Guayusa

Ilex guayusa

Family: Aquifoliaceae

By Josef Brinckmann and Thomas Brendler

INTRODUCTION

Ilex guayusa is one of the 500 to 600 *Ilex* species[1] and belongs to the holly family (Aquifoliaceae) of shrubs and trees, which includes only two genera (*Ilex* and *Nemopanthus*).[2] While the taxonomic status of *Nemopanthus* species remains accepted by some authors, others now consider *Nemopanthus* species to be members of the genus *Ilex*.[3] *Ilex* species are distributed in tropical and subtropical to temperate regions, mainly in tropical Central and South America but also Asia.[2] The perennial *I. guayusa* tree, native to Bolivia, Colombia, Ecuador, Peru, and Venezuela,[4] is dioecious (male and female flowers occur on separate plants) and reaches about 10 m (32.8 ft) when cultivated and up to 25 m (82 ft) when unmanaged or wild.[5] Other authors give a range of 6-30 m (19.7-98.4 ft). Guayusa is fast-growing, and commercial harvesting of the leaves may commence about one year after planting, with increasing annual yields until leveling off with tree maturity at around five years.[6]

Domesticated in the pre-Columbian era, guayusa is now grown in traditional agroforestry systems by indigenous farmers of the western Amazon region. In recent years, scaled-up production of certified organic and fair trade guayusa leaf has linked some indigenous farmers in the Ecuadorian Amazon to a global market for sustainable herbs, helping to conserve biodiversity (prevent forest clearing) and improve traditional economies in rural and remote indigenous communities.[6] Emerging evidence suggests that traditional agroforestry systems support climate change adaptation because they enable measurably higher levels of carbon sequestration and tree diversity compared to other forms of cultivation.[7]

HISTORY AND CULTURAL SIGNIFICANCE

Ilex guayusa is known as *waysa*[7] or *guayusa* in Kichwa, a dialect of the Quechua language group, the latter also used by Spanish speakers,[8] and as *waís* in the Shuar language in Ecuador.[9] A standard common name for this species is not provided in the American Herbal Products Association's *Herbs of Commerce*, 2nd edition.[10] In his 1737 work *Genera Plantarum*, Swedish botanist Carl Linnaeus (1707-1778) assigned the genus name *Ilex*,[11] which was already the Latin name for the Mediterranean holly oak (*Quercus ilex*, Fagaceae), probably due to the similar glossy leaves.[12] German botanist Ludwig Eduard Theodor Loesener (1865-1941) assigned the Kichwa name guayusa as the species name, forming the Latin binomial *Ilex guayusa*, in his 1901 publication *Monographia Aquifoliacearum*.[13]

Archaeobotanical evidence suggests that guayusa has been used medicinally and traded since at least 500 BCE in the greater Andes-Amazon region.[5] The contents of a tomb dated to that time, found at Niño Korin in the Bautista Saavedra Province of Bolivia, included pouches of guayusa leaves as well as *Anadenanthera colubrina* (Fabaceae) along with specialized medical equipment (e.g., enema syringes and snuff trays) believed to have belonged to a medicine person of the pre-Incan Kallawaya society of traditional healers, descendants of the Tiwanaku culture.[14] Although cultivation may have begun earlier, evidence suggests that guayusa was grown extensively and processed by at least 350 CE.[15] In 1972, American renowned Harvard University ethnobotanist Richard Evans Schultes, PhD, (1915-2001) reported discovering the vestiges of an ancient guayusa plantation in Putumayo Department of southwestern Colombia, with tall trees that were hundreds of years old.[16]

A 1683 letter from Jesuit priest Juan Lorenzo Lucero to the Viceroy of Peru, Don Melchor de Navarra y Rocafull,

