Critical Review Report:

Coca leaf

Agenda item 3.1.1

Expert Committee on Drug Dependence

Forty-eighth Meeting

Geneva, 20-22 October 2025

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization.

Contents

Executive Summary

This report synthesizes current scientific evidence on the chemistry, pharmacology, toxicology, traditional/therapeutic applications, and epidemiology of use of coca leaf in response to a Member State request for a critical review by the 48th Expert Committee on Drug Dependence. Coca leaf is currently listed under Schedule I of the 1961 Single Convention (substances whose liability to abuse constitutes an especially serious risk to public health and which have very limited, if any, therapeutic usefulness).

Coca leaf refers to the unprocessed leaf of the coca bush, excluding those from which cocaine and related alkaloids have been removed. Four primary cultivated varieties are reviewed: E. coca var. coca, E. coca var. ipadu, E. novogranatense var. novogranatense, and E. novogranatense var. truxillense. Cocaine content varies across species and regions, ranging from 0.11% to 1.02% (dry weight).

The alkaloid cocaine can be extracted from the coca leaf using several solvents without altering its molecular structure. The simplicity and profitability of extraction contribute to its role in illicit cocaine production. One hectare of coca yields approximately 0.9 kg of cocaine hydrochloride annually.

Coca leaf contains a complex mixture of alkaloids, flavonoids, terpenes, and phenols. Its pharmacological effects include:

- Stimulant activity via inhibition of dopamine and norepinephrine reuptake.
- Antihypertensive and vasodilatory effects observed in several Erythroxylum species.
- Antioxidant, anti-inflammatory, and antimicrobial properties, with preclinical evidence supporting potential therapeutic applications.
- Hepatoprotective, antidiabetic, and anorectic effects, with limited human data.

Coca leaf exhibits low acute toxicity in animal models. No fatal overdoses have been reported from traditional use. Adverse effects are primarily localized (e.g., oral mucosa irritation) and dose-dependent. Coca leaf use is not associated with significant dependence or abuse potential in limited ethnographic studies, though high-dose extracts may mimic cocaine-like effects in animal models.

Traditional use in Andean regions includes coca leaf chewing and infusion (coca tea) for energy, altitude sickness, and digestive health. Studies suggest coca leaf may modulate glucose metabolism, improve exercise tolerance, and support nutritional intake, though clinical evidence remains limited.

1 Substance identification

"Coca leaf" means the leaf of the coca bush, except a leaf from which all ecgonine, cocaine, and any other ecgonine alkaloids have been removed. "Coca bush" means the plant of any species of the genus Erythroxylon (United Nations, 1961).

A comprehensive description of the taxonomy of the genus *Erythorxylum,* comprising both major and minor species, is provided below.

1. Taxonomy

The genus *Erythroxylum* P. Browne (or *Erythroxylon* Linnaeus. T. (Plowman, 1976) includes over 250 species. As of 2024, Kew's Plants of the World Online listed 270 species (Proctor, 2012), distributed across the tropical and pantropical regions of the world (Plowman & Hensold, 2004).

1.1 Major *Erythroxylum* species

Since the 1970s, cultivated coca plants have been distinguished into two species of the genus *Erythroxylum*: *Erythroxylum coca* Lamark and *Erythroxylum novogranatense* (Morris) Hieron (Johnson et al., 2003). Each comprises two subspecies described below (Evans et al., 2009). These four major varieties are reported in Table 1.

1) *Erythroxylum coca* Lam. is the most primitive cultivated coca and is less adapted to dry habitats. Two varieties can be identified:

   1.1) *Erythroxylum coca* var. *coca* [(*E. coca* var. *coca*); 'Bolivian' or 'Huánuco coca'] is produced on the eastern slopes of the Andes in Bolivia and Peru. The cocaine content can vary between 0.23% and 0.96% with an average of 0.63% (dry weight) (Plowman & Rivier, 1983).

   1.2) *Erythroxylum coca* var. *ipadu* Plowman [(*E. coca* var. *ipadu*); 'Amazonian coca'] is cultivated in the western area of the Amazon basin. The cocaine content is significantly lower compared to *E. coca* var. *coca* (0.11-0.41% with an average of 0.25% based on dry weight) (Plowman & Rivier, 1983).

2) *Erythroxylum novogranatense*: similarly to *E. coca* species, two varieties can be identified:

   2.1) *Erythroxylum novogranatense* var. *novogranatense* (Morris) Hieron [(*E. novo*. var. *novogranatense*); 'Colombian coca'] has been cultivated throughout the mountains of present Colombia and Venezuela since pre-Columbian times. It thrives at lower altitudes and in hotter and drier climates than does *E. coca*; this variety was widely cultivated in the Old-World tropics, especially in the

former British colonies, as an ornamental plant with a lower content of cocaine. The cocaine content can vary between 0.55% and 0.93% with an average of 0.77% (dry weight) based on the data reported by Plowman and Rivier on three laboratory-cultivated samples (Plowman & Rivier, 1983).

2.2) *Erythroxylum novograntense* var. *truxillense* (Rusby) Plowman [*(E. novo*. var. *truxillense*); 'Trujillo coca'], is well adapted to the desert conditions of North Peru and was cultivated specifically for 'coca chewing' and the manufacture of coca-based soft drinks (devoid of cocaine). The cocaine content ranges between 0.42% and 1.02% with an average of 0.72% (dry weight) (Plowman & Rivier, 1983).

Geographic origin and cocaine content for each subspecies are summarized in Table 1.

Table 1. Major species and varieties of Erythroxylum with reference images, geographic origin, and cocaine content.

Species	Subspecies[a]	Geographic origin	% Cocaine content (avg..)[b]
Erythroxylum coca	*Erythroxylum coca* var. *coca* (*E. coca* var. *coca*) 'Bolivian coca' or 'Huánuco coca'	Eastern slopes of the Andes in Bolivia and Peru	0.23-0.96 (0.63)
	Erythroxylum coca var. *ipadu* Plowman (*E. coca* var. *ipadu*) 'Amazonian coca'	Western area of the Amazon basin	0.11-0.41 (0.25)
Erythroxylum novogranatense	*Erythroxylum novogranatense* var. *novogranatense* (Morris) Hieron (*E. novo*. var. *novogranatense*) 'Colombian coca' or 'Java coca'	Mountains of present-day Colombia and Venezuela	0.55-0.93 (0.77)
	Erythroxylum novograntense var. *truxillense* (Rusby) Plowman *(E. novo*. var. *truxillense*) 'Trujillo coca'	North Peru	0.42-1.02 (0.72)

[a] Scientific name (abbreviation of the scientific name) 'other names'; [b] based on dry weight according to (Plowman & Rivier, 1983)

1.2 Other *Erythroxylum* species

The wide variety of over 250 existing *Erythroxylum* species is spread throughout the tropical and semi-tropical regions of the world. The majority of the non-cocaine-producing species examined were found to contain a range of other tropane alkaloids, including pervilleines, catuabines, and calystegins. Esters of trimethoxybenzoic acid and trimethoxycinnamic acid seem to commonly occur in all *Erythroxylum* species. A study of 51 wild species of *Erythroxylum* from South America reported the presence of cocaine in 23 of them, with *E. laetevirens* having the highest cocaine content (Evans et al., 2009).

A. International Nonproprietary Name (INN)

N/A

B. Chemical Abstract Service (CAS) Registry Number

N/A

C. Other Chemical Names

Bolivian leaf; Coca; Coca folium; Coca levelek; Cocablatt; Cocae folium; Cuca; Daun coca; Erythroxylon; Erythroxylum coca; Erythroxylum truxillense; Foglia di coca; Foi de coca; Folha de coca; Folia coca,-o; Folia erytroxyli cocae; Folium cocae; Hayo; Huanuco leaf; Ipadá,-ò,-ù; Kkoka; Koka; Koka yapraggi; Kokablad; Kokablatt; Kookanlehti; Lisc koka; Listy kokadové; Listy rudodreva koka; Peruvian leaf; Trujillo coca; Trujillo herb; Truxillo leaf; Waraquol koka; Ypadu (United Nations, 2006).

D. Trade names

Raw or dried coca leaves, whole or chopped, are marketed as coca tea and are available either in loose form or in individually packaged serving bags sold under brand names ' (Siegel et al., 1986).

Coca Leaf Powder (Coca flour) is marketed as a nutritional supplement by Enaco S.A. (Lima, Peru) (ENACO, 2021).

E. Street Names

See other chemical names.

F. Physical Appearance

Coca leaves are similar in appearance to *Laurus nobilis* leaves, especially the oval shape, but size and appearance vary among different plant varieties (see Section 1.1). The common characteristic traits in all species are the darker color of the upper side compared to the underside of the leaf, and two lines parallel to the midrib of the leaf (NicDaéid & Savage, 2013).

Based on the species, the leaves have different physical appearances:

> *E. coca* var. *coca:* the leaves are elliptic in shape (2.5-7.5 cm long and 1.5-4 cm wide), thick, pointed at the apex, greenish brown to brown in color, and glabrous with the margin entire. The midrib is prominent on the lower surface and presents a ridge on its upper surface, protruding slightly beyond the lamina as an apiculus. The lamina is often broken in the commercial product, but the leaves are fairly entire. The leaves have a characteristic aromatic odor and a bitter and slightly aromatic taste, although the alkaloids cause the numbness of the tongue and lips afterwards (Evans et al., 2009).

E. coca var. *ipadu:* the leaves are broadly elliptic and rounded at the base (Evans et al., 2009) with size and shape intermediate between the Bolivian coca and the Colombian coca (Plowman, 1982). The characteristic 'parallel lines' on the lower surface described in the *E. coca* var. *coca* are often indistinct or lacking.

E. novo. Var. *novogranatense: t*he leaves are smaller, narrower, thinner, rounded at the apex, and bright yellow-green colored compared to those of the *E. coca* species (Evans et al., 2009).

E. novo. Var. *truxillense:* the leaves are 1.6-5 cm long, pale green in colour, paperier in texture than the Bolivian coca, and are usually broken. The lamina is about 1.6-5 cm long, and the 'parallel lines' on the lower surface are usually indistinct (Evans et al., 2009).

Coca leaves can also be more or less finely pulverized and appear as a greenish powder with variable granulometry.

2 CHEMISTRY

A. ***Chemical Name***

IUPAC Name:

N/A

CA Index Name:

N/A

B. ***Chemical Structure***

Free base:

N/A

Molecular Formula:

N/A

Molecular Weight:

N/A

C. ***Stereoisomers***

N/A

D. ***Methods and Ease of Illicit Manufacturing***

Cultivation and collection differ depending on the geographical source. For the coca cultivated in the Andean region at an altitude of 500-2000 m, the plants grow from seed. Seeds are usually

gathered from December through March from plants that are two to three years old, planted in small plots kept shaded from the sun. The seedbeds are kept well-watered and weeded frequently, and the seeds usually germinate within 20 to 30 days. Seedlings are usually transplanted after about two months when they are about 12 inches tall (United States Department of Justice, 1991). During the first few days, the transplanted seedlings are continuously irrigated and reach the mature stage for harvest after 12 months, but there have been reports of fields harvested after 8 months from transplantation due to the use of fertilizer. After the harvesting, pesticides are applied to the bushes to protect the crop from a variety of pests, including larvae, fungus, and ants. At 4-5 years old, the plant is totally pruned, leaving only the base of the trunk, a practice called *pillu* that significantly increases the crop yield of the next harvest, which starts not earlier than 6-8 months. The life of a coca plant is about 30 years. After harvesting, the leaves are dried artificially or by the sun and packed into bags for commercial use (UNODC, 2006)

In the Amazon basin, plants grow from cuttings, often in jungle clearings and interplanted between other staple crops (Evans et al., 2009). The cuttings are planted at the beginning of the rainy season, then the shrub grows sparsely with the stems eventually covered completely with lichens. After 18 months, the bush is ready for harvest and may yield leaves for 20 to 30 years (Schultes, 1980).

E. *Chemical Properties*

Melting point

N/A

Boiling point

N/A

Solubility

N/A

Stability

N/A

E1. Chemical composition

A total of 383 compounds from 67 *Erythroxylum* species have been reported to date (Lv et al., 2022). These compounds mainly belong to the classes of alkaloids, terpenes, flavonoids, tannins, and phenols (Lv et al., 2022). The total alkaloid content can reach up to 2.4% (calculated on a dry weight basis) in *E. coca*, *E. coca* var. *coca*, and *E. novo.* var. *novogranatense* (Aynilian et al., 1974).

The production of total phenols can be up to 17.97%, while those of tannins and flavonoids are reported to be up to 8.4% and 3.87%, respectively. Such amounts were reported for *E. suberosum, E. tortuosum, and E. deciduum* (Rodrigues et al., 2015). Total diterpene content was found to be up to 1.8% in stems of *E. australe* and *E. pictum* (Lv et al., 2022).

E1.1 Moisture

Coca leaf can be traded either as fresh, as in Colombia, or dried, as in Peru and Bolivia. When comparing the two types of coca leaf, it should be taken into account that the fresh one has been assessed to contain about 57% moisture as reported in a survey conducted by UNODC in 2004 (UNODC, 2006). Moreover, due to the different post-harvest processing methods in the Andean regions, coca leaf yield and production can be expressed in fresh, sun-dry, or oven-dry leaves. Sun-drying, which is typically carried out for traditional uses (tea preparation and chewing), causes a weight loss of more than 50%, while oven-drying reduces the weight of fresh leaves by about 70% (UNODC, 2010).

Indeed, experiments carried out by Johnson et al. showed that 4 g fresh leaves afforded 1.1 g dry weight after 2 h in the oven at 70 °C (removed about 72±3% of the fresh leaves' weight) (Johnson, 1995).

Additionally, analysis of moisture contents of seven commercially dried leaves from *E. coca* var. *coca* varied from 13% to 16%, except for a commercially processed coca flour sold as a nutritional supplement and bought as a dried, micropulverized leaf flour, which had a moisture content of 8% (Penny et al., 2009).

E1.2 Nutritional components

Nutritional values are reported for 100 g of dry leaves (with a maximum moisture content of 0.5%) of *E. coca* Lam. from Chapare, Bolivia (Duke et al., 1975) and *E. coca* var. *coca* from seven different regions of Peru (with a maximum moisture content of 11.68%) (Penny et al., 2009) (Table 2).

Table 2. Nutritional values based on 100 g of product.

	Value/100 g	
Nutritional component	(Duke et al., 1975)	(Penny et al., 2009)[a]
Energy	305 calories	346 calories
Proteins	18.9 g	20.28 g
Carbohydrates	46.2 g	-
Fibers	14.4 g	15.46 g
Fat	5.0 g	6.12 g
Ash	9.0 g	5.65 g
Calcium	1540 mg	990.18 and 1033.17 mg[b]

Phosphorous	911 mg	-
Iron	4.8 mg	29.16 and 29.16 mg[b]
Iodine	5.0 mg	-
Magnesium	213 mg	225.19 and 196.69 mg[b]
Zinc	2.70 mg	2.71 and 2.63 mg[b]
Copper	1.21 mg	-
Biotin	0.0863 mg	-
Pantothenic acid	0.684 mg	-
Sodium	40.6 mg	-
Potassium	2.02 g	-
Aluminium	39.5 mg	-
Barium	4.67 mg	-
Stronzium	9.71 mg	-
Boron	5.35 mg	-
Manganese	6.65 mg	-
Chromium	0.359 mg	-
Vitamin A (β-carotene)	11000 IU	3.51 mg
Vitamin B2 (riboflavin)	1.91 mg	-
Vitamin C (ascorbic acid)	1.4 mg	-
Vitamin E (α-tocopherol)	43.5 IU	16.72 mg
Vitamin B6	0.508 mg	-
Folic acid	0.13 mg	-
Vitamin B12	1.05 mg	-
Oil	5.0 g	-
Thiamine	0.35 mg	-
Niacin	1.29 mg	-
Histidine	-	0.418 mg
Isoleucine	-	0.728 mg
Leucine	-	1.323 mg
Lysine	-	0.801 mg
Methionine	-	0.337 mg
Cysteine	-	0.200 mg
Phenylalanine	-	0.790 mg
Tyrosine	-	0.570 mg
Threonine	-	0.711 mg
Tryptophan	-	0.265 mg
Valine	-	0.902 mg

[a] Values are reported as the mean of eight samples; [b] Data from two different laboratories.

E1.3 Terpenes

Erythroxylum comprises 11 types of diterpene scaffolds for a total of 78 compounds, which can be classified into three subclasses: 12 bicyclic, 22 tricyclic, and 44 tetracyclic diterpenes. Besides

diterpenes, a total of 19 triterpenoids with a pentacyclic structure have been identified in the genus *Erythroxylum*, 10 of which are fatty acid esters of triterpenes. Most diterpenes have been isolated not only from the leaves but also from the timber and roots of the plants, while triterpenes were identified from aerial organs (Lv et al., 2022). Diterpenes and triterpenes found in *Erythroxylum* species are reported in Table 3.

Table 3. Diterpenes and triterpenes found in the *Erythroxylum* genus.

Diterpenes			Triterpenes
Bicyclic diterpenes	Tricyclic diterpenes	Tetracyclic diperpenes	
ent-labda-8(17),14-dien-13*R*-ol	7-oxo-16-hydroxy-abiet-15(17)-en-19-al	*ent*-beyer-15-ene ((+)-hibaene)	*β*-amyrin palmitate and stearate
ent-13*R*-hydroxylabda-8(17)-dien-3-one	7-oxo-abiet-15(17)-en-16-ol	*ent*-beyer-15-en-19-ol (erythroxylol A)	erythrodiol palmitate and stearate
ent-labda-8(17),14-dien-3*β*,13*R*-diol	7*α*,16-dihydroxy-abiet-15(17)-en-19-al	*ent*-beyer-15-en-17-ol	oleanolic acid
ent-labda-8(17),14-dien-13*R*,18-diol	*ent*-pimara-8(14),15-dien-3*α*-ol	*ent*-beyer-15-en-17,19-diol	*β*-amyrin palmitate
ent-labda-8(17),13*E*-dien-15-ol	*ent*-3*α*,11*β*-dihydroxypimara-8(14),15-diene	*ent*-beyer-15-en-1*α*-ol	3*β*-hydroxy-11-oxo-olean-12-enylpalmitate
ent-labda-8(17),13*E*-dien-15,16-diol	erythroxydiol Y (allodevadarool)	*ent*-beyer-15-en-12*β*-ol	3*β*,11*β*-dihydroxy-olean-12-enyl palmitate
ent-15*ξ*,16-dihydroxypictan-4(18)-en-5-one	*ent*-dolabr-4(18)-ene-15*S*,16-diol	*ent*-beyer-15-en-7-one	3*β*,28-dihydroxy-olean-12-enyl palmitate
ent-4,15*ξ*,16-trihydroxypictan-5-one	*ent*-5*β*-dolabr-4(18)-ene-15*R*,16-diol	*ent*-2-hydroxybeyer-2,15-dien-1-one	3*β*-hydroxy-11,12-epoxy–friedoolean-14-enyl palmitate
ent-4,15*ξ*,16,18-tetrahydroxypictan-5-one	*ent*-15,16-dihydroxydolabr-4(18)-en-1-one	*ent*-2,17-dihydroxybeyer-2,15-dien-1-one	lupenyl palmitate
ent-15*ξ*,16-dihydroxy-4,18-epoxypictane-5-one	*ent*-1*α*-acetoxydolabr-4(18)-ene-11*α*,15*ξ*,16-triol	*ent*-2,19-dihydroxybeyer-2,15-dien-1-one	lupenyl acetate
ent-16-hydroxypictan-4(18)-ene-5,15-dione	*ent*-dolabr-4(18)-ene-11*α*,15*ξ*,16-triol	*ent*-15,16-epoxy-beyer-1-one	*α*-amyrin esters
ent-4,13*α*-dihydroxy-15*ξ*,16-bisnorpictan-5-one	*ent*-11*α*-acetoxydolabr-4(18)-ene-15*ξ*,16-diol	*ent*-15,16-epoxy-beyerene	*α*-amyrin
	ent-dolabr-4(18)-ene-7*β*,15*S*,16-triol	erythroxylol A epoxide	*β*-amyrin
	ent-dolabr-4(18)-ene-7*β*,15*R*,16-triol	erythroxylol A acetate epoxide	erythrodiol
	ent-5*β*-ros-1(10)-en-15*ξ*,16-diol	4*β*-hydroxy-18-norhibaene	lupeol

	ent-11*α*-acetoxy-5*α*-ros-1(10)-en-15*ξ*,16-diol	4*α*-hydroxy-18-norhibaene	lupenone
	ent-2-oxo-ros-1(10),15-diene	*ent*-beyer-15-en-19-al	friedelanol
	ent-rosane-5*α*,15*ξ*,16-triol	*ent*-17-hydroxybeyer-15-en-1-one	friedelan-3-one
	ent-5*α*,16-dihydroxyrosan-15-one	*ent*-2*α*,17-dihydroxybeyer-15-en-1-one	taraxerol
	ent-rosane-5*α*,16-diol	*ent*-2*α*,19-dihydroxybeyer-15-en-1-one	
	ent-ros-5-en-15*ξ*,16-diol	*ent*-beyer-15-en-1-one	
	ent-rosan-1-one-5*β*,15*ξ*,16-triol	*ent*-2*α*-hydroxybeyer-15-en-1-one	
		ent-19-hydroxybeyer-15-en-1-one	
		ent-1*α*-hydroxybeyer-15-en-2-one	
		ent-1*α*,17-dihydroxybeyer-15-en-2-one	
		ent-1*α*,19-dihydroxybeyer-15-en-2-one	
		isoatisirene	
		atisirene	
		ent-kauran-16-ol	
		ent-kauran-16,17-diol	
		erythroxylisin A	
		erythroxylisin B	
		ent-12*β*-hydroxy-kaur-16-en-19-al	
		methylent-7*β*,15*α*-dihydroxy-kaur-16-en-19-oate	
		(+)-devadarene	
		ent-devadarane-15*ξ*,16-diol	
		ent-devadaran-l*α*,11*α*,15*ξ*,16-tetrol	
		ent-l*α*-acetoxydevadaran-11*α*,15*ξ*,16-triol	
		triol Q	
		ent-11*α*-acetoxy-devadarane-15*ξ*,16-diol	
		ent-devadarane-11*α*,15*ξ*,16-triol	
		ent-devadarane-7*β*,15*ξ*,16-triol	

		ryanodanol	
		14-O-methyl-ryanodanol	

Monoterpenes and sesquiterpenes have been also investigated in fresh leaves of *E. ovalifolium* and *E. subsessile* (Cruz et al., 2018). Acyclic, monocyclic, and bicyclic compounds can be distinguished in the monoterpenes class (Table 4).

Table 4. Monoterpenes and sesquiterpenes found in the *Erythroxylum* genus.

Diterpenes			Triterpenes
Bicyclic diterpenes	Tricyclic diterpenes	Tetracyclic diperpenes	
ent-labda-8(17),14-dien-13*R*-ol	7-oxo-16-hydroxy-abiet-15(17)-en-19-al	*ent*-beyer-15-ene ((+)-hibaene)	*β*-amyrin palmitate and stearate
ent-13*R*-hydroxylabda-8(17)-dien-3-one	7-oxo-abiet-15(17)-en-16-ol	*ent*-beyer-15-en-19-ol (erythroxylol A)	erythrodiol palmitate and stearate
ent-labda-8(17),14-dien-3*β*,13*R*-diol	7*α*,16-dihydroxy-abiet-15(17)-en-19-al	*ent*-beyer-15-en-17-ol	oleanolic acid
ent-labda-8(17),14-dien-13*R*,18-diol	*ent*-pimara-8(14),15-dien-3*α*-ol	*ent*-beyer-15-en-17,19-diol	*β*-amyrin palmitate
ent-labda-8(17),13*E*-dien-15-ol	*ent*-3*α*,11*β*-dihydroxypimara-8(14),15-diene	*ent*-beyer-15-en-1*α*-ol	3*β*-hydroxy-11-oxo-olean-12-enylpalmitate
ent-labda-8(17),13*E*-dien-15,16-diol	erythroxydiol Y (allodevadarool)	*ent*-beyer-15-en-12*β*-ol	3*β*,11*β*-dihydroxy-olean-12-enyl palmitate
ent-15*ξ*,16-dihydroxypictan-4(18)-en-5-one	*ent*-dolabr-4(18)-ene-15*S*,16-diol	*ent*-beyer-15-en-7-one	3*β*,28-dihydroxy-olean-12-enyl palmitate
ent-4,15*ξ*,16-trihydroxypictan-5-one	*ent*-5*β*-dolabr-4(18)-ene-15*R*,16-diol	*ent*-2-hydroxybeyer-2,15-dien-1-one	3*β*-hydroxy-11,12-epoxy–friedoolean-14-enyl palmitate
ent-4,15*ξ*,16,18-tetrahydroxypictan-5-one	*ent*-15,16-dihydroxydolabr-4(18)-en-1-one	*ent*-2,17-dihydroxybeyer-2,15-dien-1-one	lupenyl palmitate
ent-15*ξ*,16-dihydroxy-4,18-epoxypictane-5-one	*ent*-1*α*-acetoxydolabr-4(18)-ene-11*α*,15*ξ*,16-triol	*ent*-2,19-dihydroxybeyer-2,15-dien-1-one	lupenyl acetate
ent-16-hydroxypictan-4(18)-ene-5,15-dione	*ent*-dolabr-4(18)-ene-11*α*,15*ξ*,16-triol	*ent*-15,16-epoxy-beyer-1-one	*α*-amyrin esters
ent-4,13*α*-dihydroxy-15*ξ*,16-bisnorpictan-5-one	*ent*-11*α*-acetoxydolabr-4(18)-ene-15*ξ*,16-diol	*ent*-15,16-epoxy-beyerene	*α*-amyrin
	ent-dolabr-4(18)-ene-7*β*,15*S*,16-triol	erythroxylol A epoxide	*β*-amyrin
	ent-dolabr-4(18)-ene-7*β*,15*R*,16-triol	erythroxylol A acetate epoxide	erythrodiol
	ent-5*β*-ros-1(10)-en-15*ξ*,16-diol	4*β*-hydroxy-18-norhibaene	lupeol
	ent-11*α*-acetoxy-5*α*-ros-1(10)-en-15*ξ*,16-diol	4*α*-hydroxy-18-norhibaene	lupenone

ent-2-oxo-ros-1(10),15-diene	*ent*-beyer-15-en-19-al	friedelanol
ent-rosane-5*α*,15*ξ*,16-triol	*ent*-17-hydroxybeyer-15-en-1-one	friedelan-3-one
ent-5*α*,16-dihydroxyrosan-15-one	*ent*-2*α*,17-dihydroxybeyer-15-en-1-one	taraxerol
ent-rosane-5*α*,16-diol	*ent*-2*α*,19-dihydroxybeyer-15-en-1-one	
ent-ros-5-en-15*ξ*,16-diol	*ent*-beyer-15-en-1-one	
ent-rosan-1-one-5*ϐ*,15*ξ*,16-triol	*ent*-2*α*-hydroxybeyer-15-en-1-one	
	ent-19-hydroxybeyer-15-en-1-one	
	ent-1*α*-hydroxybeyer-15-en-2-one	
	ent-1*α*,17-dihydroxybeyer-15-en-2-one	
	ent-1*α*,19-dihydroxybeyer-15-en-2-one	
	isoatisirene	
	atisirene	
	ent-kauran-16-ol	
	ent-kauran-16,17-diol	
	erythroxylisin A	
	erythroxylisin B	
	ent-12*ϐ*-hydroxy-kaur-16-en-19-al	
	methylent-7*ϐ*,15*α*-dihydroxy-kaur-16-en-19-oate	
	(+)-devadarene	
	ent-devadarane-15*ξ*,16-diol	
	ent-devadaran-l*α*,11*α*,15*ξ*,16-tetrol	
	ent-l*α*-acetoxydevadaran-11*α*,15*ξ*,16-triol	
	triol Q	
	ent-11*α*-acetoxy-devadarane-15*ξ*,16-diol	
	ent-devadarane-11*α*,15*ξ*,16-triol	
	ent-devadarane-7*ϐ*,15*ξ*,16-triol	
	ryanodanol	
	14-O-methyl-ryanodanol	

Examples of the chemical structure of the terpenes present in *Erythroxylum* are shown in Figure 1.

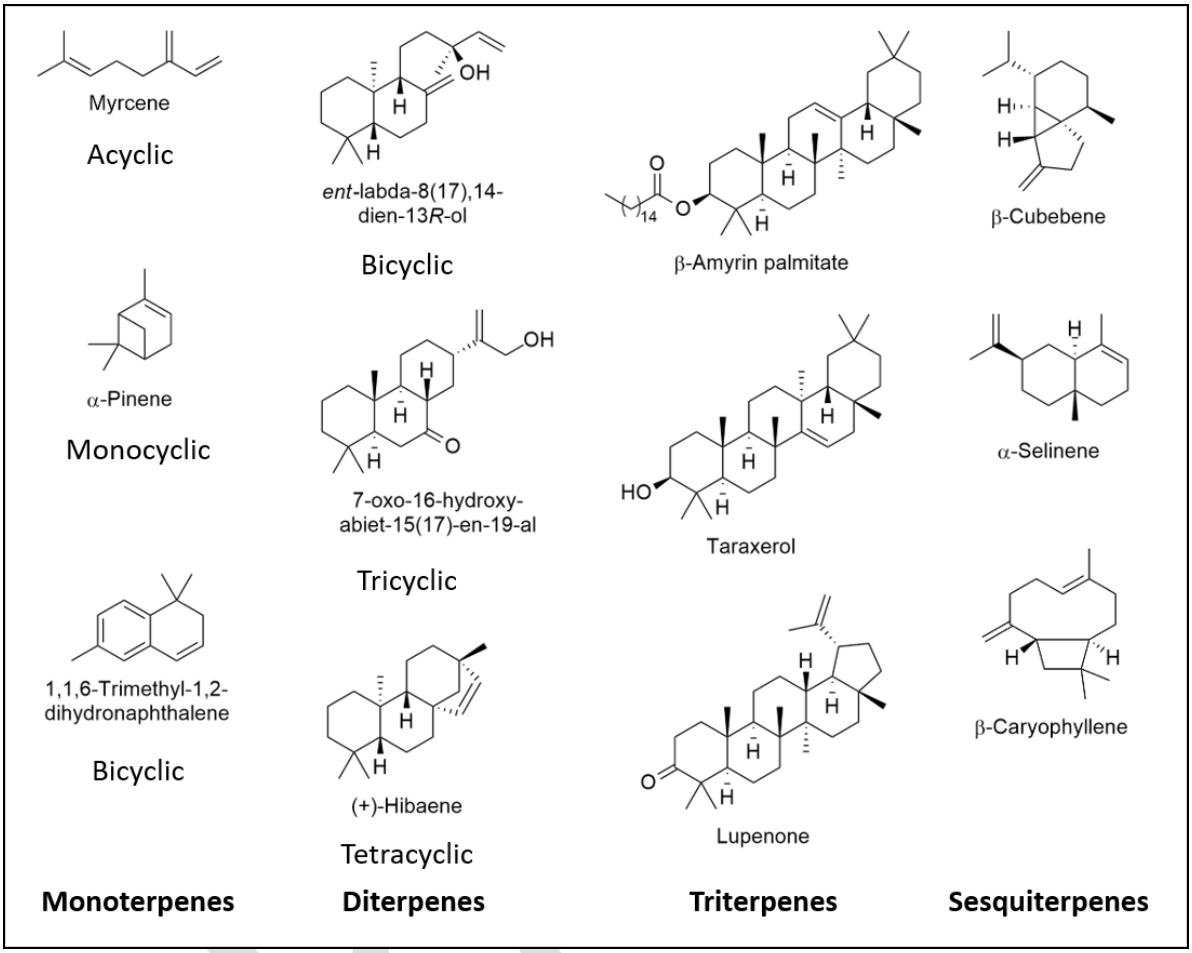

Figure 1. Chemical structure of examples of terpenes found in *Erythroxylum*.

E1.4 Alkaloids

The *Erythroxylum* genus is characterized by the production of tropane alkaloids, which bear a tropane skeleton (8-azabicyclo[3.2.1]octane). The most updated review of such compounds dates back to 2022 and reports 197 tropane alkaloids from 53 *Erythroxylum* species (Lv et al., 2022). The tropane skeleton is characterized by a two-ring structure with two carbons and the nitrogen atom at the bridge position of a pyrrolidine and piperidine rings (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2013). Most compounds of this class are represented by esters derived from ecgonine and organic acids, including acetic, tiglic, isovaleric, 2-methylbutyric, phenylacetic, 2-hydroxy-3-phenylpropionic, benzoic, cinnamic, 3,4,5-trimethoxybenzoic, 3,4,5-trimethoxycinnamic, pyrrole-2-carboxylic, and *N*-methylpyrrole-2-carboxylic acids. Pyrrole-2-carboxylic acid and 2-furoic acid are typical acid moieties of alkaloids in *E. vacciniifolium* and *E. dekindtii*, respectively. The latter species is also characterized by a limited range of alkaloids, which include tropine and pseudotropine esters. In particular, esters of tiglic acid seem to be unique to *E. australe* (Evans, 1981).

Typical acid moieties found in *Erythroxylum alkaloids* are reported in Figure 2.

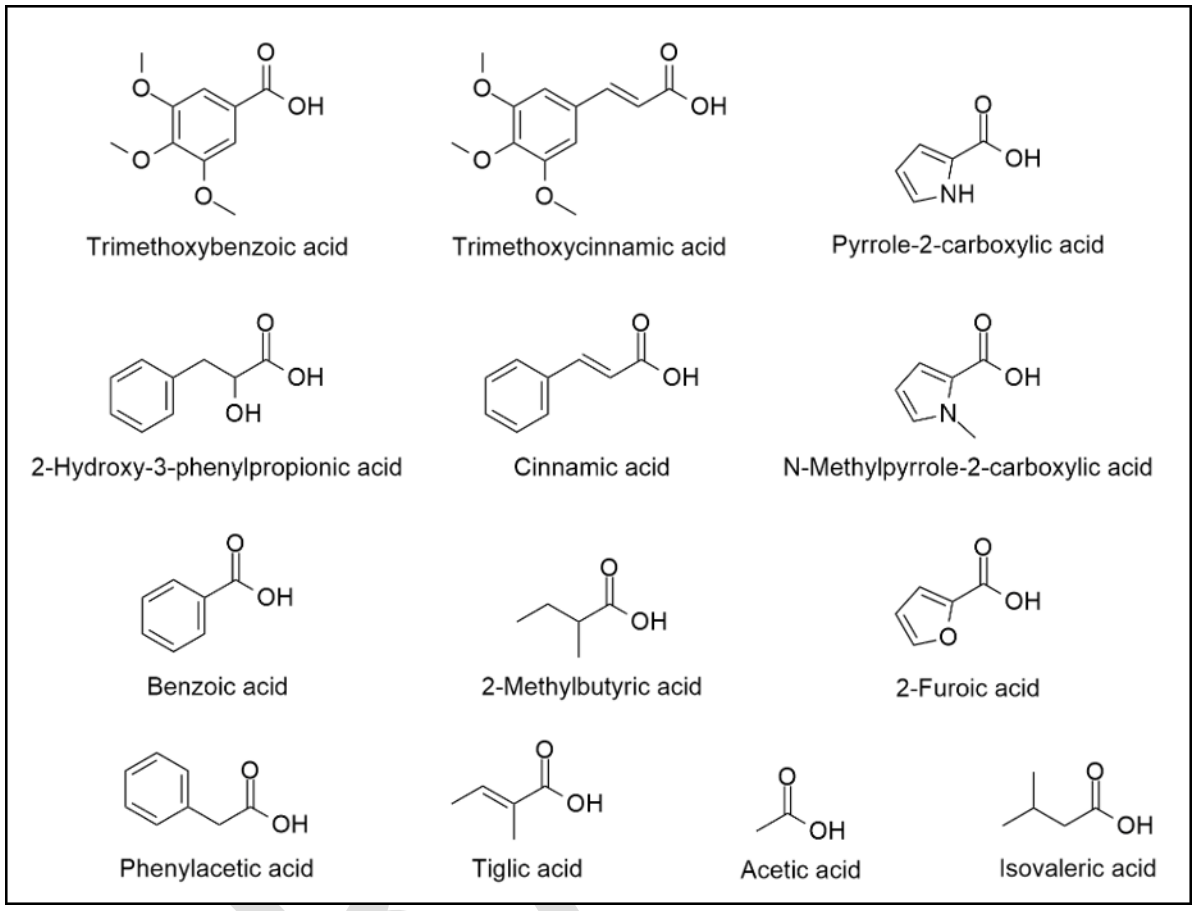

Figure 2. Acid moieties found in *Erythroxylum* alkaloids.

The total content of alkaloids in coca leaves ranges between 0.7 and 1.5% with the predominant components being cocaine (methylbenzoylecgonine), *cis*- and *trans*-cinnamoylcocaine and α-truxilline (Evans et al., 2009). However, other studies in the literature report different concentration ranges, such as 0.5-2.4% (Aynilian et al., 1974; Johnson & Foy, 1996). They occur in different proportions in different cultivated varieties. Javanese leaves usually present the highest total alkaloid content with the most abundant compound being the cinnamoylcocaines. In contrast, the Bolivian and Peruvian leaves contain a lower total alkaloid content but a higher proportion of cocaine. Other compounds of this class isolated from different varieties of *Erythroxylum* include hygrine, hygroline, cuscohygrine, dihydrocuscohygrine, and tropacocaine (3β-benzoyloxytropane). 1-Hydroxytropacocaine has been isolated as a major alkaloid of greenhouse-cultivated *E. novo.* var. *novogranatense* (Evans et al., 2009).

In addition to cocaine, cis- and trans-cinnamoylcocaine, hygrine, cuscohygrine, and tropacocaine, many studies analyzing coca leaf alkaloids also report ecgonine derivatives, such as ecgonine

methyl ester (methylecgonine), benzoylecgonine, anhydroecgonine methyl ester, and tropinone as target analyte (Johnson, 1995; Turner et al., 1981).

Cocaine is produced in significant amounts only in cultivated varieties, whereas wild species either do not contain this alkaloid or it is present only in small quantities (0.00008-0.00882%). All varieties share the common presence of ecgonine derivatives together with hydroxytropanes and their esters (Evans, 1981).

The alkaloids in coca leaf that have received the most research attention are shown in Figure 3.

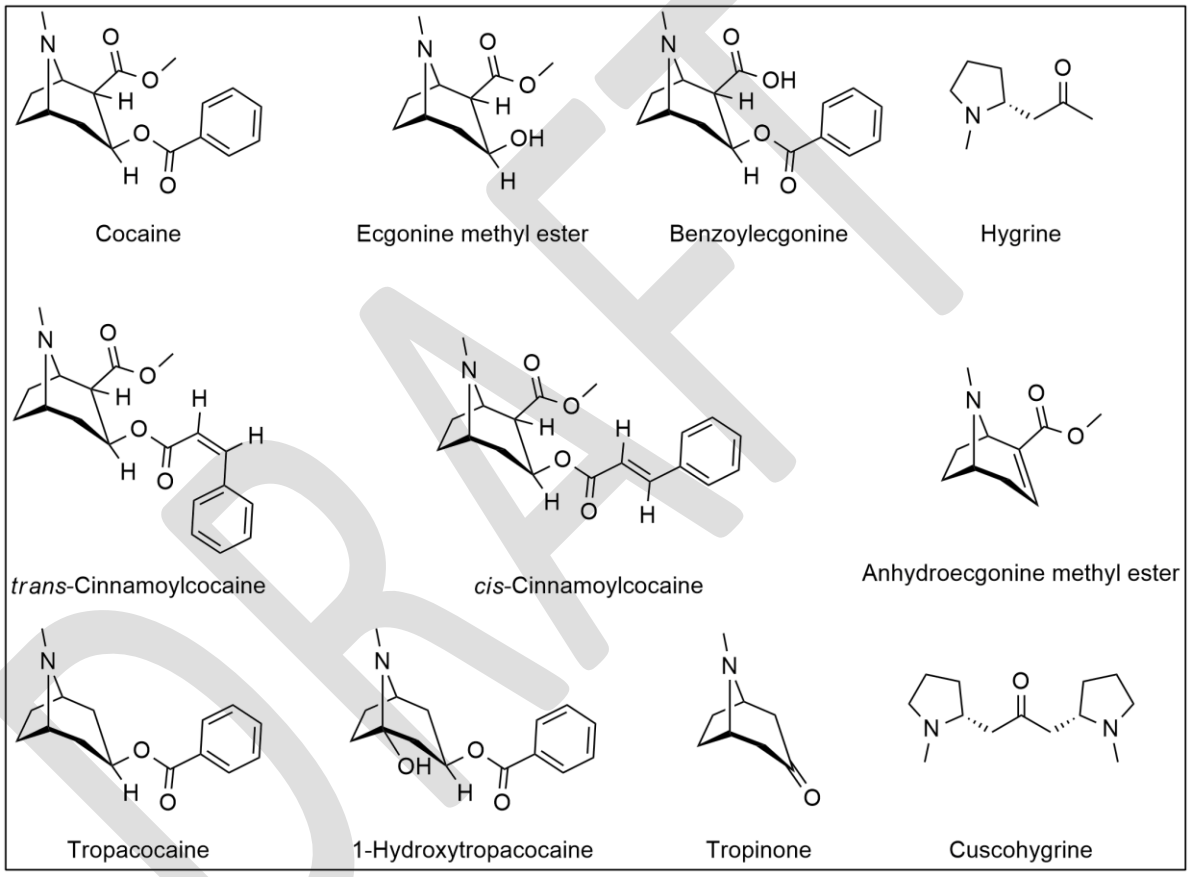

Figure 3. Most investigated alkaloids in coca leaf.