Guayusa *Ilex guayusa*
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described the drinking of a decoction of guayusa throughout the day by the indigenous Jivaroan peoples of Ecuador and Peru for the purpose of remaining awake for many nights at times when an enemy invasion was feared.[17] Seventeenth-century Jesuit missionaries planted guayusa in mission gardens and established commercial trade to highland Andean markets, including Quito.[18] According to Schultes, the Jesuits also established a market for guayusa leaf in Europe as a cure for syphilis, among other diseases.[19] With the expulsion of the Jesuits from the Spanish colonies in the 1760s, small-scale cultivation and regional trade were taken over by indigenous peoples, and guayusa is still found today in Ecuadorian village markets.[18] In 1894, anthropologist Charles Dolby Tyler wrote that guayusa, also known as "Napo tea," was the favorite beverage of the Záparo people, who lived along the Napo River in Ecuador. The Záparo drank the tea in the morning as an emetic to rid the stomach of undigested food. Tyler also noted their use of coca (*Erythroxylum coca*, Erythroxylaceae) leaf, which was chewed and mainly taken before long journeys.[20]

Shamans of the indigenous Shuar people in Amazonian Ecuador and Peru include guayusa in hallucinogenic herbal formulations, although it is a stimulant rather than a hallucinogen. For example, guayusa is combined with *Banisteriopsis caapi* (known by the local common name *ayahuasca*) and *Diplopterys cabrerana* (both in the family Malpighiaceae) and prepared as an aqueous decoction.[9] Guayusa tea is also reportedly used by Canelos-Kichwa people before and after drinking ayahuasca tea (i.e., the blend of *Banisteriopsis caapi* and other plants), as it is believed to mitigate the bitter taste of the ayahuasca, prevent hangover, and strengthen the ability to cope with the hallucinogenic effects.[21] As a daily ritual, men of the Jivaroan Achuar community in Ecuador and Peru drink aqueous decoctions of guayusa leaf, called *wayus*, before sunrise, and then vomit, for stimulating effects. Boys are taught how to vomit using a feather or finger, and they join the men in the daily ritual after puberty.[22,23]* A study looking at obstetrical practices of Canelos-Kichwa women living in communities along the Bobonaza River in the Pastaza Province of Ecuador, near the Peruvian border, found that guayusa tea is drunk for the purpose of reducing blood loss during menstruation, with concomitant avoidance of both salt and chili (*Capsicum* spp., Solanaceae) for one to three days. Postpartum, women are also given guayusa tea to drink in order to "prevent blood drying up inside her and thus cause other complications."[24]

In a study of traditional plant usage among the indigenous Kichwa people of Canton Loreto in Ecuador, guayusa was found to be the most used, harvested, and significant plant in daily life.[25] In another recent study that surveyed indigenous Shuar and *mestizos* about traditional ecological knowledge and medicinal plant diversity in Ecuadorian Amazon home gardens, guayusa ranked among the highest in importance. The study asserts that guayusa and other medicinal plants grown in these home gardens are ecosystem service providers that support human well-being, biodiversity conservation, and traditional knowledge in agroecosystems.[26]

CURRENT AUTHORIZED USES IN COSMETICS, FOODS, AND MEDICINES

In the United States, guayusa is marketed as a beverage tea for energy, similar to caffeine-containing leaves of other *Ilex* species such as yerba maté (*I. paraguariensis*) and yaupon (*I. vomitoria*).[27] It may also be used as a component of dietary supplement products, which require notification with the US Food and Drug Administration within 30 days of marketing if a structure-function claim is made.[28] In Canada, guayusa is regulated as a medicinal ingredient of licensed natural health products (NHPs), which require pre-marketing authorization from the Natural and Non-prescription Health Products Directorate (NNHPD).[29] At the time of this writing, two licensed NHPs in Canada list *I. guayusa* as an active ingredient.[30] In the EU, use of

* Although English botanist William Townsend Aiton (1766-1849) assigned the Latin binomial *Ilex vomitoria* to the related North American yaupon,[66] and both guayusa and yaupon have been used traditionally in indigenous vomiting rituals,[67] constituents that could be responsible for emetic action have not been identified in either species.[68]