E1.5 Flavonoids

In total, 73 flavonoids from 37 species of *Erythroxylum* have been identified in leaves or branches: predominant flavoinoid aglycones found in *Erythroxylum* are quercetin, ombuin (7,4′-dimethylquercetin), kaempferol, fisetin, epicatechin, eriodictyol and taxifolin. Additionally, isofavone, isofavanone and other favone derivatives can be found and the major glycosides of these favonoids include mono-glucosyl rhamnosyls and dirhamnosyl-glucosides, as well as mono-galactosyl and mono-arabinosyl (Lv et al., 2022).

The chemical structures of the most abundant flavonoids and sugar residues found in *Erythroxylum* species are shown in Figure 4.

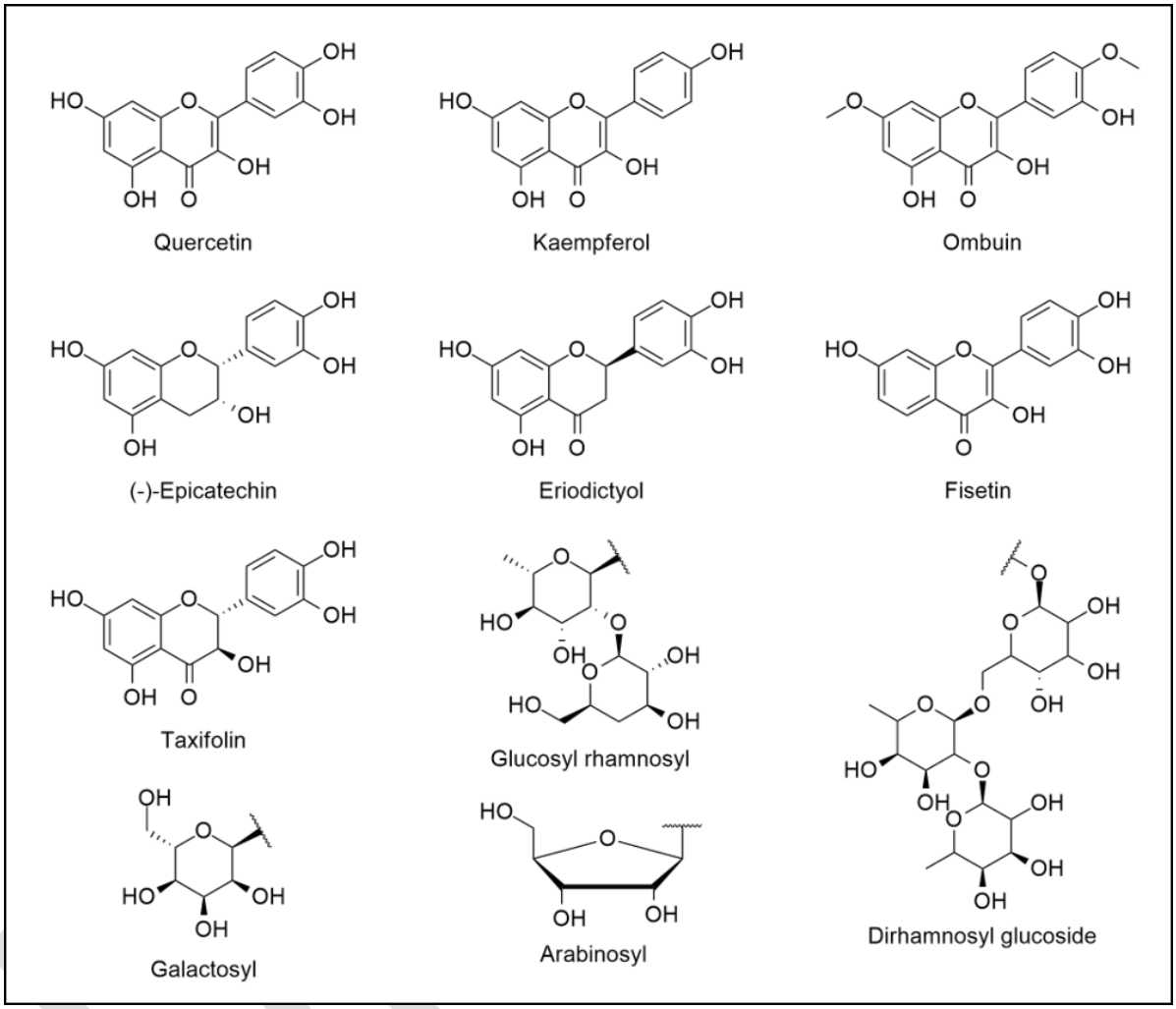

Figure 4. Chemical structure of the most abundant flavonoids and sugar residues found in *Erythroxylum*.

E1.6 Other constituents

Other compounds contributing to the chemical composition of the *Erythroxylum* genus include megastigmanes (norisoprenoid compounds) characterized in the leaves of *E. cuneatum* and three steroids including 4-methyl ergosta-7,23-dien-3*β*-ol and 4-methyl ergosta-7,24(28)-dien-3*β*-ol from *E. monogynum* leaves and *β*-sitosterol from *E. barbatum*, *E. daphnites*, *E. rimosum*, *E. nummularia*, and *E. passerinum* leaves (Lv et al., 2022).

E1.7 Botanical variation in coca plant and differences in component substances (types and proportions), distribution in coca leaf

The chemical composition of the coca leaf can vary depending on the species and the climate it is grown in (Restrepo et al., 2019). In relation to the alkaloids, their content is known to vary due to the growth environment, method of storage after harvest, growth stage, and treatment during extraction (Restrepo et al., 2019; Turner et al., 1981). Among the different parts of the coca plant, the leaves exhibit the highest alkaloid content (Johnson, 1996). The leaves of *E. coca*, *E. coca* var. *coca*, and *E. novogranatense* var. *novogranatense* show different concentrations of alkaloids ranging from 0.5% to 2.4% (Lv et al., 2022). Among the alkaloid class, cocaine concentrations are lower in the *E. coca* var. *ipadu* (Amazonian coca) with 0.11-0.41%. *E. coca* var. *coca* (Bolivian coca) contains an average of 0.63% cocaine, while the highest levels have been registered in the *E. novogranatense* varieties with 0.77% in *E. novo.* var. *novogranatense* (Colombian coca) and 0.72% in *E. novo.* var. *truxillense* (Trujillo coca) (Plowman & Rivier, 1983). Of the 51 plants from wild species investigated by S. Bieri et al. in 2006, 23 showed the presence of cocaine with amounts lower than 0.001% (dry leaves). *E. suberosum*, *E. tortuosum*, and *E. deciduum* registered a high production of total phenols, total tannins and total flavonoids of up to 17.97%, 8.4%, and 3.87% (dry leaves), respectively. Moreover, the total diterpenes content determined in stems of *E. australe* and *E. pictum* ranged from 0.09% to 1.8% (dry mass) (Bieri, Brachet, et al., 2006).

Light intensity does not significantly affect the alkaloid production, while lower temperatures seem to negatively influence this process in all cultivars studied by Acock et al. in 1996 (Acock et al., 1996).

A study on the alkaloid distribution over the leaf growth stages showed that cocaine peaked in 7-day old rolled leaves (0.75%) and declined to 0.39% at leaf drop. Cocaine, ecgonine methyl ester, hygrine, tropinone, *trans*-cinnamoylcocaine, *cis*-cinnamoylcocaine, cuscohygrine, and tropacocaine content in mature (35-day old) leaves was 0.61%, 0.59%, 0.68%, 0.08%, 0.31%, 0.55%, 0.52%, and 0.05%, respectively. Of these alkaloids, cocaine, ecgonine methyl ester, hygrine, *cis*-cinnamoylcocaine, and cuscohygrine gradually decreased from week 2 to week 36 (at leaf drop). *Cis*-cinnamoylcocaine content was higher than cocaine at week 12, 16, and weeks 19 to 23. *Trans*-cinnamoylcocaine was higher in rolled leaves (week 1) and in expanded leaves after week 30 (Johnson & Emche, 1994). Similarly, L. River investigated the content of cocaine and the cinnamoylcocaines at different growth stages. In *E. coca* var. *coca* and *E. novo.* var. *novogranatense*, the cinnamoylcocaines were more abundant in younger leaves, while cocaine content increased with leaf age, although the amounts varied dramatically between the two subspecies. In *E. novo.* var. *truxillense*, although the alkaloid pattern was the same as in the other two subspecies, the proportion of cinnamoylcocaines was greater in young leaves than in old ones when compared to cocaine levels (Rivier, 1981).

Even within the same species, plants grown in different geographical areas can produce different amounts of alkaloids. Indeed, notwithstanding similar cocaine concentrations, the

cocaine/cinnamoylcocaine and the *cis*-/*trans*-cinnamoylcocaine ratios varied between samples of *E. coca* collected from three different areas. The registered values for cocaine, *cis*-cinnamoylcocaine and *trans*-cinnamoylcocaine were respectively in the range of 0.57-0.60%, 0.03-0.08% and 0.01-0.07% (*w/w*) for the *E. coca* of Tingo Maria, Cuzco, and Trujillo (Turner et al., 1981).

Greenhouse cultivated plants of *E. coca* var. *coca* were analysed at 35-70 days from leaf formation. Each harvested leaf was divided into four primary sections (petiole, base, mid and anterior) and three subsections (lamina periphery, false midrib, and true midrib) to determine the distribution and content of hygrine, cuscohygrine, *trans*-cinnamoylcocaine, *cis*-cinnamoylcocaine, tropacocaine, tropinone, ecgonine methyl ester, and cocaine. Cocaine, ecgonine methyl ester, and hygrine showed the highest concentration in the lamina periphery with a content of 0.48%, 0.46%, and 0.32%, respectively. *Trans*-cinnamoylcocaine was the predominant of the cinnamoylcocaines with higher levels in the petiole (0.24%), while the distribution of *cis*-cinnamoylcocaine, tropinone, cuscohygrine and tropacocaine was not significantly different among the tissue sections analysed with concentrations of 0.14%, 0.004%, 0.16%, and 0.04%, respectively (Johnson, 1995).

E1.8 Preparations of coca leaf and available information as to chemical composition

E1.8.1 Coca tea

Coca tea bags from Peruvian (1.09 g per bag) and Bolivian (0.82 g per bag) coca leaf were found to contain cocaine in the highest amount (5.02 mg and 4.86 mg in the Peruvian and Bolivian tea bags, respectively), followed by ecgonine methyl ester (1.15 mg and 2.93 mg in the Peruvian and Bolivian tea bags, respectively) (Jenkins et al., 1996). Moreover, traces of benzoylecgonine and *trans*-cinnamoylcocaine were also found, along with trace amounts of anhydroecgonine methyl ester (also known as methylecgonidine or anhydromethylecgonine).

Tea was made from the same tea bags by the addition of 180 mL of deionized water at 94 °C. The tea bag was maintained in the hot water for 3, 6, 9, 12, and 15 min, then removed. A cup of the resultant tea was found to contain the same alkaloids contained in the tea bags with cocaine being the most abundant (4.14 mg and 4.29 mg in the tea from the Peruvian and Bolivian coca tea bag, respectively), followed by ecgonine methyl ester (1.15 mg and 1.81 mg in the Peruvian and Bolivian tea, respectively), benzoylecgonine (0.50 mg and 0.26 mg in the Peruvian and Bolivian tea, respectively), and trace amounts of *trans*-cinnamoylcocaine and anhydroecgonine methyl ester (Jenkins et al., 1996).

E1.8.2 Nutritional supplements

'Coca leaf flour' or 'coca flour' is powdered coca leaves sold as a nutritional supplement (e.g. coca leaf powder sold by ENACO S.A., Lima, Peru) and usually added to food and drinks with a recommended intake of 2 spoonfuls (5 g) (Penny et al., 2009). The inclusion of 5% coca flour in bread flour has also been proposed for public nutrition programs (emol.com, 2006).

In the study by Penny et al., it was calculated that a school-aged child consuming two wheat bread rolls of 30 g each would ingest 3 g of coca flour. In the same study, the nutrients (see Table 2) and alkaloid content of eight coca leaf powder samples, including that from ENACO, were analyzed. Two spoonfuls of coca leaf flour (5 g) would satisfy less than 10% of the dietary intake requirements for schoolchildren and adults for critical, commonly deficient nutrients in the diet (Penny M.E. et al., 2009). Cocaine was found in the amount of 15 mg in two bread rolls (based on an average 0.56% concentration in the raw powdered leaves). As noted in Section 9, the authors conclude that a daily supplement of 5 g of dried powder does not represent substantial nutritional value, and a higher intake, on the order of 100 g daily, would provide unsafe amounts of cocaine (Penny et al., 2009).

Additionally, anhydroecgonine methyl ester and ecgonine methyl ester were detected at 0.02% and 0.18%, respectively (dry weight), likely derived from cocaine degradation. Lastly, trans- and cis-cinnamoylcocaine were found at concentrations of 0.04% and 0.07%, respectively (dry weight) (Penny et al., 2009).

E1.8.3 Essential Oil

Essential oil is obtained by hydrodistillation of fresh leaves with distilled water. A work by R. A. S. Cruz reports hydrodistillation for 4 h of two *Erytroxylum* species (*E. ovalifolium* and *E. subsessile*) collected in January 2009 at Restinga de Jurubatiba National Park, Rio de Janeiro, Brazil. The yields of the two essential oils were 0.04% and 0.05% (*w/w*), respectively. Gas chromatography coupled to mass spectrometry (GC-MS) analysis revealed a total of 20 constituents in *E. ovalifolium* essential oil (91.3% of the total relative composition) and 22 constituents in *E. subsessile* essential oil (99.7% of the total relative composition) (Cruz et al., 2018). A less recent work depicts the volatile components of the species *E. coca* var. *coca* (Novak & Salemink, 1987). The relative percentages are reported in Table 5.

Table 5. Relative amount (%) of each volatile component in three Erythroxylum species.

Compound	*E. ovalifolium* (Cruz	*E. subsessile* (Cruz	*E. coca* var. *coca* (Novák
N-methylpyrrole	-	-	3.7
trans-2-hexenal	24.1	41.0	10.4
cis-3-hexen-1-ol			16.1

1-hexanol	-	2.9	5.2
N,N-Dimethylbenzylamine	-	-	0.5
Methyl salicylate	2.0	4.4	13.6
2-Hexenol	-	3.2	-
α-Pinene	-	20.0	-
β-Pinene	-	5.1	-
Mircene	-	0.5	-
3*Z*-Hexenyl acetate	1.2	0.3	-
α-Terpinene	-	0.4	-
o-Cimene	-	0.8	-
Limonene	-	0.8	-
Z-*β*-Ocimene	0.8	0.4	-
E-*β*-Ocimene	23.2	8.1	-
Terpinolene	-	1.3	-
3*Z*-Hexenyl butanoate	2.6	-	-
Tetrahydrolinalool	1.6	-	-
Linalool	-	1.2	-
3*Z*-Hexenyl-2-methyl	1.6	-	-
E-*β*-Damascenone	1.2	-	-
β-Cubebene	4.4	-	-
1,1,6-Trimethyl-1,2-	1.0	-	-
Italicene	0.9	-	-
E-Caryophyllene	0.9	4.0	-
trans-*α*-Bergamotene	0.7	-	-
β-Selinene	-	1.5	-
δ-Selinene	-	1.3	-
E,E-*α*-Farnesene	3.7	0.5	-
δ-Amorfene	-	1.1	-
trans-Calamenene	-	0.4	-
3*Z*-Hexenyl benzoate	1.3	-	-
Z-Dihydroapofarnesol	1.0	-	-
epi-Cubenol	-	0.5	-
6*E*,10*Z*-Pseudophytol	8.1	-	-
Nonacosane	8.2	-	-
Untriacontane	2.8	-	-

E1.9 Stability of component substances and changes in the coca leaf during growth and in different environmental conditions

The stability of the component substances in coca leaf was evaluated, focusing on the alkaloid class, while no literature was found describing the other components. In particular, cocaine,

benzoylecgonine, and ecgonine were analysed in the coca tea, indicating that their degradation was less than 30%. Both cocaine and benzoylecgonine degraded into ecgonine, which was not present in the original plant material (Marín-Sáez et al., 2019).

It is also reported that some alkaloids detected during chemical analysis are likely to be artifacts generated by the extraction reagents used. For example, ecgonine methyl ester is probably formed during acidic extraction, as it was not present in the ethanolic extract, while ecgonine methyl ester could be derived from the breakdown of cocaine during prolonged extraction with chloroform. As far as the cinnamoylcocaines are concerned, no conversion of the *cis* to the *trans* isomer has been observed in whole leaves because variable amounts of both compounds were found in the different plant specimens and some samples showed only the presence of the *cis* isomer (Rivier, 1981).

Cuscohygrine is reported to be very unstable and to degrade rapidly to hygrine in standard solution (10 µg/mL). After one week its GC-MS signal was no longer detected. In urines preserved at-20 °C with sodium fluoride 1% and acidic pH the initial ratios between cuscohygrine and hygrine varied between 2% and 6%, whereas after four months it varied between 30% and 45%, suggesting a high instability of cuscohygrine also in these biological samples (Rubio et al., 2014).

Bieri et al. evaluated the stability of cocaine during extraction by focused microwave-assisted extraction (FMAE) and subsequent solid phase microextraction (SPME) with alkaline aqueous solutions at different temperatures over a time period of 150 min. The stability experiments were carried out with pure cocaine standard solutions prepared in various buffers (pH 8.1 and 8.6: phosphate; pH 9.1 and 9.6: borax; pH 10.6: carbonate), while the experiments with the plant material were performed employing the conditions found ideal to preserve cocaine concentrations. Cocaine has a pK_a value of 8.6, thus it is efficiently extracted at pH values above 10. However, under these conditions it spontaneously undergoes hydrolysis. In particular, its lability increases with increasing pH and/or temperature (Bieri S. et al., 2006b).

E. novo. var. *novogranatense*, *E. novo.* var. *truxillense*, and *E. coca* var. *ipadu* are native to Colombia and cultivated for illicit cocaine production. In the mid to late 1990s, stricter law enforcement against shipments of crude Peruvian cocaine base to Colombia led to a shift in cultivation, with new coca plantations established in Colombia that expanded to about 167,000 ha. Coca farmers started to select plants with specific traits, including resistance to glyphosate, dense biomass, and high cocaine content, thus generating 15 new cultigens throughout Colombia (Casale et al., 2014). Analysis of the alkaloids produced from *E. novo.* var. *novogranatense* and *E. novo.* var. *truxillense* showed elevated concentrations of truxillines, tropacocaine, and 1-hydroxytropacocaine relative to cocaine (Moore & Casale, 1994)(Moore J.M. and Casale J.F., 1994) while being void of trimethoxy-substituted alkaloids

compared to *E. coca* var. *ipadu* (Casale & Moore, 1994)(Casale J. and Moore J., 1994). Of the new cultigens, ten showed a profile compatible with that of *E. coca* var. *ipadu,* and four presented a mixed profile between *E. coca* var. *ipadu* and either *E. novo. v*ar. *novogranatense* or *E. coca* var. *truxillense* with high concentrations of truxillines, tropacocaine, and 1-hydroxytropacocaine relative to a typical *E. coca* var *ipadu* profile (Casale et al., 2014). Moreover, one cultigen showed a heterogeneous alkaloid profile and could not be classified. Amplified fragment length polymorphism (AFLP) DNA analysis later confirmed the presence of hybridized plants (Johnson et al., 2003; Johnson et al., 2005).

F. Identification and Analysis

Coca leaf can be analysed by physical identification assays and chemical analysis.

F.1 Physical identification assays

Physical identification can be carried out on either whole coca leaf or powdered coca leaf material (UNODC, 2012). A macroscopic and a microscopic assay can be performed for the whole coca leaf, while only a microscopic assay can be performed for the powdered material. However, these assays should always be followed by chemical analysis for confirmation.

F.1.1 Macroscopic assay

Macroscopic analyses include the visual examination of coca leaves, assessing their color, size, shape, and texture. Coca leaves are similar in appearance to *Laurus nobilis* leaves, especially for the oval shape, but size and appearance vary among different plant varieties. The common characteristic traits in all species are the darker color of the upper side compared to the underside of the leaf and two lines parallel to the midrib of the leaf (NicDaéid & Savage, 2013).

The physical traits of the leaves vary among the four major subspecies (see paragraph F – Physical appearance)

F.1.2 Microscopic assay

Microscopic analysis can be carried out on either fragmented, pulverized, or semi-carbonized plant material using either a stereoscopic microscope, a light microscope, a transmission electron microscope (TEM), or a scanning electron microscope (SEM) (M. T. Castro et al., 2004; Cortella & Pochettino, 1994; Dillehay et al., 2010). A cross-section of a coca leaf reveals the upper epidermis, palisade parenchyma containing calcium oxalate prisms, spongy parenchyma, and a lower papillose epidermis with numerous stomata, which is the main distinctive trait in a microscopic assay (Cortella & Pochettino, 1994; Dillehay et al., 2010). The midrib is partially encircled by a ring of pericytic fibers, surrounded above and below by a substantial amount of collenchyma tissue. When examining the lower epidermis under a surface preparation, the

papillae appear as well-defined circles, accompanied by numerous stomata, each featuring four subsidiary cells, two of which align their long axes parallel to the pore (Evans et al., 2009).

F.2 Chemical analysis

Chemical analysis is performed with two main objectives: a) qualitative and/or quantitative determination of coca leaf constituents in plant material or plant material preparations; b) qualitative and/or quantitative determination of coca leaf constituents and their metabolites in biological samples. Chemical analysis can be carried out on either whole or pulverized plant material. Based on the aim of the analysis (qualitative or quantitative), different sample preparation procedures and techniques should be adopted.

F.2.1 Sample preparation

F.2.1.1 Plant material and plant material preparations

For qualitative analysis, chopped or pulverized leaves are extracted with either ethanol or methanol at ambient temperature by pounding them in a mortar. The alcoholic extract is usually spotted onto thin layer chromatography (TLC) or injected into either a GC- or a liquid chromatography (LC) system (Perera et al., 2021; UNODC, 2012).

Quantitative analysis of alkaloids, instead, requires a more systematic protocol for sample preparation starting from pulverized material and using either boiling ethanol or methanol. After removal of the solid material and evaporation of the solvent, the residue is dissolved in chloroform and extracted with citric acid (1.5%, *w/v*). The pH is then adjusted to 8.2 and the solution extracted with chloroform. After solvent evaporation an appropriate internal standard (IS) is added and the sample is analyzed by either GC or HPLC (Turner et al., 1981; UNODC, 2012). Alternatively, many research works report the direct analysis of the alcoholic extract using an alcoholic IS solution as the extracting solvent (Ferreira et al., 1998).

It is also reported that focused microwave-assisted extraction (FMAE) at atmospheric pressure at the standard frequency of 2450 MHz using methanol as the solvent can efficiently extract several endogenous plant substances. An additional purification step by solid phase microextraction (SPME) with an aqueous buffer (pH 8.1) allows for a higher selectivity for cocaine and *cis*- and *trans*-cinnamoylcocaine (Bieri, Ilias, et al., 2006).

One study reports the trituration of coca leaf powder with an aqueous solution saturated with sodium bicarbonate. This basified mixture was extracted with water-saturated toluene (with IS) at 60-65°C for 1 h with occasional mixing. The extract is then passed through a chromatographic column packed with a mixture of 0.18 M sulphuric acid and Celite. After washing with water-

saturated toluene, the coca alkaloids are eluted by the addition of water-saturated chloroform (Moore et al., 1994).

Heating a coca leaf bag for coca tea in hot distilled water (94 °C) allows for to transfer of over 80% of the cocaine originally present in the coca tea bag. The amount of cocaine, along with that of ecgonine methyl ester, increased with the infusion time (from 3 to 15 min), while the amount of benzoylecgonine remained almost unchanged (Jenkins et al., 1996).

Flavonoids can also be extracted from coca leaves as reported in E. L. Johnson et al., first with 72% aqueous methanol, then with water. After centrifugation, the supernatants are dried and dissolved in 1% acetic acid (*v/v*). The extract is loaded onto SPE columns, washed, and the flavonoids eluted with 70% methanol. The analyte-containing fraction can be analysed as such, or the solvent can be removed and replaced by 1% acetic acid (*v/v*) for storage due to the weak acidic character of these compounds (Johnson et al., 2002).

F.2.1.2 Biological samples

For biological specimens, the procedure for the extraction of coca leaf alkaloids changes according to the sample type. For hair samples from people who chewed coca leaf or drank coca tea, a preliminary washing step with water and acetone and drying should be undertaken, then the samples undergo extraction, which can consist of a mixture of methanol/acetonitrile/2 mM ammonium formate (25:25:50, *v/v/v*) with gentle shaking at 37 °C (Rubio, Krumbiegel, et al., 2019). Another example reports the washing of the hair samples with methanol, then extraction with 0.05 M sulphuric acid, neutralization with 1 M sodium hydroxide, and pH adjustment to 4 with 2 M sodium acetate (Springfield et al., 1993).

Oral fluid analysis of people who chewed coca leaf or drank coca tea is reported to require extraction with borate buffer (pH 9.2) before analysis (Cabarcos-Fernandez et al., 2024) or protein precipitation with acidic acetonitrile (pH 4.2) (Rubio, Bermejo-Barrera, et al., 2019).

Whole blood, plasma, and urine of coca leaf consumers can be diluted with acetate buffer (pH 4) before extraction (Jenkins et al., 1996; Rubio et al., 2025).

F.2.2 Thin Layer Chromatography (TLC)

TLC is generally performed on extracts of seized material by spotting individually the sample(s) and a cocaine standard solution on a silica gel plate and running an appropriate solvent system as mobile phase. A recommended procedure for the detection of cocaine reported by the UNODC includes the choice of one solvent system between: a) chloroform/dioxane/ethyl acetate/ammonia (29%) (25:60:10:5, *v/v/v/v*), b) methanol/ammonia (29%) (100:1.5, *v/v*), and c) cyclohexane/toluene/diethylamine (75:15:10, *v/v/v*) (UNODC, 2012). The literature mentions

other examples of solvent systems, such as methanol for TLC analysis of the leaves from *E. coca* var. *coca* and *E. novo.* var. *novogranatense* (Ferreira et al., 1998) and toluene/ethyl acetate (9:1, *v/v*) for the HPTLC (high-performance TLC) analysis of the leaves of *E. monii* (Perera et al., 2021).

Visualization of the spots can be achieved by different methods (UNODC, 2012):

a) UV light at 254 nm: cocaine appears as a dark spot over a green background

b) Acidified potassium iodoplatinate reagent: cocaine appears as a blue spot when the plate is sprayed with the reagent.

c) Dragendorff's reagent (Munier): cocaine appears as an orange spot when the plate is sprayed with the reagent.

F.2.3 Liquid Chromatography (LC)

F.2.3.1 Plant material and plant material preparations

Liquid chromatography can be interfaced to either a UV (HPLC-UV) or a mass spectrometry detector (HPLC-MS).

HPLC-UV detection of coca alkaloids is recommended by the UNODC, in particular with the use of a C18 column and methanol:water:1% phosphoric acid:n-hexylamine (300:700:1000:14 v/v/v/v; pH = 2.5) as mobile phase. The UV detector should be set at 230 nm, and the calibration should be performed to have a limit of quantification (LOQ) of 0.05 mg/mL for cocaine (UNODC, 2012).

An HPLC-UV method has been developed for the determination of cocaine and cis- and trans-cinnamoylcocaine in 110 samples of E. coca var. coca collected in the Yungas mountains and the Chapare lowlands (Bolivia) between the end of 1991 and the middle of 1992. The method was developed in reversed-phase mode using a C18 column heated at 35°C for the determination of cocaine and a C8 column for the cinnamoylcocaines. The mobile phase for cocaine consisted of 0.05 M phosphate buffer (pH 5) containing 25% (v/v) acetonitrile, while for the cinnamoylcocaines, the solvent was a mixture of acetonitrile:tetrahydrofuran:0.1% diethylamine in water (40:10:50, v/v). The detector was set at 220 nm for cocaine and 280 nm for cis and trans-cinnamoylcocaine. Results indicated a concentration of cocaine of 0.33% and 0.60% (based on dry weight) in the wet and dry seasons respectively in the Youngas, while concentrations of 0.32% and 0.50% (based on dry weight) were recorded in the same seasons in the Chapare. Cis-cinnamoylcocaine registered levels of 0.016% and 0.08% in the wet and dry seasons respectively in the Youngas and levels of 0.021% and 0.01% in the same seasons in the Chapare. Trans-cinnamoylcocaine was lower than the cis isomer with amounts of 0.003% in both seasons in the Youngas and 0.003% and 0.005% in the wet and dry seasons respectively in the Chapare. LOQs were 0.037% for cocaine, 0.0065% for cis-cinnamoylcocaine, and 0.0015% for trans-cinnamoylcocaine (Sauvain et al., 1997).

An example of the use of the HPLC-MS technique involves the separation of cocaine, norcocaine, benzoylecgonine, ecgonine methyl ester, cocaethylene, cinnamoylcocaine, anhydroecgonine methyl ester, hygrine, cuscohygrine, and tropacocaine contained in coca leaves or coca tea. The chromatographic separation was achieved on a HILIC (hydrophilic interaction liquid chromatography) stationary phase kept at 40 °C with a mobile phase composed of ammonium formate buffer (pH 4.2) and acetonitrile. The chromatographic apparatus was interfaced to a quadrupole-time of flight mass spectrometer (HPLC-QToF) and to a triple quadrupole mass spectrometer in multiple reaction monitoring mode (MRM) (HPLC-MS/MS). The LOQ is not specified. The results showed that the main components were cocaine, cinnamoylcocaine, ecgonine methyl ester, and cuscohygrine in similar ranges (0.10-0.35%, w/w), while lower amounts were detected for anhydroecgonine methyl ester (0.006%, w/w), and benzoylecgonine (0.02%, w/w), and tropacocaine was undetectable (Rubio, Krumbiegel, et al., 2019).

Leaf extracts from Amazonian field-grown coca (E. coca var. ipadu) were analysed for flavonoids by LC-MS. Eight O-conjugated flavonoids were detected: two O-conjugates of taxifolin, one O-conjugate of quercetin, two O-conjugates of eriodictyol, and three O-conjugates of kaempferol. An O-ethyl ester typically found in E. coca var. coca, kaempferols, and a 7-O-rutinoside commonly encountered in the E. novogranatense taxons were also detected in the Amazonian coca leaf samples, suggesting that the field under investigation in Colombia derives from a cross between E. coca var. coca and E. novo. var. truxillense. The data obtained in the study suggested that flavonoids can be used as biomarkers of the Erythroxylum taxon (Johnson et al., 2002).

F.2.3.2 Biological samples

Oral fluid analysis by HPLC-MS/MS (Q-TRAP) in MRM mode allowed for the quantitative determination of cocaine, benzoylecgonine, hygrine, cuscohygrine, tropacocaine, ecgonine methyl ester, trans-cinnamoylcocaine, and anhydroecgonine methyl ester from coca leaf consumers (coca leaf chewers and coca tea drinkers). Chromatographic separation was achieved using 20 mM ammonium formate in ultrapure water (pH 4.2) and an acetonitrile/methanol (4:1) mixture as a mobile phase on a HILIC stationary phase at 40 °C. The LOQ was established at 5 ng/mL for cocaine, benzoylecgonine, trans-cinnamoylcocaine, and cocaethylene, 10 ng/mL for ecgonine methyl ester and anhydroecgonine methyl ester, and 50 ng/mL for cuscohygrine. Cocaine concentrations ranged from 11.3 to 253.4 ng/mL. In comparison to people who use cocaine, people who use coca leaves were positive for hygrine and cuscohygrine (Rubio, Bermejo-Barrera, et al., 2019).

The quantitative determination of cocaine, benzoylecgonine, ecgonine methyl ester, trans-cinnamoylcocaine, tropacocaine, anahydroecgonine methyl ester, and cuscohygrine, and the detection of hygrine were undertaken in oral fluid samples of three volunteers after drinking a cup of coca tea using an HPLC-MS/MS (Q-TRAP) method exploiting the MRM transitions of the analytes. The separation was achieved using a mobile phase made of 20 mM ammonium formate in ultrapure water (pH 4.2) and an acetonitrile/methanol (4:1) mixture on a HILIC column. The LOQ was determined to be 1 ng/mL for cocaine and benzoylecgonine, 5 ng/mL for ecgonine methyl

ester, trans-cinnamoylcocaine, and tropacocaine, 10 ng/mL for anahydroecgonine methyl ester, and 15 ng/mL for cuscohygrine. Oral fluid samples were diluted in borate buffer (pH 9.2) and then subjected to SPE, eluting the analytes of interest with 2% (v/v) acetic acid in methanol. The samples were taken from volunteer 1 at 30, 60, 120, and 180 min after drinking, and from volunteers 2 and 3 at 30 and 180 min after drinking. After 30 min, all volunteers tested positive for hygrine, and 2 of them even after 180 min. Anahydroecgonine methyl ester was detected in one volunteer up to 60 min after consumption of the tea, while tropacocaine was not detected in any samples. After 30 min, the cocaine levels ranged from 330 to 840 ng/mL, and after 180 min, from 1.1 to 7.0 ng/mL. Ecgonine methyl ester, trans-cinnamoylcocaine, and benzoylecgonine were found at levels above 14 ng/mL even after 180 min (Alvarez-Freire et al., 2023).

HILIC separation combined with tandem MS (QToF/MS) analysis of hair samples of 10 people who used coca leaves or coca tea occasionally or moderately was used to quantify the amount of cocaine, norcocaine, benzoylecgonine, ecgonine methyl ester, cocaethylene, cinnamoylcocaine, anhydroecgonine methyl ester, hygrine, cuscohygrine, and tropacocaine. The latter was not detected. Due to the lack of an analytical standard for hygrine, this substance was not quantified, but the peak area ratio hygrine/cocaine was used as a relative measure of the concentration. The LOQ of all analytes in hair was in the range of 10-30 pg/mg, and the average concentration for cocaine was 2 ng/mg (the average content of the leaves and tea was 0.42%). Cocaethylene usually results from the concomitant use of alcoholic beverages, while the detection of anhydroecgonine methyl ester was excluded to be an artifact in the LC-MS/MS analysis, as it was demonstrated to be also present in coca leaves and coca tea by several works, thus it does not unambiguously prove smoking of cocaine products (Rubio, Krumbiegel, et al., 2019).

Urine samples collected over 72 h after consumption of a coca tea cup (3.8 mg of cocaine) from five volunteers were analysed by UHPLC-MS/MS (triple quadrupole detector) using formate buffer adjusted to pH 3 and 0.1% formic acid in acetonitrile as mobile phase and a C18 stationary phase. The LOQ was 5 ng/mL for cocaine, benzoylecgonine, and ecgonine methyl ester. Cocaine was detectable for 20 h in urine (concentration range 6-91 ng/mL), and its metabolites, benzoylecgonine and ecgonine methyl ester, were detectable for 70 and 60 h, respectively, after consumption of a single cup of coca tea (Feisthauer et al., 2022). In the same work, hair samples were analysed one month after the consumption of a single coca tea cup, and the UHPLC-MS/MS analysis provided a negative response for cocaine with a LOQ of 10 pg/mg (Feisthauer et al., 2022).

Urine samples stored for 6 years with sodium fluoride 1% (w/v) in an acidic environment (pH close to 5) at -20 °C were qualitatively analysed by both GC-MS and LC-MS/MS (Q-Trap). LC-MS/MS analysis was performed on a HILIC column at 40 °C using 20 mM ammonium formate in ultrapure water (pH 4.2) and 4:1 acetonitrile/methanol as a mobile phase. The limit of detection (LOD) was established at 50 ng/mL for cocaine and trans-cinnamoylcocaine, 100 ng/mL for ecgonine methyl ester, and 200 ng/mL for cuscuhygrine by GC-MS. The LC-MS/MS method provided LODs of 5 ng/mL for cocaine and trans-cinnamoylcocaine, 10 ng/mL for ecgonine methyl ester, and

50 ng/mL for cuscohygrine. The LC-MS/MS method showed a higher rate of positive results for all analytes, especially hygrine (putatively identified) and cuscohygrine, compared to the GC-MS method (Rubio, Moreda-Piñeiro, Alvarez-Freirec, et al., 2019).

In the same work, the authors indicated the factors that affect the detection of coca leaf alkaloids in urine samples (Rubio, Moreda-Piñeiro, Alvarez-Freirec, et al., 2019):

- frequency of coca leaf consumption
- The method of coca leaf consumption as chewing and drinking coca tea, leads to different concentrations of coca alkaloids in urine (higher in chewers)
- use of alkaline substances during chewing, which enhances the absorption of the coca alkaloids from the leaf
- use of alkaline pH during the extraction as it favours the chemical hydrolysis of the analytes with ester moieties like cocaine, ecgonine methyl ester, and *trans*-cinnamoylcocaine.

F2.4 Gas Chromatography (GC)

Qualitative analysis by means of GC-MS is based on the comparison of the retention time and mass spectrum of the analyte with that of a reference standard obtained in the same operating conditions.

Quantitative analysis, instead, is accomplished by means of either GC-MS or GC coupled to flame ionization detector (GC-FID) and can be applied to all sample types, including both seized material and biological specimens.

F.2.4.1 Plant material and plant material preparations

UNODC recommends the analysis of coca leaf to be performed by GC-FID without derivatization using a reference external standard of either cocaine free base or hydrochloride salt with only one point for calibration (0.27 mg/mL) (UNODC, 2012).

GC-FID (Johnson & Emche, 1994; Turner et al., 1981) and GC-MS (Johnson & Emche, 1994; Rivier, 1981) analyses showed that the cocaine/cinnamoylcocaine and the cis-/trans-cinnamoylcocaine ratios can vary substantially according to geographical area of origin, age, and subspecies of Erythroxylum. Results for cocaine, cis-cinnamoylcocaine, and trans-cinnamoylcocaine were respectively in the range of 0.57-0.60%, 0.03-0.08%, and 0.01-0.07% (w/w) for the E. coca of three different areas, Tingo Maria, Cuzco, and Trujillo (the LOD for cocaine is reported to be 0.5 ng) (Turner et al., 1981). Other alkaloid determined were ecgonine methyl ester, hygrine, tropinone, cuscohygrine, and tropacocaine in various concentration ranges: cocaine varied from 0.18% in the buds to 0.75% in young rolled leaves and 0.61% in mature leaves; ecgonine methyl ester was found

to be 0.47%, 0.78% and 0.59% in the buds, young and mature leaves respectively; hygrine was 0.19%, 1.80% and 0.68% in the same tissues; tropinone followed the same trend with 0.11%, 0.33% and 0.08% in buds, young and mature leaves; trans-cinnamoylcocaine was found at 0.19%, 3.9% and 0.31% in the three tissues; its cis isomer had concentrations of 0.06% in buds and young leaves and 0.55% in mature leaves; cuscohygrine was found at 0.23%, 1.97% and 0.52% in buds, young and mature leaves respectively; lastly, tropacocaine had concentrations of 0.05% in buds and mature leaves and higher concentration of 0.12% in young leaves. All results were reported as % of substances based on the dry weight of plant material (Johnson & Emche, 1994).

The leaves of 51 Erythroxylum species were analysed for their cocaine content by GC-MS in single reaction monitoring (SIM) mode. The LOQ of the method is reported to be 0.0001% of cocaine based on dry weight. Among the cocaine containing wild species, E. laetevirens presented markedly lower cocaine levels compared to other cultivated E. coca species (0.11-1.02%), as well as to a commercially available "Mate de coca" (0.60%)., Moreover, a qualitative chromatographic profile of the E. laetevirens alkaloid content was carried out and compared with those of cultivated coca species. The tropane alkaloid pattern was similar for all species, with hygrine, anhydroecgonine methyl ester, ecgonine methyl ester, cocaine, and the cinnamoylcocaines unambiguously identified.

Cocaine, ecgonine methyl ester, benzoylecgonine, and trans-cinnamoylcocaine were found after derivatization and GC-MS analysis in both coca tea and in coca tea bags from which the tea was made. An average concentration of 4.14 mg of cocaine was transferred to the coca tea from the tea bag (81% extraction efficiency). Coca tea also contained an average of 1.15 mg of ecgonine methyl ester, similar to the amount found in coca tea bags. In addition, benzoylecgonine was found in amounts (0.50 mg) 10-fold higher than those contained in the tea bag (Jenkins et al., 1996).

SPE-GC-MS analysis of a coca leaf extract obtained after stirring with a mixture of methanol/acetonitrile/2 mM ammonium formate (25:25:50, v/v/v) for 15 min was used to quantify several coca alkaloids, including hygrine, cuscohygrine, ecgonine methyl ester, trans-cinnamoylcocaine, and cocaine in coca tea extracts and compare the content with oral fluid samples. However, the quantitative results have not been discussed (Cabarcos-Fernandez et al., 2024).

Derivatization and GC-MS with isotope ratio mass spectrometry analysis were applied to a sample from a seized illicit coca field in Chapas (Mexico), showing the ability of this technique to identify the geographical origin of the plant, which depicted a profile not comparable to other coca plants in South America. The leaves were classified as belonging to E. novo. var. truxillense containing 0.36% (w/w) cocaine, but with extraordinary levels of 1-hydroxytropacocaine (21.3%) and cinnamoylcocaines (242%) relative to cocaine (Casale & Mallette, 2016).

Capillary GC coupled to either FID (cGC-FID) or electron-capture detector (cGC-ECD) was used to analyse South American coca and greenhouse- and tropical-cultivated field coca and determine

coca alkaloids. Quantitative data were obtained using a standard mixture of cocaine, cuscohygrine, ecgonine methyl ester, and trans-cinnamoylcocaine at the final concentrations of 0.100 mg/mL, 0.050 mg/mL, 0.050 mg/mL, and 0.030 mg/mL. The results indicated the presence of cocaine, cis- and trans-cinnamoylcocaine, tropacocaine, hygrine, cuscohygrine, and the isomeric truxillines in the coca leaf extracts of South American fields obtained with water-saturated toluene. The cocaine content varied from 0.36% to 0.72% (dry weight), while cis-cinnamoylcocaine represented 5.8-28%, trans-cinnamoylcocaine was 2.9-33%, tropacocaine 0.25-4.9%, and cuscohygrine 11-78% of the cocaine content. Total truxilline content was in the range 2.9-61.2% relative to cocaine, while hygrine was between 1.4% and 24% of cocaine. The highest amount of all analytes was found in the plants of Colombia. In comparison, the greenhouse and tropical samples extracted in the same way did not show detectable levels of either hygrine or the truxillines. The content of cocaine in the greenhouse cultivated plants varied from 0.37% to 0.60% (dry weight). The relative content of cis-cinnamoylcocaine, trans-cinnamoylcocaine, ecgonine methyl ester, tropacocaine, and cuscohygrine was 7.2-50%, 18-98%, 38-63%, 0.3-4.6%, and 3.8-57%, respectively. The content of cocaine in the tropical plants varied from 0.43% to 0.67% (dry weight). The relative content of cis-cinnamoylcocaine, trans-cinnamoylcocaine, ecgonine methyl ester, tropacocaine, and cuscohygrine was 18-53%, 22-170%, 29-47%, 0.16-3.8% and 5.8-61%, respectively. The samples from both South America and the greenhouse belonged to the E. coca var. coca and E. novo. var. novogranatense, while the tropical samples also included the E. novo. var. truxillense. Further extraction of some of the samples with acid phthalate buffer (pH 4) and chloroform, and subsequent basification, led to the isolation of numerous trace-level coca alkaloids of unknown structure (Moore et al., 1994).

F.2.4.2 Biological samples

SPE-GC/MS analysis of urine samples of an individual who had assumed a coca tea cup made from a Peruvian coca tea bag showed that the concentrations of benzoylecgonine and ecgonine methyl ester peaked at 10 h (3368 and 2520 ng/mL, respectively), while those of cocaine at 5 h (196 ng/mL). Thereafter, concentrations declined, but benzoylecgonine and ecgonine methyl ester remained at detectable concentrations for 48 h (23 and 22 ng/mL, respectively), while cocaine was negative. The same experiment carried out with a coca tea cup made from a Bolivian coca tea bag revealed the peak concentrations of all analytes after 3.5 h (4155, 587, and 2314 ng mL of benzoylecgonine, cocaine, and ecgonine methyl ester, respectively). After 52.5 h, in urine, benzoylecgonine and ecgonine methyl ester concentrations were still detectable (21 and 12 ng/mL, respectively), while cocaine was negative. LOQs of the analytes were 6.25 ng (Jenkins et al., 1996).

Oral fluid collection after consumption of a coca tea cup, followed by SPE-GC/MS analysis, revealed that the sample collection method affects the concentration of coca alkaloids due to different extraction recoveries. Hygrine, cuscohygrine, ecgonine methyl ester, and trans-cinnamoylcocaine were not detectable after 120 min when Quantisal® was used, but they remained in the samples

obtained by passive drooling (above 0.04 ng/mL). Tropacocaine was negative in all samples, while cocaine always remained detectable, although at lower levels in the Quantisal® samples (0.08 and 0.28 ng/mL) compared to the passive drooling collection (0.24 and 1.11 ng/mL). It should, though, be taken into account that cuscohygrine and trans-cinnamoylcocaine presented a high matrix effect with both collection methods. LOQs were 10 ng/mL for cocaine, trans-cinnamoylcocaine, ecgonine methyl ester, and tropacocaine, and 50 ng/mL for cuscohygrine. The authors also highlight that hygrine, cuscohygrine, tropacocaine, and trans-cinnamoylcocaine are not included in routine forensic and toxicological analyses (Cabarcos-Fernandez et al., 2024).

SPE-GC-MS analysis (with derivatization) has also been applied to hair samples of ancient Peruvian coca chewers (dated 1000 AD), revealing detectable amounts of ecgonine methyl ester (2.4 ng/mg) and benzoylecgonine (2.1 ng/mg), which resulted in 10-fold higher amounts than cocaine (0.25 ng/mg). LOQ of the analytes with the GC-MS method is reported to be 10 ng (Springfield et al., 1993).

Another example of the use of GC-MS analysis is the study of cocaine levels in plasma after chewing either the whole leaves with the alkaline mixture *llipta* or the powder with ashes of leaves of *Cecropia sciadophylla*. The amount of cocaine in leaves and powder was 0.39-0.48% and 0.24% based on dry weight, respectively (Holmstedt et al., 1979).

F2.5 Matrix-assisted laser desorption/ionization mass spectrometry coupled to Fourier-transform ion cyclotron resonance imaging mass spectrometry (MALDI-FT-ICR IMS)

Matrix-assisted laser desorption/ionization mass spectrometry has recently been considered as a valuable technique for the identification and analysis of the distribution of alkaloids on the surface of coca leaves. The instrumental platform operated in positive-ion mode using the Fourier-transform ion cyclotron resonance imaging mass spectrometry (MALDI(+)FT-ICR IMS). For this type of analysis, a piece of leaf was frozen and sectioned horizontally. The results suggested that cocaine is distributed over the whole leaf surface with small areas of greater abundance in the central region of the inner part of the leaf tissue, where benzoylecgonine and cinnamoylcocaine also are colocalized. Additionally, the molecule was seen to be present both in the adaxial (front) and abaxial (back) surfaces, but it was less abundant on the back than on the front of the leaf. On the other hand, the truxilline detected showed a greater abundance in the peripheral regions of the leaf tissue. Lastly, six flavonoids (isoquercitrin, kaempferol, herbacetin, carlinoside, peltatoside, and rutin) were monitored on the E. coca leaf: in particular, isoquercitrin had a greater abundance in the inner and central parts of the leaf. The other flavonoids, kaempferol, herbacetin, carlinoside, peltatoside, and rutin, showed greater abundance in the outer part of the leaf (dos Santos et al., 2021).

F2.6 DNA analysis

E. L. Johnson et al. analyzed 132 known and unknown coca leaf accessions by the amplified fragment length polymorphism (AFLP) approach (genetic fingerprinting) to define specific genetic traits that could distinguish the four Erythroxylum varieties cultivated for cocaine production (E. novo. var. novogranatense, E. novo. var. truxillense, E. coca var. coca, and E. coca var. ipadu). Based on the DNA profiling, it was possible to establish that the Colombian coca had changed its classical signature to become a hybridization of E. coca var. ipadu (Johnson et al., 2003). The same authors investigated with the same approach 86 Erythroxylum accessions using a capillary genotyping system to assess the pattern and level of genetic variation among and within the taxa. They found a clear distinction between E. coca and E. novogranatense. At the intra-specific level, significant differentiation was observed between E. coca var. coca and E. coca var. ipadu; on the other hand, no differentiation could be appreciated between E. novo. var. novogranatense and E. novo. var. truxillense. Interestingly, E. coca var. ipadu had a significantly lower amount of diversity than the E. coca var. coca, with a clear genetic distinction from the E. coca var. ipadu cultivated in Colombia during the early 2000s (Johnson et al., 2005).

3 EASE OF CONVERTIBILITY INTO CONTROLLED SUBSTANCES

As described in Section 1, the coca leaf plant contains complex mixtures of chemicals that vary across subspecies. Many subspecies of coca leaf contain cocaine, an alkaloid that is naturally synthesized by the plant (see Section 1.1). Hence, chemical transformation of these subspecies of coca leaf into a controlled drug is not required. Rather, the production of cocaine and other alkaloids from coca leaf falls within the IUPAC definition of solvent extraction: “the process of transferring a substance from any matrix to an appropriate liquid phase” (IUPAC, 2025). It is a physical separation process in which a compound is removed from a complex matrix using selective solvents based on differential solubility or affinity. This operation does not involve any modification of the molecular structure of the extracted alkaloids. To obtain pure cocaine base, the extract must be purified (i.e., other extracted substances must be removed), and the resulting product may be transformed into cocaine hydrochloride (one of the typical forms found on the illicit market). Of note, the processes described below do not apply to any of the subspecies of coca leaf that do not contain cocaine. None of the chemicals contained in these subspecies could be easily converted into cocaine or another controlled substance.

Two common procedures for extracting cocaine from coca leaves are described by UNODC 2012 and Casale et al. 1993 (Casale & Klein, 1993; UNODC, 2012). The first is the preparation of a coca paste from coca leaves using an acid-base extraction, as described in the next paragraph. Alternatively, cocaine sulphate can be directly extracted from the coca leaf with dilute sulphuric acid. After filtration, an excess of lime or carbonate is added to the aqueous solution, obtaining a precipitate of crude coca paste. Because this paste contains cocaine (as well as other alkaloids), it is controlled under drug control regulations that pertain to cocaine.

The acid–base extraction of cocaine from coca leaf involves the extraction of coca paste (Schedule I of the 1961 Single Convention according to the Yellow list Annex to Forms A, B, and C, 63rd edition, July 2024) by mixing coca leaves with water and lime. The resulting alkaline mixture is crushed, and the alkaloids are extracted with kerosene, while the waxy material is removed by heating, then cooling the kerosene mixture and solidifying the unwanted wax. The kerosene fraction is then back-extracted with dilute acidified water to convert the free base of the alkaloids to their sulphate form and transfer them into the aqueous layer. Lime or ammonia is then used to convert the sulphates back to the free bases, which results in the precipitation of crude cocaine along with the more basic alkaloids and inorganic salts. The product is then filtered and dried to give coca paste. Purification of cocaine base from coca paste is accomplished by dissolving the latter in dilute sulphuric acid and slowly adding potassium permanganate that turns the solution from a yellow-brown colour to a colourless liquid. The solution is then filtered and made basic with ammonia, resulting in precipitation of cocaine base and other alkaloids. The cocaine base is filtered, washed with water, dried, and dissolved in diethyl ether. Cocaine hydrochloride is eventually obtained as a precipitate by adding concentrated hydrochloric acid and acetone (Casale & Klein, 1993; UNODC, 2012).

Practicability and profitability

The extraction of coca paste from coca leaf and the purification of cocaine from coca paste are easy to follow and do not require specialist expertise. Except for kerosene, the chemicals and reagents used for the processes (sulphuric acid, potassium permanganate, hydrochloric acid, acetone, and diethyl ether) are listed in the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988 (CND & United Nations Commission on Narcotic Drugs, 2024).

According to INCB Precursors Report 2024 – VIII Annex (INCB, 2024c), approximately 1-3 liters of sulfuric acid, 0.2-0.55 kg potassium permanganate, 10-20 liters of solvent (e.g., ethyl ether and/or acetone), and 0.2-0.4 liters of hydrochloric acid are needed to obtain 1 kg of cocaine hydrochloride.

Yield

According to UNODC field surveys conducted in 2008–2009, supplemented with information provided by the US Drug Enforcement Administration (DEA), the following national average conversion ratios were reported for Colombia (UNODC, 2009): one hectare of coca cultivation produces approximately 4.2 tonnes of fresh leaves per year; one tonne of fresh leaves is processed into about 1.5 kg of coca paste or 1.4 kg of cocaine base; one kilogram of cocaine base results in roughly 0.9 kg of cocaine hydrochloride; the latter typically contains around 85% pure cocaine (EMCDDA, 2010).

4 GENERAL PHARMACOLOGY

4.1 Routes of administration and dosage

Coca leaf products are traditionally administered through two primary routes: chewing and infusion. Chewing coca leaves is a widespread and culturally accepted habit in the Andean highlands, often referred to as “coqueo” or “acullico”, that involves placing a wad of dried leaves in the buccal cavity, either alone or with an alkaline substance such as plant ash or sodium bicarbonate that enhances the extraction of alkaloids through the oral mucosa.

The traditional technique for preparing coca leaves begins with harvesting the leaves and drying them by exposure to the sun (Plowman, 1984; Restrepo et al., 2019) or over a low fire (Plowman, 1981). The leaves are stripped of their veins, placed in the mouth and moistened with saliva, forming a quid with the tongue, which is then placed between the gum and cheek. As several authors point out, the English translation "coca chewing" is inaccurate because the quid is not actually chewed but rather is sucked as its juice is released. Occasionally, a leaf or two is added to refresh the *acullico*, which is eventually discarded and replaced with a fresh one (Heath, 1990; Restrepo et al., 2019).

The absorbed dose depends on the duration of the mastication process, the amount of leaves used (typically 8–50 grams per session), and the type of alkali added (Bauer, 2019; Biondich et al., 2016). Traditional coca chewers practice their habit daily; agricultural laborers or mine workers are identified as the people that most perform the practice since they start chewing early in the morning and keep it up throughout their working hours. Typically, a chewer keeps a quid of leaves in his mouth between two and three hours and renews it three to four times a day. This amounts to an average daily consumption of about 50 grams of dry leaves (Negrete, 1978).

When comparing research describing the effects of coca leaf chewing, the dose used must be taken into account, as it varies widely between individuals and studies. The levels of alkaloid absorption—and their effects—can therefore be very different. Using a study from the Bolivian Institute of High Altitude Biology (where many of the studies described below were done) as an example, the variability in the amount of leaf consumed and the associated plasma cocaine concentrations was analyzed. In a group of 17 people who reported long-term use of coca leaf by chewing, the consumption quantities ranged from 3 to 77 g, with a mean of 31 +/- 21 g, and plasma cocaine levels ranged from 28 to 299 ng/mL, with a mean of 98 +/- 75 ng/mL. Following an exercise test, plasma levels ranged from 30 to 211 ng/mL, with a mean of 86 +/- 54 ng/mL. In another experiment where the amounts of coca leaf consumed were more uniform (12 +/- 3 g), the resulting plasma cocaine levels were also less variable (89 +/- 25 ng/mL after chewing and 80 +/- 22 ng/mL after exercise) (Rerat et al., 1997).

Coca leaves are also infused in water and consumed as tea (Bedi & Scully, 2014). In the Andean countries, it is called "Mate de Coca". It is sold in small, 1-gram filter bags of coca leaf, which can contain approximately 4 mg of cocaine (Jenkins et al., 1996). When prepared in hot water, up to 80% of the cocaine it contains can be extracted (Baselt, 1983; Carmona et al., 2000). The gastrointestinal absorption rate of ingested cocaine is approximately 33% (Skopp et al., 2001), which shows that up to 1.0–1.3 mg of cocaine per filter bag would be absorbed into the bloodstream. This is a much lower dose of cocaine than the estimated 10 to 35 mg for a recreational nasal dose, or about 15 mg for intravenous use (Nogué Xarau et al., 2002).

Coca leaf as flour (finely ground coca leaves) can be used like coffee in a coffee machine to make a stronger, more concentrated tea. Coca flour with a coca leaf concentration of 5% is also sold as nutritional supplement (ENACO S.A., Lima, Peru) with a recommended intake of 2 spoonfuls (5 g) added to soups or drinks (Penny et al., 2009). However, oral consumption of coca flour is uncommon compared to other routes of administration described above (Bauer, 2019).

Use of coca leaves by other routes (smoked, inhaled) is not described as regular consumption practices.

4.2 Pharmacokinetics

Pharmacokinetic studies are vital for understanding how a substance is absorbed, distributed, metabolized, and excreted in the human body. However, when it comes to traditional herbal preparations such as the leaves of *Erythroxylum coca* and *Erythroxylum novogranatense*, current scientific literature presents significant limitations that hinder the clinical relevance and generalizability of available data (Khan et al., 2005; Schwitzer et al., 2005).

Furthermore, the number of published clinical trials specifically focusing on the pharmacokinetic aspects of coca leaf in its traditional forms—such as infusions (teas or mates) or leaf chewing ("chacchado" in Peru)—is limited, largely to that published several decades ago (Barnett et al., 1981).

The process of standardizing whole plant extracts is inherently complex. The chemical composition of coca leaves can vary not only between species (e.g., E. coca vs. E. novogranatense), but also due to environmental factors such as soil type, altitude, climate, and seasonal harvest (Bohm et al., 1982; Johnson & Foy, 1996; Sauvain et al., 1997).

Preparation techniques have a substantial impact on the phytochemical composition of coca leaf products. Whether consumed as an infusion or chewed with alkaline agents such as lime or ash, each method influences the spectrum and concentration of bioactive compounds. These differences pose challenges when attempting to extrapolate pharmacokinetic findings from controlled laboratory settings to traditional use contexts (Hilgert et al., 2001).

In addition, cultural practices often play a key role in modifying compound absorption and bioavailability. The “chacchado” technique, for instance, entails slowly masticating dried coca leaves in combination with alkaline substances, facilitating gradual alkaloid release through the oral mucosa (Hilgert et al., 2001). This prolonged exposure contrasts markedly with experimental models that rely on brief administration of standardized extracts.

Another limitation to interpreting evidence on the pharmacokinetics of coca leaf for traditional use is that, despite widespread cultural use in some regions, evidence-based research on traditional herbal medicines, including coca leaf, is scarce. Pharmacological studies on herbal medicines, including coca leaf, often focus on isolated active ingredients, rather than the complex mixtures present in whole-plant preparations, further limiting translational value (Biondich et al., 2016; Chang, 2000).

In fact, the current pharmacokinetic data on coca leaf, derived from a small number of studies, is insufficient to reflect the complexity and variability of its traditional forms of use. The limited scope, methodological heterogeneity, and lack of cultural-contextual integration suggest caution is needed when interpreting this information and extrapolating it to other contexts.

4.2.1 Absorption

4.2.1.1 Chewing coca leaves and drinking coca leaf tea

When coca leaves are chewed, a combination of several constituents, including cocaine, is absorbed from the mucous membranes of the mouth and by swallowing. Absorption of these constituents through oro-buccal membranes avoids first-pass liver metabolism, whereas swallowed products are absorbed from the gastrointestinal tract.

Although the genus Erythroxylum includes several hundred species, trace amounts of cocaine have been detected in 23 species of Erythroxylum, but with content below 0.001% (Aniszewski, 2007), and from this small amount of cocaine present in coca leaves, only 30% of it is absorbed through the mucous membranes of the mouth, stomach, or duodenum (Grabowski, 1984). For example, when exposed to 50 g of chewed coca leaves for 2 hours of chewing, the peak concentrations of metabolites in blood is 150 ng/ml plasma, and 249 ng/ml after 3 hours, while detection persisted in the plasma for more than 7 hours measured by mass fragmentography (Hilgert et al., 2001; Sauvain et al., 1997). A second study indicated that chewing 4.4 g of whole leaves leads to a higher amount of cocaine determined in the plasma (150 ng/mL) compared to chewing 20 g of powder (140 ng/mL). In addition, the study reported a faster absorption rate (half-life 0.2-0.6 h) compared to the elimination rate (1.0-1.9 h). The peak plasma concentration occurred between 0.4 and 2.0 hours (Holmstedt et al., 1979).

Experimental evidence on coca chewing was scientifically gathered by Holmstedt et al. (Holmstedt et al., 1979). When coca leaves (5–10 g) were taken orally by human subjects replicating traditional indigenous practices in South America, cocaine was immediately detected in the blood, reaching peak plasma concentrations between 10 and 150 ng/mL within 0.38 to 1.95 hours, and remaining

detectable in plasma for more than 7 hours. The elimination half-life of cocaine ranged from 1.0 to 1.9 hours, while absorption half-lives ranged from 0.2 to 0.6 hours.

The metabolite concentrations produced by chewing coca leaves are relatively low in contrast with the levels observed following cocaine recreational consumption (inhaled or intravenous). For example, intravenous or smoked cocaine use in humans can produce plasma cocaine concentrations up to approximately 1,200 ng/mL, with benzoylecgonine (BE) also present at substantial levels, though typically lower than the parent compound in early post-use timepoints (Isenschmid et al., 1992). In emergency department patients with recreational cocaine use, plasma cocaine levels ranged roughly from 16 to 130 ng/mL, while BE concentrations reached up to about 1,390 ng/mL (Williams et al., 2000). Similarly, in forensic blood samples from drivers under the influence, typical cocaine concentrations were around 95 ng/mL, and BE levels averaged 700–1,010 ng/mL, often an order of magnitude higher than parent drug concentrations (Jones et al., 2008). According to Javaid et al. (Javaid et al., 1978), intranasal administration of 32 mg of cocaine resulted in peak plasma concentrations ranging from 100 to 500 ng/mL within 30–60 minutes. Similarly, Cone et al. (1995) reported that intravenous administration of 25 mg cocaine produced peak levels around 200 ng/mL, and intranasal administration of 32 mg cocaine produced peak levels more than 100 ng/mL.

These levels are often higher compared with those seen with coca chewing, which typically results in peak concentrations of 10 to a maximum of 149 ng/mL, as shown by Holmstedt et al. (Holmstedt et al., 1979).

Compared to modern cocaine use (either inhaled-one "line" of cocaine contains 10-35 mg- or intravenously-an average dose has 15 mg) (Nogué Xarau et al., 2002), traditional coca consumption involves much lower doses.

Coca tea bags contain 4.86–5.11 mg of cocaine depending on origin (Biondich et al., 2016).

Indigenous population and mining workers are the largest consumers of chewed coca leaves, who may consume up to 52 to 60 g of coca leaves daily. However, the considering that coca leaf contains a minimum 0.1% of cocaine alkaloid (United States Department of Justice, 1991), and the bioavailability fraction for oral cocaine component is 0.20 (Coe et al., 2018) then the expected absorption when coca leaf is chewed is limited and scattered throughout the day, reaching with very low whole plasma levels compared with other ways of administration.

Authors like Hurtado-Gumucio (Hurtado-Gumucio, 2000) state that only 10g of coca leaves can be held at a time because of the limitations of the mouth’s size. Extraction of the components is slow and relatively inefficient; since the mouth, in addition to crushing the leaves, must also soak the leaves for a while in the weak acids of saliva.

A study of over 3,000 people who use coca leaf demonstrated that mine workers, considered the largest consumers, chew an average of 13 ounces a week (368 g), i.e., extract an average of 3.9 net

grams of cocaine per week (Carter & Mamani, 1986). Therefore, the theoretical maximum cocaine dose is 500mg per 24 h (assuming 100% efficiency by oral extraction, which is not true).

Research performed in the High Biological Bolivian Institute -IBBA (Villena et al., 1997) demonstrated that the absorption of cocaine is limited after chewing about 30g of leaves (around 98ng/ml in blood analysis using High Pressure Liquid Chromatography) which differs from levels obtained after cocaine nasal shot which is 4890 ng/ml in whole blood (Javaid et al., 1978; Van Dyke et al., 1978). Hence, the whole blood concentration of cocaine is almost 50 times greater after using the pure isolate in comparison to chewing coca leaf (Biondich et al., 2016).

Thus, while coca leaf chewing does lead to low, but measurable, plasma metabolites, the magnitude and duration of exposure often differ from those following active cocaine intake (Barnett et al., 1981; Rubio et al., 2015).

In other studies, using gas chromatography-mass spectrometry, researchers quantified cocaine levels over time in plasma. Cocaine absorbed was detectable in plasma 5 minutes after the chewing began, and peak plasma concentrations (10–150 ng/ml) occurred between 0.4 and 2.0 hours, depending on the quantity used. Absorption half-lives ranged from 0.2 to 0.6 hours. The rapid onset of effects correlated with the rising phase of the plasma concentration curve and matched subjective stimulant sensations reported by participants.

These findings confirm lower systemic exposure when coca leaves are chewed or drunk in tea (Biondich et al., 2016).

Other products that can be extracted from the coca leaf are alkaloid metabolites. The most common alkaloid metabolites are hygrine (HIG), cuscohygrine (CUS), cinnamoylcocaine (CIN), and tropococaine (TRO). Interestingly, HIG and CUS are not extracted from coca leaves during the clandestine production of cocaine hydrochloride; hence, these compounds are not present in biological samples from people who use cocaine (Rubio et al., 2015).

Low concentrations of cocaine were found in the hair of seven people who used coca leaves or coca tea occasionally (0.010–0.051 ng/mg). For three moderate chewers of coca leaves, all compounds except tropacocaine (TRO) were detected, including anhydroecgonine methyl ester (AEME). Cuscohygrine (CUS) remains the most suitable marker in hair for chewing coca leaves or drinking coca tea (Rubio, Bermejo-Barrera, et al., 2019; Rubio et al., 2015). By contrast, the two main metabolites of cocaine (benzoylecgonine (BE) and methylecgonine (MEE) are present at high frequency in people who use cocaine, but not in people who use coca leaf, which may help to distinguish between the consumption of processed cocaine and natural coca leaves. In one preliminary study with two healthy volunteers, BE and MEE were present in the oral fluid for approximately 12 hours after chewing 5 g of coca leaf for approximately 1 hour (Rubio, Bermejo-Barrera, et al., 2019; Rubio, Krumbiegel, et al., 2019; Rubio, Moreda-Piñeiro, Bermejo-Barrera, et al., 2019).

CUS and HIG also remain positive in the oral fluid of the volunteers who chewed coca leaves, even when cocaine (COC) and its metabolites, such as benzoylecgonine, have decreased in concentration below the cut-off values proposed by international guidelines for screening (15 to 20 ng/mL) and confirmatory (8 to 10 ng/mL) purposes. CUS and HIG remain positive up to 1 hour after ingestion of the tea, whereas cocaine and BE can no longer be detected. Therefore, CUS and HIG, if measured in oral fluid, could also be useful markers to corroborate recent coca leaf use (through chewing or ingesting coca tea) and discriminate against cocaine use (Rubio et al., 2013; Rubio, Bermejo-Barrera, et al., 2019; Rubio, Krumbiegel, et al., 2019; Rubio, Moreda-Piñeiro, Bermejo-Barrera, et al., 2019).

In another study, hair analysis was shown to be a suitable method for distinguishing between alkaloid absorption from coca leaf chewers and users of manufactured cocaine (Rubio et al., 2015). As mentioned above, one study used the coca alkaloids hygrine (HYG) and cuscohygrine (CUS) as markers, demonstrating that CUS remains the most reliable marker for identifying frequent coca leaf chewing or coca tea consumption (more than twice per month), as it is not found in the hair of Argentinean PACO smokers or German cocaine users (Rubio, Bermejo-Barrera, et al., 2019; Rubio, Krumbiegel, et al., 2019).

Other components of coca leaves may be absorbed and detected in humans' blood and tissues, including numerous flavonoids (600 mg/gr of leaf). Flavonoid absorption is usually very low, and their absorption pathways and metabolites are poorly understood (Bešlo et al., 2023; Chen et al., 2022).

4.2.2 Distribution

When coca leaves are chewed or drunk as a tea infusion, a combination of several constituents, including cocaine and several alkaloids, might be absorbed. The distribution of these coca leaf components is demonstrated through the presence of these substances in several tissues of the body. The general pharmacokinetic profile of terpenes, common in essential oils, shows biphasic elimination, indicating distribution from blood into tissues; however, their high clearance and short half-lives make accumulation unlikely. Despite this general understanding of terpene pharmacokinetics in herbal medical plants (Kohlert et al., 2000), the specific presence and composition of terpenoids in coca leaves are not extensively documented in current literature.

The flavonoids absorbed after coca leaf oral administration pass from the small intestine to the liver through the portal vein, where they are metabolized by hepatic enzymes and released into circulation for distribution. After a short plasma stage, flavonoids quickly enter peripheral tissues, with peak values reached after 0.25–0.5 h (Schröder-van der Elst et al., 1997). Unabsorbed flavonoids enter the large intestine, where abundant gut microbiomes cleave their pyranone rings. They then undergo dehydroxylation, decarboxylation, and other reactions, resulting in further metabolites, which are subsequently absorbed, distributed, or excreted in the feces (Hu et al., 2025).

Coca leaf alkaloids, including cocaine itself, have fast distribution to the tissues and easily diffuse across the blood-brain barrier (Roque Bravo et al., 2022).

Giordano et al. revealed the presence of alkaloids of the Erythroxylum species in brain tissue (Giordano et al., 2024). After coca leaf exposure, an undefined amount of these components may undergo enterohepatic circulation (Gosselin et al., 1984).

Coca leaf compounds, including cocaine bind to albumin and α1-acid glycoprotein at a level of around 90% and they can be found at the highest concentrations in the brain, spleen, kidney, and lungs, followed by blood, the heart, and muscle tissue (Bertol et al., 2022).

Authors describe that the volume of distribution of cocaine and its alkaloids ranges between 1.2 to 3 L/kg (Cunha-Oliveira et al., 2013; Edwards & Bowles, 1988).

Studies focusing on pharmacokinetic parameters when cocaine itself is administered orally showed kinetic parameters demonstrated that the mean ± SEM oral cocaine bioavailability was 0.32 ± 0.04 after a dose of 100 mg and 0.45 ± 0.06 after 200 mg, while the volume of distribution (Vd) and clearance (CL) were both greatest after an oral dose of 100 mg (Vd = 4.2 L/kg; CL = 116.2 mL/[min kg]) compared to 200 mg oral administration (Vd = 2.9 L/kg; CL = 87.5 mL/[min kg]) and 40 mg IV (Vd = 1.3 L/kg; CL = 32.7 mL/[min kg]) (Coe et al., 2018).

4.2.3 Biological half-life

In a study performed by Holmstedt et al. (1979) coca leaves were taken orally by chewing or by drinking tea infusion by human subjects in the same way as Indigenous people of South America. The absorption half-life of cocaine after ingestion of 50 g of coca leaf ranged from 0.2 to 0.6 hours. It was quickly detected in the blood, reached peak concentrations from 10–150 ng/ml plasma at 0.38–1.95 hours, and persisted in the plasma for more than 7 hours. The elimination half-life ranged from 1.0 to 1.9 hours (Holmstedt et al., 1979).

Cocaine itself is rapidly cleared from the plasma and can be detected in the brain, ocular fluid, and liver for 8 hours after initial inhaled usage (Boghdadi & Henning, 1997). Plasma half-life and blood concentrations are both known to be dose dependent (Coe et al., 2018; Firenzuoli & Gori, 2007).

When coca leaf is ingested as tea bag infusion, benzoylecgonine was detected in the urine of some coca tea drinkers by gas chromatography with nitrogen phosphorus detection and gas chromatography/mass spectrometry (GC/MS) for 29 h following consumption of one cup of Health Inca tea (estimated to contain 4.8-5.7 mg of cocaine per tea bag) (ElSohly et al., 1986). Peak benzoylecgonine concentrations occurred 2 h after ingestion and decreased to 274 ng/ml by 22 h. The total amount of benzoylecgonine excreted after 29 h was 0.82 mg. Peak benzoylecgonine concentrations ranged from 1.4–2.8 mg/1 and occurred 4–11 h post ingestion. Positive immunoassay results (300 ng/ml cutoff) were obtained for 21–26 h.

Floren and Small (Floren & Small, 1993) reported a peak urine concentration of 2608 ng/ml for benzoylecgonine in a 100-kg subject 4 h after drinking one cup (240 ml) of 'Mate de Coca' purchased in Bolivia. Urine drug screens for two individuals were negative (no cutoff concentration reported) 24 h after drinking two cups of coca tea.

4.2.4 Metabolism

Coca leaf components are rapidly and extensively metabolized by hepatic metabolism. Enzyme esterase, specifically plasma cholinesterase, plays an important role in the metabolism of cocaine, and the activity of cholinesterase can vary greatly between individuals. Metabolites conjugated with methyl, glucuronate, and sulfate groups are the predominant forms present in plasma (Schröder-van der Elst et al., 1997).

The cocaine component of Coca leaf is largely metabolized to water soluble metabolites through four pathways (Bencharit et al., 2003; Brzezinski et al., 1994; Stewart et al., 1977): (i) liver carboxylesterase 1 (hCE1) hydrolyzes the methyl ester linkage of cocaine to form benzoylecgonine (BZE), (ii) intestinal carboxylesterase (hCE2) hydrolyzes the benzoate linkage to form ecgonine methyl ester (EME), (iii) serum butyrylcholinesterase (BchE) also produces EME (though with low catalytic efficiency) (Carmona et al., 2000) and (iv) CYP450 3A4 demethylates cocaine to form norcocaine (NCOC). Further oxidative metabolism produces several minor hydroxy (e.g., m- and p-HOCOC; m- and p-HOBZE) metabolites. It has also been reported that cocaine can spontaneously hydrolyze in vitro at physiological temperature and pH to form BZE and EME (Baselt, 1983) at a rate of 4.8% total cocaine/h (Warner & Norman, 2000).

The major products of metabolism are ecgonine methyl ester (32 to 49%) and benzoylecgonine (29 to 45%). Other metabolites, including hydroxycocaine, methylecgonidine, and norcaine, have been identified (Coe et al., 2018; Roque Bravo et al., 2022).

Additionally, other compounds like flavonoids undergo extensive metabolism in enterocytes and hepatocytes, including glucuronidation, sulfation, and methylation, significantly altering their active forms and reducing systemic availability. Glucuronidation, sulfation, and methylation serve to enhance the water solubility of these substances, promoting their excretion through bile and urine (Hu et al., 2025; Naeem et al., 2022). Recent studies have highlighted the modulatory role of the gut microbiota in flavonoid metabolism, which may enhance or reduce their bioactivity, depending on diet, health status, and genetics (Hu et al., 2025).

4.2.5 Elimination

The metabolites of coca leaf components, including flavonoids, alkaloids, and cocaine, are excreted in urine and can be identified up to 48 hours after oral ingestion.

Following metabolism, cocaine and its main metabolites are finally excreted in urine. Ecgonine methyl ester (EME) and benzoylecgonine (BE) constitute the major excretion products, irrespective of the route of administration (Jeffcoat et al., 1989). Moreover, approximately 1–3% of cocaine

metabolic products excreted in urine are those resulting from N-demethylation to a norecgonine base, such as norbenzoylecgonine (NBE), in addition to ecgonine (EC) (Goldstein et al., 2009).

There are almost no differences in composition between Peruvian and Bolivian teas. After consumption of one cup of tea made of 1 g of coca (determined by Jenkins et al. in this study to contain an average of 4.14- 4.29 mg of cocaine per cup), cocaine metabolites like benzoylecgonine and ecgonine methyl ester were detected in urine (Jenkins et al., 1996). Levels of benzoylecgonine were 3368 ng/ml at 10 h, 1000 ng/ml at 17 h, 300 ng/ml at 20 h, 100 ng/ml at 45 h, and 23 ng/ml after coca tea consumption, with a cumulative urinary excretion of benzoylecgonine of 3.11 mg after 48 h. The excretion profile of ecgonine methyl ester was 2520 ng/ml at 10 h, and 22 ng/ml at 48 h.

After metabolism, 1 to 9 % of cocaine is excreted unchanged in the urine (Chang, 2000; Paul et al., 2005). Urine excretion of cocaine after consumption of 1 g of coca leaf was 196 ng/ml at 5 h, with undetectable levels after 48 h (Jenkins et al., 1996; Williams et al., 2000).

Although the route of administration impacts the metabolic profile of cocaine, Cone et al. (1998) observed that cocaine was rapidly absorbed, metabolized, and excreted, and it was usually identified in the first urine void regardless of route of administration, including intravenous, intranasal, or smoking routes.

BE is a cocaine metabolite that is required by many countries for regulated urine drug testing programs (DHHS, 2004). Cocaine can be converted to BE in urine when the pH is basic, allowing the possibility of a positive test due to external contamination (Isenschmid et al., 1989). Hence, some authorities have suggested testing for EME to circumvent this problem, but Klette et al. (Klette et al., 2000) demonstrated that cocaine can be converted to EME when urine pH is > 7. Because of these bias risks, testing for m-hydroxybenzoylecgonine (mOHBE) and p-hydroxybenzoylecgonine (pOHBE) is recommended. These metabolites are lower in concentration than BE or EME, but they are not produced in vitro (Huestis et al., 2007).

4.3 Pharmacodynamics

The pharmacodynamics of coca leaf primarily depends on the alkaloids, phenols, tannins, flavonoids and diterpenes that it contains (see section 1) The pharmacodynamics of cocaine, the most important alkaloid in coca leaves, includes its inhibitory action on the sodium pump, which explains its local anesthetic effect, and its inhibition of the presynaptic reuptake of monoamines such as norepinephrine, dopamine, and 5-HT. However, the effects of cocaine are not the focus of this report. There is no evidence available yet on the mechanism of action of the other components of the coca leaf (Roque Bravo et al., 2022).

4.4 Preclinical effects

The biological and pharmacological effects of coca leaf use are described below, according to in vivo or in vitro studies carried out. In the following paragraphs, several species of Erythroxylum will be discussed, so it should be kept in mind that the only ones cultivated to obtain cocaine are *E. coca* and *E. novogranatense*.

4.4.1 Antihypertensive effect

Several Erythroxylum species demonstrate antihypertensive potential through ACE inhibition, vasodilation, and diuretic effects. Ethanol extract of E. gonocladum inhibited ACE in vitro, with astilbin identified as a key active compound (Lucas-Filho et al., 2010; Matos de Macêdo et al., 2022). Crude extracts and semipurified fractions of E. argentinum leaves reduced blood pressure in vivo (Matos de Macêdo et al., 2022; Takahashi et al., 1988). E. laurifolium extract inhibited ACE by 64% at 0.33 mg/mL, with activity linked to proanthocyanidins, quercitrin, and afzelin, which showed synergistic ACE inhibition and blood pressure–lowering effects in animal models (Fukunaga et al., 1989; Hansen et al., 1996; Matos de Macêdo et al., 2022; Novoa et al., 1985; Restrepo et al., 2019).

E. macrocarpum displayed diuretic effects via inhibition of fluid absorption, attributed to tropane alkaloids (Mahomoodally et al., 2005; Restrepo et al., 2019). E. campestre methanolic fraction reduced blood pressure, renal and aortic vascular resistance in hypertensive rats, likely due to glycosylated flavonoids (de Lima et al., 2024). E. passerinum ethanolic extract induced dose-dependent hypotension, bradycardia, and vasorelaxation, mediated by polyphenols through nitric oxide, COX metabolites, and potassium channels (Santos et al., 2022). E. pungens caused hypotension and tachycardia in vivo and vasorelaxation in vitro, with tachycardia attributed to baroreflex (Oliveira et al., 2012).

Overall, E. gonocladum, E. argentinum, E. laurifolium, E. macrocarpum, E. campestre, E. passerinum, and E. pungens have shown ACE inhibitory, diuretic, and vasodilatory effects in vitro and in vivo, supporting their traditional antihypertensive use.

4.4.2 Anticancer activity

4.4.2.1 Cytotoxic effect

Cytotoxicity assays of Erythroxylum species have demonstrated variable activity across different extracts and cell lines. Araújo Neto et al. (2021) reviewed 21 species against 45 cell lines, grouping them into alkaloid-rich species with high cytotoxic potential (e.g., E. caatingae, E. pervillei, E. rotundifolium, E. vacciniifolium), alkaloid-containing species with low activity, and non-alkaloid species. Some extracts showed activity below the NCI antitumor threshold.

Specific studies report cytotoxic effects of triterpenes from E. daphnites on oral carcinoma cells via apoptosis (Elias et al., 2016; Lv et al., 2022; Matos de Macêdo et al., 2022); alkaloid-rich fractions of E. pungens against cervical, prostate, and renal cancer lines (Araújo Neto et al., 2021; Macedo Pereira et al., 2018); and aqueous E. cuneatum extracts against HepG2 cells without genotoxicity (Matos de Macêdo et al., 2022; Prayong et al., 2008; Wesam et al., 2013). E. suberosum extracts enhanced radiotherapy efficacy in oral and hypopharyngeal carcinoma (Macedo et al., 2016; Matos de Macêdo et al., 2022).

Other findings include cytotoxic activity of E. coca morphotypes against murine fibroblasts (Marentes-Culma & Orduz-Díaz, 2025), E. campestre extracts with strong activity against S180 and HeLa cells (Araújo Neto et al., 2021), E. deciduum extracts showing effects comparable to cisplatin (Araújo Neto et al., 2021; Mesquita et al., 2017), and E. macrocarpum extracts selective for tumor cells (Araújo Neto et al., 2021). Extracts of E. tortuosum and E. anguifugum also displayed cytotoxicity against HeLa and leukemia lines, respectively (Araújo Neto et al., 2021; Liu et al., 2025).

Some preparations showed radiosensitising effects (E. suberosum, E. subrotundum), often comparable to cisplatin (Elias et al., 2015; Macedo et al., 2016). Selective or protective effects were also reported, such as hepatoprotective properties of E. confusum (Araújo Neto et al., 2021; Rodeiro, Donato, Lahoz, et al., 2008; Rodeiro, Donato, Martínez, et al., 2008) and lack of cytotoxicity for rutin (Cristina Marcarini et al., 2011). Early animal studies (Schulz et al., 1980) and small human studies on coca products (Descailleaux, 1990) suggest both antitumor and antimutagenic effects.

Overall, Erythroxylum species show diverse cytotoxic and radiosensitising properties, with some extracts displaying activity comparable to standard chemotherapy agents.

4.4.3 Anti-oxidant and anti-inflammatory activities.

Several Erythroxylum species have been evaluated for antioxidant activity using in vitro methods, including DPPH, ABTS, ORAC, NO, SO, H2O2, XO inhibition, and FRAP assays. Sterols isolated from E. monogynum leaves, 4-methyl ergosta-7,23-dien-3β-ol and 4-methyl ergosta-7,24-dien-3β-ol, showed strong antioxidant and anti-glycation activity (G & Suripeddi, 2021; Lv et al., 2022). Leaf alkaloid extract of E. cuneatum demonstrated both antioxidant and anti-inflammatory effects (Li et al., 2020; Lv et al., 2022). In vivo, crude extract and semipurified fractions of E. argentinum leaves reduced carrageenan-induced paw edema in laboratory animals (Matos de Macêdo et al., 2022; Takahashi et al., 1988).

E. sideroxyloides exhibited strong protective effects in microsomal lipid peroxidation systems with IC50 values of 0.0435 ± 0.001 mg FW/mL (Fe3+/ascorbate) and 0.05 ± 0.002 mg FW/mL (AAPH),

surpassing other Mauritian endemic plants (Soobrattee et al., 2008). Comparative evaluation of 64 Mascarene Island plants confirmed high antioxidant capacity for E. laurifolium and E. sideroxyloides, with IC50 values in ABTS, FRAP, and ORAC assays reported for leaf and bark extracts of both species (Ledoux et al., 2018; Matos de Macêdo et al., 2022).

Antioxidant activity varied widely across species, extraction methods, and assays. Extracts of E. macrocarpum ranged from low to strong activity depending on site and methodology (F. M. Mahomoodally et al., 2012; Matos de Macêdo et al., 2022; Ramhit et al., 2018). In E. alaternifolium, only polar fractions showed detectable activity (Perera Córdova et al., 2012). Moderate antioxidant activity was reported for alcoholic extracts of E. novogranatense and E. coca (Gamarra Ochoa et al., 2017), while E. Coca infusions also demonstrated measurable effects (Poblete et al., 2009). By contrast, steroids from E. monogynum consistently exhibited strong antioxidant activity (G & Suripeddi, 2021).

Anti-inflammatory testing of E. mexicanum extracts in LPS-stimulated RAW 264.7 macrophages found no significant cytotoxicity, but also no inhibition of NO production at concentrations from 1 to 100 µg/mL (Hurtado-Díaz et al., 2024). In a comparative study, ethanol extract of E. suberosum leaves showed superior antioxidant activity across DPPH, FRAP, and cyclic voltammetry assays compared to ethyl acetate extract, likely due to higher phenolic content (de Fátima Souza de Oliveira et al., 2015). Isoquercitrin, quercetin, catechin, and epicatechin isomers identified in the extract support this explanation (Barros et al., 2017).

Overall, extracts of E. cuneatum, E. argentinum, E. sideroxyloides, E. macrocarpum, E. laurifolium, E. alaternifolium, E. novogranatense, E. coca, E. monogynum, E. suberosum, and E. mexicanum show variable but sometimes strong antioxidant and anti-inflammatory effects in vitro and in vivo, suggesting potential for future development of therapeutic agents.

4.4.4 Antimicrobial effects

Antimicrobial activity (against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa*, and *Salmonella typhi*) and antiviral effect on herpes simplex have been found . Although many of these properties are invoked for traditional medicine, they do not yet have sufficient evidence for their use in therapeutics (Restrepo et al., 2019).

The hydro-alcoholic extract of Erythroxylum coca leaves was evaluated under cell culture conditions for its effects on human granulocytes and mononuclear cells. The study assessed cell viability, mitochondrial and cytoplasmic oxidoreductase activity, and innate immune functions, including phagocytosis, chemotaxis, endocytosis, and microbicidal activity, as well as cytokine release related to inflammatory response (Padilla et al., 2023). At doses equivalent to traditional human consumption (0.13 µg/ml) and up to higher concentrations (130 µg/ml), leukocyte

viability was preserved. Within this safety range, the extract did not impair oxidoreductase enzyme activity; instead, low doses stimulated it. Chemotactic and endocytic functions were enhanced at intermediate doses, while microbicidal activity remained unchanged, with cells effectively processing Staphylococcus aureus similarly to untreated controls. The extract also promoted mitochondrial enzymatic activity and increased bacterial ingestion and polymorphonuclear cell migration. Regarding cytokine modulation, E. coca stimulated TNF release and inhibited IL-10, favoring a pro-inflammatory profile. Overall, the extract demonstrated no harmful effects on leukocyte viability or functionality at traditionally recommended doses and showed immunomodulatory potential by enhancing certain innate immune responses and promoting a pro-inflammatory cytokine profile.

The ability to trigger myeloperoxidase activities of phagocytes by methanolic and aqueous extracts of *E. macrocarpum* leaves was evaluated. At concentrations of 25, 50, and 100 µg/mL, the extracts showed low immunomodulatory activity when compared with the control (F. M. Mahomoodally et al., 2012; Matos de Macêdo et al., 2022).

The influence of a coca leaf 95% ethanol extract was studied in a model of cellular immune response induction in mice. Animals that received coca derivatives orally during the first 4 days of the immune challenge showed a 53% lower response than controls. The inhibitory effect of the extract was greater than that of pure cocaine, suggesting that the extract contains other inhibitory components (Watson et al., 1983).

The preparations used are generally alcoholic extracts of coca leaves. Ethanol used as a vehicle serves as a negative control, and chlorhexidine or an antibiotic serves as positive controls. The alcoholic extracts have an area of microbial inhibition intermediate between these two controls.

4.4.5 Antibacterial effects

Crude extracts of E. delagoense, E. emarginatum and E. pictum showed significant antibacterial activity (Lv et al., 2022; Wet, 2011). Similarly, E. coca leaf extract (1 g/mL) demonstrated broad inhibition zones against S. epidermidis, E. coli, P. aeruginosa and S. aureus, confirming notable antimicrobial potential (Gamarra Ochoa et al., 2017; Matos de Macêdo et al., 2022).

Alcoholic extracts of E. novogranatense leaves were active against multiple oral and pathogenic bacteria, including Streptococcus, Lactobacillus, Actinomyces, Prevotella, Fusobacterium, E. coli, P. aeruginosa, and S. epidermidis (Alvarado Villanueva & Moromi Nakata, 2010; Gamarra Ochoa et al., 2017; Luna-Vílchez et al., 2017). E. macrocarpum also showed strong to moderate activity against both Gram-positive and Gram-negative strains (Mahomoodally et al., 2005; Matos de Macêdo et al., 2022; Ramhit et al., 2018). Comparative testing of E. macrocarpum, E. hypericifolium, E. laurifolium, and E. sideroxyloides revealed antimicrobial effects against S.

aureus, E. coli, P. aeruginosa, and S. typhi, linked to quercitrin, isoquercitrin, and catechin. E. macrocarpum was active against all strains, while E. hypericifolium also inhibited Aspergillus niger (Gurib-Fakim et al., 2005; Matos de Macêdo et al., 2022; Restrepo et al., 2019). Extracts from E. laurifolium further inhibited Salmonella enteritidis, P. aeruginosa, Enterobacter cloacae, and B. subtilis (Matos de Macêdo et al., 2022).

Direct comparisons between coca leaf varieties highlight species differences: ethanolic extracts of E. coca var. coca showed stronger activity against Streptococcus mutans than E. novogranatense var. truxillense, with significant dose–response effects, though neither matched chlorhexidine (Salcedo Calderón & Moromi Nakata, 2022). Other studies confirmed ethanolic E. coca extracts inhibited S. mutans and S. sanguis but were less effective than chlorhexidine (Cormejo Cruz & Quispe Condori, 2017; Loyola et al., 2020). In contrast, aqueous E. coca extracts lacked activity (Diaz Velasquez, 2022). Essential oil from E. novogranatense var. truxillense also inhibited S. mutans (Castro Luna, 2008).

Additional species demonstrate broad-spectrum effects: alcoholic E. pulchrum extract inhibited B. subtilis, E. coli, P. aeruginosa, S. aureus, and S. mutans (Albuquerque, 2013). In E. mexicanum, methanolic leaf extract was ineffective against Gram-positive strains up to 500 µg/mL, but stem extracts and fractions displayed promising antibacterial activity (Hurtado-Díaz et al., 2024).

4.4.5.1 Antifungal effect

E. daphnites and *E. subrotundum* showed activity against the yeast strains with a Minimal Inhibitory Concentration (MIC) value of 1000 µg/dis. The ethanol extract of *E. daphnites* leaves failed to show any inhibitory activity. The aqueous extract of *E. daphnites* leaves showed inhibitory effect only against C. glabrata (24 and 25 mm). The aqueous extract of *E. subrotundum* leaves was effective against three Candida species and showed comparable antifungal activity against C. parapsilosis (10 and 11 mm), C. guilliermondii (10 mm), and C. glabrata (15 and 30 mm). The ethanolic extract of *E. subrotundum* revealed antifungal activity against C. parapsilosis (10 mm) and C. glabrata (20 to 25 mm) (Fernandes Correia et al., 2016).

The aqueous and ethanolic extracts of *E. coca* leaves did not show any effect on the growth of Candida albicans and Trichophyton mentagrophytes, but did show an effect on Trichophyton rubrum and Microsporum canis (Luna-Vílchez et al., 2017; Matos de Macêdo et al., 2022).

Extracts from *E. ovalifolium* leaves exhibited antifungal activity for Stryphnodendron adstringens, Styrax spp., Synadenium sp. and Symphytum officinale (Matos de Macêdo et al., 2022; Sales et al., 2016).

Extracts from the leaves of *E. laurifolium* were reported to exhibit antifungal activity against C. albicans (Matos de Macêdo et al., 2022).

4.4.5.2 Antiprotozoal activity

Species of the genus Erytroxylum were analyzed for their antiplasmodial properties. Extracts from the leaves of *E. monogynum* showed interesting antimalarial activity, with the methanolic extract being the most promising, with an IC50 of 12.23 µg/mL against Plasmodium falciparum (Venkatesalu V et al., 2012). In contrast, extracts from the leaves and bark of *E. laurifolium and E. sideroxyloides* were only able to reduce the population of P. falciparum at concentrations greater than 50 µg/mL (Ledoux et al., 2018; Matos de Macêdo et al., 2022).

The antiparasitic activity of 174 compounds and plant extracts from the semi-arid region of Bahia was study, among them, a pure substance isolated from *E. passerinum*, which at a concentration of 0.1 mg/mL presented 21.39% inhibition for Trypanosoma cruzi epimastigotes and 5.88% inhibition for Leishmania amazonensis promastigotes (Matos de Macêdo et al., 2022).

4.4.5.3 Antiviral activity

The antiviral properties of methanolic extracts of the leaves and bark of *E. laurifolium* against Herpes simplex virus type 1 (HSV-1) and Poliovirus type 2 (PV-2), were analyzed. It was observed that the extracts did not show the ability to inhibit the growth of PV-2; however, they were active against HSV-1 with an IC50 of 125 µg/mL and a selectivity index of 16 (Fortin et al., 2002). In addition, the tannin-enriched extract from the leaves and bark of *E. laurifolium* at a concentration of 2 mg/mL showed time-dependent virucidal activity against HSV-1. This property is explained by the fact that tannins can affect virus replication due to their ability to complex with cell envelope proteins (Lohezic et al., 1999; Matos de Macêdo et al., 2022).

Hydroalcoholic extracts of *E. areolatum* or *E. confusum* leaves showed antiherpetic activity (Lv et al., 2022).

Extracts form leaves of E. laurifolium, E. areolatum and E. confusum have antiherpetic activity. This genus seems relevant as a source of bioactive compounds with antiviral properties.

4.4.6 Stimulant activity

Despite an abundance of information on the psychostimulant effects of purified cocaine, there is little research on the acute stimulant effects of coca leaf preparations. In 1984, Novák (Novák et al., 1984) reported the bioactivities of tropane alkaloids (TAs) from leaves of E. coca and E. novogranatense that had stimulant activity, inhibiting effect on dopamine uptake.

Methylecgonine, benzoyltropine, and propacocaine were found to inhibit dopamine reuptake in various animal preparations, an action associated with psychostimulant effects (Novák et al., 1984; Williams et al., 1977).

Benzoyltropine shows both potency and selectivity as an antagonist of 5 hydroxytryptamine (serotonine) on the rabbit heart. In rats, benzoyltropine inhibits the radiolabeled [3H] norepinephrine and [3H] dopamine uptake in the cortex and striatum, respectively (Novák et al., 1984).

Psychostimulant effects in humans are reviewed in section 9.

4.4.7 Hepatoprotective effects

Extracts of *E. minutifolium or E. confusum* leaves showed hepatoprotective effects (Lv et al., 2022; Rodeiro, Donato, Lahoz, et al., 2008).

The protective effect on oxidative damage induced by toxic models in rat hepatocyte cultures was studied for extracts of E. *minutifolium* and *E. confusum*. Both extracts showed hepatoprotective activity, reducing hepatocyte damage caused by tert-butyl hydroperoxide (EC50 72 to 83 µg/mL) and carbon tetrachloride (EC50 86 to 33 µg/mL), as well as ethanol and lipopolysaccharide with EC50 >100 µg/mL (Matos de Macêdo et al., 2022; Rodeiro, Donato, Martínez, et al., 2008).

E. minutifolium leaves extract (25, 50, and 100µg/mL, sub-toxic concentrations) exhibited hepatoprotective effects and also showed antioxidant potential by the reduction in the production of malondialdehyde (MDA). The maximum effect was observed with a 50 µg/mL concentration (Rodeiro, Donato, Martínez, et al., 2008).

The methanolic and hydroalcoholic extracts of *E. monogynum* leaves demonstrated hepatoprotective activity in vivo on the toxicity induced by paracetamol and CCl4 in rats, respectively. The administration of CCl4 (1 ml/kg) and paracetamol (2 mg/kg) resulted in significant hepatocellular damage, evidenced by a significant increase in serum biomarkers SGPT, SGOT, and total bilirubin compared to control groups. There was a reduction in SGOT, SGPT, and total bilirubin levels, in addition to hepatocyte regeneration (Araújo Neto et al., 2021; Syed & Namdeo, 2013).

The presence of glycosylated flavonoids, especially rutin (quercetin-3-O-β-rutinoside), is thought to be responsible for the hepatoprotective effect observed by the hydroalcoholic extracts of the leaves of *E. confusum* and *E. monogynum* and by the methanolic extract of the leaves of *E. monogynum*. The potent antioxidant capacity of rutin has been demonstrated by different antioxidant assays. The ability to neutralize or sequester free radicals has been proven in tests such as the hydroxyl radical scavenging test, superoxide radical scavenging test, 1,1-diphenyl-2-picrylhydrazyl radical scavenging test (DPPH), sequestration of 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) radicals (ABTS), and lipid peroxidation assay (Araújo Neto et al., 2021).

4.4.8 Antidiabetes activity

The methanolic extract of the leaf of *E. laurifolium* showed significant inhibition of α-amylase (IC50 7472.92 µg/mL) and α-glucosidase (IC50 1.02 µg/mL) when compared with acarbose. It was then demonstrated that *E. laurifolium* has a potent antidiabetic activity, with strong inhibition especially of α-glucosidase (Picot et al., 2014; Shori, 2015). At concentrations between 250 and 2000 µg/mL, the extracts and fractions of *E. macrocarpum* showed low antiglycation properties, with an IC50 of 0.11 to 9.36 µg/mL when compared with the aminoguanidine standard (M. F. Mahomoodally et al., 2012). On the other hand, the steroids 4-methyl ergosta-7, 23-dien-3β-ol and 4-methyl ergosta-7, 24(28)-dien-3β-ol, isolated from the leaves of *E. monogynum*, demonstrated high antiglycation capacity, with more than 90% inhibition of advanced glycation end products (AGE) at a concentration of 100 mg/mL and with IC50 of 35.12 and 39.28 mg/mL, respectively (G & Suripeddi, 2021; Matos de Macêdo et al., 2022).

Furthermore, it was observed that Coca *(E. coca)* reduces postprandial glycemia in people without a metabolic pathologic background, and it's statistically significant in the two ways of cultural consumption, in a control group post-intake mate of 5 gr. Coca and a post-chewing group 5 gr. Coca leaf (Hurtado Sánchez et al., 2013).

4.4.9 Cholinergic and adrenergic activity

The tropane alkaloid 7β-acetoxy-3β, 6β-dibenzoyloxytropane, isolated from the leaves of E. rimosum, was evaluated for inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), presenting IC50 values of 4.67 × 103 mmol/L and 2.71 × 104 mmol/L, respectively, an effect that was significant when compared to that obtained by the control with physostigmine (Ribeiro et al., 2013). Furthermore, it was also described that the extract (Acetone/water (70/30, v/v) of the leaves of E. macrocarpum presents a potent and significant inhibitory activity of AChE with an IC50 of 0.04 mg of fresh weight per mL (Lv et al., 2022; Matos de Macêdo et al., 2022; Ramhit et al., 2018). Furthermore, TA from the leaves of E. coca and E. novogranatense, tropacocaine, and benzoyltropine exhibited cholinolytic action. Benzoyltropine has mild mydriatic properties but a limited anesthetic effect (Novák et al., 1984).

4.4.10 Antiparkinsonian activity

Astilbin (AST), a flavonoid isolated from the aerial parts of *E. gonocladum*, has been reported to have anti-inflammatory, antioxidant, and neuroprotective properties. In this sense, AST was evaluated for its potential to treat Parkinson's disease (PD) induced with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice. AST showed the ability to exert neuroprotective effects in MPTP-induced PD mice, suppressing gliosis, α-synuclein overexpression, and oxidative stress, suggesting that AST could be used for the development of medicines for the treatment of PD (Matos de Macêdo et al., 2022; Zhu et al., 2019).

4.4.11 Myorelaxant activity

E. caatingae was investigated for its muscle relaxant effect on muscle tissue by analyzing its ability to reduce the contractility of the ovine cervix. The ethanolic extract of *E. caatingae* leaves at cumulative concentrations (1-729 g/mL) decreased the amplitude of contractility in vitro, with an EC50 of 17.9 g/mL. The muscle relaxant effect may involve nitric oxide signaling mediated by cellular cGMP transduction, related to intracellular calcium sequestration (Matos de Macêdo et al., 2022; Santos et al., 2016).

Other species also demonstrated interesting effects on the muscular system; the aqueous and methanolic extracts of the leaves and bark of *E. sideroxyloides, E. hypericifolium, E. laurifolium, and E. macrocarpum* presented in vivo contraction and relaxation responses of smooth muscles, aortal and tracheal muscles in cold-blooded animals (Gurib-Fakim et al., 2005; Matos de Macêdo et al., 2022).

4.4.12 Cytochrome P450 system modulating activity

A study reported the ability of extracts from the leaves of *E. minutifolium* and *E. confusum* to modulate the cytochrome P450 system of rat hepatocytes. Both extracts produced a decrease in the activities of CYP1A2, CYP2E1, and SM4OH, whereas no influence on the values of CYP3A1, 2D2, and 2C6 was observed (Rodeiro, Donato, Lahoz, et al., 2008). Another study evaluated volatile mixtures induced by jasmonic acid from two Erythroxylum species. The study concluded that CYP79D60, CYP79D61, and CYP79D62 accept L-phenylalanine, L-leucine, L-isoleucine, and L-tryptophan as substrates, and that these in vivo contribute to the production of volatile and semivolatile nitrogenous defense compounds in E. coca and E. fischeri (Luck et al., 2016). Quantitative real-time PCR revealed that CYP79D60, CYP79D61, and CYP79D62 were significantly upregulated in jasmonic acid-treated Erythroxylum leaves (Matos de Macêdo et al., 2022).

4.4.13 Larvicide activity

Regarding larvicidal activity, the methanolic and ethyl acetate extracts of the leaves and fruits of *E. passerimum and E. nummularia* were inactive against Aedes aegypti larvae. However, the compound 14-O-methyl-ryanodanol, a diterpene isolated from *E. nummularia*, showed slight activity in the larvicidal test with an LC50 of 82 ppm (Barreiros et al., 2007; Matos de Macêdo et al., 2022).

4.4.14 Metabolic activity

There is clinical evidence of the association between coca leaf use and lower total cholesterol levels. See section 9, “Lipid Lowering Effects”. Supplementation with a powdered preparation of coca leaf has also been studied on bone turnover in postmenopausal women. See section 9, “Effects on Bone Metabolism”.

4.4.15 Analgesic and anesthetic effects of coca leaves

The local anesthetic effect of cocaine is well known (Calatayud & Gonzalez, 2003; Tsuchiya, 2017), but studies of these effects from the whole coca leaf or other derived preparations are very scarce.

Different fractions obtained from an alcoholic extract of *E. coca* were studied in a laboratory model of rat tail withdrawal from electric shock, with cocaine as a positive control and the excipient as a negative control. The efficacy of the most potent preparations, containing 2% cocaine, was 20% lower than that of purified cocaine. Remarkably, a cocaine-free fraction reached 30% of the effect observed with cocaine. It was concluded that the local anesthetic effect of these extracts appears to depend on their cocaine content, although the contribution of other components of the coca leaf was not ruled out. (Bedford et al., 1984).

4.4.16 Anorectic activity

Experiments in animal research have shown that oral and intraperitoneal administration of *E. coca* extracts in rats increased locomotor activity and reduced food consumption in treated animals. (Bedford et al., 1980). It's possible that the reduction in appetite is not solely attributable to the cocaine content: after removing the alkaloid, intraperitoneally administered *E. coca* extracts in rats resulted in decreased food-seeking behavior without affecting general motor activity (Bedford, Wilson, et al., 1981).

Rats fed decocainized coca leaves at a high dose of 150 mg demonstrated a significant decrease in weight gain compared with control animals receiving the vehicle, but not at any of the lower doses (1.5 or 15 mg (Valentine et al., 1988).

In addition, a study by Vee GL et al. demonstrated that a coca extract given orally reduced food intake with an ED50 of 52.6 mg/kg ± 1.7 SEM. Significant tolerance developed over 30 days associated with an increase in the ED50 to >100mg/kg (Vee et al., 1983).

4.4.17 Effects on the Gastrointestinal System

Pizarro, F et al. (1994) measured the amount of tannins in coca leaf when used as a tea. They found the levels to be intermediate and similar to matico, boldo, avocado, bay leaf, orange, and fennel. They concluded that regular Coca tea use may reduce the GI absorption of iron (Fe), zinc (Zn), and copper (Cu), essential metals that are needed for normal physiological function (Pizarro et al., 1994).

4.4.18 Effects on Locomotor Activity

We did not identify any peer-reviewed research directly studying the effect of coca leaf (as traditionally consumed, e.g., coca tea or chewing) on driving performance or driving under the influence of drugs in humans or animals.

Studies on locomotor activity in male Wistar rats were performed to test whether two extracts of the coca leaf have effects comparable to the effects of cocaine. Coca leaf extracts were prepared using 95% ethanol, then the ethanol was evaporated, and any residue was partitioned between water and chloroform. The doses of the extracts studied were 60, 120, 240, and 480 mg/kg body weight. The doses of cocaine studied were 3.45, 6.9, 13.8, and 27.6 mg/kg. The chloroform layer of the extract, when given orally or intraperitoneal at the doses of 240 mg/kg or 480 mg/kg, produced significant increases in locomotor activity and decreases in food consumption (Bedford et al., 1980). Further studies by this group demonstrated that the coca leaf does contain constituents other than cocaine that are biologically active in increasing locomotion and reducing food consumption. This activity is thought to be qualitatively different from that observed with cocaine (Bedford, Wilson, et al., 1981).

A study by Silva-Filha et al. investigated the effects of an ethanolic extract of Erythroxylum mucronatum on the strength and muscle performance of resistance-trained Wistar rats. A daily dose of either 50 or 150 mg/kg/day was administered in two groups of rats through gavage during the 20 days of training. Supplemented groups had significantly lower body fat content, a reduction in oxidative stress, and increased antioxidant activity compared to the control groups ($P < .05$) (Silva-Filha et al., 2022).

Decocainized (cocaine removed) i.v. injections of large doses (200 mg/kg) can produce hyperglycemia, a significant reduction in heart rate, and a significant decrease in blood pressure in dogs, as well as a reduction in the oxygen utilization in mice (240 to 800 mg/kg). Coca extract may have the potential to produce slower growth rates at high elevation (6,705 m) in rats, as well as a potential to demonstrate addictive properties at high levels of coca extract (60 and 120 mg/kg). In several rat and mouse studies, there were significant signs of coca leaf extract causing increased locomotor activity, decreased food consumption, increased respiratory quotient, and reduced oxidative stress.

Water-soluble nonalkaloid fractions of E. coca were screened by observation as well as by utilizing an open field locomotor screen assay in mice for central nervous system (CNS) activity. No CNS effects were demonstrated in mice (Harland et al., 1982).

4.4.19 **Other activity**

A study sought to determine the effect of the alkaloid extract of the leaves of *E. cuneatum* against chronic morphine dependence and the influences on neurotransmission processes in vitro. The extract of E. cuneatum was postulated to treat dependence symptoms after chronic morphine, with properties similar to methadone, increasing vesicle traffic and neurotransmitter release. (Matos de Macêdo et al., 2022; Suliman et al., 2016).

In a small study in anemic rats, *E. coca* ethanol extract showed an incipient antianemic effect, as evidenced by the improvements in serum hemoglobin levels observed in the treated group (Gonzales-Carazas et al., 2013).

Cuscohygrine (*alkaloid of E. coca and E. novogranatense*) was found to inhibit the delayed type hypersensitivity response to 2,4-dinitrofluorobenzene in mice; it produced 24% inhibition at daily doses of 60 mg/kg. Mice dosed with 60 mg/kg cuscohygrine had suppressed plaque-forming cell/10^6 spleen cell responses (Novák et al., 1984).

A study was conducted to determine whether cocaine-free extracts would produce changes in oxygen utilization, blood glucose levels, respiration, and/or cardiovascular effects that could be related to improved physical endurance in humans (Harland et al., 1982).

Water-soluble non-alkaloid fractions of *E. coca* were analyzed in mice for their effects on oxygen utilization and central nervous system (CNS) activity. In dogs, these fractions were analyzed for cardiovascular, glycemic, and respiratory changes. No CNS effects were observed in mice; however, a reduction in the rate of oxygen utilization and locomotor activity was observed. The decrease in locomotor activity was not the only cause of decreased oxygen consumption. Intravenous administration of the extract to dogs produced hyperglycemia, a reduction in heart rate, and a decrease in blood pressure. Since hard work or heavy exercise tends to increase cardiac output and mean arterial pressure, the sustained hypotensive effect and decrease in heart rate could be partially responsible for the enhanced work performance and endurance experienced by natives using coca. Blood glucose levels reached their peak 45 min after dosing and began to decline after 60 min. This could explain a ready energy source, which would improve the short-term ability to do work and alleviate hunger. The blood glucose levels begin to decline in 1 hr. This is the approximate length of time that chewing of coca leaves is reported to give stimulatory effects, without affecting liver glycogen stores (Harland et al., 1982).

No substantial changes were observed in respiratory rate or tidal or minute volumes.

A single 200-mg/kg dose IV of a butanol fraction cocaine-free given to conscious dogs produced an effect on the autonomic nervous system. Shallow, rapid panting and increased salivation, swallowing, and defecation began immediately after injection. Cyanosis and inactivity were

produced and lasted-1 hr postdose. These effects, exclusive of defecation, appeared to be masked in the anesthetized animals (Harland et al., 1982).

These data suggest that noncocaine-containing fractions may contribute to the beneficial effects seen in subjects chewing coca leaves (Harland et al., 1982).

5 Toxicology

The toxicology of the coca leaf or the Erythroxylum genus is defined here as the study of the mechanisms of action, the damage caused, testing methods, and prevention and repair strategies, including dose-response relationships, exposure pathways, and susceptibility factors. This section will detail the toxicology (study of toxicity) of the coca leaf, whether chewed or in sources of powder, flour, food, drink, as well as utilized as pigments, in materials, fertilizers, agricultural products, etc., on living organisms. The majority of the evidence for possible toxicity associated with the use of coca comes from animal studies or tissue isolated from humans and Erythroxylum coca Lam. or Erythroxylum novogranatense (Morris) Hieron.

The vast majority of toxicology research has focused on pure, isolated cocaine; this concentrated and rapidly acting single constituent is far more toxic than the whole coca leaf (Novák et al., 1984). The coca leaf contains a mix of less harmful alkaloids and a lower concentration of cocaine (Novák et al., 1984). Extrapolating these findings to traditional coca use is of limited use, and drug scheduling has greatly restricted toxicology research specific to the leaf itself.

We were unable to locate in our extensive literature search any studies, human or otherwise, that determine the impact of coca leaf consumption on health or specific health conditions and involved an extensive, multi-center, longitudinal cohort study that objectively assessed outcomes in both coca consumers and matched non-consumers over time, while rigorously controlling for confounding variables and ensuring cultural and demographic representativeness. Such a design would provide more robust and generalizable evidence on the causal relationship between coca leaf chewing, specific health conditions, and overall health. Below is a synopsis of the studies that entail the use of the coca leaf and its outcomes towards measures of toxicity and adverse events in animals and humans.

5.1 Lethality

The estimated minimum lethal dose of cocaine remains a topic of ongoing debate and discussion among researchers, with some studies suggesting a dose as low as 1.2g, while others report different estimates or question current estimates due to the complexities of cocaine toxicity and its effects on individual physiology. Predicting toxic reactions following cocaine use is

complicated by multiple factors, including individual sensitivity, acute tolerance, cocaine purity, and the type of impurities and adulterants (Barceloux, 2012).

There is no evidence in ethnographic or medical literature of a fatal coca leaf overdose in humans, even in regions where chewing is traditional and widespread.

The 24-hour lethal effects of cocaine were compared to those of a crude ethanol extract of the coca leaf (E. coca) in male Swiss mice. Coca leaf extracts as well as cocaine were suspended in a Tween 60, Arlacel 83, and distilled water vehicle and administered intraperitoneal (IP) injections to cohorts of 10 mice each. The LD50 for the coca extract was very high at 3450 mg/kg. As a comparison, the LD50 for cocaine was 95.1 mg/kg- a 36-fold difference (Bedford et al., 1982).

5.2 Effects on the cardiovascular and hematologic systems

Water-soluble, non-alkaloid fractions of E. coca were screened in dogs for their cardiovascular, blood glucose, and respiratory effects. Crude ethanol extract of coca leaves was partitioned between water (fraction A) and chloroform (fraction B). Fraction A was made cocaine and alkaloid-free by dissolving in ammonium hydroxide solution and extracting 10 times with chloroform. Each chloroform fraction was subjected to analytical (GLC) analysis. These fractions each showed the absence of cocaine peaks. Fraction A was further partitioned between butanol and water, yielding two fractions: fraction C, the butanol phase; fraction D, the water phase. Intravenous administration of fraction C (200 mg/kg) to dogs produced hyperglycemia, a significant reduction in heart rate, and a significant decrease in blood pressure. The authors concluded that the other constituents in the coca leaf (not cocaine nor alkaloids) are causing the outcomes (Harland et al., 1982).

5.3 Effects on the respiratory system

Water-soluble nonalkaloid fractions of Erythroxylum coca were screened in mice for their effects on oxygen utilization. Crude ethanol extract of coca leaves was partitioned between water (fraction A) and chloroform (fraction B). Fraction A was made cocaine and alkaloid-free by dissolving in ammonium hydroxide solution and extracting 10 times with chloroform. Each chloroform fraction was subjected to GLC analysis. These fractions each showed the absence of cocaine peaks. Fraction A was further partitioned between butanol and water, yielding two fractions: fraction C, the butanol phase; fraction D, the water phase. There was a significant ($p<0.01$) reduction in the oxygen utilization rate in mice at doses of 240 to 800 mg/kg of all fractions. Intravenous administration of the extract to dogs caused no significant changes in respiratory rate, tidal volume, or minute ventilation (Harland et al., 1982).

5.4 Effects on the immune system

In our search, we were unable to identify any reputable, well-designed, peer-reviewed studies that directly investigate the immunomodulatory effects of coca leaves on the human or animal immune system.

5.5 Mutagenicity and cancer

5.5.1 Potential oral carcinoma effects

A study was conducted to determine if coca leaf consumption causes genotoxic effects in humans that may lead to carcinogenesis. A buccal cytome assay was used to analyze oral cells from 45 uni- and bilateral chewers and 23 controls living in the Altiplano of the Peruvian Andes. In total, 123,471 cells were evaluated from the chewers, and 57,916 from the controls. Chewing of the leaves did not induce nuclear anomalies reflecting genetic damage such as micronuclei (MNi) and nuclear buds. In the highest exposure group, a significant decrease in the frequency of cells with MNi (by 64%) was observed. Yet, the study did find a significantly elevated level of other nuclear anomalies (karyorrhexis or nucleus fragmentation and karyolysis or dissolution of a cell nucleus), which reflect cytotoxic effects in the coca users. The frequencies of these anomalies increased with daily consumption, and when lime was used to improve the release of the alkaloids. In contrast to other chewing habits (betel, tobacco, and khat), consumption of coca leaves does not appear to induce genetic instability in cells from the oral cavity, as measured by the buccal cytome assay, and their findings indicate that no adverse health effects took place in chewers that are associated with DNA damage. However, the significant increase in certain anomalies shows that acute toxic effects are caused by coca consumption (Nersesyan et al., 2013).

In one observational study, 68.4% of 150 coca leaf chewers exhibited hyperparakeratosis and notable intracellular edema in the stratum corneum and the basal cell layer, without any inflammatory signs in the lamina propria (Borghelli et al., 1973). Coca chewing also suppresses salivary glandular activity and contributes to xerostomia by decreasing the secretion of saliva and slowing salivary flow (Indriati & Buikstra, 2001).

In a 1969 study by Hamner, J. E., and Villegas, O. L., forty-six biopsy specimens from the buccal mucosa of Bolivian Indians who had chewed a coca leaf/lime mixture for a variable number of years (0.5 to 65 years) were examined (36 men and 10 women). Histologic leukoedema was a prominent finding on the side in which the chew was held. Large, spongy, vacuolated epithelial cells were noted in the stratum spinosum in many of the samples. No clinical or histologic evidence was found to support the idea that the leukoedema may be a premalignant condition. None of these patients displayed buccal carcinoma, despite lengthy exposure to coca leaf and calcium hydroxide (Hamner & Villegas, 1969).

5.5.2 Potential cytotoxic effects

Utilizing extracts from Erythroxylum suberosum, Erythroxylum subrotundum, and Erythroxylum daphinites, a study on oral squamous cell carcinoma, hypopharyngeal carcinoma, and a keratinocyte cancer cell line examined cytotoxic effects in the absence and presence of radiation. E. suberosum alone demonstrated significant cytotoxic effects, which were further enhanced in the presence of radiation, on all types of cancer cells tested. E. daphinites demonstrated significant cytotoxicity only in the hypopharyngeal carcinoma cells. E. subrotundum did not demonstrate any cytotoxicity (Elias et al., 2015).

Extracts from coca leaves exhibited moderate cytotoxic activity against the L929 murine fibroblast cell line, with one morphotype (Palo) showing a 60.95% inhibition and the other (Caimo) showing a 48.57% inhibition. Clinical implications of this activity have yet to be elucidated (Marentes-Culma & Orduz-Díaz, 2025).

To better understand the activity and toxicity of E. coca, the authors tested E. coca extract on human peripheral blood mononuclear cells in vitro. E. coca extract at physiological doses (1.3ug/ml-130ug/ml) did not demonstrate increased toxicity in the mononuclear cells measured by trypan blue and MTT assay at 24 and 48 hours (Padilla et al., 2023).

5.5.3 Fertility and teratogenesis

In our search, we were unable to identify any reputable, well-designed, peer-reviewed studies that directly investigate the teratogenic effects of coca leaf use in humans or animals.

6 ADVERSE REACTIONS IN HUMANS

The adverse events associated with the Erythroxylum genus primarily deal with E. coca and E. novogranatense. Adverse events are defined as any unfavorable and unintended medical occurrence in humans, and may include a wide range of outcomes, from abnormal laboratory findings to death or potential birth defects. This section will detail the adverse events of the coca leaf, whether chewed or in sources of powder, flour, food, drink, as well as utilized as pigments, in materials, fertilizers, agricultural products, etc., on living organisms. Most of the evidence for possible adverse events associated with coca leaf use comes from published observational reports in humans, population-based studies, and involved participants who were existing coca leaf consumers without clear controls or adequate methodology to explore important themes like causality.

6.1 Oral and periodontal system

A case-control study was conducted from 2013 to 2018 at the Senor del Milagro Hospital, Salta, Argentina (Molina-Avila et al., 2024). This study consisted of 62 patients with Oral Squamous Cell

Carcinoma (OSCC) and 180 control patients, adjusted for sex and age. Findings identified that OSCC was significantly associated with coca leaf chewing ($P < 0.001$), tobacco use ($P = 0.001$), as well as poor oral condition ($P = 0.02$). The study employed a multivariate analysis, which demonstrated that all three items remained independently associated with OSCC development in individuals who chewed coca ($P = 0.0007$). This finding suggests that chewing coca leaves may be considered a risk factor for oral cancer (Molina-Avila et al., 2024).

A case report of a 62-year-old male who had chewed coca leaves for more than six hours per day for 40 years presented with an ulcerated, indurated, and fixed lesion located on the lower left gingivojugal complex, accompanied by a leukoedematous white mucosa observed near the lesion. On the contralateral buccal mucosa, a whitish lesion with a leukoedematous surface was noted. The patient did not smoke, drink, or have exposure to environmental or occupational carcinogens. No inherited history of cancer was recorded. A biopsy of the left-sided lesion revealed a well-differentiated OSCC. The specimen obtained from the contralateral side showed a stratified epithelium with areas of reactive keratosis and underlying chronic inflammatory infiltrate (Molina-Avila et al., 2020).

A case-control study was conducted to determine whether long-term coca leaf chewing in inhabitants of the highland region of Peru is associated with histological periodontal changes (Mendoza-Azpur et al., 2021). The study included 50 individuals who were habitual coca leaf chewers and 50 non-users of coca. Study participants were between 60 and 80 years old, had at least 20 teeth, were systemically healthy (without controlled systemic disease), and were not currently using medications that might affect the gingiva. Chronic tobacco smokers were excluded, and based on gingival biopsies, coca leaf chewers reported several oral changes, such as bitterness, numbness, and mouth dryness. None of the non-chewers reported experiencing such changes ($P = 0.014$). In addition, histological changes of coca chewing participants demonstrated a higher number of inflammatory cells in the stratum spinosum ($P=0.011$), with more acanthosis ($P<0.001$), clear cell and eosinophils ($P<0.001$), loss of dyskeratotic cells (altered maturation process within the epidermis) ($P=0.001$) and higher number of blood vessels as compared to controls ($P=0.001$) (Mendoza-Azpur et al., 2021).

A study examined the oral health of 301 subjects from Venezuela (male and female), aged from 30 to 87; 150 were habitual coca leaf chewers, and the remaining subjects were non-coca chewers. They found that the coca chewers had a significant increase in oral leukoedema (a non-cancerous, whitish or grayish appearance) and leukoplakia (thickened, white or grayish patches) (Borghelli et al., 1975).

A non-experimental, cross-sectional study was conducted to examine the association between oral disease and coca leaf chewing among residents in Peru. The results revealed that 70% of

participants (n = 49) reported chewing coca leaves, with the practice being most prevalent among males and individuals aged 46 to 52 years, indicating a notable demographic pattern. The prevalence of oral diseases within the study population was considerable: gingivitis was observed in 43% of participants, periodontitis in 53%, and dental caries in 56%. Statistical analysis revealed a significant association between coca leaf chewing and both gingivitis ($p = 0.008$) and dental caries ($p = 0.024$). These findings suggest that while coca leaf chewing may increase susceptibility to gingivitis, it may concurrently exert a protective effect against the development of dental caries (Daga Mauricio et al., 2024).

A second cross-sectional study examined the oral health in Peruvian coca chewers. Participants (n = 200) were divided into two groups: 100 non-coca chewers and 100 coca chewers. Participants completed a validated oral health instrument where temporomandibular joint (TMJ), oral cavity, and coca leaf chewing characteristics were assessed. The authors found no association between dental wear, fracture, or mobility and coca chewing. Coca chewing was associated with alteration of the gums (OR=42.67) and increased right insertion masseter muscle pain (OR=17.47) compared to those who did not chew coca (Lucas-Espeza et al., 2023).

A study of 81 male construction workers investigating the relationship of periodontal disease and E. coca chewing with lime found no relationship with periodontal disease and coca chewers with lime ($p=0.458$) (Ordinola Ramírez et al., 2020).

Borghelli et al. reported data from 2,174 military recruitment exams in Argentina. A total of 655 individuals had one or more lesions of the oral mucosa (30.1%). 110 of these cases were clinically compatible with previously reported signs of coca chewing. The authors confirmed that 71.8% of the 110 cases involved coca chewers, and the lesions on the oral mucosa were consistent with leucoedema (Borghelli et al., 1973).

Histopathological changes in the gingival mucosa were evaluated in men aged 40-61 years from Yauyos Province, Peru. Thirty men who reported coca chewing were compared to 30 non-coca chewers. The ages and characteristics were similar between the coca-chewing and non-coca-chewing groups. A significant association was found between the coca chewing group and an increased incidence of acanthosis and hyperparakeratosis ($P < 0.05$) (Ayón Haro & Chu Morales, 2005).

6.2 Cardiovascular system

Human studies show that coca chewing produces measurable cardiovascular effects, including increases in heart rate, mean arterial pressure, hemoconcentration, and peripheral vasoconstriction, particularly during exercise or cold exposure, but these changes were generally

within normal physiological ranges and did not indicate overt harm in healthy individuals (Carmel et al., 2022).

6.3 Gastrointestinal system

In a prospective cohort study conducted between 2000 and 2006 on patients admitted with sigmoid volvulus at the Bolivian-Japanese Gastroenterology Institute, a university tertiary Hospital in Cochabamba, Bolivia, coca-chewing was found to be an independent risk factor for higher inpatient mortality (aOR: 6.1, $p<0.05$), surgical intervention (not reported), and hospital readmission (aOR: 2.5, CI: 1.1-5.6, $p<0.05$). Post-surgical complications were not found to be associated with coca-chewing, but alcohol abuse was a significant risk factor (Simons-Linares et al., 2018).

A second publication, also conducted at the Bolivian-Japanese Gastroenterology Institute, found that among 814 patients with lower intestinal obstruction, 74.7% had sigmoid volvulus, often associated with megacolon. Chagas disease was the most common cause (22% seropositive), but another 21.4% of patients were seronegative and had a history of coca leaf chewing, suggesting coca may also contribute to megacolon (Saravia Burgos & Acosta Canedo, 2015).

6.4 Hormonal and endocrine effects

In studies of Andean populations, coca-leaf chewing dramatically increased apparent salivary progesterone levels—averaging a 716% rise at 30 minutes post-chewing—likely due to assay interference rather than true hormonal change, with habitual users showing higher levels than infrequent users. Additionally, a high-altitude study found that coca leaf infusion during submaximal exercise influenced prolactin, FSH, LH, and testosterone levels, though the clinical significance of these hormone changes remains unclear.

6.5 Visual system

In a published abstract of 111 individuals in Peru all exposed to biomass fuels (burning of things like wood, leaves, etc.) with 60 (54%) of the individuals coca leaf chewers they found more blurred vision 70% (coca chewers) vs. 47% (controls) ($p=0.01$), double vision 39% (coca chewers) vs. 18%(controls) ($p=0.01$), dry eye sensation 58% (coca chewers) vs. 42% (controls) ($p=0.08$) In addition to vision issues they found that increased cough 41,4% (coca chewers) vs. 16% (controls) ($p<0.01$), allergic rhinitis symptoms 18,6% (coca chewers) vs. 3,9% (controls) ($p=0.01$) and had more days per week with expectoration (4,5 vs. 3,1 days, $p<0.05$). They also found that chewers had higher peripheral blood white cell counts ($p= 0.037$). Overall, individuals exposed to biomass fuels and those who chew coca leaves may experience more difficulties with vision, cough, expectoration, and allergies (Sánchez-Sierra et al., 2010).

6.6 Nutritional state and overall health

An epidemiological study of the inhabitants of several small Peruvian villages investigated whether regular coca chewers and non-chewers demonstrated a statistically significant difference in weight-to-height ratios. They found that coca chewers showed a slight decrease in both weight and height compared to non-chewers, although the difference was not statistically significant. In the same study investigating nutritional state, they found no significant difference in skin thickness; however, coca chewers exhibited a slight reduction in skin thickness compared to the controls. They found that serum albumin levels were significantly lower ($p = 0.05$) and cholesterol levels were lower ($p = 0.01$) in coca chewers compared to the control group. Personal hygiene was evaluated, with the prevalence of pyoderma being more significant in coca chewers compared to controls ($p = 0.03$). This same study measured hemoglobin and hematocrit, finding a decrease in coca-chewers compared to controls, which may be induced in those with hookworm, a common issue among this population (Buck et al., 1968).

7 DEPENDENCE POTENTIAL

Studies conducted in animals to assess dependence potential were not identified in the literature.

The dependence potential of coca leaf use has been assessed through clinical observations.

Several ethnographic studies conducted in Andean and Amazonian regions during the 1970s–2000s consistently reported low potential for dependence on coca leaf chewing. Field observations from long-term residence among habitual users (Hanna, 1974; Hurtado Gumucio, 2000; Negrete, 1980; Weil, 1978) found no evidence of tolerance, withdrawal symptoms, or compulsive patterns of use. On the contrary, coca chewing was described as easily discontinued, particularly when users migrated to urban areas or when regular consumption was interrupted by circumstances such as hospitalization.

A recent study explored dependence on the use of coca leaf in a more systematic way with a large representative random sample of the Andean rural highlanders of Peru, applying the ICD-10 diagnostic criteria for dependence syndrome. The results show that coca leaf chewing is common (41.2% of those who have ever chewed coca leaf and 21.4% of current users). Furthermore, 2.3 % (95% CI: 1.4%- 3.5%; SE 0.5) of those who reported chewing coca leaf met criteria for ICD-10 dependence syndrome within the past 12 months, and this dependence syndrome has compromised their quality of life. These initial findings should be followed by rigorous causal studies to assess the clinical features of coca leaf chewing dependence syndrome (Cruz, 2020).

Additional information on presentations to drug dependence treatment can be found in Annex I.

8 ABUSE POTENTIAL

Some experimental studies in animals explored the abuse potential of the coca leaf. In one study, Wistar rats were trained to discriminate 5.0 mg/kg cocaine from 2.0 ml/kg saline using a two-lever food reinforcement (FR 30) drug discrimination paradigm. After training, they were tested with chloroform extracts from the coca leaf. The two largest doses of the chloroform fraction (60 and 120 mg/kg, IP) generalized to cocaine, while the other three doses did not, suggesting that high doses of coca leaf extract may produce subjective effects similar to cocaine (Bedford, Nail, et al., 1981).

In a recent epidemiological study in Peru, Cruz (Cruz, 2020) reported that among 1,333 individuals with a history of coca leaf chewing, the 12-month prevalence of harmful use was virtually absent (0.1%).

No other rigorously conducted animal or human research studies have been found that evaluate the abuse potential of coca leaf use.

9 THERAPEUTIC APPLICATIONS AND TRADITIONAL USE, EXTENT OF THERAPEUTIC USE, AND EPIDEMIOLOGY OF MEDICAL USE

9.1 Therapeutic applications and traditional uses of coca leaf

In addition to *E. coca* and *E. novogranatense*, the two species associated with licit and illicit cocaine production, there are more than 230 other species of the genus Erythroxylum. Although minimal concentrations of cocaine have been detected in some of them, on the order of one hundredth of that of E. coca (Aynilian et al., 1974; Oliveira et al., 2010), their traditional use in phytotherapy and modern research exploring possible therapeutic uses focus on other components (Restrepo et al., 2019).

The potential therapeutic effects of crude extracts of different Erythroxylum species have been investigated in *in vitro* and animal models and have been recently reviewed (Lv et al., 2022; Matos de Macêdo et al., 2022; Restrepo et al., 2019). By 2022, studies had been conducted on some of the species of the genus Erythroxylum, primarily for their antioxidant, antibiotic, anticancer, antihypertensive, antidiabetic, and neuroprotective effects (Matos de Macêdo et al., 2022). These effects are of great interest for future developments to establish their efficacy and safety for use in human medicine.

Although progress in research on these other Erythroxylum species is notable, clinical trials exploring their therapeutic potential were not found. Further details on these investigations can be found in section 4 of this report.

9.1.1 Traditional use as an “energizer”

Although the "energizing" effect is not a standard pharmacological term, this is the most frequently cited reason for traditional use. Bolton (1976) points out that the motives given by his research subjects for chewing coca leaves did not appeal to its sacred nature but to three practical reasons: coca gave them energy to work, reducing fatigue; it kept them warm; and it helped alleviate hunger (Bolton, 1976). Although the geographic distribution of coca use has been explained by this combination of effects, which makes it an ideal means of adaptation to altitude, it has been suggested that the persistence of ancestral native cultures also increases with altitude, which could better explain the level of use for cultural rather than physiological reasons (Bray & Dollery, 1983). Similar reasons are reported by the members of the Kogui communities in the Sierra Nevada de Santa Marta, Colombia. Uses of coca leaf include aiding in performing regular tasks and improving locomotor strength and stamina. Consumption is perceived as reliable and free of adverse physical or psychological effects (Zambrano Calderón & Vaca, 2002).

One approach to the rigorous study of the effects of coca leaf is the evaluation of the cardiovascular, respiratory, and metabolic response to controlled exercise under laboratory conditions, which is detailed in the following sections. The evidence reviewed corresponds to observational studies comparing outcomes between coca leaf users and non-users. No well-designed randomized clinical trials exploring the therapeutic potential of coca leaf were found.

9.1.2 Cardiovascular and respiratory responses to coca leaf consumption

Multiple studies have examined the physiological effects of coca chewing on cardiorespiratory function and exercise response. The initial research indicated that chewing coca leaves (around 100 g per dose) acutely increased heart rate, blood pressure (especially systolic), respiratory rate, core body temperature, and caused mild pupil dilation (Risemberg Mendizábal, 1944).

Studies comparing coca chewers and non-chewers at high altitude (4000 m) in Peru revealed that coca users had lower heart rates but higher blood pressure throughout controlled exercise, with no significant differences in ventilation or oxygen uptake (Hanna, 1970). In subsequent experiments, coca chewers showed higher heart rates during submaximal exercise, but similar oxygen consumption and maximal exercise duration compared to non-chewers (Hanna, 1971, 1974).

From 1996 onward, collaborative research at Bolivia's High Altitude Biology Institute with French laboratories explored deeper metabolic and cardiovascular effects (Ayala Pío & Meneses, 2024; Instituto Boliviano de biología de altura : cooperación Francesa, 2008). One study compared habitual coca chewers of the Bolivian Altiplano to non-chewers, finding similar baseline plasma norepinephrine and epinephrine levels, oxygen consumption, and work efficiency (Spielvogel et al., 1996). Another study examined cardiovascular and metabolic responses during one hour of submaximal exercise. They also exhibited a lower VO_2 drift, meaning oxygen consumption increased less during prolonged effort, potentially enabling longer exercise durations and better tolerance (Favier et al., 1996).

Additional research involving people who consumed larger amounts of coca leaf (about 50 g daily) showed that coca leaf chewing increased resting heart rate and blood pressure, as well as hematocrit levels, indicating plasma volume shifts associated with adrenergic activation. Heart rate and blood pressure remained elevated after 60 minutes of exercise, with higher norepinephrine and epinephrine levels in coca users. Hematocrit increases suggested plasma volume reduction, consistent with sympathetic stimulation, which was more prominent in heavy users (Spielvogel et al., 1997).

Studies of male coca chewers riding a bicycle ergometer found no differences in VO_2, VCO_2, maximal work output, oxygen saturation, or pulmonary ventilation when comparing coca vs. non-chewing conditions. However, muscle efficiency at low workloads (around 32% VO_2 max) was slightly higher with coca, implying metabolic adaptation, though the significance for performance remains uncertain (Brutsaert et al., 1995).

Research at high altitude (3950 m) with 80 men indicated that habitual coca chewers showed no structural lung changes but had bronchodilation and increased heart rates after chewing. They displayed heightened sensitivity to hypoxic and hyperoxic stimuli, aligning with the known effects of low-dose cocaine absorption. Baseline lung function was similar between chewers and non-chewers, supporting that coca use does not impair lung mechanics (Villena et al., 1997).

In summary, although some conflicting results exist, the body of evidence indicates that coca chewing produces effects consistent with adrenergic stimulation: increased blood pressure, heart rate, bronchodilation, mild pupil dilation, and elevated blood glucose and free fatty acids. These effects do not appear to increase overall oxygen consumption or enhance maximum work performance but may improve submaximal exercise tolerance through metabolic shifts and delayed fatigue.

9.1.3 Muscle performance

A study of 10 individuals using an ergographic curve of the bicep muscle recorded muscle fatigue as a baseline recording. Twenty minutes of coca chewing and the repetition of the ergographic curve of the bicep muscle resulted in no significant difference in muscle fatigue (Schwab et al., 1952).

The effect of coca leaf chewing on athletic performance was compared with ten different strength/endurance tests between 10 coca chewers (C) and 10 controls (NC), who were training in the same gym. Although users reported less fatigue and greater feelings of strength with coca use, performance in objective tests showed no differences between the C and non-C groups (Bravo, 2021).

9.1.4 Temperature regulation and cold tolerance

The traditional view that coca leaf improves cold tolerance was experimentally examined by Hanna (1974). Core and peripheral body temperature (measured on fingers and toes) was recorded during two hours of exposure to a temperature of 15.5°C, comparing the results obtained with and without coca chewing. It was found that during coca leaf use, peripheral temperature dropped more, but core temperature remained higher than in the absence of coca. Coca's effect was interpreted as producing vasoconstriction and less heat loss, which could explain the traditional attribution of improved cold tolerance (Hanna, 1974).

9.1.5 Carbohydrate and lipid metabolism

Coca chewers experienced increased blood glucose, elevated plasma free fatty acids, and greater fat utilization during exercise, which might delay exhaustion. This metabolic shift could improve endurance by sparing glycogen stores (Spielvogel et al., 1996; Spielvogel et al., 1997).

Bolton (1976) found higher coca leaf use among individuals with a hypoglycemic response after a glucose tolerance test. Conversely, another study showed that, following a glucose load, control subjects experienced more frequent hypoglycemia at 120 minutes than coca users (57% vs. 6.6%), suggesting coca may regulate insulin secretion, though insulin levels were not measured (Galarza Guzman et al., 1997).

Casikar et al. (2010) studied the impact of coca chewing during exercise in Peruvian adults. Cutaneous microdialysis catheters were introduced into the forearm for real-time monitoring of tissue levels of metabolic products. They report no significant changes in oxygen saturation, blood pressure, or pulse compared to controls. However, coca users had increased glucose, pyruvate, lactate, and glycerol, suggesting that coca impedes glycolysis, leading to reliance on fatty acid beta-oxidation for energy. These effects may benefit sustained physical activity (Casikar et al., 2010).

Although the physiological evidence is suggestive, any potential clinical benefit should be evaluated in a clinical trial.

9.1.6 Altitude sickness

Findings on the use of coca leaf products for the prevention or treatment of altitude sickness are mixed, with no clear evidence of clinical benefit despite widespread tourist use and long-standing cultural practices. Bauer has reviewed the use of coca derivatives in travel medicine for the prevention or treatment of altitude sickness, with a focus on clarifying the possible confusion between the properties of the coca leaf and those of cocaine (Bauer, 2019). Aside from the cultural considerations and current use among travelers, the limited scientific evidence regarding its efficacy and safety is reviewed here.

The effects of coca leaf products may be different for a native who has adapted to high altitude and is a chronic user than for a traveler using it for the first time to prevent or treat acute altitude sickness. The technique of use itself requires training, which is why coca infusions are the most studied method of administration in travel medicine.

In a review of the use of coca derivatives to prevent altitude sickness in tourists, Salinas Piélago (2016) found that coca tea is the predominant form in which it is offered to tourists, although no evidence of its effectiveness was found, which the author attributed to the low alkaloid content of coca tea (see 4.1) (Salinas-Piélago, 2016).

In an observational study conducted in Cusco, Peru, at 3,400 meters above sea level, nearly 1,000 visitors boarding their return flight at the city's airport were asked about the presence of symptoms of acute mountain sickness (AMS) and the preventive and/or therapeutic measures they had used. Approximately two-thirds of travelers had used coca leaf derivatives, including infusions, leaf chewing, and even coca candies. Symptoms were very common, and 48.5% of tourists met criteria for AMS. Preventive use of coca-containing products was associated with a moderately increased risk of developing AMS (OR: 1.37; 95% CI: 1.0–1.89). Due to the observational and retrospective nature of the study, the possibility of indication bias, i.e., the onset of symptoms precedes the use of the coca derivative, cannot be ruled out (Salazar et al., 2012).

In a study conducted in Bolivia and Peru, tourists visiting destinations above 3,100 meters above sea level were surveyed. Of the 136 respondents (average age 26 years), 89% reported coca leaf consumption, of which 55% consumed coca tea, 22% chewed coca leaves, and the remaining 23% used both preparations. While the majority used coca to prevent or treat altitude sickness, a third of respondents had other motives, such as a desire to participate in the local culture or simple curiosity (Conway et al., 2012).

A cohort of 142 students aged 20 to 25 years who visited Cusco, Peru, at 3,350 meters above sea level, was studied. Upon arrival, they were surveyed about the measures planned to prevent AMS and, after 4 to 5 days of stay, about the measures used and the presence of AMS symptoms. Thirty-four percent of the young people drank coca mate, but it was not found to be effective in preventing the development of AMS (RR: 1.43 [95% CI 0.95-2.15, p = 0.09]) compared to those who did not use it (Caravedo et al., 2022).

Mujica et al. conducted an experimental study of acute physiological adaptation to altitude in males living at sea level who ascended to an altitude of 3,280 m above sea level. The response to submaximal exercise was studied at 150 m above sea level, upon arrival at altitude, and after drinking half a liter of coca tea. Cardiorespiratory, metabolic, and hormonal aspects were analyzed. Summaries of the results have been published, but we were unable to locate the full report. Cardiorespiratory function was assessed with EKG, heart rate, blood pressure, SaO2, and spirometry. After coca tea administration, there were slight, nonsignificant changes in spirometry, a slight increase in systolic blood pressure, and no changes in the EKG. Blood glucose, total cholesterol, HDL cholesterol, and triglyceride levels also did not change significantly. The hormonal profile showed a decrease in prolactin and LH after coca mate ingestion. In summary, no clear cardiorespiratory or metabolic effects were observed immediately after consumption of a single dose of coca mate in people who had recently ascended to altitude (Mujica, Ronceros, et al., 2012; Mujica, Saavedra, Huamán, Díaz, Carrión, et al., 2012; Mujica, Saavedra, Huamán, Díaz, Ronceros, et al., 2012).

In a placebo-controlled, single-blinded, non-randomized study, 11 hikers were given homeopathic coca at 200°C daily for 12 days starting from an altitude of 8,000 ft. until they arrived at the Mt. Everest base camp, 17,600 ft. Thirteen hikers were the control group that took neutral homeopathic pellets once daily for 12 days over the same hike. Oxygen saturation in the homeopathic coca group was significantly higher. A questionnaire detailing the occurrence and severity of altitude sickness symptoms included items regarding nausea, headaches, and difficulty breathing while asleep. The homeopathic coca group demonstrated a statistically significant decrease in nausea, headache, and difficulty in breathing compared to the control group (Shackleton et al., 2000).

An earlier hypothesis by Fuchs suggested that coca leaf alkaloids may pharmacologically inhibit excessive red blood cell production induced by hypoxia at high altitudes, potentially reducing symptoms of mountain sickness and polycythemic stress (Fuchs et al., 1978). However, controversy remains related to this hypothesis (Burchard, 1980). New research suggests a potential genetic role, and a definitive answer is yet to be determined (Mary, 2025).

9.1.7 Nutrition

9.1.7.1 Nutritional value of coca leaves

Nutritional analysis has led to the proposal to use coca leaves as a dietary supplement, recommended for their high protein, iron, and calcium content, compared to other plant foods. (Aibar Ozejo, 2006).

After reviewing the nutrient contents, the authors conclude that the nutritional value of coca leaves is similar to that of other leaves such as oregano, parsley, and coriander, and that a daily supplement of 5 g of dried powder does not represent a substantial nutritional contribution. Furthermore, they consider that a higher intake, on the order of 100 g daily, would provide unsafe amounts of cocaine (Penny et al., 2009).

Marentes et al. (2025) analyzed coca leaves collected in Colombia from the Palo and Caimo morphotypes. The average crude fiber values were 18.48 +/- 0.09 and 21.05 +/- 0.41 g/100 g of dry leaf, respectively. The protein content was strikingly lower than that reported by Penny et al. (2009): 6.59 +/- 0.61 and 9.26 +/- 1.91 g/100 g of leaf, for the Palo and Caimo morphotypes, respectively (Marentes-Culma & Orduz-Díaz, 2025).

Previous studies of the nutritional properties of coca leaves showed a similar micro- and macronutrient profile, although the mineral content varies by region and season. The favorable nutritional properties for its use as a nutritional supplement are emphasized, but with a cautionary note due to the alkaloid content and possible insecticide contamination (Duke et al., 1982; Duke et al., 1975).

9.1.7.2 Anorectic effect of coca leaves

Although there is agreement on the existence of an anorectic effect of coca leaf chewing, its implications in addressing food scarcity at altitude gave rise to a prolonged debate centering on whether proper nutrition should be the remedy for food scarcity, rather than the use of an anorectic agent (Ayala Pío & Quintana-Salinas, 2019).

In field studies conducted over 50 years ago among natives of the Peruvian village of Cachimoto, coca chewing was associated with poorer nutritional status (weight-for-height ratio, skinfold thickness, serum albumin, and cholesterol) and a higher frequency and severity of hookworm anemia (Buck et al., 1968). However, confounding socioeconomic factors cannot be ruled out in this study, since, despite matching controls for age, sex, and ethnicity, educational and social differences persisted between groups (Negrete, 1978).

To investigate the use of coca leaves as a hunger-suppressing strategy, a nutritional survey was conducted among 120 men from two populations in the Bolivian plateau, comparing the intake of the C and NC groups. A similar distribution of energy composition was found, with a high

predominance of carbohydrates (84% carbohydrates, 10% protein, and 6% fat), but with lower daily caloric intake in C than in NC groups (2266 kcal vs. 3040 kcal, respectively, in the 17- to 35-year-old group, $p < 0.01$, and 2389 kcal vs. 2488 kcal, respectively, in those over 36 years of age, $p < 0.05$). Unfortunately, anthropometry and biochemical markers of nutrition are not described, nor is the additional caloric intake that could result from coca chewing mentioned (Lujan, 1997).

The use of coca derivatives has been proposed as a weight loss aid (Weil, 1978), though no clinical trials have been identified.

9.1.7.3 Lipid-lowering effect

In a cross-sectional study conducted in Ayacucho, Peru, at approximately 2,700 m above sea level, total cholesterol and plasma triglyceride levels were compared between 100 people who regularly chew coca leaves (*E. coca*) with those of non-users. Total cholesterol levels were 23% lower among coca users than in controls (155 mg/dL vs. 201.7 mg/dL in men and 150 mg/dL vs. 193.5 mg/dL in women, respectively). The difference in triglyceride levels was even greater, with levels among coca chewers less than half those of controls (84 mg/dL vs. 174 mg/dL in men and 55 mg/dL vs. 134 mg/dL in women, respectively). The findings are suggestive, although the influence of confounding variables such as older age and lower height, and body weight of coca leaf users cannot be ruled out (Ñaccha-Urbano, 2021).

9.1.7.4 Antidiabetic properties of coca leaves

An experimental study conducted in Cochabamba, Bolivia, selected 90 young men with no history of metabolic disease, and compared blood glucose levels 2 hours after an oral glucose load of 75 g between control group, another group who chewed 5 g of coca leaves (*E. coca*) after the load, and a third group that received 500 mL of tea prepared with 5 g of coca. The average blood glucose levels at 2 hours were 100.4 mg/dL, 81.8 mg/dL, and 82.1 mg/dL for the control, coca tea, and chewing groups, respectively, with significant differences between the groups that received coca and the control group. The authors conclude that coca reduces postprandial blood glucose in healthy subjects (Hurtado Sánchez et al., 2013).

The hypoglycemic effect of coca leaves was studied in 30 patients with type 2 diabetes mellitus, who were administered a 5 g coca leaf infusion daily for 14 days. Blood glucose levels decreased from a mean (SD) of 235.63 (118.7) mg/dL at baseline to 168.70 (72.4) mg/dL after 2 weeks of treatment. Despite the magnitude of the observed effect, confidence in the results is very low due to the before-and-after design in the same population, without a control group. The very high initial blood glucose levels likely led to measures for improved glycemic control in the following days. Furthermore, there was no clear description of the conditions under which blood glucose was measured or of the concomitant use of antidiabetic medications (López Espinoza et al., 2023).

9.1.8 Effects on bone metabolism

Based on its calcium and fiber content and antioxidant properties of coca leaf, Trigo-Pérez et al. (2017) studied whether a powder preparation of *E.coca* leaves favorably modified bone turnover in postmenopausal women. They administered 4 g of coca leaf powder daily for 90 days, comparing bone markers at the beginning of the study with those obtained at 45 and 90 days of treatment. They observed a significant decrease in the N-terminal telopeptide of type 1 collagen (NTX1), a marker of bone resorption, but also a decrease in bone alkaline phosphatase (BALP), a marker of new bone formation. There were no significant changes in the levels of beta-crosslaps (βCTX) or the N-terminal propeptide of type 1 procollagen (P1NP). These findings do not demonstrate a benefit of this coca leaf derivative for bone health but highlight the need for further research (Trigo-Pérez & Suárez-Cunza, 2017).

9.1.9 Hematology and immunology

The influence of coca leaf chewing on platelet function and hemoglobin concentration was studied in 10 coca leaf users and 10 controls. Baseline values were measured one hour after consuming 10 g of coca leaf and remaining at rest, and at the end of one hour of submaximal effort on the cycle ergometer. Baseline values for platelet aggregation tests were similar in groups C and NC, with lower values of ADP-induced platelet aggregation after exercise in group C. Baseline hemoglobin concentration was similarly elevated in both groups (17.6 g/dL), reflecting altitude adaptation, and increased somewhat more at rest and after exercise in group C. The potential clinical impact of these differences is unknown (Rodrigues et al., 1997).

9.1.10 Psychological effects

Research on the psychological effects of coca leaf use is limited, with most studies conducted over 80 years ago and under experimental conditions that differ from traditional practices, meaning no firm conclusions can be drawn about its therapeutic value as a psychostimulant. Early reports describe initial stimulation followed by withdrawal: after chewing about 100 g of coca leaf, habitual users first experienced euphoria, sociability, and a sense of well-being, then became quiet, withdrawn, and absorbed in thought, a state they reported as favourable for concentration and work (Risemberg Mendizábal, 1944). In another study, reaction time to auditory stimuli lengthened as chewing progressed, while attention tasks were completed faster but with more errors (Zapata Ortiz, 1944).

More recent investigations have not shown consistent benefits. A randomised crossover trial of 20 university employees found that coca tea (1 g leaf infusion daily for 15 days) did not significantly reduce work-related stress compared to water (Rivera Encinas, 2015). In eight cases of mild to moderate depression, daily coca tea use was linked with marked symptom reduction

on the Beck Inventory over three weeks, but without a control group, placebo effects cannot be excluded (Bolo & Ocampo, 2004).

Coca leaf chewing has also been explored as a harm reduction approach for cocaine dependence. In an uncontrolled study of 50 cocaine users, prolonged coca leaf use (average 27 months) was associated with improved social and economic functioning and a trend toward better mental health, with the proportion classified as having 'good' mental health rising from 2% to 35%. However, the absence of controls, lack of standardised measures, and limited methodological detail make interpretation difficult, and rigorous trials are needed (Hurtado Gumucio, 2000).

9.2 Extent and epidemiology of therapeutic use

The traditional use of coca leaves in the Andean regions of Peru, Bolivia, Chile, northwestern Argentina, Colombia, Ecuador, and some areas of the Amazon basin has been extensively described in the historical, anthropological, and medical literature.

The use of phytotherapy was studied in the Bolivian community residing in Barcelona, where 58% of those surveyed used herbal medicines, most of them as self-medication. Among 60 reported plant species, *E. coca* was the second most cited, accounting for 49% of cases. Indications reported included stomach pain, menstrual cramps, headaches, high blood pressure, diabetes, stress, maintaining alertness, and also as a ritual offering to Pachamama, known as *k'hoa*, which is celebrated on the first Friday of each month (Antih et al., 2016).

Some species of the genus Erythroxylum are part of the traditional herbal medicine of Mauritius. Preparations of *E. laurifolium* are included in herbal remedies for rheumatoid arthritis (Neergheen-Bhuiyan et al., 2014) and in preparations for diabetes, perhaps explained by its amylase inhibition, similar to that of acarbose (Rummun et al., 2018). Tea made from *E. hypericifolium* leaves (*bois ronde*) is traditionally used in Mauritius as a treatment for anemia (Suroowan & Mahomoodally, 2013). Derivatives of *E. macrocarpum* and *E. sideroxyloides* are used for urinary calculi, and *E. laurifolium* is also claimed to have antibacterial, antifungal, and antihypertensive effects (Rummun et al., 2018).

Cano et al. (2004) investigated the traditional use of herbal mixtures in Eastern Cuba. They compiled references to 170 species, used in 199 formulas. *E. havanense*, an endemic species from Cuba, appears in 15 of them, with indications such as biliary or urinary lithiasis, rheumatic conditions, pneumonia, tuberculosis, asthma, muscle pain, and venereal diseases (Cano & Volpato, 2004).

A case report from Pelotas, Brazil, describes the use of *E. argentinum* ("cocão") for prevention and complementary treatment of prostate cancer (Andrade et al., 2011). It is also used for digestive and respiratory conditions (Chaves et al., 1988).

An infusion of the bark of E. vacciniifolium (and other components) is used in Brazil as a popular medicine called “catuaba”, with tonic and aphrodisiac properties. These effects have been linked to the tropane content, including catuabines A, B, and C. The leaves are used as a stimulant, and the antimicrobial and cytotoxic properties of derivatives of the plant have been described (Restrepo et al., 2019). Despite its widespread use as a medicinal plant, Magalhaes et al. found no pharmacological studies investigating the popular use of catuaba as a treatment for anemia, impotence, or nervousness (Magalhães et al., 2019).

In India, preparations of coca leaf have recognized homeopathic uses, and a detailed monograph on coca leaf and preparations of coca leaf exists (*Homeopathic pharmacopeia of India*, 1974)

The Government of Colombia has suggested that coca leaf compounds be considered for registration as plant-based medicinal products, in the context of natural and traditional medicine (de Colombia, 2024).

10 LISTING ON THE WHO MODEL LIST OF ESSENTIAL MEDICINES

Neither coca leaf nor its derivatives are included in the WHO Model List of Essential Medicines nor the WHO Model List of Essential Medicines for Children (WHO, 2023a).

11 MARKETING AUTHORIZATIONS (AS A MEDICINAL PRODUCT)

See Annex 1: Member State Questionnaire

The products sold in Latin America generally fall into the following categories: food and drinks, dietary supplements, cosmetic products, and only in Bolivia, as medicinal products.

11.1.1 Bolivia

Bolivia has authorized different kinds of marketed products derived from the coca leaf. The vast majority are for traditional medicine use, and the proposed indications include anti-inflammatory, anesthetic, pain reliever, nervous system stimulant, cardiovascular, antidepressant, diabetes prevention, antispasmodic, expectorants, cough suppressants, rheumatic pain, arthritis, and gout. Despite this, the Regulatory Agency “Agencia Estatal de Medicamentos y Tecnologías en Salud” (AGEMED) only has one product registration, for an ointment (Tara Tara Pino y Coca) (AGEMED, 2025)

In February 2025, the "Catalogue of Coca Leaf Derived Products and Their Application in Traditional Medicine 2024-2025" was presented, with a list of coca leaf derivatives produced by 62 companies, laboratories, and gastronomical schools.

The full list of commercial products for medicinal, food and drinks, dietary supplements, and cosmetic products is available in English and Spanish (Vicepresidencia del Estado Plurinacional de Bolivia, 2025). It contains 10 medicinal products classified as: Traditional Medicine – Pharmaceutical Industry, Natural Medicine, or Natural Pharmacopoeia.

11.1.2 Colombia

Products in Colombia must be completely devoid of active alkaloids, such as cocaine, for authorization. The categories include food and drinks, dietary supplements, and cosmetic products, but not medicinal products (INVIMA, 2025).

Products must come from licit crops, such as those authorized by the government in Indigenous areas or substitution programs.

11.1.3 Peru

Peru does not have any medicines or pharmaceutical products authorized by the General Directorate of Medicines, Supplies and Drugs (DIGEMID) that contain cocaine or any of its derivatives. However, at the national level, there are products derived from coca leaves that are authorized as industrial foods by the General Directorate of Environmental Health (DIGESA), which, like DIGEMID, are general directorates that belong to the Ministry of Health.

There is a national company, the National Coca Company (ENACO SA), authorized to collect, market, and process coca leaves (Erythroxylum coca) and their derivatives for legal and health-promoting purposes.

ENACO manufactures finished products with coca leaf derivatives for direct use by the consumer, as well as coca leaf concentrates without alkaloids for use in the food industry. ENACO offers 10 products, 3 of which are authorized by DIGESA (ENACO, 2025).

The industrialization of coca leaves includes the production of pharmaceutical products provided by ENACO, Empresa Nacional de la Coca S.A. (Art. 41 of DL 22095, Art. 6 of DL 1241, Art. 11 of DS 006-2016-IN)(DEVIDA, 2012). This industrial use of coca leaves has expanded in Peru, with applications in the production of cosmetics and other derivatives. ENACO produces cocaine base for the industrial production of local anesthetic ampoules and flours to produce analgesic capsules or ointments. (DEVIDA, 2021).

12 Industrial use

Coca products include food and nutraceuticals, cosmetics and other personal care products, and agricultural inputs (e.g., fertilizer). Coca products developed for legal trade are described below.

12.1 Food and Nutraceuticals

Coca flour (micronized coca leaf powder) is noted for its content of protein, dietary fiber, calcium, phosphorus, and vitamins such as A, B1, B2, C, and E (Penny et al., 2009; Trigo-Pérez & Suárez-Cunza, 2017). Coca flour is currently used to produce breads, cookies, nutritional bars, cereals, and shakes (Trigo-Pérez & Suárez-Cunza, 2017). Coca tea (mate de coca) is widely consumed in high-altitude Andean regions, promoted for its stimulating and digestive properties and its efficacy in preventing altitude sickness (DIGEMIC et al., 2024; Estado Plurinacional de Bolivia, 2023; Olivier et al., 2012). Dietary supplements derived from coca extracts have also been proposed for use in metabolism regulation and enhancing physical endurance (de Colombia, 2024).

12.2 Cosmetics and Personal Care:

Coca leaf extracts are incorporated into soaps, shampoos, creams, and facial masks that are promoted for their anti-aging, antimicrobial, and regenerative properties (de Colombia, 2024; DIGEMIC et al., 2024).

12.3 Agricultural and Environmental Applications:

Residues from coca processing are being explored for use as organic fertilizers, with potential to enhance soil quality and crop yield in high-altitude agricultural systems (de Colombia, 2024; Lozada Centurión, 2022; Valencia & Courtheyn, 2023). In addition, the coca plant's high biomass yield and ecological adaptability make it a promising candidate for sustainable agro-industrial systems (DIGEMIC et al., 2024).

12.4 Textile and Pigment Industry

Natural pigments extracted from coca leaves are used in textile dyeing, a practice rooted in traditional Andean culture and currently under reevaluation for ecological textile production (de Colombia, 2024).

12.5 Government-Endorsed Industrial Product Catalogs

Both Bolivia and Peru have documented and promoted a range of coca-derived commercial products, including energy drinks and herbal tonics, functional teas and coca liqueurs, chewing

gum, nutritional tablets and capsules, toothpastes, balms, and muscle-relief creams (DIGEMIC et al., 2024; Estado Plurinacional de Bolivia, 2023).

Since 2009, the Bolivian Constitution has recognized the traditional, medicinal, and cultural use of coca leaves. In 2022, the Bolivian Coca Leaf Industrialization Productive Public Company (KOKABOL) was created to develop coca leaf derivatives for industrial and other uses.

13 NON-MEDICAL USE, ABUSE, AND DEPENDENCE

Research on modes of consumption, dependence potential, and abuse potential of coca leaf is reviewed in Sections 4, 7, and 8, respectively (see also 12-14)

14 NATURE AND MAGNITUDE OF PUBLIC HEALTH PROBLEMS RELATED TO MISUSE, ABUSE, AND DEPENDENCE

Research on coca and public health has been sporadic over time and has been constrained by the plant's complicated legality (Marentes-Culma & Orduz-Díaz, 2025). Nevertheless, research reviewed for this report did not reveal evidence of clinically meaningful public health harms associated with coca leaf use, and the contemporary scientific literature on the public health impact of coca leaf remains consistent with the 1995 WHO Cocaine Report (WHO & UNICRI, 1995). The research record does, however, robustly document the substantial public health harms associated with coca control strategies at all scales (see Section 19). For additional information related to health problems related to misuse, abuse, and dependence, please refer to Section 5.) Toxicology and 6.) Adverse Reactions in Humans as well as 7.) Dependence Potential and 8.) Abuse Potential of this report.

15 LICIT PRODUCTION, CONSUMPTION, AND INTERNATIONAL TRADE

The International Narcotics Control Board (INCB) publishes data reported by member states on licit coca leaf production, utilization, imports, and exports. Those data are referenced below.

15.1 Licit production

15.1.1 Bolivia

Bolivia authorizes licit coca-leaf growing by registered producers in upland and lowland growing areas (Brewer-Osorio, 2021; UNODC, 2023b).

Over a five-year period (2019-2023), Bolivia reported producing between 24.5 to 30.9 million kg of coca leaf annually (INCB, 2024b).

15.1.2 Colombia

Indigenous peoples in Colombia have a constitutional right to grow coca leaf for traditional use and for the protection of Indigenous cultural identity (de Colombia, 2024; Estado Plurinacional de Bolivia, 2023). They are also permitted to commercialize coca leaf products (Fernández, 2017; Snapp & Quintero, 2024). In recent years, the Colombian government introduced legislation to regulate coca leaf use for medical, scientific, and industrial purposes. The bill also permits scientific study of coca, which had previously been restricted (Marentes-Culma & Orduz-Díaz, 2025).

National INCB production estimates of licit coca leaf for Colombia were not available.

15.1.3 Peru

Legal coca leaf in Peru is regulated by its National Coca Company (ENACO, founded 1949). The General Drug Law of 1978 establishes licit coca bush cultivation for traditional and medicinal uses by farmers registered in the General Register of Coca Leaf Producers, who may sell only through ENACO. This arrangement also supplies coca leaf for its use in soft drinks (Estado Plurinacional de Bolivia, 2023; Gootenberg, 2007; Plowman, 1984). ENACO has exclusive control over coca leaf distribution and pricing. The agency also sets the upper limit for total licit production (currently 81 tons annually) within an allowance of 12,000 ha nationwide for permitted cultivation (Busnel & Manrique Lopez, 2023; Niño de Guzmán Tapia & Medina Rivas Plata, 2025). Coca leaf production reported by Peru varied between 2019-2023, ranging from a low of 339,303 kg in 2022 to a high of 2.1 million kg in 2020 (INCB, 2024b).

The INCA 2019 study conducted by DEVIDA estimated that ENACO supplied approximately 12.3% of the licit market demand for coca leaf in the Lima metropolitan area and around 11% of the quantity required for coca tea production. These figures suggest a notable gap between formal supply and consumer demand. As a result, coca leaf products are increasingly produced and distributed outside ENACO's regulatory framework, with some lacking traceability and formal oversight (DEVIDA, 2020).

15.2 Consumption

15.2.1 Patterns and prevalence

Coca leaf use is widespread across rural and urban areas in the western Amazon and Andes regions, except for Ecuador (DIGEMIC et al., 2024; Estado Plurinacional de Bolivia, 2023; Hirschkind, 2005). Migrant populations have contributed to the emergence of coca use in

diasporic communities in other South American countries and Europe (Avilés & Bouso, 2024). In addition to traditional chewing practices, niche markets for coca-based products—such as tea, flour, and energy drinks—have expanded, particularly in South America and Europe (Avilés & Bouso, 2024; Ghehiouèche & Riboulet-Zemouli, 2024; Olivier et al., 2012; Snapp & Quintero, 2024).

Reliable cross-national estimates of the prevalence of coca leaf consumption are limited. Coca leaf is not included in the UNODC Annual Report Questionnaire's module on drug use prevalence, complicating efforts to monitor its use systematically (UNODC, 2025). Nonetheless, national and regional surveys provide insight into consumption patterns:

- In Bolivia, a 1984 survey found that 89% of adult women and 95% of adult men used coca in some form (Carter et al., 1984). A 2009–2010 census-based estimate placed the number of coca consumers at approximately 3 million (Estado Plurinacional de Bolivia, 2023; Viceministerio de Relaciones Exteriores, 2019).
- In Colombia, among Indigenous populations, coca leaf use is estimated at 1 to 1.5 million individuals (National Commission of Indigenous Territories, 2018).
- In Peru, national surveys indicate shifting patterns of use over time, from exclusively rural use in the 1940s (Gutierrez-Noriega, 1948) to more widespread use today. In 2005, 35.7% of urban respondents aged 12–64 reported having ever chewed coca (*Centro de Información y education para la Prevención del Abuso de Drogas,*, 2006). Subsequent surveys estimated that the number of coca consumers over age 12 increased from 4.6 million in 2003 to nearly 6 million in 2019—approximately 20% of the population in that age group (Busnel & Manrique Lopez, 2023; DEVIDA, 2020).

Some consumption estimates are inferred from trade data. For example, the coca leaf trade between Bolivia and Argentina suggests a user base of approximately 300,000 in Argentina (Estado Plurinacional de Bolivia, 2023). However, the coexistence of licit and illicit supply chains limits the reliability of such estimates (Busnel & Manrique Lopez, 2023).

Prevalence of coca leaf use is generally higher among men, older adults, and Indigenous populations (*Centro de Información y Educación para la Prevención del Abuso de Drogas*, 2006; DEVIDA, 2020; Oliva, 2016). Occupational factors also influence use: high rates of coca chewing have been reported among miners and agricultural laborers, particularly those engaged in physically demanding work (J. R. d. Castro et al., 2004; Schinder & Ruder, 1989). Coca leaf is also used by university students in some areas of Latin America, with reported motivations including staying awake for study, social use, and perceived stimulant effects (Cuellar B et al., 2020; Enriquez Flores & Villar-Luis, 2004; Martins et al., 2020; Mercado Antelo & K. Schulmeyer, 2021).

Scientific literature documents the widespread use of coca leaf among Aymara and Quechua populations in both urban and rural settings, including diasporic communities (Antih et al., 2016). Coca leaf chewing is an important marker of cultural identity and is commonly used in social, ceremonial, religious, and divinatory practices (Allen, 1981; Fernández Droguett et al., 2024; Garcia-Yi, 2014a, 2014b; Goddard et al., 1969; Henman, 1990; INCB, 2009; Ministerio de Relaciones Exteriores, 2009; Pereira, 2010; Plowman, 1984; Sandagorda, 1984; Sauvain et al., 1997; Scrivener, 1871; Seminario, 2024; South, 1977; Von Glascoe et al., 1977; WHO & UNICRI, 1995). Bolivia's 2009 Constitution recognizes chewing coca leaf as intangible cultural heritage.

Among Andean Indigenous groups, coca leaf use often begins in adolescence and is linked to social transitions, such as entry into adulthood and participation in adult forms of work (Baker & Mazess, 1963; Carter, 1982; Carter et al., 1984; Mendoza-Azpur et al., 2021; Plowman, 1984; Uscategui M, 1959; Von Glascoe et al., 1977; WHO & UNICRI, 1995)(13, 14, 29, 47-51). The use of coca leaf has also expanded beyond Indigenous populations. In Bolivia, coca chewing became widespread among working-class individuals during the Chaco War (1932–1935), when it was distributed to mestizo troops (Ehrinpreis, 2020). In northern Argentina, coca chewing is socially comparable to gum or tobacco use and is common among middle-class populations (Cattani, 1984; Cusicanqui, 2005; Goddard et al., 1969). Coca tea consumption in Peru and Bolivia became widespread following independence and is not typically associated with Indigenous identity (Estado Plurinacional de Bolivia, 2023; WHO & UNICRI, 1995).

15.3 International Trade

The 1961 Convention permits the import and export of coca leaf under two specific scenarios. First, Article 27 of the Convention allows trade destined for the preparation of leaves as a flavoring agent if the resulting product contains no alkaloids. Second, the Convention allows trade in the leaf to produce limited amounts of cocaine for medical and pharmaceutical uses, including to produce pharmaceutical cocaine, which is used primarily in ear, nose, and throat surgeries (Wang et al., 2022).

Between 2019-2023, Peru reported exporting between 68,140 and 169,410 kg of coca leaf annually (INCB, 2024b). No other countries reported exporting coca leaf. During the same period, the United States of America reported importing between 52,940 kg and 148,503 kg of coca leaf annually, while the Netherlands and France reported sporadic imports of 100 kg or less (INCB, 2024b). These trends reflect the fact that much of the market for flavoring agents and medical cocaine is met by raw coca leaf imported from Peru to the USA to produce a de-cocainized extract for soft-drink production, and to produce and sell medical-grade cocaine (Gootenberg, 2007).

INCB estimates of requirements for coca leaf by country for 2024 show very small requirements for Argentina (1 g), Brazil (50 g), China (2g), Costa Rica (20 g), Czechia (1g), Iran (2 g), Ireland (10 g), Mexico (1 g), Romania (2 g), Rwanda (5 g), Trinidad and Tobago (5 g), and Turkey (1 g). Other countries have larger estimated coca leaf requirements: Australia (3 million grams), Canada (11,300 g), France (4,427 g), Italy (183,200 g), Netherlands (150,000 g) and the United States of America (148 million grams). Because coca leaf production is not reported in any of these countries, these requirements are necessarily met by coca leaf importation (INCB, 2024a).

16 ILLICIT MANUFACTURE AND TRAFFIC AND RELATED INFORMATION

The UNODC Global Illicit Crop Monitoring Program was established in 1998 and supports coca bush surveys in Bolivia, Colombia, and Peru. Those efforts allow assessment of trends in the total area cultivated in non-registered coca bush ("illicit" coca) at the national scale. In addition, data on law enforcement eradication of coca bush, or seizures of harvested coca leaf, offer some insight into the magnitude and routes of illicit production and traffic in coca leaf.

16.1 Bolivia

In 2023, Bolivia reported 31,000 ha under coca cultivation, of which 22,000 were permitted. The country reported eradicating 10,302 ha that year (UNODC, 2023b). Bolivia reported seizing 331 MT of coca leaf in 2022 and 372 MT in 2023 (UNODC, 2023b).

16.2 Colombia

In 2023 (the most recent year data are available), Colombia reported over 250,000 ha in illicit coca (UNODC, 2023a).

Recent efforts to control illicit coca leaf production and trade within Colombia have transitioned significantly in their scope, priorities, and mechanisms since the early 2000s. At the center of early strategies was Plan Colombia, a militarized counternarcotics initiative that featured aerial spraying of coca crops with glyphosate, a practice that continued until 2015 when a public health approach to drug policy was adopted (Huezo, 2017). This policy shift culminated in a new phase of national drug control following the 2016 Peace Accords, a cornerstone of which was the National Program for the Substitution of Illicit Crops (PNIS), a voluntary program designed to transition smallholder farmers out of coca production through cash incentives, technical support, and rural development.

Colombia manually eradicated 68,974 hectares of coca in 2022 and 20,325 hectares in 2023. The country has reported hundreds of thousands of kilograms of coca leaf seized annually since 2012 (UNODC).

16.3 Peru

Peru reported 92,784 ha of illicit coca bush cultivation in 2023 (UNODC, 2024b), and reported manually eradicating 22,600 ha of illicit coca in locations across the country in 2023 (UNODC, 2024b). Peru targets illicit coca plantations with manual eradication and alternative development policies. The country also seizes 'illicit' leaf grown by registered growers but sold outside the ENACO monopoly (Busnel & Manrique Lopez, 2023).

16.4 Other countries

Coca-growing is reported in Venezuela, Ecuador, and Brazil, particularly in borderland and frontier contexts (Salisbury & Fagan, 2013)(142). In response, state and federal forces in those countries have implemented periodic manual crop eradication campaigns and have seized harvested coca leaves (UNODC, 2013, 2023a, 2024a).

Coca leaf consumption has been legal in Argentina since 1989 (Cusicanqui, 2005). The Argentinian market is supplied by Bolivian coca, and Argentina has reported seizing thousands of kilogram-equivalents of coca leaf annually (UNODC). The legality of the Bolivia/Argentina cross-border trade is currently under review (Estado Plurinacional de Bolivia, 2023).

Coca is increasingly being grown in Central America, particularly in Honduras and Guatemala. There is no reported coca bush monitoring in Central America. The Honduran and Guatemalan police and military routinely report on their efforts to manually eradicate coca fields. In 2023, Honduran authorities reported manually eradicating 461 ha, and Guatemalan authorities reported eradicating 27 ha in 2022 (Murillo-Sandoval et al., 2024). The two countries also sporadically report seizing (presumably harvested) coca leaf (Murillo-Sandoval et al., 2024; UNODC).

17 CURRENT INTERNATIONAL CONTROLS AND THEIR IMPACT

17.1 WHO Review History

Coca-leaf chewing was discussed at the 3rd (1952) and 4th (1954) meetings of the WHO Expert Committee on Drugs Liable to Produce Addiction and classified as a form of "addiction" (with the report referencing a study conducted in 1949-50 by the United Nations Commission of Enquiry on the Coca Leaf). (UNODC, 1950; WHO, 1952, 1954).

Coca leaf was placed under Schedule I of the 1961 Single Convention. The treaty required that the practice of coca-leaf chewing cease within 25 years of the convention coming into force (by December 1989).

At its 28th meeting in 1992, the ECDD conducted a pre-review of coca leaf. At that time, the Committee advised that coca leaf was appropriately scheduled under Schedule I of the 1961 Single Convention since cocaine is readily extractable from the leaf (WHO, 1993).

In 2023, who received an official notification from a Member State to conduct a critical review of coca leaf. Accordingly, in accordance with the Guidance on the WHO review of psychoactive substances for international control, a critical review was initiated for conclusion in 2025

17.2 Current international controls

Coca leaf (Erhyroxylum coca, Folium cocae) and preparations of coca leaf are currently listed as a Schedule I substance under the 1961 Single Convention on Narcotic Drugs (substances whose liability to abuse constitutes an especially serious risk to public health and which have very limited, if any, therapeutic usefulness).

Extracts and tinctures of coca leaf: As per Table 2 of the INCB Yellow List, one kilogram of tincture of coca leaf containing 0.1 per cent of cocaine, i.e., 1 gram of cocaine, should be considered to be equivalent to 200 grams of coca leaf. One kilogram of fluid extract of coca leaf containing 0.5 per cent of cocaine, i.e., 5 grams of cocaine, is equivalent to 1 kilogram of coca leaf. For the calculation of estimates and statistics in accordance with the terms of the 1961 Convention, coca leaf preparations containing more than 0.1 per cent of cocaine and made directly from coca leaf should be considered to be coca leaf (preparations).

Cocaine (methyl ester benzoylecgonine) and certain preparations of cocaine (e.g., coca base, coca paste, delcaine, depsocaine, dextrocaine,erytroxyline) are currently controlled separately under Schedule I of the 1961 Single Convention on Narcotic Drugs. Ecgonine (and cocaethylene, benzoylecgonine,cinnamylcocaine, ethylcocaine) is also controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs.

Preparations of cocaine “containing not more than 0.1 per cent of cocaine calculated as cocaine base and that are compounded with one or more other ingredients and in such a way that the drug cannot be recovered by readily applicable means or in a yield which would constitute a risk to public health” are listed under Schedule III of the 1961 Convention as preparations of narcotic drugs that are exempted from some provisions (substances whose liability to abuse constitutes a substantial risk to public health and which have moderate to great therapeutic usefulness).

The chemicals and reagents used for the extraction of cocaine from coca leaf (sulphuric acid, potassium permanganate, hydrochloric acid, acetone, and diethyl ether) are listed in the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988 (as at 3 December 2024, https://docs.un.org/en/ST/CND/1/Add.3/Rev.7).

17.3 Provisions of international control

To cultivate, use, trade, or to study coca leaf can only be granted through special government authorization (e.g., export and import licenses) (Fernández Droguett et al., 2024; McAllister, 2004; United Nations, 1961).

Article 26 of the 1961 Single Convention on Narcotic Drugs states the following:

1. If a Party permits the cultivation of the coca bush, it shall apply thereto and to coca leaves the system of controls as provided in Article 23 respecting the control of the opium poppy (e.g., the establishment of a national agency to carry out functions required under Article 23)
2. Parties may permit the use of coca leaves for the preparation of a flavouring agent, which shall not contain any alkaloids, and, to the extent necessary for such use, may permit the production, import, export, trade in, and possession of such leaves
3. Parties shall furnish separately estimates (article 19) and statistical information(article 20) in respect of coca leaves for the preparation of the flavouring agent, except to the extent that the same coca leaves are used for the extraction of alkaloids and the flavouring agent, and so explained in the estimates and statistical information

17.4 Impact of international control

This section reviews the scientific literature that has assessed the direct and indirect effects of these programs at multiple scales and over time. At the national scale, the data indicated that coca control efforts have not curbed overall cultivation in Colombia and Peru, while Bolivia shows more stability.:

- Colombia: Coca bush cultivation dropped from 2005–2013 (Rincon-Ruiz et al., 2016), but has expanded markedly since. Peru estimated <100,000 ha in 2005, which rose to >250,000 ha by 2023 (UNODC, 2023a)
- Peru: The area in coca bush rose from 40,300 ha in 2015 to 92,784 ha in 2023, despite a slight decline in 2022 (UNODC, 2013).
- Bolivia: Coca cultivation has fluctuated but shows a net decrease over 20 years. In 2023, 31,000 ha were reported, with 22,000 ha permitted—indicating some growth in illicit production (UNODC, 2003, 2023b).

At the sub-national scale, coca cultivation trends in Peru, Bolivia, and Colombia are more complex than at the national scale, with coca acreage declining and expanding depending on the municipality or department (UNODC, 2003, 2013, 2023a, 2023b).

18 CURRENT AND PAST NATIONAL CONTROLS

See Annex 1: Member State Questionnaire for additional information.

In the United States, coca leaf is categorized as Schedule 2, in recognition of the plant's medicinal benefits (United States Department of Justice, 2024). Like the U.S., other coca-leaf importing countries have created their own regulatory responses to coca (Executive Board, 2007). For example, in 1989, Argentina legalized the chewing of coca leaves, but the importation of coca leaves into Argentina remains illicit (Cusicanqui, 2005). In Canada, coca leaf is a Schedule 1 substance, but businesses have obtained licenses to import coca leaf for the development of commercial products ("Coca-based flavor enhancer allows sugar cut in sodas," 2024).

19 OTHER MEDICAL AND SCIENTIFIC MATTERS RELEVANT FOR A RECOMMENDATION ON THE SCHEDULING OF THE SUBSTANCE

19.1 Effects of coca controls on human health

Some research has explored the effects of glyphosate spraying on human health in Colombia. An early study using retrospective surveys of ~2500 women across rural Colombia found no increase in time to pregnancy for women in areas exposed to aerial eradication (Sanin et al., 2009). Subsequent research, however, used a panel of individual health records to measure the impacts of aerial spraying over 5 years. Results show that exposure to glyphosate from aerial spraying campaigns increased the number of miscarriages and the number of medical consultations related to dermatological and respiratory illnesses in targeted communities (Camacho & Mejia, 2017).

Other studies have linked coca control efforts to cocaleros' heightened exposure to potentially toxic agro-chemicals more generally. For example, a 2021 study from Putumayo, Colombia, showed that forced coca eradication by the police incentivized coca farmers to intensify and diversify their use of toxic agro-chemicals in remaining or subsequent coca plots, increasing their exposure to those chemicals (Acero et al., 2023; Bolognesi et al., 2009; Rhodes et al., 2023; Varona et al., 2010).

Similarly, in Bolivia's Chapare, where 'social control' programs limit the extensification of coca acreage, farmers can be incentivized to intensify production through increased agrochemical use. This pressure has likely led to agro-chemically resistant coca fungus that is depressing leaf production, further intensifying agro-chemical dependence (Pearson, 2016). Chronic exposure to agro-chemicals increases any health risks associated with their use, including neurological damage, organ failure, and reproductive health problems (Bolognesi et al., 2009; Pearson, 2016; Rhodes et al., 2023; Varona et al., 2010). To date, these effects have yet to be fully studied in a systematic epidemiological framework. Nevertheless, what emerges clearly from ethnographic research is that coca growers have a pervasive fear of the long-term effects of these exposures, compounded by the fact that medical support and environmental monitoring in these rural areas are minimal to nonexistent (Acero et al., 2023). Rhodes et al. (2023) conclude that the normalization of toxic chemical use and the lack of institutional response have created environments of chronic vulnerability among coca producers (Rhodes et al., 2023).

Pesticides and other agrochemicals commonly used in the cultivation of unregulated crops may influence both the safety profile and health risks associated with plant use (Ehrinpreis, 2020; Plowman, 1984).

The broader literature highlights that persistent pesticide contamination may or may not pose significant risks to human health and food safety, with potential for acute poisoning, neurological disorders, and carcinogenicity, especially in settings lacking regulatory oversight (Giordano et al., 2024; Hirschkind, 2005; Plowman, 1984). The intersection of plant toxicology and chemical contaminants is a critical consideration for any future comprehensive risk assessment.

19.2 Methodological considerations on therapeutic effects

The evaluation of the therapeutic properties of a medicinal product requires experimental studies, in particular randomized clinical trials. However, in contrast to the abundant literature on the botanical, historical, and cultural aspects of coca leaves, adequately designed studies evaluating their clinical effects are scarce. Most research consists of preclinical studies, whether in vitro or in animal models (See Section 4.4 Biological / Pharmacological Effects). Human studies consist of self-administered surveys, open interviews, cross-sectional studies, observational studies (some without a control group, with small sample sizes and little consideration of potential confounding factors), cohort studies, and a few experimental studies in laboratory conditions with surrogate endpoints. By their nature, these studies are brief and limited and do not allow a full appreciation of their clinical significance. Therefore, from a formal drug regulatory standpoint, the evidence supporting the effectiveness and safety of these specific therapeutic applications is still considered preliminary.

However, care should be taken to apply suitable frameworks when analysing traditional medical practices. Since 1976, the WHO has developed a framework for international collaboration on herbal medicines, aiming to define strategies, standards, and benchmarks. The International Regulatory Cooperation for Herbal Medicines (IRCH) is the formal forum for this task; as of January 2025, the number of participating countries reached 46. Generally speaking, Traditional and Complementary Medicine (T&CM) products and practices are subject to the same scrutiny (regulation, safety, and quality control) as pharmaceuticals. As of 2023, 124 WHO Member States have passed laws or regulations for herbal medicines. To support Member States, WHO has published several guidelines for the quality, safety, and efficacy of herbal medicine (WHO, 2023b).

20 References

Acero, C., Ordonez, L., Harris, M., Rhodes, T., Holland, A., & Gutierrez-Sanin, F. (2023). Navigating chemical toxicity in coca production in the Colombian borderlands of putumayo. *Medical Anthropology*, *42*(7), 650-666. https://doi.org/10.1080/01459740.2023.2249202

Acock, M. C., Lydon, J., Johnson, E., & Collins, R. (1996). Effects of temperature and light levels on leaf yield and cocaine content in two Erythroxylum species. *Annals of Botany*, *78*(1), 49-53. https://doi.org/10.1006/anbo.1996.0094

AGEMED. (2025). *Registro sanitario de productos tradicionales artesanales nacional. Actualizado al 15 septiembre 2025.* [Report]. Agencia Estatal de Medicamentos y Tecnologías en Salud (AGEMED). https://www.agemed.gob.bo/archivo_regsan/registro_sanitario/reg-trad_arte.xlsx

Aibar Ozejo, M. E. (2006). Los efectos del consumo de hoja de coca [The Effects of Coca Leaf Consumption]. *Revista Peruana de Obstetricia y Enfermería*, *2*(1), 71-80. https://pesquisa.bvsalud.org/gim/resource/en/lil-504389

Albuquerque, C. H. d. (2013). *Constituintes químicos e atividade farmacológica de Erythroxylum pulchrum St. Hil. (Erythroxylaceae)* [Dissertation, Universidade Federal da Paraiba]. João Pessoa. https://repositorio.ufpb.br/jspui/handle/tede/6788

Allen, C. J. (1981). To be Quechua - the symbolism of coca chewing in highland Peru. *American Ethnologist*, *8*(1), 157-171. https://doi.org/10.1525/ae.1981.8.1.02a00100

Alvarado Villanueva, V., & Moromi Nakata, H. (2010). Plantas medicinales: Efecto antibacteriano in vitro de plantago major l, Erythroxylum novogranatense, plowman var truxillense y camellia sinensis sobre bacterias de importancia estomatológica. *Odontología Sanmarquina*, *13*(2), 21-25. https://doi.org/10.15381/os.v13i2.2853

Alvarez-Freire, I., Cabarcos-Fernandez, P., Rubio, N. C., Moreda-Pineiro, A., Tabernero-Duque, M. J., Sanchez-Sellero, I., Bermejo-Barrera, P., & Bermejo-Barrera, A. M. (2023). Detection of coca alkaloids in oral fluid from coca leaf (tea) consumers: Using solid phase extraction to improve validation parameters and widen the detection window. *Analytical Methods*, *15*(45), 6177-6183. https://doi.org/10.1039/d3ay01298k

Andrade, F. P., Muniz, R. M., Wenzel, F. A., Barbieri, R. L., Heck, R. M., & Schwartz, E. (2011). Plantas medicinais utilizadas por sobreviventes do câncer no tratamento e prevenção desta doença [Medicinal plants used for cancer survivors in the treatment and prevention of this disease]. *Revista de Enfermagem UFPE On Line*, *5*(4), 944-950. https://doi.org/10.5205/reuol.1302-9310-1-LE.0504201113

Aniszewski, T. (2007). *Alkaloids - secrets of life alkaloid chemistry, biological significance, applications and ecological role*. Elsevier.

Antih, J., Cañigueral, S., & Heinrich, M. (2016). Uso de plantas medicinales por la comunidad boliviana en el área metropolitana de Barcelona [Use of medicinal plants by the Bolivian community in the Metropolitan Region of Barcelona]. *Revista Fisioterapia*, *16*(2), 141-152. https://pesquisa.bvsalud.org/portal/resource/en/ibc-161080

Araújo Neto, J. F., de O. Ribeiro, E. M., do Vale, A. E., David, J. M., & David, J. P. (2021). Cytotoxic activity of tropane alkaloides of species of Erythroxylum. *Mini-Reviews in Medicinal Chemistry*, *21*(17), 2458-2480. https://doi.org/10.2174/1389557521666210119123409

Avilés, C. S., & Bouso, J. C. (2024). A decade of providing legal defence support for coca leaf cases in spain. *Drugs Habits and Social Policy*, *25*(2), 132-145. https://doi.org/10.1108/DHS-10-2023-0041

Ayala Pío, S., & Meneses, G. (2024). Efectos fisiológicos del hábito de la coca. Una aproximación histórica durante el siglo xx. *Anales de la Facultad de Medicina*, *85*(4), 481-485. https://doi.org/10.15381/anales.v85i4.29372

Ayala Pío, S., & Quintana-Salinas, M. (2019). Síntesis histórica de estudios biosociales de la coca y la alimentación en perú, 1948-1994 *Anales de la Facultad de Medicina*, *80*(3), 383-388. https://doi.org/10.15381/anales.803.16868

Aynilian, G. H., Duke, J. A., Gentner, W. A., & Farnsworth, N. R. (1974). Cocaine content of Erythroxylum species. *Journal of Pharmaceutical Sciences*, *63*(12), 1938-1939. https://doi.org/10.1002/jps.2600631223

Ayón Haro, E., & Chu Morales, M. d. P. (2005). Cambios histopatológicos de la mucosa gingival en masticadores de hoja de coca varones del distrito de laraos, provincia de Yauyos [Hystopathological changes of the gingival mucosa in the coca leaves chewer's males of district of Laraos, Province of Yauyos]. *Kiru*, *2*(1), 18-26. https://portalrevistas.aulavirtualusmp.pe/index.php/Rev-Kiru0/article/view/274/241

Baker, B. T., & Mazess, R. B. (1963). Calcium: Unusual sources in the highland Peruvian diet. *Science*, *142*(3598), 1466-1467. https://doi.org/10.1126/science.142.3598.1466

Barceloux, D. G. (2012). Cocaine. In D. G. Barceloux (Ed.), *Medical toxicology of drug abuse* (pp. 805-866). https://doi.org/10.1002/9781118105955.ch56

Barnett, G., Hawks, R., & Resnick, R. (1981). Cocaine pharmacokinetics in humans. *Journal of Ethnopharmacology*, *3*(2), 353-366. https://doi.org/10.1016/0378-8741(81)90063-5

Barreiros, M. L., David, J. P., David, J. M., Xavier Lopes, L. M., de Sá, M. S., Costa, J. F. O., Almeida, M. Z., de Queiróz, L. P., & Sant'Ana, A. E. G. (2007). Ryanodane diterpenes from two

Erythroxylum species. *Phytochemistry*, *68*(13), 1735-1739. https://doi.org/10.1016/j.phytochem.2007.05.007

Barros, I. M. d. C., Leite, B. H. M., Leite, C. F. M., Fagg, C. W., Gomes, S. M., Resck, I. S., Fonseca-Bazzo, Y. M., Magalhães, P. O., & Silveira, D. (2017). Chemical composition and antioxidant activity of extracts from Erythroxylum suberosum a.St. Hil.Leaves. *Journal of Applied Pharmaceutical Science*, *7*(3), 088-094. https://doi.org/10.7324/JAPS.2017.70314

Baselt, R. C. (1983). Stability of cocaine in biological fluids. *Journal of Chromatography A*, *268*(3), 502-505. https://doi.org/10.1016/S0021-9673(01)95449-4

Bauer, I. (2019). Travel medicine, coca and cocaine: Demystifying and rehabilitating Erythroxylum - a comprehensive review. *Tropical Diseases Travel Medicine & Vaccines*, *5*, 20. https://doi.org/10.1186/s40794-019-0095-7

Bedford, J. A., Lovell, D. K., Turner, C. E., Elsohly, M. A., & Wilson, M. C. (1980). The anorexic and actometric effects of cocaine and two coca extracts. *Pharmacology, Biochemistry and Behavior*, *13*(3), 403-408. https://doi.org/10.1016/0091-3057(80)90246-4

Bedford, J. A., Nail, G. L., Elsohly, H. N., Wilson, M. C., & Turner, C. E. (1981). Comparative stimulus properties of two fractions of the coca leaf (E. coca). *Pharmacology, Biochemistry and Behavior*, *15*(6), 907-909. https://doi.org/10.1016/0091-3057(81)90052-6

Bedford, J. A., Turner, C. E., & Elsohly, H. N. (1982). Comparative lethality of coca and cocaine. *Pharmacology, Biochemistry and Behavior*, *17*(5), 1087-1088. https://doi.org/10.1016/0091-3057(82)90499-3

Bedford, J. A., Turner, C. E., & Elsohly, H. N. (1984). Local anesthetic effects of cocaine and several extracts of the coca leaf (E. coca). *Pharmacology, Biochemistry and Behavior*, *20*(5), 819-821. https://doi.org/10.1016/0091-3057(84)90207-7

Bedford, J. A., Wilson, M. C., Elsohly, H. N., Elliott, C., Cottam, G., & Turner, C. E. (1981). The effects cocaine free extracts of the coca leaf on food consumption and locomotor activity. *Pharmacology, Biochemistry and Behavior*, *14*(5), 725-728. https://doi.org/10.1016/0091-3057(81)90138-6

Bedi, R., & Scully, C. (2014). Tropical oral health. In J. Farrar, P. J. Hotez, T. Junghanss, G. Kang, D. Lalloo, & N. J. White (Eds.), *Manson's tropical infectious diseases (23rd edition)* (pp. 1073-1083e). W.B. Saunders. https://doi.org/10.1016/B978-0-7020-5101-2.00074-1

Bencharit, S., Morton, C. L., Xue, Y., Potter, P. M., & Redinbo, M. R. (2003). Structural basis of heroin and cocaine metabolism by a promiscuous human drug-processing enzyme. *Nature Structural Biology*, *10*(5), 349-356. https://doi.org/10.1038/nsb919

Bertol, E., Favretto, D., Goldberger, B. A., & Karch, S. B. (2022). Pharmacokinetics: Drug absorption, distribution, and elimination. In *Karch's drug abuse handbook: Third edition.* (Vol. 1, pp. 133-178). CRC Press. https://doi.org/10.4324/9781315155159-2

Bešlo, D., Golubić, N., Rastija, V., Agić, D., Karnaš, M., Šubarić, D., & Lučić, B. (2023). Antioxidant activity, metabolism, and bioavailability of polyphenols in the diet of animals. *Antioxidants*, *12*(6), 1141. https://doi.org/10.3390/antiox12061141

Bieri, S., Brachet, A., Veuthey, J., & Christen, P. (2006). Cocaine distribution in wild Erythroxylum species. *Journal of Ethnopharmacology*, *103*(3), 439-447. https://doi.org/10.1016/j.jep.2005.08.021

Bieri, S., Ilias, Y., Bicchi, C., Veuthey, J. L., & Christen, P. (2006). Focused microwave-assisted extraction combined with solid-phase microextraction and gas chromatography-mass spectrometry for the selective analysis of cocaine from coca leaves. *Journal of Chromatography. A*, *1112*(1-2), 127-132. https://doi.org/10.1016/j.chroma.2005.12.028

Biondich, A. S., Joslin, J. D., & Avner, J. R. (2016). Coca: The history and medical significance of an ancient Andean tradition. *Emergency Medicine International*, *2016*(2016), 36-40. https://doi.org/10.1155/2016/4048764

Boghdadi, M. S., & Henning, R. J. (1997). Cocaine: Pathophysiology and clinical toxicology. *Heart & Lung: The Journal of Cardiopulmonary and Acute Care*, *26*(6), 466-483. https://doi.org/10.1016/S0147-9563(97)90040-6

Bohm, B. A., Ganders, F. R., & Plowman, T. (1982). Biosystematics and evolution of cultivated coca (Erythroxylaceae) [Erythroxylum spp.]. *Systematic Botany*, *7*(2), 121-133. https://doi.org/10.2307/2418321

Bolo, L. L., & Ocampo, S. P. (2004). Mate de coca y episodio depresivo. *Medicina Naturista*, *5*, 223-232.

Bolognesi, C., Carrasquilla, G., Volpi, S., Solomon, K. R., & Marshall, E. J. (2009). Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: Association to occupational exposure to glyphosate. *Journal of Toxicology and Environmental Health. Part A*, *72*(15-16), 986-997. https://doi.org/10.1080/15287390902929741

Bolton, R. (1976). Andean coca chewing: A metabolic perspective. *American Anthropologist*, *78*(3), 630-634. https://doi.org/10.1525/aa.1976.78.3.02a00110

Borghelli, R. F., Stirparo, M., Andrade, J., Barros, R., Centofanti, M., & Estevez, O. T. (1975). Leukoedema in addicts to coca leaves in Humahuaca, Argentina. *Community Dentistry and Oral Epidemiology*, *3*(1), 40-43. https://doi.org/10.1111/j.1600-0528.1975.tb00277.x

Borghelli, R. F., Stirparo, M. A., Andrade, J. H., Centofanti, M. H., & Barros, R. E. (1973). Lesiones de la mucosa bucal por el uso de bojas de coca (Erythroxylon coca) en el grupo etario de varones de 20 anos de la provincia de Jujuy (Argentina) [Lesions of the oral mucosa caused by the use of coca leaves (Erythroxyloncoca) in 20 year old men in the Province of Jujuy (Argentina)]. *Revista de la Asociación Odontológica Argentina*, *61*(7), 250-254.

Bravo, O. I. (2021). *La influencia del consumo de hoja de coca en la actividad física-deportiva* [Dissertation, Universidad Abierta Interamericana]. https://repositorio.uai.edu.ar/handle/123456789/829

Bray, W., & Dollery, C. (1983). Coca chewing and high-altitude stress: A spurious correlation. *Current Anthropology*, *24*(3), 269-282. https://doi.org/10.1086/202995

Brewer-Osorio, S. (2021). Turning over a new leaf: A subnational analysis of 'coca yes, cocaine no' in Bolivia. *Journal of Latin American Studies*, *53*(3), 573-600, Article Pii s0022216x21000456. https://doi.org/10.1017/S0022216X21000456

Brutsaert, T., Milotich, M., Frisancho, A. R., & Spielvogel, H. (1995). Coca chewing among high altitude natives: Work and muscular efficiencies of nonhabitual chewers. *American Journal of Human Biology*, *7*(5), 607-616. https://doi.org/10.1002/ajhb.1310070508

Brzezinski, M. R., Abraham, T. L., Stone, C. L., Dean, R. A., & Bosron, W. F. (1994). Purification and characterization of a human liver cocaine carboxylesterase that catalyzes the production of benzoylecgonine and the formation of cocaethylene from alcohol and cocaine. *Biochemical Pharmacology*, *48*(9), 1747-1755. https://doi.org/10.1016/0006-2952(94)90461-8

Buck, A. A., Sasaki, T. T., Hewitt, J. J., & Macrae, A. A. (1968). Coca chewing and health. An epidemiologic study among residents of a Peruvian village. *American Journal of Epidemiology*, *88*(2), 159-177. https://doi.org/10.1093/oxfordjournals.aje.a120875

Burchard, R. E. (1980). Coca chewing and the polycythemia hypothesis. *Current Anthropology*, *21*(1), 108-109. https://doi.org/10.1086/202410

Busnel, R., & Manrique Lopez, H. (2023). The political economy of a failed drug reform: Insights from Peru's main legal coca valley. *International Journal of Drug Policy*, *117*, 104050. https://doi.org/10.1016/j.drugpo.2023.104050

Cabarcos-Fernandez, P., Alvarez-Freire, I., Rubio, N. C., Bermejo-Barrera, A. M., Moreda-Pineiro, A., Sanchez-Sellero, I., & Tabernero-Duque, M. J. (2024). Evaluation of an oral fluid collection device and a solid-phase extraction method for the determination of coca leaf alkaloids by gas chromatography-mass spectrometry. *Molecules*, *29*(3), 25. https://doi.org/10.3390/molecules29030592

Calatayud, J., & Gonzalez, A. (2003). History of the development and evolution of local anesthesia since the coca leaf. *Anesthesiology*, *98*(6), 1503-1508. https://doi.org/10.1097/00000542-200306000-00031

Camacho, A., & Mejia, D. (2017). The health consequences of aerial spraying illicit crops: The case of Colombia. *Journal of Health Economics*, *54*, 147-160. https://doi.org/10.1016/j.jhealeco.2017.04.005

Cano, J. H., & Volpato, G. (2004). Herbal mixtures in the traditional medicine of eastern cuba. *Journal of Ethnopharmacology*, *90*(2-3), 293-316. https://doi.org/10.1016/j.jep.2003.10.012

Caravedo, M. A., Mozo, K., Morales, M. L., Smiley, H., Stuart, J., Tilley, D. H., & Cabada, M. M. (2022). Risk factors for acute mountain sickness in travellers to cusco, Peru: coca leaves, obesity and sex. *Journal of Travel Medicine*, *29*(5), 20. https://doi.org/10.1093/jtm/taab102

Carmel, B., Moraes, B., Fox, D., Danckers, M., & Cabrera, R. (2022). Let's spill the tea: Acute aortic dissection. *Chest*, *162*(4), A1140. https://doi.org/10.1016/j.chest.2022.08.904

Carmona, G. N., Jufer, R. A., Goldberg, S. R., Gorelick, D. A., Greig, N. H., Yu, Q.-S., Cone, E. J., & Schindler, C. W. (2000). Butyrylcholinesterase accelerates cocaine metabolism: In vitro and in vivo effects in nonhuman primates and humans. *Drug Metabolism and Disposition*, *28*(3), 367-371. https://doi.org/10.1016/S0090-9556(24)15375-5

Carter, W. E. (1982). Coca in Bolivia. Final report, box 1. In *William E Carter papers*: National Anthropological Archives, Smithsonian Institution.

Carter, W. E., & Mamani, M. (1986). *Coca en Bolivia* (1.ª ed.). Libr. Editorial Juventud.

Carter, W. E., Parkerson, P., & Mamani, M. (1984). *Traditional and changing patterns of coca use in Bolivia* [Conference paper]. Cocaine 1980: Proceedings of the interamerican seminar on medical and sociological aspects of coca and cocaine, Lima, Peru. https://hdl.handle.net/2027/pur1.32754050100092

Casale, J. F., & Klein, R. F. (1993). Illicit production of cocaine. *Forensic Science Review*, *5*(2), 95-107.

Casale, J. F., & Mallette, J. R. (2016). Illicit coca grown in Mexico: An alkaloid and isotope profile unlike coca grown in South America. *Forensic Chemistry*, *1*, 1-5. https://doi.org/10.1016/j.forc.2016.05.001

Casale, J. F., Mallette, J. R., & Jones, L. M. (2014). Chemosystematic identification of fifteen new cocaine-bearing Erythroxylum cultigens grown in Colombia for illicit cocaine production.

Forensic Science International, *237*, 30-39. https://doi.org/10.1016/j.forsciint.2014.01.012

Casale, J. F., & Moore, J. M. (1994). 3',4',5'-trimethoxy-substituted analogs of cocaine, cis-/trans-cinnamoylcocaine and tropacocaine: Characterization and quantitation of new alkaloids in coca leaf, coca paste and refined illicit cocaine. *Journal of Forensic Sciences*, *39*(2), 462-472. https://doi.org/10.1520/jfs13617j

Casikar, V., Mujica, E., Mongelli, M., Aliaga, J., Lopez, N., Smith, C., & Bartholomew, F. (2010). Does chewing coca leaves influence physiology at high altitude? *Indian Journal of Clinical Biochemistry*, *25*(3), 311-314. https://doi.org/10.1007/s12291-010-0059-1

Castro, J. R. d., Gallo, J., & Loureiro, H. (2004). Cansancio y somnolencia en conductores de ómnibus y accidentes de carretera en el perú: Estudio cuantitativo *Revista Panamericana de Salud Publica*, *16*(1), 11-18.

Castro Luna, A. (2008). *Composición química del aceite esencial de las hojas de Erythroxylum novogranatense (morris) "coca", actividad antioxidante y determinación antibacteriana frente a streptococcus mutans* [Dissertation, Universidad Nacional Mayor de San Marcos]. Lima, Perú. https://core.ac.uk/outputs/323351216/

Castro, M. T., Raviña, M. G., Nájera, M. T., Carpano, S. M., Iácona, L. A., & Spegazzini, E. D. (2004). Micrographic analysis of Erythroxylum coca, phaseolus vulgaris, and canavalia ensiformis samples from the archaeological textile collection of the museo de la plata, Argentina. *Acta Farmaceutica Bonaerense*, *23*(3), 315-322.

Cattani, R. (1984). *Legal background of the argentinian sanitary policy about coca chewing* [Conference paper]. Cocaine 1980: Proceedings of the interamerican seminar on medical and sociological aspects of coca and cocaine, Lima, Peru. https://hdl.handle.net/2027/pur1.32754050100092

Centro de informacion y education para la prevencion del abuso de drogas, . (2006). [Report].

Chang, J. (2000). Medicinal herbs: Drugs or dietary supplements? *Biochemical Pharmacology*, *59*(3), 211-219. https://doi.org/10.1016/S0006-2952(99)00243-9

Chaves, C. G., Schapoval, E. E. S., Zuanazzi, J. A., Diehl, E., De Siqueira, N. C. S., & Henriques, A. T. (1988). Erythroxylum-argentinum assays for antiinflammatory activity. *Journal of Ethnopharmacology*, *22*(1), 117-120. https://doi.org/10.1016/0378-8741(88)90237-1

Chen, L., Cao, H., Huang, Q., Xiao, J., & Teng, H. (2022). Absorption, metabolism and bioavailability of flavonoids: A review. *Critical reviews in food science and nutrition*, *62*(28), 7730-7742. https://doi.org/10.1080/10408398.2021.1917508

CND, & United Nations Commission on Narcotic Drugs. (2024). *Tables of the United Nations convention against illicit traffic in narcotic drugs and psychotropic substances of 1988, as at 3 December 2024* [Report]. https://docs.un.org/en/ST/CND/1/Add.3/Rev.7

Coca-based flavor enhancer allows sugar cut in sodas. (2024). *Sugar Iundustry International*, *149*(11).

Coe, M. A., Jufer Phipps, R. A., Cone, E. J., & Walsh, S. L. (2018). Bioavailability and pharmacokinetics of oral cocaine in humans. *Journal of Analytical Toxicology*, *42*(5), 285-292. https://doi.org/10.1093/jat/bky007

Cone, E. J. (1995). Pharmacokinetics and pharmacodynamics of cocaine. *Journal of Analytical Toxicology*, *19*(6), 459-478. https://doi.org/10.1093/jat/19.6.459

Cone, E. J., Tsadik, A., Oyler, J., & Darwin, W. D. (1998). Cocaine metabolism and urinary excretion after different routes of administration. *Therapeutic Drug Monitoring*, *20*(5), 556-560. https://doi.org/10.1097/00007691-199810000-00019

Conway, R., Evans, I., & Weeraman, D. (2012). Assessing travelers' knowledge and use of coca for altitude sickness. *Wilderness & Environmental Medicine*, *23*(4), 373-374. https://doi.org/10.1016/j.wem.2012.06.005

Cormejo Cruz, S., & Quispe Condori, H. L. (2017). *Actividad antibacteriana in vitro del extracto etanólico de la hoja de Erythroxylum coca Lam. (coca) frente a cepas: Streptococcus mutans atcc 25175, streptococcus sanguis atcc 10556 y formulación de una pasta dental* [Dissertation, Universidad Nacional de San Antonio Abad del Cusco]. https://repositorio.unsaac.edu.pe/handle/20.500.12918/3313

Cortella, A. R., & Pochettino, M. L. (1994). Starch grain analysis as a microscopic diagnostic feature in the identification of plant material. *Economic Botany*, *48*(2), 171-181. https://doi.org/10.1007/BF02908212

Cristina Marcarini, J., Ferreira Tsuboy, M. S., Cabral Luiz, R., Regina Ribeiro, L., Beatriz Hoffmann-Campo, C., & Ségio Mantovani, M. (2011). Investigation of cytotoxic, apoptosis-inducing, genotoxic and protective effects of the flavonoid rutin in htc hepatic cells. *Experimental and Toxicologic Pathology*, *63*(5), 459-465. https://doi.org/https://doi.org/10.1016/j.etp.2010.03.005

Cruz, R. A. S., Botas, G. D., Fernandes, C. P., Santos, M. G., & Rocha, L. (2018). Chemical constituents of essential oils from leaves of two Erythroxylum species. *Chemistry of Natural Compounds*, *54*(1), 185-187. https://doi.org/10.1007/s10600-018-2292-4

Cruz, V. O. (2020). *Epidemiology of coca leaf chewing in the 21st century Peru* [Dissertation, Michigan State University]. https://d.lib.msu.edu/etd/49410

Cuellar B, S. L., Aranibar S, G. J., Orellana, N. I., Lopez C, R. A., Cervantes F, M. R., Chavarría D, J. P., Avalos M, L., & López H, K. L. (2020). Psicoestimulantes menores consumidos por estudiantes de la universidad san francisco xavier de chuquisaca, 2019 [Minor psychostimulants consumed by students of San Francisco Xavier de Chuquisaca University, 2019]. *Bio scientia*, *3*(5), 1-11. https://revistas.usfx.bo/index.php/bs/article/view/341/264

Cunha-Oliveira, T., Rego, A. C., Carvalho, F., & Oliveira, C. R. (2013). Medical toxicology of drugs of abuse. In P. M. Miller (Ed.), *Principles of addiction* (pp. 159-175). Academic Press. https://doi.org/10.1016/B978-0-12-398336-7.00017-6

Cusicanqui, S. R. (2005). "Here, even legislators chew them": Coca leaves and identity politics in Northern Argentina. In W. v. Schendel & I. Abraham (Eds.), *Illicit flows and criminal things: States, borders, and the other side of globalization* (pp. 128-152). Indiana University Press.

Daga Mauricio, K. M., Castillo Saavedra, E. F., Reyes Alfaro, C. E., Salas Sánchez, R. M., & Vargas Vigo, J. E. (2024). Enfermedad bucodental y masticación de hoja de coca en pobladores peruanos [Oral disease and coca leaf chewing in Peruvian residents]. *Avances en Odontoestomatologia*, *40*(2), 78-83.

de Colombia, G. (2024). *Dosier de la república de Colombia para el proceso de revisión critica de la actual clasificación de la hoja de coca en la lista i de la convención Única sobre estupefacientes de 1961* [Report]. Ministerio de Relaciones Exteriores.

de Fátima Souza de Oliveira, F., Coelho Aguiar, P. N., Gomes Ribeiro, G. d. J., Lozer de Amorim, M. L., Santos Guimaraes, P. S., Mendonca Filho, C. V., Goncalves Sivieri, R. R., Lins Brandão, M. d. G., Pio dos Santos, W. T., & Fuzer Grael, C. F. (2015). Antioxidant activity and phytochemical screening of extracts of Erythroxylum suberosum a.St.-hil (Erythroxylaceae). *Research Journal of Phytochemistry*, *9*(2), 68-78. https://doi.org/10.3923/rjphyto.2015.68.78

de Lima, L. H., Gomes, M. W., Curado, T. S., Naves, L. M., Marques, S. M., Oliveira, M. S., Ogbu, J. I., Menezes, A. C., Vila Verde, G. M., Fajemiroye, J. O., & Pedrino, G. R. (2024). Cardiovascular effects of a glycosylated flavonoids-rich leaf extract from Brazilian Erythroxylum campestre: A potential health bio-input. *Pharmaceuticals*, *17*(11). https://doi.org/10.3390/ph17111456

Descailleaux, J. (1990). Averiguación de la acción mutagénica de la hoja de coca y derivados en consumidores rutinarios. *Psicoactiva*, *4*(7), 133-160. https://pesquisa.bvsalud.org/gim/resource/en/lil-107062

DEVIDA. (2012). *Informe ejecutivo encuesta nacional sobre consumo de drogas en la población general del perú 2010* [Report]. Comisión Nacional para el Desarrollo y Vida sin Drogas -

DEVIDA. https://www.gob.pe/institucion/devida/informes-publicaciones/3057373-informe-ejecutivo-encuesta-nacional-sobre-consumo-de-drogas-en-la-poblacion-general-del-peru-2010

DEVIDA. (2020). *Informe sobre la demanda de hoja de coca para fines tradicionales e industriales* [Report]. Comisión Nacional para el Desarrollo y Vida sin Drogas - DEVIDA. https://cdn.www.gob.pe/uploads/document/file/1348630/Informe%20-%20Demanda%20Hoja%20de%20Coca.pdf

DEVIDA. (2021). *La cadena de suministro de la hoja de coca para fines industriales en el perú* [Report]. Comisión Nacional para el Desarrollo y Vida sin Drogas - DEVIDA. https://www.gob.pe/institucion/devida/informes-publicaciones/2062359-la-cadena-de-suministro-de-la-hoja-de-coca-para-fines-industriales-en-el-peru

DHHS. (2004). Mandatory guidelines for Federal workplace drug testing programs. *Federal Register*, *69*(71), 19644-19673. https://www.govinfo.gov/content/pkg/FR-2004-04-13/pdf/04-7985.pdf

Diaz Velasquez, L. J. S. (2022). *Efecto antibacteriano del extracto acuoso de hoja de stevia rebaudiana y erythroxylum coca solos y en combinación sobre streptococcus mutans atcc 25175, trujillo 2019* [Dissertation, Universidad Católica Los Ángeles de Chimbote]. https://renati.sunedu.gob.pe/handle/renati/2578258

DIGEMIC, ENACO, & DEVIDA. (2024). *Revision de la literatura cientifica actulaizada en farmacologia, toxicologia, epidemiologia y uso terapeuticao/traditional de la hoja de coca y su impacto en la salud publica* [Report].

DIGESA. (2025). *Consulta de registros sanitarios de alimentos* https://consultas-digesa.minsa.gob.pe/ConsultaWebRS/Consultas/Consulta_Registro_Sanitario.aspx

Dillehay, T. D., Rossen, J., Ugent, D., Karathanasis, A., Vásquez, V., & Netherly, P. J. (2010). Early holocene coca chewing in northern Peru. *Antiquity*, *84*(326), 939-953. https://doi.org/10.1017/S0003598X00067004

dos Santos, N. A., de Almeida, C. M., Goncalves, F. F., Ortiz, R. S., Kuster, R. M., Saquetto, D., & Romao, W. (2021). Analysis of Erythroxylum coca leaves by imaging mass spectrometry (MALDI-FT-ICR IMS). *Journal of the American Society for Mass Spectrometry*, *32*(4), 946-955. https://doi.org/10.1021/jasms.0c00449

Duke, J., Aulik, D., & Plowman, T. (1982). El valor alimenticio de la coca. In W. E. Carte (Ed.), *Ensayos científicos sobre la coca* (pp. 71-77). Juventud.

Duke, J. A., Aulik, D., & Plowman, T. (1975). Nutritional value of coca. *Botanical Museum Leaflets, Harvard University*, *24*(6), 113-119.

Edwards, D. J., & Bowles, S. K. (1988). Protein binding of cocaine in human serum. *Pharmaceutical Research*, *5*(7), 440-442. https://doi.org/10.1023/A:1015992502509

EFSA Panel on Contaminants in the Food Chain (CONTAM). (2013). Scientific opinion on tropane alkaloids in food and feed. *EFSA journal*, *11*(10), 3386. https://doi.org/10.2903/j.efsa.2013.3386

Ehrinpreis, A. (2020). Green gold, green hell: Coca, caste, and class in the Chaco War, 1932-1935. *Americas*, *77*(2), 217-245. https://doi.org/10.1017/tam.2019.110

Elias, S. T., Borges, G. A., Amorim, D. A., Rego, D. F., Simeoni, L. A., Silveira, D., Fonseca-Bazzo, Y. M., Paula, J. E., Fagg, C. W., Barros, I. M., Abreu, W. C., Pinto-Junior, D. S., Magalhães, P. O., Neves, F. A., Lofrano-Porto, A., & Guerra, E. N. (2015). Radiation induced a supra-additive cytotoxic effect in head and neck carcinoma cell lines when combined with plant extracts from the Brazilian cerrado biome. *Clinical Oral Investigations*, *19*(3), 637-646. https://doi.org/10.1007/s00784-014-1289-z

Elias, S. T., Macedo, C. C., Simeoni, L. A., Silveira, D., Magalhães, P. O., Lofrano-Porto, A., Coletta, R. D., Neves, F. A., & Guerra, E. N. (2016). Cytotoxic effect of Erythroxylum daphnites extract is associated with G1 cell cycle arrest and apoptosis in oral squamous cell carcinoma. *Cell Cycle*, *15*(7), 948-956. https://doi.org/10.1080/15384101.2016.1151583

ElSohly, M. A., Stanford, D. F., & ElSohly, H. N. (1986). Coca tea and urinalysis for cocaine metabolites. *Journal of Analytical Toxicology*, *10*(6), 256-256. https://doi.org/10.1093/jat/10.6.256

EMCDDA. (2010). *Cocaine: A European Union perspective in the global context* [Report]. https://www.euda.europa.eu/publications/joint-publications/cocaine_en

emol.com. (2006, March 7). *Candidato humala propone dar pan de coca en desayunos escolares*. https://www.emol.com/noticias/internacional/2006/03/07/213022/candidato-humala-propone-dar-pan-de-coca-en-desayunos-escolares.html

ENACO. (2021). *Hoja de coca natural en polvo* [Online]. Empresa Nacional de la Coca S.A. https://comercial.enaco.com.pe/coca-en-polvo/

ENACO. (2025). *Catálogo de productos de enaco*. https://www.gob.pe/26676-conocer-el-catalogo-de-productos-de-enaco

Enriquez Flores, I. E., & Villar-Luis, M. A. (2004). Uso y actitudes relacionados a las drogas en las estudiantes de enfermería de la universidad mayor de san andrés [Use and attitudes about drugs among nursing students at the Universidad Mayor de San Andres]. *Revista Latino-Americana de Enfermagem*, *12*(spe), 376-382. https://doi.org/10.1590/S0104-11692004000700012

Estado Plurinacional de Bolivia. (2023). *Dossier complementario en el marco del examen critico de la hoja de coca de la oms* [Report].

Evans, W. C. (1981). The comparative phytochemistry of the genus Erythroxylon. *Journal of Ethnopharmacology*, *3*(2-3), 265-277. https://doi.org/10.1016/0378-8741(81)90057-x

Evans, W. C., Evans, D., & Trease, G. E. (2009). *Trease and evans pharmacognosy* (16th / rev. with the assistance of Daphne Evans. ed.). Saunders/Elsevier.

Executive Board. (2007). *Contribution of traditional medicine to public health: coca leaf. Report by the secretariat* [Report](120th Session, Provisional agenda item 4.13). World Health Organization. https://iris.who.int/handle/10665/21977

Favier, R., Caceres, E., Koubi, H., Sempore, B., Sauvain, M., & Spielvogel, H. (1996). Effects of coca chewing on hormonal and metabolic responses during prolonged submaximal exercise. *Journal of Applied Physiology*, *80*(2), 650-655. https://doi.org/10.1152/jappl.1996.80.2.650

Feisthauer, E., Ameline, A., Gheddar, L., Arbouche, N., Raul, J. S., & Kintz, P. (2022). Analysis of cocaine and its metabolites in urine after consumption of coca tea by five subjects and subsequent hair testing. *Journal of Analytical Toxicology*, *46*(1), 108-113. https://doi.org/10.1093/jat/bkaa190

Fernandes Correia, A., Silveira, D., Fonseca-Bazzo, Y. M., Magalhães, P. O., Fagg, C. W., da Silva, E. C., Gomes, S. M., Gandolfi, L., Pratesi, R., & de Medeiros Nóbrega, Y. K. (2016). Activity of crude extracts from Brazilian cerrado plants against clinically relevant Candida species. *BMC Complementary and Alternative Medicine*, *16*(1), 203. https://doi.org/10.1186/s12906-016-1164-3

Fernández Droguett, F., Berrios Osores, M. V., & Díaz Ugarte, M. A. (2024). (des)penalización del uso de la hoja de coca entre comunidades andinas y migrantes del norte de Chile. *Textual*(83), 41-58. https://doi.org/10.5154/r.textual/2020.83.2

Fernández, J. (2017). The norm prohibiting the chewing of coca leaf: From the international system to the Colombian state. *Desafíos*, *29*(2), 61-83. https://doi.org/10.12804/revistas.urosario.edu.co/desafios/a.5228

Ferreira, J. F. S., Duke, S. O., & Vaughn, K. C. (1998). Histochemical and immunocytochemical localization of tropane alkaloids in Erythroxylum coca var. coca and E. Novogranatense var. Novogranatense. *International Journal of Plant Sciences*, *159*(3), 492-503. https://doi.org/10.1086/297566

Firenzuoli, F., & Gori, L. (2007). Herbal medicine today: Clinical and research issues. *Evidence-Based Complementary and Alternative Medicine*, *4*(S1), 594728. https://doi.org/10.1093/ecam/nem096

Floren, A. E., & Small, J. W. (1993). Mate de coca equals cocaine. *Journal of Occupational and Environmental Medicine*, *35*(2). https://doi.org/10.1097/00043764-199302000-00006

Fortin, H., Vigor, C., Lohézic-Le Dévéhat, F., Robin, V., Le Bossé, B., Boustie, J., & Amoros, M. (2002). In vitro antiviral activity of thirty-six plants from La Réunion Island. *Fitoterapia*, *73*(4), 346-350. https://doi.org/10.1016/S0367-326X(02)00080-1

Fuchs, A., Burchard, R. E., Curtain, C. C., De Azeredo, P. R., Frisancho, A. R., Gagliano, J. A., Katz, S. H., Little, M. A., Mazess, R. B., Picón-Reátegui, E., Sever, L. E., Tyagi, D., & Wood, C. S. (1978). Coca chewing and high-altitude stress: Possible effects of coca alkaloids on erythropoiesis [and comments and reply]. *Current Anthropology*, *19*(2), 277-291. https://doi.org/10.1086/202075

Fukunaga, T., Nishiya, K., Kajikawa, I., Takeya, K., & Itokawa, H. (1989). Studies on the constituents of Japanese mistletoes from different host trees, and their antimicrobial and hypotensive properties. *Chemical & Pharmaceutical Bulletin*, *37*(6), 1543-1546. https://doi.org/10.1248/cpb.37.1543

G, B., & Suripeddi, R. K. (2021). Development and validation of HPTLC method for identification and quantification of sterols from leaves of Erythroxylum monogynum Roxb. And in vitro evaluation of anti-oxidant and anti-glycation activities. *South African Journal of Botany*, *137*, 24-34. https://doi.org/10.1016/j.sajb.2020.10.005

Galarza Guzmán, M., Penaloza Imana, R., Echalar Afcha, L., Aguilar Valerio, M., Spielvogel, H., & Sauvain, M. (1997). Efectos del acullico de coca en la prueba de tolerancia a la glucosa [Effects of coca chewing on the glucose tolerance test]. *Medicina*, *57*(3), 261-264.

Gamarra Ochoa, V., Fuertes R, C., Chavez S, N., Contreras C, D., Goya S, E., Huamantumba B, K., Retuerto P, F., & Ruiz Pacco, G. (2017). Metabolitos en las hojas de Erythroxylum coca Lam y erithroxylum novogranatense (morris) vieron y evaluacion de sus propiedades biologicas mediante bioensayos. *Revista Peruana de Medicina Integrativa*, *2*(4), 828-834. https://doi.org/10.26722/rpmi.2017.24.70

Garcia-Yi, J. (2014a). Heterogeneous motivations for coca growing: The case of an indigenous Aymara community in Peru. *International Journal of Drug Policy*, *25*(6), 1113-1123. https://doi.org/10.1016/j.drugpo.2014.05.011

Garcia-Yi, J. (2014b). Social control as supply-side harm reduction strategy. The case of an indigenous coca-growing community in Peru. *Iberoamerican Journal of Development Studies*, *3*(1), 58-82.

Ghehiouèche, F., & Riboulet-Zemouli, K. (2024). Amigos de la hoja de coca: History of a pioneering coca leaf fair-trade. *Drugs Habits and Social Policy*, *25*(2), 155-172. https://doi.org/10.1108/DHS-10-2023-0040

Giordano, G., Mattia, M., Biehler-Gomez, L., Boracchi, M., Porro, A., Sardanelli, F., Slavazzi, F., Galimberti, P. M., Di Candia, D., & Cattaneo, C. (2024). Forensic toxicology backdates the use of coca plant (Erythroxylum spp.) in europe to the early 1600s. *Journal of Archaeological Science*, *170*, Article 106040. https://doi.org/10.1016/j.jas.2024.106040

Goddard, D., De Goddard, S. N., & Whitehead, P. C. (1969). Social factors associated with coca use in the Andean region. *International Journal of the Addictions*, *4*(4), 577-590.

Goldstein, R. A., DesLauriers, C., Burda, A., & Johnson-Arbor, K. (2009). Cocaine: History, social implications, and toxicity: A review. *Seminars in Diagnostic Pathology*, *26*(1), 10-17. https://doi.org/10.1053/j.semdp.2008.12.001

Gonzales-Carazas, E. F., Melgarejo-García, G. C., Chávez-Conde, L. K., Arellán-Bravo, L. J., Carbajal-Lázaro, E., Cabrera-Gómez, Y. A., Quiróz-Sáenz, G. M., García-Antúnez, I. N., Llanto-Aguirre, M., & Choque-Nolasco, F. G. (2013). Efecto terapéutico del extracto etanólico de Erythroxylum coca spp. En anemia ferropénica inducida en ratas Holtzman macho [Therapeutic effect of Erythroxylum coca spp. ethanol extract in experimental iron-deficiency anemia in male Holtzman rats]. *Anales de la Facultad de Medicina*, *74*(1), 7-10.

Gootenberg, P. (2007). The "pre-Colombian" era of drug trafficking in the Americas: Cocaine, 1945-1965. *The Americas*, *64*(2), 133-176.

Gosselin, R. E., Smith, R. P., Hodge, H. C., & Baraddock, J. E. (1984). *Clinical toxicology of commercial products* (5th. ed.). Williams & Wilkins.

Grabowski, J. (1984). *Cocaine: Pharmacology, effects, and treatment of abuse.* [Report](DHHS-ADM-84-1326). Issue 50). National Inst. on Drug Abuse (DHHS/PHS). https://eric.ed.gov/?id=ED260938

Gurib-Fakim, A., Subratty, H., Narod, F., Govinden-Soulange, J., & Mahomoodally, F. (2005). Biological activity from indigenous medicinal plants of mauritius. *Pure and Applied Chemistry*, *77*(1), 41-51. https://doi.org/10.1351/pac200577010041

Gutierrez-Noriega, C. (1948). Observaciones sobre el cocaismo obtenidas en un viaje al sur del Peru. *Revista de Farmacologia y Medicina Experimental*, *1*(2), 232-252.

Hamner, J. E. r., & Villegas, O. L. (1969). The effect of coca leaf chewing on the buccal mucosa of Aymara and Quechua Indians in Bolivia. *Oral Surgery, Oral Medicine, Oral Pathology*, *28*(2), 287-295. https://doi.org/10.1016/0030-4220(69)90299-0

Hanna, J. M. (1970). The effects of coca chewing on exercise in the Quechua of Peru. *Human Biology*, *42*(1), 1-11.

Hanna, J. M. (1971). Further studies on the effects of coca chewing on exercise. *Human Biology*, *43*(2), 200-209.

Hanna, J. M. (1974). Coca leaf use in Southern Peru - biosocial aspects. *American Anthropologist*, *76*(2), 281-296. https://doi.org/10.1525/aa.1974.76.2.02a00020

Hansen, K., Adsersen, A., Smitt, U. W., Nyman, U., Christensen, S. B., Schwartner, C., & Wagner, H. (1996). Angiotensin converting enzyme (ACE) inhibitory flavonoids from Erythroxylum laurifolium. *Phytomedicine*, *2*(4), 313-317. https://doi.org/10.1016/S0944-7113(96)80075-4

Harland, E. C., Murphy, J. C., Elsohly, H., Greubel, D., Turner, C. E., & Watson, E. S. (1982). Biological effects of nonalkaloid-containing fractions of Erythroxylon coca. *Journal of Pharmaceutical Sciences*, *71*(6), 677-679. https://doi.org/10.1002/jps.2600710618

Heath, D. B. (1990). Coca in the Andes: Traditions, functions and problems. *Rhode Island Medical Journal*, *73*(6), 237.

Henman, A. R. (1990). Coca and cocaine: Their role in 'traditional' cultures in South America. *Journal of Drug Issues*, *20*(4), 577-588.

Hilgert, N., Reyes, S., & Schmeda-Hirschmann, G. (2001). Alkaline substances used with coca (Erythroxylum coca, Erythroxylaceae) leaf insalivation in northwestern Argentina. *Economic Botany*, *55*(2), 325-329. https://doi.org/10.1007/BF02864567

Hirschkind, L. (2005). The enigmatic evanescence of coca from Ecuador. *Ethnobotany Research and Applications*, *3*(1), 97-106. https://www.ethnobotanyjournal.org/vol3/I1547-3465-03-097.pdf
http://ezproxy.library.arizona.edu/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=lhh&AN=20073207943&site=ehost-live

Holmstedt, B., Lindgren, J. E., Rivier, L., & Plowman, T. (1979). Cocaine in blood of coca chewers. *Journal of Ethnopharmacology*, *1*(1), 69-78. https://doi.org/10.1016/0378-8741(79)90017-5

Homeopathic pharmacopeia of India. (1974). (Vol. II). Ministry of Ayurveda Yoga and Naturopahty Unani Siddha and Homeopathy.

Hu, L., Luo, Y., Yang, J., & Cheng, C. (2025). Botanical flavonoids: Efficacy, absorption, metabolism and advanced pharmaceutical technology for improving bioavailability. *Molecules*, *30*(5). https://doi.org/10.3390/molecules30051184

Huestis, M. A., Darwin, W. D., Shimomura, E., Lalani, S. A., Trinidad, D. V., Jenkins, A. J., Cone, E. J., Jacobs, A. J., Smith, M. L., & Paul, B. D. (2007). Cocaine and metabolites urinary

excretion after controlled smoked administration. *Journal of Analytical Toxicology*, *31*(8), 462-468. https://doi.org/10.1093/jat/31.8.462

Huezo, A. (2017). Eradication without prior consultation: The aerial fumigation of coca in the black communities of the Colombian pacific. *Canadian Journal of Latin American and Caribbean Studies*, *42*(3), 375-399. https://doi.org/10.1080/08263663.2017.1378406

Hurtado Gumucio, J. (2000). Coca leaf chewing as therapy for cocaine maintenance. *Annales de Médecine Interne*, *151*, B44-48.

Hurtado Sánchez, C. A., Cartagena Triveño, D., & Erostegui Revilla, C. P. (2013). Evaluación de la respuesta glucemica post-ingesta de la hoja de coca (Erythroxylum coca) en personas sin antecedente patológico metabólico *Revista Científica Ciencia Médica*, *16*(1), 20-24.

Hurtado-Díaz, I., Ramírez-Cisneros, M. Á., Alvarez, L., Sánchez-Carranza, J. N., Columba-Palomares, M. C., Silva-Guzmán, J. A., Cruz-Sosa, F., & Bernabé-Antonio, A. (2024). Metabolites profile of extracts and fractions of Erythroxylum mexicanum kunth by uhplc-qtof-ms/ms and its antibacterial, cytotoxic and nitric oxide inhibitory activities. *Chemistry & Biodiversity*, *21*(3), e202301474. https://doi.org/10.1002/cbdv.202301474

INCB. (2009). *The report of the international narcotics control board* [Report]. U. Nations.

INCB. (2024a). *Estimated world requirements of narcotic drugs in grams for 2024 (september update)*. INCB. https://www.incb.org/documents/Narcotic-Drugs/Status-of-Estimates/2024/EstSep24.pdf

INCB. (2024b). *Narcotic drugs 2024: Estimated world requirements for 2025, statistics for 2023*. International Narcotics Control Board. https://www.incb.org/incb/en/narcotic-drugs/Technical_Reports/2024/narcotic-drugs-technical-report-2024.html

INCB. (2024c). *Precursors report 2024 – Annex VIII*. United Nations Publications. https://www.incb.org/documents/PRECURSORS/TECHNICAL_REPORTS/2024/E/Annex_VIII_E.pdf

Indriati, E., & Buikstra, J. E. (2001). Coca chewing in prehistoric coastal Peru: Dental evidence. *American Journal of Physical Anthropology*, *114*(3), 242-257. https://doi.org/10.1002/1096-8644(200103)114:3<242::Aid-ajpa1023>3.0.Co;2-j

Instituto Boliviano de Biología de Altura: cooperación francesa. (2008). Sobre la influencia del acullico de coca en la capacidad física [On the influence of coca acullico in the physical ability]. *Cuaderno Hospital de Clínicas*, *53*(1), 9-14. http://biblioteca.fment.umsa.bo/docs/tc/v530101.pdf

INVIMA. (2025). *Consultas de datos de productos* https://consultaregistro.invima.gov.co/Consultas/consultas/consreg_encabcum.jsp

Isenschmid, D. S., Fischman, M. W., Foltin, R. W., & Caplan, Y. H. (1992). Concentration of cocaine and metabolites in plasma of humans following intravenous administration and smoking of cocaine. *Journal of Analytical Toxicology*, *16*(5), 311-314. https://doi.org/10.1093/jat/16.5.311

Isenschmid, D. S., Levine, B. S., & Caplan, Y. H. (1989). A comprehensive study of the stability of cocaine and its metabolites. *Journal of Analytical Toxicology*, *13*(5), 250-256. https://doi.org/10.1093/jat/13.5.250

IUPAC. (2025). Solvent extraction. In *IUPAC Compendium of Chemical Terminology, 5th ed.* International Union of Pure and Applied Chemistry, Online version 5.0.0. https://doi.org/10.1351/goldbook.S05752

Javaid, J. I., Fischman, M. W., Schuster, C. R., Dekirmenjian, H., & Davis, J. M. (1978). Cocaine plasma concentration: Relation to physiological and subjective effects in humans. *Science*, *202*(4364), 227-228. https://doi.org/10.1126/science.694530

Jeffcoat, A. R., Perez-Reyes, M., Hill, J. M., Sadler, B. M., & Cook, C. E. (1989). Cocaine disposition in humans after intravenous injection, nasal insufflation (snorting), or smoking. *Drug Metabolism and Disposition*, *17*(2), 153-159. https://doi.org/10.1016/S0090-9556(25)08737-9

Jenkins, A. J., Llosa, T., Montoya, I., & Cone, E. J. (1996). Identification and quantitation of alkaloids in coca tea. *Forensic Science International*, *77*(3), 179-189. https://doi.org/10.1016/0379-0738(95)01860-3

Johnson, E. L. (1995). Content and distribution of Erythroxylum coca leaf alkaloids. *Annals of Botany*, *76*(4), 331-335. https://doi.org/10.1006/anbo.1995.1104

Johnson, E. L. (1996). Alkaloid content in Erythroxylum coca tissue during reproductive development. *Phytochemistry*, *42*(1), 35-38. https://doi.org/10.1016/0031-9422(96)00864-3

Johnson, E. L., & Emche, S. D. (1994). Variation of alkaloid content in Erythroxylum coca leaves from leaf bud to leaf drop. *Annals of Botany*, *73*(6), 645-650. https://doi.org/10.1006/anbo.1994.1081

Johnson, E. L., & Foy, C. D. (1996). Biomass accumulation and alkaloid content in leaves of Erythroxylum coca and Erythroxylum novogranatense var. Novogranatense grown in soil with varying pH. *Journal of Plant Physiology*, *149*(3), 444-450. https://doi.org/10.1016/S0176-1617(96)80147-7

Johnson, E. L., Saunders, J. A., Mischke, S., Helling, C. S., & Emche, S. D. (2003). Identification of Erythroxylum taxa by AFLPAFLP DNA analysis. *Phytochemistry*, *64*(1), 187-197. https://doi.org/10.1016/s0031-9422(03)00206-1

Johnson, E. L., Schmidt, W. F., & Cooper, D. (2002). Flavonoids as chemotaxonomic markers for cultivated Amazonian coca. *Plant physiology and biochemistry*, *40*(1), 89-95. https://doi.org/10.1016/S0981-9428(01)01348-1

Johnson, E. L., Zhang, D., & Emche, S. D. (2005). Inter- and intra-specific variation among five Erythroxylum taxa assessed by AFLP. *Annals of Botany*, *95*(4), 601-608. https://doi.org/10.1093/aob/mci062

Jones, A. W., Holmgren, A., & Kugelberg, F. C. (2008). Concentrations of cocaine and its major metabolite benzoylecgonine in blood samples from apprehended drivers in Sweden. *Forensic Science International*, *177*(2), 133-139. https://doi.org/10.1016/j.forsciint.2007.11.009

Kauroo, S., Govinden-Soulange, J., Ranghoo-Sanmukhiya, V. M., Miranda, K., Cotham, W. E., Walla, M. D., Nagarkatti, M., & Nagarkatti, P. (2021). Extracts of select endemic plants from the Republic of mauritius exhibiting anti-cancer and immunomodulatory properties. *Scientific Reports*, *11*(1), 4272. https://doi.org/10.1038/s41598-021-83461-0

Khan, M. T. H., Ather, A., Thompson, K. D., & Gambari, R. (2005). Extracts and molecules from medicinal plants against herpes simplex viruses. *Antiviral Research*, *67*(2), 107-119. https://doi.org/10.1016/j.antiviral.2005.05.002

Klette, K. L., Poch, G. K., Czarny, R., & Lau, C. O. (2000). Simultaneous GC-MS analysis of meta- and para-hydroxybenzoylecgonine and norbenzoylecgonine: A secondary method to corroborate cocaine ingestion using nonhydrolytic metabolites. *Journal of Analytical Toxicology*, *24*(7), 482-488. https://doi.org/10.1093/jat/24.7.482

Kohlert, C., van Rensen, I., März, R., Schindler, G., Graefe, E. U., & Veit, M. (2000). Bioavailability and pharmacokinetics of natural volatile terpenes in animals and humans. *Planta Médica*, *66*(06), 495-505. https://doi.org/10.1055/s-2000-8616

Ledoux, A., Cao, M., Jansen, O., Mamede, L., Campos, P.-E., Payet, B., Clerc, P., Grondin, I., Girard-Valenciennes, E., Hermann, T., Litaudon, M., Vanderheydt, C., Delang, L., Neyts, J., Leyssen, P., Frédérich, M., & Smadja, J. (2018). Antiplasmodial, anti-chikungunya virus, and antioxidant activities of 64 endemic plants from the Mascarene Islands. *International Journal of Antimicrobial Agents*, *52*(5), 622-628. https://doi.org/10.1016/j.ijantimicag.2018.07.017

Li, L. S., Chiroma, S. M., Hashim, T., Adam, S. K., Mohd Moklas, M. A., Yusuf, Z., & Rahman, S. A. (2020). Antioxidant and anti-inflammatory properties of *Erythroxylum cuneatum* alkaloid leaf extract. *Heliyon*, *6*(6). https://doi.org/10.1016/j.heliyon.2020.e04141

Liu, S., Farias, K. S., Zanuncio, V. S. S., Damasceno Júnior, G. A., Alves, F. M., Paredes-Gamero, E. J., de Souza, K. F. S., Pessatto, L. R., Torquato, H. F. V., Carollo, C. A., & Silva, D. B. (2025).

Deciphering steroidal and aporphine alkaloids as antileukemic agents by approaches of molecular networking and metabolomics. *ACS Omega*, *10*(10), 10327-10339. https://doi.org/10.1021/acsomega.4c10160

Lohezic, F., Amoros, M., Boustie, J., & Girre, L. (1999). In-vitro antiherpetic activity of Erythroxylon laurifolium (Erythroxylaceae). *Pharmacy and Pharmacology Communications*, *5*(3), 249-253. https://doi.org/10.1211/146080899128734695

López Espinoza, J., Paredes Iribarren, N., Y Reyes Medina, G. (2023). *Infusión de la hoja de coca (Erythroxylum coca) como hipoglucemiante en pacientes adultos y adultos mayores con diabetes mellitus tipo 2, provincia de Huánuco y Ambo – 2021* [Dissertation, Universidad Nacional Hermilio Valdizán]. https://repositorio.unheval.edu.pe/item/10cebda4-09e2-4f57-9f4b-ff14fc559f80

Loyola, D., Mendoza, R., Chiong, L., Rueda, M., Alvítez-Temoche, D., Gallo, W., & Mayta-Tovalino, F. (2020). Ethanol extract of Schinus molle l. (molle) and Erythroxylum coca Lam (coca): Antibacterial properties at different concentrations against: Streptococcus mutans: : An: In vitro: Study. *Journal of International Society of Preventive and Community Dentistry*, *10*(5). https://doi.org/0.4103/jispcd.JISPCD_237_20

Lozada Centurión, E. M. (2022). *Efectos de la harina de coca (Erythroxylum coca) en raciones de cuyes sobre su carcasa y órganos internos* [Dissertation, Universidad Nacional Pedro Ruiz Gallo].

Lucas-Espeza, L. P., y la Cruz-Rodríguez, R., & Aguirre-Siancas, E. E. (2023). Coca leaf chewing as a risk factor for oral health [Masticación de la hoja de coca como factor de riesgo para la salud bucal]. *Revista de Salud Pública*, *25*(5). https://doi.org/10.15446/rsap.v25n5.109421

Lucas-Filho, M. D., Silva, G. C., Cortes, S. F., Mares-Guia, T. R., Perpétua Ferraz, V., Serra, C. P., & Braga, F. C. (2010). Ace inhibition by astilbin isolated from Erythroxylum gonocladum (Mart.) o.E. Schulz. *Phytomedicine*, *17*(5), 383-387. https://doi.org/10.1016/j.phymed.2009.09.008

Luck, K., Jirschitzka, J., Irmisch, S., Huber, M., Gershenzon, J., & Köllner, T. G. (2016). Cyp79d enzymes contribute to jasmonic acid-induced formation of aldoximes and other nitrogenous volatiles in two Erythroxylum species. *BMC Plant Biology*, *16*(1), 215. https://doi.org/10.1186/s12870-016-0910-5

Lujan, M. C. (1997). Ingesta alimentaria en acullicadores y no acullicadores de dos comunidades rurales. In M. S. M. Villena Cabrera (Ed.), *Usos de la hoja de coca y salud pública* (pp. 83-86). Instituto Boliviano de Biología de Altura.

Luna-Vílchez, M., Díaz-Vélez, C., & Baca-Dejo, F. (2017). Efecto del extracto acuoso, ácido y alcohólico de las hojas secas de Erythroxylum coca var. coca (coca) en Trichophyton rubrum, Trichophyton mentagrophytes, Microsporum canis y Candida albicans in vitro [effect of the aqueous, acidic and alcoholic extract of dried leaves of Erythroxylum coca var. coca (coca) in Trichophyton rubrum, Trichophyton mentagrophytes, Microsporum canis and Candida albicans in vitro]. *Horizonte Médico (Lima)*, *17*(1), 25-30.

Lv, Y., Tian, T., Wang, Y.-J., Huang, J.-P., & Huang, S.-X. (2022). Advances in chemistry and bioactivity of the genus Erythroxylum. *Natural Products and Bioprospecting*, *12*(1), 15. https://doi.org/10.1007/s13659-022-00338-z

Macedo Pereira, G., Moreira, L. G. L., Neto, T., Moreira de Almeida, W. A., Almeida-Lima, J., Rocha, H. A. O., Barbosa, E. G., Zuanazzi, J. A. S., de Almeida, M. V., Grazul, R. M., Navarro-Vazquez, A., Hallwass, F., Ferreira, L. S., Fernandes-Pedrosa, M. F., & Giordani, R. B. (2018). Isolation, spectral characterization, molecular docking, and cytotoxic activity of alkaloids from Erythroxylum pungens o. E. Shulz. *Phytochemistry*, *155*, 12-18. https://doi.org/10.1016/j.phytochem.2018.07.003

Macedo, T. B. C., Elias, S. T., Torres, H. M., Yamamoto-Silva, F. P., Silveira, D., Magalhães, P. O., Lofrano-Porto, A., Guerra, E. N. S., & Silva, M. A. G. (2016). Cytotoxic effect of Erythroxylum suberosum combined with radiotherapy in head and neck cancer cell lines. *Brazilian Dental Journal*, *27*. https://doi.org/10.1590/0103-6440201600014

Magalhães, K. D. N., Guarniz, W. A. S., Sá, K. M., Freire, A. B., Monteiro, M. P., Nojosa, R. T., Bieski, I. G. C., Custódio, J. B., Balogun, S. O., & Bandeira, M. A. M. (2019). Medicinal plants of the caatinga, northeastern Brazil: Ethnopharmacopeia (1980–1990) of the late ProfessorProfessor Francisco José de Abreu Matos. *Journal of Ethnopharmacology*, *237*, 314-353. https://doi.org/10.1016/j.jep.2019.03.032

Mahomoodally, F. M., Mesaik, A., Choudhary, M. I., Subratty, A. H., & Gurib-Fakim, A. (2012). In vitro modulation of oxidative burst via release of reactive oxygen species from immune cells by extracts of selected tropical medicinal herbs and food plants. *Asian Pacific Journal of Tropical Medicine*, *5*(6), 440-447. https://doi.org/10.1016/S1995-7645(12)60075-3

Mahomoodally, M. F., Gurib-Fakim, A., & Subratty, A. H. (2005). Antimicrobial activities and phytochemical profiles of endemic medicinal plants of Mauritius. *Pharmaceutical Biology*, *43*(3), 237-242. https://doi.org/10.1080/13880200590928825

Mahomoodally, M. F., Subratty, A. H., Gurib-Fakim, A., Choudhary, M. I., & Nahar Khan, S. (2012). Traditional medicinal herbs and food plants have the potential to inhibit key carbohydrate-hydrolyzing enzymes in vitro and reduce postprandial blood glucose peaks in vivo. *The Scientific World Journal*, *2012*(1), 285284. https://doi.org/10.1100/2012/285284

Marentes-Culma, R., & Orduz-Díaz, L. L. (2025). From tradition to science: Chemical, nutritional, and cytotoxic characterization of Erythroxylum coca from indigenous Colombian communities. *ACS Omega*, *10*(15), 15009-15017. https://doi.org/10.1021/acsomega.4c10491

Marín-Sáez, J., Romero-González, R., & Garrido Frenich, A. (2019). Effect of tea making and boiling processes on the degradation of tropane alkaloids in tea and pasta samples contaminated with Solanaceae seeds and coca leaf. *Food Chemistry*, *287*, 265-272. https://doi.org/10.1016/j.foodchem.2019.02.091

Martins, M. F., Vanoni, S., & Carlini, V. P. (2020). Consumo de psicoestimulantes como potenciadores cognitivos por estudiantes de medicina de la Universidad Nacional de Córdoba [Psychostimulants consumption for neuroenhancement among medical students from National University of Córdoba]. *Revista de la Facultad de Ciencias Médicas de Córdoba*, *77*(4), 254-259. https://doi.org/10.31053/1853.0605.v77.n4.28166

Mary, C. (2025). Genetic links to high altitude found to reduce inflammation, speed response to PV therapy. *Evidence-Based Oncology*, *31*, SP28. https://www.ajmc.com/view/genetic-links-to-high-altitude-found-to-reduce-inflammation-speed-response-to-pv-therapy (January 2025)

Matos de Macêdo, L., Cardoso de Souza Neta, L., de Oliveira Ribeiro, E. M., & Lacerda Braga Teles, A. (2022). Atividades biológicas avaliadas in vitro de espécies do gênero Erythroxylum: Uma revisão de literatura. *Revista Colombiana de Ciencias Químico-Farmacéuticas*, *51*, 316-347. http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0034-74182022000100316&nrm=iso

McAllister, W. B. (2004). The global political economy of scheduling: The international-historical context of the Controlled Substances Act. *Drug Alcohol Depend*, *76*(1), 3-8. https://doi.org/10.1016/j.drugalcdep.2004.02.012

Mendoza-Azpur, G., Cruz, M., Bahamonde, A., Ponce, C., Mauricio, J. M., & Shibli, J. A. (2021). Clinical and histological manifestations of chronic coca leaf chewing in a Peruvian population: A cross-sectional study. *Journal of the International Academy of Periodontology*, *23*(1), 11-16.

Mercado Antelo, M. A., & K. Schulmeyer, M. (2021). Motivos, práctica y percepción social del boleo de la hoja de coca en universitarios de Santa Cruz, Bolivia [motives, practice and social perception of coca leaf balling in university students in Santa Cruz, Bolivia] [Motives, Practice and Social Perception of Coca Leaf Balling in University Students in Santa Cruz, Bolivia]. *Revista Aportes de la Comunicación y la Cultura (31)*, 2-22. http://www.scielo.org.bo/scielo.php?script=sci_arttext&pid=S2306-86712021000200002&lang=en

Mesquita, E. C., Consolaro, H. N., Ribeiro, R. I. M. d. A., & Severino. (2017). Estudo químico de espécies do gênero Erythroxylum (Erythroxylaceae). Em *Tecnologias em pesquisa: Ciências exatas e biológicas* (pp. 71-84). Blucher.

Ministerio de Relaciones Exteriores. (2009). *Aprendiendo nuevos protocolos el akhulli la hoja de coca en la diplomacia de los pueblos* [Report].

Molina-Avila, I., Pimentel Sola, J. M., Vides Almonacid, G., & Gilligan, G. (2020). Oral squamous cell carcinoma could be related to coca chewers in Northern Argentina. *Oral Oncology*, *108*, 104927. https://doi.org/10.1016/j.oraloncology.2020.104927

Molina-Avila, I., Pimentel-Sola, J. M., Buschiazzo, E., Echazu, A., Piemonte, E., & Gilligan, G. (2024). Association between coca (Erythroxylum coca) chewing habit and oral squamous cell carcinoma: A case-control study from Argentina. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *138*(2), 279-288. https://doi.org/10.1016/j.oooo.2024.04.011

Moore, J. M., & Casale, J. F. (1994). In-depth chromatographic analyses of illicit cocaine and its precursor, coca leaves. *Journal of Chromatography. A*, *674*(1-2), 165-205. https://doi.org/10.1016/0021-9673(94)85224-3

Moore, J. M., Casale, J. F., Klein, R. F., Cooper, D. A., & Lydon, J. (1994). Determination and in-depth chromatographic analyses of alkaloids in South American and greenhouse-cultivated coca leaves. *Journal of Chromatography. A*, *659*(1), 163-175. https://doi.org/10.1016/0021-9673(94)85018-6

Mujica, E., Ronceros, G., Torres, J., Pinto, R., Ponciano, W., Bravo, Y., López, M., Gallardo, D., Salinas, C., Calderón, S., Villareal, C., & Yampufé, M. (2012). Estudio de parámetros metabólicos en sujetos jóvenes sometidos a ejercicio submáximo después de la administración de mate de coca, en la exposición aguda a la altura. *Anales de la Facultad de Medicina*, *73*(Suppl 1), S34. https://doi.org/10.15381/anales.v73i1.2190

Mujica, E., Saavedra, C., Huamán, J., Díaz, J., Carrión, M., Zúñiga, H., Aliaga, J., Ortiz, J., Cebreros, H., Casikar, V., Córdova, H., López, N., & Murillo, A. (2012). Efecto del mate de coca en la función cardio-respiratoria en sujetos jóvenes sometidos a ejercicio submáximo, en la exposición aguda a la altura. *Anales de la Facultad de Medicina*, *73*(Suppl 1), S33. https://doi.org/10.15381/anales.v73i1.2187

Mujica, E., Saavedra, C., Huamán, J., Díaz, J., Ronceros, G., Zúñiga, H., Aliaga, J., Casikar, V., Cebreros, H., Ortiz, J., Carranza, E., & Florentino, E. (2012). Efecto del mate de coca en la función hormonal en sujetos jóvenes sometidos a ejercicio sub-máximo, en la exposición aguda a la altura. *Anales de la Facultad de Medicina*, *73(Suppl. 1)*, S33. https://doi.org/10.15381/anales.v73i1.2189

Murillo-Sandoval, P. J., Sesnie, S. E., Armas, M. E. O., Magliocca, N., Tellman, B., Devine, J. A., Nielsen, E., & McSweeney, K. (2024). Central America's agro-ecological suitability for cultivating coca, Erythroxylum spp. *Environmental Research Letters*, *19*(10), Article 104068. https://doi.org/10.1088/1748-9326/ad7276

Ñaccha-Urbano, J. J. (2021). Efecto de la masticación de Erythroxylum coca Lamarck (coca) sobre los niveles de colesterol y triglicérido sérico en personas altoandinas *Journal of the Selva Andina Research Society*, *12*(1), 64-76.

Naeem, A., Ming, Y., Pengyi, H., Jie, K. Y., Yali, L., Haiyan, Z., Shuai, X., Wenjing, L., Ling, W., Xia, Z. M., Shan, L. S., & Qin, Z. (2022). The fate of flavonoids after oral administration: A comprehensive overview of its bioavailability. *Critical Reviews in Food Science and Nutrition*, *62*(22), 6169-6186. https://doi.org/10.1080/10408398.2021.1898333

National Commission of Indigenous Territories. (2018). *Cultural and spiritual use of coca leaf in Colombian indigenous communities* [Report]. Ministry of the Interior.

Neergheen-Bhujun, V. S., Munogee, N., & Coolen, V. (2014). Antioxidant and anti-inflammatory efficacies of polyherbal formulations and elixirs traditionally used in Mauritius for the treatment of rheumatoid arthritis. *Journal of Herbal Medicine*, *4*(1), 1-9. https://doi.org/10.1016/j.hermed.2013.11.002 https://www.sciencedirect.com/science/journal/22108033

Negrete, J. C. (1978). Coca leaf chewing: A public health assessment. *British Journal of Addiction to Alcohol and Other Drugs*, *73*(3), 283-290. https://doi.org/10.1111/j.1360-0443.1978.tb00155.x

Negrete, J. C. (1980). Evaluación de salud pública sobre la masticación de hoja de coca [evaluation of public health in relation to coca leaf chewing] [Evaluation of public health in relation to coca leaf chewing]. *Boletín de la Oficina Sanitaria Panamericana (OSP)*, *88*(2), 109-118. https://pesquisa.bvsalud.org/portal/resource/en/pah-5574

Nersesyan, A., Kundi, M., Krupitza, G., Barcelos, G., Misik, M., Wultsch, G., Carrion, J., Carrion-Carrera, G., & Knasmueller, S. (2013). Induction of nuclear anomalies in exfoliated buccal cells of coca chewers: Results of a field study. *Archives of Toxicology*, *87*(3), 529-534. https://doi.org/10.1007/s00204-012-0969-1

NicDaéid, N., & Savage, K. A. (2013). Classification. In J. A. Siegel, P. J. Saukko, & M. M. Houck (Eds.), *Encyclopedia of forensic sciences* (Second edition ed.). Academic Press.

Niño de Guzmán Tapia, S. X., & Medina Rivas Plata, A. R. (2025). Analysis of the 1961 Single Convention on narcotic drugs' impact on the restructuring projects of Peru's national coca company. *Revista Andina de Estudios Politicos*, *15*(1), 57-80. https://doi.org/10.35004/raep.v15i1.258

Nogué Xarau, S., Picón Cabrera, M., Mestre Roca, G., & de la Devesa, R. C. R. (2002). Urgencias en usuarios de cocaína. *Medicina Integral*, *39*(6), 249-259.

Novak, M., & Salemink, C. A. (1987). The essential oil of Erythroxylum coca. *Planta Médica*, *53*(1), 113. https://doi.org/10.1055/s-2006-962643

Novák, M., Salemink, C. A., & Khan, I. (1984). Biological activity of the alkaloids of Erythroxylum coca and Erythroxylum novogranatense. *Journal of Ethnopharmacology*, *10*, 261-274. https://doi.org/10.1016/0378-8741(84)90015-1

Novoa, B. E., Céspedes, A. C., A. de García, L., & Olarte, C. J. E. (1985). Quercitrina: Un flavoide con actividad hipotensora, obtenido del Croton glabellus. *Revista Colombiana de Ciencias Químico-Farmacéuticas*, *4*(2), 7-13. https://revistas.unal.edu.co/index.php/rccquifa/article/view/56641

Oliva, M. V. (2016). Usos y costumbres sobre hierbas medicinales en barrios periurbanos del sudeste de la ciudad de Salta, Argentina [Uses and customs on medicinal herbs in periurban neighborhoods of southeastern Salta City, Argentina]. *Archiv. Med. Fam. Gen. (En línea)*, *13*(1), 18-26. http://revista.famfyg.com.ar/index.php/AMFG/article/view/7/4

Oliveira, A. C., Sena-Filho, J. G., Mendes-Júnior, L. G., Anjos, R. M., Ribeiro, T. P., Barbosa-Filho, J. M., Braga, V. A., & Medeiros, I. A. (2012). Erythroxylum pungens elicits vasorelaxation by reducing intracellular calcium concentration in vascular smooth muscle cells of rats. *Revista Brasileira de Farmacognosia*, *22*. https://doi.org/10.1590/S0102-695X2012005000005

Oliveira, S. L., da Silva, M. S., Tavares, J. F., Sena-Filho, J. G., Lucena, H. F., Romero, M. A., & Barbosa-Filho, J. M. (2010). Tropane alkaloids from Erythroxylum genus: Distribution and compilation of 13C-NMR spectral data. *Chemistry & Biodiversity*, *7*(2), 302-326. https://doi.org/10.1002/cbdv.200800290

Olivier, J., Symington, E. A., Jonker, C. Z., Rampedi, I. T., & Eeden, T. S. v. (2012). Comparison of the mineral composition of leaves and infusions of traditional and herbal teas. *South African Journal of Science*, *108*(1/2), 97-103. https://doi.org/10.4102/sajs.v108i1/2.623

Ordinola Ramírez, C. M., Barrena Gurbillón, M. Á., Oc Carrasco, O. J., Pizarro Salazar, O., Chicoma Roque, M. L. J., Barrena Ordinola, C. M., & Cucho Hidalgo, M. N. A. (2020). Relación de enfermedad periodontal y chacchado de hoja de "coca" erithroxylum coca (Erythroxylaceae) con cal en trabajadores de construcción civil de la Universidad Nacional Toribio Rodríguez de Mendoza de Amazonas - 2018 [Periodontal disease relationship and chew of "coca" Erithroxylum coca (Erythroxylaceae) leaf with lime in civil construction workers of the National University Toribio Rodriguez de Mendoza de Amazonas - 2018]. *Arnaldoa*, *27*(1), 129-140. https://doi.org/10.22497/arnaldoa.271.27106

Padilla, X., Terrazas, K. & Carvajal, R. (2023). La viabilidad y funcionalidad de leucocitos humanos en presencia de un extracto hidroalcohólico de E. coca x1 - the viability and functionality of human leukocytes in the presence of a hydro-alcoholic extract of E. coca. *Revista CON-CIENCIA*, *11*(2), 25-40. https://doi.org/10.53287/haxv1678ag35o

Paul, B. D., Lalani, S., Bosy, T., Jacobs, A. J., & Huestis, M. A. (2005). Concentration profiles of cocaine, pyrolytic methyl ecgonidine, and thirteen metabolites in human blood and urine: Determination by gas chromatography–mass spectrometry. *Biomedical Chromatography*, *19*(9), 677-688. https://doi.org/10.1002/bmc.495

Pearson, Z. (2016). "Coca got us here and now it's our weakness:" Fusarium oxysporum and the political ecology of a drug war policy alternative in Bolivia. *International Journal of Drug Policy*, *33*, 88-95. https://doi.org/10.1016/j.drugpo.2016.05.007

Penny, M. E., Zavaleta, A., Lemay, M., Liria, M. R., Huaylinas, M. L., Alminger, M., McChesney, J., Alcaraz, F., & Reddy, M. B. (2009). Can coca leaves contribute to improving the nutritional status of the Andean population? *Food and Nutrition Bulletin*, *30*(3), 205-216. https://doi.org/10.1177/156482650903000301

Pereira, L. (2010). Becoming coca: A materiality approach to a commodity chain analysis of hoja de coca in Colombia. *Singapore Journal of Tropical Geography*, *31*(3), 384-400. https://doi.org/10.1111/j.1467-9493.2010.00412.x

Perera Córdova, W. H., Gómez Matos, M., Tabart, J., Sipel, A., Kevers, C., & Dommes, J. (2012). In vitro characterization of antioxidant properties of Cuban endemic varieties of *Erythroxylum alaternifolium* A. Rich. Isolation of two flavonol glycosides. *Journal of the Chilean Chemical Society*, *57*, 1340-1343. https://doi.org/10.4067/S0717-97072012000400002

Perera, P., Rabinarayan, A., Pandya, P., Harisha, C. R., & Shukla, V. J. (2021). Pharmacognostic and analytical profile of leaves of Erythroxylum moonii Hochr. - an ethno-medicinal plant. *International Journal of Ayurvedic Medicine*, *12*(2), 353-359.

Picot, C. M., Subratty, A. H., & Mahomoodally, M. F. (2014). Inhibitory potential of five traditionally used native antidiabetic medicinal plants on alpha-amylase, alpha - glucosidase, glucose entrapment, and amylolysis kinetics in vitro. *Advances in Pharmacological Sciences*, *2014*, 739834. https://doi.org/10.1155/2014/739834

Pizarro, F., Olivares, M., Hertrampf, E., & Walter, T. (1994). Factores que modifican el estado de nutricion de hierro: Contenido de taninos de infusiones de hierbas [Factors which modify the nutritional state of iron: tannin content of herbal teas]. *Archivos Latinoamericanos de Nutrición*, *44*(4), 277-280.

Plowman, T. (1976). Orthography of Erythroxylum (erythroxylaceae). *Taxon*, *25*(1), 141-144. https://doi.org/10.2307/1220421

Plowman, T. (1981). Amazonian coca. *Journal of Ethnopharmacology*, *3*(2), 195-225. https://doi.org/10.1016/0378-8741(81)90054-4

Plowman, T. (1982). The identification of coca (Erythroxylum species) - 1860-1910. *Botanical Journal of the Linnean Society*, *84*(4), 329-353. https://doi.org/10.1111/j.1095-8339.1982.tb00368.x

Plowman, T. (1984). *Botanical perspectives on coca* [Conference paper]. Cocaine 1980: Proceedings of the interamerican seminar on medical and sociological aspects of coca and cocaine, Lima, Peru. https://hdl.handle.net/2027/pur1.32754050100092

Plowman, T., & Hensold, N. (2004). Names, types, and distribution of neotropical species of Erythroxylum (Erythroxylaceae). *Brittonia*, *56*(1), 1-53. https://doi.org/10.1663/0007-196X(2004)056[0001:NTADON]2.0.CO;2

Plowman, T., & Rivier, L. (1983). Cocaine and cinnamoylcocaine content of Erythroxylum species. *Annals of Botany*, *51*(5), 641-659.

Poblete, A., López-Alarcón, C., Lissi, E., & Campos, A. M. (2009). Oxygen radical antioxidant capacity (ORAC) values of herbal teas obtained employing different methodologies can provide complementary data. *Journal of the Chilean Chemical Society*, *54*, 154-157.

Prayong, P., Barusrux, S., & Weerapreeyakul, N. (2008). Cytotoxic activity screening of some indigenous thai plants. *Fitoterapia*, *79*(7-8), 598-601. https://doi.org/10.1016/j.fitote.2008.06.007

Proctor, G. R. (2012). *Flora of the cayman islands* (Second edition ed.). Kew Publishing.

Ramhit, P., Ragoo, L., Bahorun, T., & Neergheen-Bhujun, V. S. (2018). Multi-targeted effects of untapped resources from the Mauritian endemic flora. *South African Journal of Botany*, *115*, 208-216. https://doi.org/10.1016/j.sajb.2018.01.020

Rerat, C., Sauvain, M., Rop, P. P., Ruiz, E., Bresson, M., & Viala, A. (1997). Liquid chromatographic analysis of cocaine and benzoylecgonine in plasma of traditional coca chewers from Bolivia during exercise. *Journal of Ethnopharmacology*, *56*(3), 173-178. https://doi.org/10.1016/S0378-8741(97)00029-9

Restrepo, D. A., Sáenz, E., Jara-Muñoz, O. A., Calixto-Botía, I. F., Rodríguez-Suárez, S., Zuleta, P., Chávez, B. G., Sánchez, J. A., & Chávez, B. G., Sánchez, J. A., & D'Auria, J. C. (2019). Erythroxylum in focus: An interdisciplinary review of an overlooked genus. *Molecules*, *24*(20). https://doi.org/10.3390/molecules24203788

Rhodes, T., Ordonez, L. S., Acero, C., Harris, M., Holland, A., & Sanin, F. G. (2023). Caring for coca, living with chemicals: Towards ecological harm reduction. *International Journal of Drug Policy*, *120*, 104179. https://doi.org/10.1016/j.drugpo.2023.104179

Ribeiro, E. M. d. O., Lima, L. S., David, J. M., Vale, A. E. D., Lopes, L. M. X., & David, J. P. (2013). A new tropane alkaloid and other constituents of Erythroxylum rimosum (Erythroxylaceae). . *Phytochemistry Letters*, *6*(2), 232-235. http://hdl.handle.net/11449/75231

Rincon-Ruiz, A., Correa, H. L., Leon, D. O., & Williams, S. (2016). Coca cultivation and crop eradication in Colombia: The challenges of integrating rural reality into effective anti-drug policy. *International Journal of Drug Policy*, *33*, 56-65. https://doi.org/10.1016/j.drugpo.2016.06.011

Risemberg Mendizábal, F. (1944). Acción de la coca y de la cocaína en sujetos habituados. *Revista Peruana de Medicina Experimental y Salud Pública*, *3*(4), 317-328.

Rivera Encinas, M. T. (2015). *Efectividad del uso del mate de coca en la reducción del estrés laboral en administrativos de la Universidad de San martÍn de Porres en 2014* [Dissertation, Universidad de San MartÍn de Porres]. Lima, Perú. https://repositorio.usmp.edu.pe/handle/20.500.12727/1903

Rivier, L. (1981). Analysis of alkaloids in leaves of cultivated Erythroxylum and characterization of alkaline substances used during coca chewing. *Journal of Ethnopharmacology*, *3*(2-3), 313-335. https://doi.org/10.1016/0378-8741(81)90061-1

Rodeiro, I., Donato, M. T., Lahoz, A., González-Lavaut, J. A., Laguna, A., Castell, J. V., Delgado, R., & Gómez-Lechón, M. J. (2008). Modulation of p450 enzymes by Cuban natural products rich in polyphenolic compounds in rat hepatocytes. *Chemico-Biological Interactions*, *172*(1), 1-10. https://doi.org/10.1016/j.cbi.2007.10.004

Rodeiro, I., Donato, M. T., Martínez, I., Hernández, I., Garrido, G., González-Lavaut, J. A., Menéndez, R., Laguna, A., Castell, J. V., & Gómez-Lechón, M. J. (2008). Potential hepatoprotective effects of new Cuban natural products in rat hepatocytes culture. *Toxicology in Vitro*, *22*(5), 1242-1249. https://doi.org/https://doi.org/10.1016/j.tiv.2008.04.006

Rodrigues, A., Guillon, L., & M C. d. (1997). Uso de la hoja de coca y hematología [Coca leaf uses and public health]. En M. Villena Cabrera y M. Villena Cabrera & M. Sauvain (Eds.), *Usos de la hoja de coca y salud pública* (pp. 78-82). Instituto Boliviano de Biología de Altura. https://pesquisa.bvsalud.org/gim/resource/en/lil-193144

Rodrigues, G. A., Souza, W. C., Godinho, M. G. C., Ferreira, H. D., & Vila Verde, G. M. (2015). Determinação de parâmetros farmacognósticos para as folhas de Erythroxylum

suberosum A. St.-hilaire (Erythroxylaceae) coletadas no município de Goiânia, Goiás. St.-hilaire (Erythroxylaceae) coletadas no município de Goiânia, Go. *Revista Brasileira de Plantas Medicinais*, *17*(4 suppl 3), 1169-1176. https://doi.org/10.1590/1983-084X/14_114

Roque Bravo, R., Faria, A. C., Brito-da-Costa, A. M., Carmo, H., Mladěnka, P., Dias da Silva, D., Remião, F., & on behalf of The, O. R. (2022). Cocaine: An updated overview on chemistry, detection, biokinetics, and pharmacotoxicological aspects including abuse pattern. *Toxins*, *14*(4). https://doi.org/10.3390/toxins14040278

Rubio, C., Strano-Rossi, S., Tabernero, M. J., Anzillotti, L., Chiarotti, M., & Bermejo, A. M. (2013). Hygrine and cuscohygrine as possible markers to distinguish coca chewing from cocaine abuse in workplace drug testing. *Forensic Science International*, *227*(1), 60-63. https://doi.org/10.1016/j.forsciint.2012.09.005

Rubio, N. C., Álvarez-Freire, I., Cabarcos-Fernández, P., Tabernero-Duque, M. J., Sánchez-Sellero, I., Moreda-Piñeiro, A., Bermejo-Barrera, P., & Bermejo-Barrera, A. M. (2025). Cuscohygrine and hygrine as biomarkers for coca leaf chewing: Analytical challenges in GC-MS detection and implications for the differentiation of cocaine use in forensic toxicology. *Separations*, *12*(8), 201. https://doi.org/10.3390/separations12080201

Rubio, N. C., Bermejo-Barrera, P., Bermejo, A. M., & Moreda-Pineiro, A. (2019). Development of a reliable method for assessing coca alkaloids in oral fluid by HPLC-MS-MS. *Journal of Analytical Toxicology*, *43*(3), 196-202. https://doi.org/10.1093/jat/bky076

Rubio, N. C., Hastedt, M., Gonzalez, J., & Pragst, F. (2015). Possibilities for discrimination between chewing of coca leaves and abuse of cocaine by hair analysis including hygrine, cuscohygrine, cinnamoylcocaine and cocaine metabolite/cocaine ratios. *International Journal of Legal Medicine*, *129*(1), 69-84. https://doi.org/10.1007/s00414-014-1061-6

Rubio, N. C., Krumbiegel, F., Pragst, F., Thurmann, D., Nagel, A., Zytowski, E., Aranguren, M., Gorlelo, J. C., & Poliansky, N. (2019). Discrimination between chewing of coca leaves or drinking of coca tea and smoking of "paco" (coca paste) by hair analysis. A preliminary study of possibilities and limitations. *Forensic Science International*, *297*, 171-176. https://doi.org/10.1016/j.forsciint.2019.01.040

Rubio, N. C., Moreda-Piñeiro, A., Alvarez-Freirec, I., Bermejo-Barrera, P., Tabernero-Duque, M. J., & Bermejo, A. M. (2019). The probability to detect cocaine, methylecgonine, cinnamoylcocaine, hygrine and cuscohygrine in urine samples of coca leaves chewers after six years. *Microchemical Journal*, *151*, Article 104215. https://doi.org/10.1016/j.microc.2019.104215

Rubio, N. C., Moreda-Piñeiro, A., Bermejo-Barrera, P., & Bermejo, A. M. (2019). Perfil de alcaloides de la hoja de coca en el fluido oral de un mascador de hoja de coca y un bebedor de té de coca. Estudio preliminar. *Acta toxicológica argentina*, *27*(2), 72-80.

Rubio, N. C., Strano-Rossi, S., Tabernero, M. J., González-González, J. L., Anzillotti, L., Chiarotti, M., & Bermejo, A. M. (2014). Application of hygrine and cuscohygrine as possible markers to distinguish coca chewing from cocaine abuse on WDT and forensic cases. *Forensic Science International*, *243*, 30-34. https://doi.org/10.1016/j.forsciint.2014.02.024

Rummun, N., Neergheen-Bhuiyan, V. S., Pynee, K. B., Baider, C., & Bahorun, T. (2018). The role of endemic plants in Mauritian traditional medicine – potential therapeutic benefits or placebo effect? *Journal of Ethnopharmacology*, *213*, 111-117. https://doi.org/10.1016/j.jep.2017.10.006

Salazar, H., Swanson, J., Mozo, K., Clinton White Jr., A., & Cabada, M. M. (2012). Acute mountain sickness impact among travelers to Cusco, Peru. *Journal of Travel Medicine*, *19*(4), 220-225. https://doi.org/10.1111/j.1708-8305.2012.00606.x

Salcedo Calderón, M. D. R., & Moromi Nakata, H. (2022). Efecto del extracto etanólico de Erythroxylum novogranatense var. Truxillense y Erythroxylum coca var. coca frente al streptococcus mutans. *Revista Estomatológica Herediana*, *32*, 365-370. https://doi.org/10.20453/reh.v32i4.4376

Sales, M. D. C., Costa, H. B., Fernandes, P. M. B., Ventura, J. A., & Meira, D. D. (2016). Antifungal activity of plant extracts with potential to control plant pathogens in pineapple. *Asian Pacific Journal of Tropical Biomedicine*, *6*(1), 26-31. https://doi.org/10.1016/j.apjtb.2015.09.026

Salinas-Piélago, J. (2016). Revisión sobre el uso del mate de hoja de coca en la prevención del mal agudo de montaña [Review on the use of coca tea in prevention of acute mountain sickness]. *Rev. neuro-psiquiatr. (Impr.)*, *79*(3), 166-168. https://doi.org/10.20453/rnp.v79i3.2922

Salisbury, D. S., & Fagan, C. (2013). Coca and conservation: Cultivation, eradication, and trafficking in the Amazon borderlands. *GeoJournal*, *78*(1), 41-60. https://doi.org/10.1007/s10708-011-9430-x

Sánchez-Sierra, M., Noda, J. R., Bravo, Y. A., López, L. M., Zárate, L., Lazo, M. A., Sócola, F. A., Salinas, V., Del Risco, J., Sasieta, H. C., Palomino, J. D., & Accinelli, R. A. (2010). Clinical and spirometric findings among people exposed to biomass fuels associated with chewing coca leaves habits in the highlands of Peru. *American Journal of Respiratory and Critical Care Medicine*, *181*(1).

Sandagorda, A. (1984). *Socio cultural aspects of coca use* [Conference paper]. Cocaine 1980: Proceedings of the interamerican seminar on medical and sociological aspects of coca and cocaine, Lima, Peru. https://hdl.handle.net/2027/pur1.32754050100092

Sanin, L. H., Carrasquilla, G., Solomon, K. R., Cole, D. C., & Marshall, E. J. P. (2009). Regional differences in time to pregnancy among fertile women from five Colombian regions with different use of glyphosate. *Journal of Toxicology and Environmental Health, Part A*, *72*(15/16), 949-960. https://doi.org/10.1080/15287390902929691

Santos, B. L., Oliveira, A. J. d., Santos, I. V., Duarte, M. C., Cunha, P. S., dos Santos, D. M., Silva, E. A. P. d., Quintans Júnior, L. J., & Santos, M. R. V. d. (2022). Phytochemical screening and cardiovascular effects of the ethanol extract of Erythroxylum passerinum mart. *Natural Product Research*, *36*(4), 1048-1052. https://doi.org/10.1080/14786419.2020.1844690

Santos, K. C., Monte, A. P. O., Lima, J. T., Ribeiro, L. A. A., & Palheta Junior, R. C. (2016). Role of no–cgmp pathway in ovine cervical relaxation induced by Erythroxylum caatingae plowman. *Animal Reproduction Science*, *164*, 23-30. https://doi.org/10.1016/j.anireprosci.2015.11.003

Saravia Burgos, J., & Acosta Canedo, A. (2015). Megacolon y volvulo de sigmoides: Incidencia y fisiopatología. *Revista de Gastroenterología del Perú*, *35*(1), 38-44.

Sauvain, M., Rerat, C., Moretti, C., Saravia, E., Arrazola, S., Gutiérrez, E., Lema, A. M., & Muñoz, V. (1997). A study of the chemical composition of Erythroxylum coca var. coca leaves collected in two ecological regions of Bolivia. *Journal of Ethnopharmacology*, *56*(3), 179-191. https://doi.org/10.1016/s0378-8741(97)00030-5

Schinder, E. O., & Ruder, A. M. (1989). Epidemiology of coca and alcohol use among high-altitude miners in Argentina. *American Journal of Industrial Medicine*, *15*(5), 579-587. https://doi.org/10.1002/ajim.4700150510

Schröder-van der Elst, J. P., van der Heide, D., Rokos, H., Köhrle, J., & Morreale de Escobar, G. (1997). Different tissue distribution, elimination, and kinetics of thyroxine and its conformational analog, the synthetic flavonoid emd 49209 in the rat1. *Endocrinology*, *138*(1), 79-84. https://doi.org/10.1210/endo.138.1.4848

Schultes, R. E. (1980). Coca in the northwest Amazon. *Botanical Museum Leaflets, Harvard University*, *28*, 47-60.

Schulz, O. E., Estevez-Nieto, A., & Garcia, P. (1980). Antitumor effect of a purified fraction of the leaves of Erythroxylon alaternifolium A. Rich. And Erythroxylon pedicellare (GRISEB). *Revista Cubana de Farmacia*, *14*(Jan-Apr), 25-28.

Schwab, R. S., Delorme, T. L., & Zimmerman, K. (1952). Observations on the effects of chewing cocaine wax or coca leaves on muscular fatigue. *Transactions of the American Neurological Association*, *56*(77th Meeting), 256-259.

Schwitzer, G., Mudur, G., Henry, D., Wilson, A., Goozner, M., Simbra, M., Sweet, M., & Baverstock, K. A. (2005). What are the roles and responsibilities of the media in disseminating health information? *PLoS Medicine*, *2*(7), e215. https://doi.org/10.1371/journal.pmed.0020215

Scrivener, J. H. (1871). On the coca leaf, and its uses in diet and medicine. *The Medical Times and Gazette*, 407-408.

Seminario, C. B. (2024). "Coca says that the hill fell out of jealousy": Testimonies about a threatened practice and episteme in ancash, Peru. *Drugs Habits and Social Policy*, *25*(2), 116-131. https://doi.org/10.1108/DHS-11-2023-0046

Shackleton, M. F., Tondora, C. M., Whiting, S., & Whitney, M. (2000). The effect of homeopathic coca on high altitude mountain sickness: Mt. Everest base camp. *Complementary Health Practice Review*, *6*(1), 45-55.

Shori, A. B. (2015). Screening of antidiabetic and antioxidant activities of medicinal plants. *Journal of Integrative Medicine*, *13*(5), 297-305. https://doi.org/10.1016/S2095-4964(15)60193-5

Siegel, R. K., Elsohly, M. A., Plowman, T., Rury, P. M., & Jones, R. T. (1986). Cocaine in herbal tea. *JAMA*, *255*(1), 40-40. https://doi.org/10.1001/jama.1986.03370010042021

Silva-Filha, E., Silva, N. L., Macedo, F. N., Santos, L. Í. C., Santos, A. S., Santos, M. R. V., Duarte, M. C., Aragão, C. F. S., Nogueira, F. H. A., Lima, A. A. N., Zengin, G., Coutinho, H. D. M., Schimieguel, D. M., Quintans, J. S. S., & Quintans-Júnior, L. J. (2022). The effects of ethanolic extract of the leaves of Erythroxylum mucronatum (Benth.) (Erythroxylaceae) on strength and muscle performance of resistance-trained rats. *Phytomedicine Plus*, *2*(2), Article 100230. https://doi.org/10.1016/j.phyplu.2022.100230

Simons-Linares, C. R., Morgenstern, R., Acosta-Canedo, A., & Saravia-Burgos, J. (2018). Is there an association of the Andes traditional coca leaf chewing and sigmoid volvulus? A study of 441 patients in Bolivia. *American Journal of Gastroenterology*, *113*, S106-S107.

Skopp, G., Klingmann, A., Pötsch, L., & Mattern, R. (2001). In vitro stability of cocaine in whole blood and plasma including ecgonine as a target analyte. *Therapeutic Drug Monitoring*, *23*(2), 174-181. https://doi.org/10.1097.00007691-200104000-00014

Snapp, Z., & Quintero, J. (2024). Towards the fair regulation of all coca leaf derivatives in Colombia. *Drugs Habits and Social Policy*, *25*(2), 173-186. https://doi.org/10.1108/DHS-05-2024-0020

Soobrattee, M. A., Bahorun, T., Neergheen, V. S., Googoolye, K., & Aruoma, O. I. (2008). Assessment of the content of phenolics and antioxidant actions of the Rubiaceae, ebenaceae, Celastraceae, Erythroxylaceae, and Sterculaceae families of Mauritian endemic plants. *Toxicology in Vitro*, *22*(1), 45-56. https://doi.org/10.1016/j.tiv.2007.07.012

South, R. B. (1977). Coca in Bolivia. *Geographical Review*, *67*(1), 22-33. https://doi.org/10.2307/213601

Spielvogel, H., Caceres, E., Koubi, H., Sempore, B., Sauvain, M., & Favier, R. (1996). Effects of coca chewing on metabolic and hormonal changes during graded incremental exercise to maximum. *Journal of Applied Physiology*, *80*(2), 643-649. https://doi.org/10.1152/jappl.1996.80.2.643

Spielvogel, H., Rodriguez, A., Sempore, B., Caceres, E., Cottet-Emard, J. M., Guillon, L., & Favier, R. (1997). Body fluid homeostasis and cardiovascular adjustments during submaximal exercise: Influence of chewing coca leaves. *European Journal of Applied Physiology and Occupational Physiology*, *75*(5), 400-406. https://doi.org/10.1007/s004210050179

Springfield, A. C., Cartmell, L. W., Aufderheide, A. C., Buikstra, J., & Ho, J. (1993). Cocaine and metabolites in the hair of ancient Peruvian coca leaf chewers. *Forensic Science International*, *63*(1-3), 269-275. https://doi.org/10.1016/0379-0738(93)90280-n

Stewart, D. J., Inaba, T., Tang, B. K., & Kalow, W. (1977). Hydrolysis of cocaine in human plasma by cholinesterase. *Life Sciences*, *20*(9), 1557-1563. https://doi.org/10.1016/0024-3205(77)90448-9

Suliman, N. A., Mohd Moklas, M. A., Mat Taib, C. N., Adenan, M. I., Hidayat Baharuldin, M. T., Basir, R., & Amom, Z. (2016). Morphine antidependence of Erythroxylum cuneatum (Miq.) kurz in neurotransmission processes in vitro. *Evidence-Based Complementary and Alternative Medicine*, *2016*(1), 3517209. https://doi.org/10.1155/2016/3517209

Suroowan, S., & Mahomoodally, F. (2013). Complementary and alternative medicine use among Mauritian women. *Complementary Therapies in Clinical Practice*, *19*(1), 36-43. https://doi.org/10.1016/j.ctcp.2012.07.002

Syed, S. H., & Namdeo, A. G. (2013). Hepatoprotective effect of leaves of Erythroxylum monogynum Roxb. On paracetamol-induced toxicity. *Asian Pacific journal of tropical biomedicine*, *3*(11), 877-881. https://doi.org/10.1016/S2221-1691(13)60172-0

Takahashi, R. N., Calixto, J. B., Costa, I. M., Lima, T. C. M. d., Morato, G. S., Nicolau, M., Rae, G. A., Valle, R. M. R., & Yunes, R. A. (1988). Análise química e perfil farmacológico do Erythroxylum argentinum [Chemical analysis and pharmacological profile of

Erythroxylum argentinum]. *Acta Amazonica (Suplemento)*, *18*(1-2), 407-424. https://www.scielo.br/j/aa/a/TdppS4fGfdGmtxzGbRxtWSQ/?lang=pt#

Trigo-Pérez, K., & Suárez-Cunza, S. (2017). Evaluation of the effect of coca leaf powder consumption on bone turnover in postmenopausal women. *Revista Peruana de Ginecología y Obstetricia*, *63*(4), 519-527. https://doi.org/10.31403/RPGO.V63I2023

Tsuchiya, H. (2017). Anesthetic agents of plant origin: A review of phytochemicals with anesthetic activity. *Molecules*, *22*(8), 18. https://doi.org/10.3390/molecules22081369

Turner, C. E., Ma, C. Y., & Elsohly, M. A. (1981). Constituents of Erythroxylon coca. Ii. Gas-chromatographic analysis of cocaine and other alkaloids in coca leaves. *Journal of Ethnopharmacology*, *3*(2-3), 293-298. https://doi.org/10.1016/0378-8741(81)90059-3

United Nations. (1961). *Single convention on narcotic drugs, 1961* [Report]. https://www.unodc.org/pdf/convention_1961_en.pdf

United Nations. (2006). *Multilingual dictionary of narcotic drugs and psychotropic substances under international control [online]* [Report]. https://www.unodc.org/documents/scientific/-%20Part%20One%20ALL.pdf

United States Department of Justice. (1991). *Coca cultivation and cocaine processing: An overview* [Online]. https://www.ojp.gov/pdffiles1/Digitization/132907NCJRS.pdf

United States Department of Justice. (2024). *Controlled substances* [Online]. https://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf

UNODC. *World drugs reports: Previous reports 1997-2024*. https://www.unodc.org/unodc/en/data-and-analysis/Previous-reports.html

UNODC. (1950). *Commission of inquiry on the coca leaf* [Report]. https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1950-01-01_4_page005.html

UNODC. (2003). *Bolivia coca cultivation survey* [Report]. https://www.unodc.org/pdf/bolivia/bolivia_coca_survey_2003.pdf

UNODC. (2006). *Coca cultivation in the Andean region: A survey of Bolivia, Colombia, and Peru* [Report]. https://www.unodc.org/pdf/andean/Andean_full_report.pdf

UNODC. (2009). *Colombia coca cultivation survey for 2008* [Report]. http://www.unodc.org/documents/crop-monitoring/Colombia_coca_survey_2008.pdf

UNODC. (2010). *World Drug Report* [Report]. https://www.unodc.org/documents/wdr/WDR_2010/World_Drug_Report_2010_lo-res.pdf

UNODC. (2012). *Recommended methods for the identification and analysis of cocaine in seized materials* [Report]. https://www.unodc.org/documents/scientific/Cocaine_Manual_Rev_1.pdf

UNODC. (2013). *Perú monitoreo de cultivos de coca 2012* [Report]. DEVIDA. https://www.unodc.org/documents/crop-monitoring/Peru/Peru_Monitoreo_de_Coca_2012_web.pdf

UNODC. (2023a). *Colombia survey report* [Report]. https://www.unodc.org/documents/crop-monitoring/Colombia/Colombia_survey_report_EN_2023.pdf

UNODC. (2023b). *Fact sheet: Bolivia coca cultivation executive summary* [Report]. https://www.unodc.org/documents/crop-monitoring/Bolivia/Bolivia_report_2023_Fact_Sheet_Executive_summary.pdf

UNODC. (2024a). *The online world drug report 2023* [Report]. https://www.unodc.org/unodc/en/data-and-analysis/wdr-2023-online-segment.html

UNODC. (2024b). *Perú: monitoreo de cultivos de coca 2023.* [Report]. DEVIDA. https://www.unodc.org/documents/crop-monitoring/Peru/Peru_monitoreo_2023_DEVIDA.pdf

UNODC. (2025). *The annual report questionnaire*. United Nations Office on Drugs. https://www.unodc.org/unodc/en/data-and-analysis/arq.html

Uscategui M, N. (1959). The present distribution of narcotics and stimulants amongst the indian tribes of Columbia. *Botanical Museum Leaflets, Harvard University*, *18*(6), 273-304.

Valencia, O. E., & Courtheyn, C. (2023). Peace through coca? Decolonial peacebuilding ecologies and rural development in the territory of conviviality and peace of Lerma, Colombia. *Third World Quarterly*, *44*(5), 1077-1097. https://doi.org/10.1080/01436597.2023.2175656

Valentine, J. L., Fremming, B. D., Chappell, R. H., & Stephen, P. M. (1988). Effects of extended feeding of decocainized Erythroxylon coca leaves on growth and selected organs in rats and rabbits. *Human Toxicology*, *7*(1), 21-26. https://doi.org/10.1177/096032718800700104

Van Dyke, C., Jatlow, P., Ungerer, J., Barash, P. G., & Byck, R. (1978). Oral cocaine: Plasma concentrations and central effects. *Science*, *200*(4338), 211-213. https://doi.org/10.1126/science.24895

Varona, M. E., Díaz-Criollo, S. M., Lancheros-Bernal, A. R., Murcia-Orjuela, A. M., Henao-Londono, G. L., & Idrovo, A. J. (2010). Organochlorine pesticide exposure among agricultural workers in Colombian regions with illegal crops: An exploration in a hidden and dangerous world. *International Journal of Environmental Health Research*, *20*(6), 407-414. https://doi.org/10.1080/09603123.2010.491855

Vee, G. L., Fink, G. B., & Constantine, G. H. (1983). Anorexic activity of cocaine and coca extract in naive and cocaine tolerant rats. *Pharmacology, Biochemistry and Behavior*, *18*(4), 515-517. https://doi.org/10.1016/0091-3057(83)90273-3

Viceministerio de Relaciones Exteriores. (2019). *Bolivia - encuesta nacional de uso y consumo de la hoja de coca en hogares 2009-2010 [national household survey of consumption and use of coca leaf 2009-2010]* [Report].

Vicepresidencia del Estado Plurinacional de Bolivia. (2025). *Catálogo de productos derivados de la hoja de coca*. https://drive.google.com/drive/folders/1VlAhBtFPwavsSjEj3N6OKokOqDbSJQQD

Villena, M., Vargas, E., Soria, R., Alarcón, A. M., & Gonzales, C. (1997). Efectos del consumo tradicional de hojas de coca sobre la respiración [Efectos del consumo tradicional de hojas de coca sobre la respiración]. En M. Villena Cabrera y M. Villena Cabrera y M. Sauvain (Eds.), *Usos de la hoja de coca y salud pública* (pp. 62-71). http://fi-admin.bvsalud.org/document/view/65g6j

Von Glascoe, C., Metzger, D., & Palomino, A. (1977). Are you going to learn to chew coca like us? *Journal of Psychedelic Drugs*, *9*(3), 209-219.

Wang, Y.-J., Huang, J.-P., Tian, T., Yan, Y., Chen, Y., Yang, J., Chen, J., Gu, Y.-C., & Huang, S.-X. (2022). Discovery and engineering of the cocaine biosynthetic pathway. *Journal of the American Chemical Society*, *144*(48), 22000-22007. https://doi.org/10.1021/jacs.2c09091

Warner, A., & Norman, A. B. (2000). Mechanisms of cocaine hydrolysis and metabolism in vitro and in vivo: A clarification. *Therapeutic Drug Monitoring*, *22*(3). https://doi.org/10.1097/00007691-200006000-00006

Watson, E. S., Murphy, J. C., ElSohly, H. N., ElSohly, M. A., & Turner, C. E. (1983). Effects of the administration of coca alkaloids on the primary immune responses of mice: Interaction with delta 9-tetrahydrocannabinol and ethanol. *Toxicology and Applied Pharmacology*, *71*(1), 1-13. https://doi.org/10.1016/0041-008x(83)90040-6

Weil, A. T. (1978). Coca leaf as a therapeutic agent. *The American Journal of Drug and Alcohol Abuse*, *5*(1), 75-86. https://doi.org/10.3109/00952997809029262

Wesam, R. K., Ghanya, A. N., Mizaton, H. H., Ilham, M., & Aishah, A. (2013). Assessment of genotoxicity and cytotoxicity of standardized aqueous extract from leaves of Erythroxylum cuneatum in human HepG2 and WRL68 cells line. *Asian Pacific Journal of Tropical Medicine*, *6*(10), 811-816. https://doi.org/10.1016/S1995-7645(13)60143-1

Wet, H. D. (2011). Antibacterial activity of the five South African Erythroxylaceae species. *African Journal of Biotechnology*, *10*(55), 11511-11514. https://doi.org/10.5897/AJB11.720

WHO. (1952). *Expert committee on drugs liable to produce addiction: Third report* [Technical Report Series N. 57]. World Health Organization.

WHO. (1954). *Expert committee on drugs liable to produce addiction: Fourth report* [Technical Report Series N. 76]. World Health Organization.

WHO. (1993). *Expert committee on drug dependence: Twenty-eighth report* [Technical Report Series N. 836]. World Health Organization.

WHO. (2023a). *The selection and use of essential medicines: Report of the WHO expert committee on selection and use of essential medicines, 2023 (including the 23rd WHO model list of essential medicines and the 9th WHO model list of essential medicines for children)* [Online]. World Health Organization. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.01

WHO. (2023b). *Traditional medicine. Questions and answers* [Online]. World Health Organization. https://www.who.int/es/news-room/questions-and-answers/item/traditional-medicine

WHO, & UNICRI. (1995). *Cocaine project* [Report]. World Health Organization.

Williams, N., Clouet, D. H., Missa, A. L., & Mule, S. (1977). Cocaine and metabolites: Relationship between pharmacological activity and inhibitory action on dopamine uptake into striatal synaptosomes. *Progress in Neuro-Psychopharmacology*, *1*(3), 265-269. https://doi.org/10.1016/0364-7722(77)90049-2

Williams, R. H., Maggiore, J. A., Shah, S. M., Erickson, T. B., & Negrusz, A. (2000). Cocaine and its major metabolites in plasma and urine samples from patients in an urban emergency medicine setting. *Journal of Analytical Toxicology*, *24*(7), 478-481. https://doi.org/10.1093/jat/24.7.478

Zambrano Calderón, K. V., & Vaca, G. H. M. (2002). Aspectos farmacológicos y socioculturales del consumo de hoja de coca en indígenas koguis respecto al consumo de cocaína en ambientes urbanos. *Revista Internacional de Psicología*, *3*(2). https://doi.org/10.33670/18181023.v3i02.16

Zapata Ortiz, V. (1944). Modificaciones psicológicas y fisiológicas producidas por la coca y la cocaína en los coqueros. *Revista Peruana de Medicina Experimental y Salud Pública*, *3*(2), 132-162. http://www.scielo.org.pe/pdf/rins/v3n2/a04v3n2.pdf

Zhu, Y.-L., Sun, M.-F., Jia, X.-B., Cheng, K., Xu, Y.-D., Zhou, Z.-L., Zhang, P.-H., Qiao, C.-M., Cui, C., Chen, X., Yang, X.-S., & Shen, Y.-Q. (2019). Neuroprotective effects of astilbin on mptp-induced parkinson's disease mice: Glial reaction, α-synuclein expression and oxidative stress. *International Immunopharmacology*, *66*, 19-27. https://doi.org/10.1016/j.intimp.2018.11.004