Guayusa *Ilex guayusa*
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an extract of the leaves in cosmetic products is authorized specifically for skin-protecting function.[31] However, for oral ingestion, *I. guayusa* is presently classified as an unauthorized novel food in the EU. According to EU regulatory authorities, *I. guayusa* was not used as a food or food ingredient in the EU before May 15, 1997, and, therefore, a premarketing safety assessment under the Novel Food Regulation is required.[32]

MODERN RESEARCH

Largely seen as a stimulant traditional beverage among indigenous communities,[9,16,17,22] with some medicinal uses therein (e.g., to avoid postpartum complications; as a tonic, diuretic, flu remedy, mouth wash, and insect repellent; for dysmenorrhea, diabetes, venereal diseases, and weight loss[5,24,26,33-35]), guayusa only recently attracted interest from the research community for its health benefits. Published research on its actions and effects remains limited. Many recent academic theses investigating medicinal and cosmetic applications of guayusa[36-42] indicate new interest, likely also stimulated by international commercialization and regulatory requirements.[35,43,44] There are no known human clinical trial publications to date.

Plants in the genus *Ilex* are known to contain a significant number of secondary metabolites, such as xanthines, chlorogenic acid derivatives, flavonoids, and triterpenoids.[33,34,45,46] Wise and Santander (2018) provide a comprehensive summary of the composition of dried guayusa leaves, including total and free amino acids, chemical elements, nutritional values, and caffeine content.[47] Earlier research addressing the composition of guayusa focused on its high caffeine content (e.g., Lewis et al., 1991).[22] More recently, triterpenoids in guayusa leaf, specifically ursolic acid, have gained attention due to their antihyperglycemic, antibacterial, and antiparasitic effects.[33-35]

Ursolic acid is a known activator of the G protein-coupled bile acid receptor 1 (GPBAR1), which is involved in energy homeostasis, bile acid homeostasis, glucose metabolism, inflammatory response, cancer progression, and liver regeneration, giving guayusa a potential role in the management of diabetes and metabolic syndrome. Swanston-Flatt et al. (1989, 1991)[48,49] showed that guayusa had a hypoglycemic effect in normal mice and in mice with streptozotocin-induced diabetes. In addition, guayusa reduced hyperphagia (increased appetite), polydipsia (excessive thirst), body weight loss, and glycated hemoglobin. These results were confirmed by Stoyell-Conti et al. (2018),[50] who showed positive effects on metabolic, cardiovascular, and oxidative stress in mice with streptozotocin-induced diabetes. Espinosa Soto et al. (2015)[51] reported the presence of ursolic acid, which was confirmed by Chianese et al. (2019),[52] who determined a similar triterpenoid profile for *I. guayusa* and *I. paraguariensis*, as well as the presence of amyrin esters. They characterized amyrin palmitate, palmitoleate, and corresponding isomers as the primary constituents of the amyrin complex from both plants.

García-Ruiz et al. (2017)[53] identified a total of 14 phenolic compounds and five carotenoids in guayusa leaf, and

further showed high antioxidant capacity for blanched and untreated leaves. This antioxidant capacity was much reduced during fermentation. Pardau et al. (2017)[54] demonstrated protection from oxidative stress in the Caco-2 cellular antioxidant assay and anti-inflammatory activity in lipopolysaccharide-stimulated RAW 264.7 cells, and these effects were attributed to the phenolic mono- and dicaffeoylquinic acid derivatives in guayusa leaves. Cadena-Carrera et al. (2019)[55] studied the biological activities of guayusa leaf extracts using supercritical CO_2 as the solvent and ethanol as the co-solvent and showed antifungal activity against *Trichophyton rubrum*, *T. mentagrophytes*, *Microsporum gypseum*, and *M. canis*. Caffeine, squalene, and α-amyrin were the main compounds found; antioxidant activity varied with extraction technique, solvent, and conditions (e.g., pressure, temperature). Gamboa et al. (2018)[56] demonstrated an antimicrobial effect for an ethanolic extract of guayusa leaves, inhibiting *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Fusobacterium nucleatum*, bacteria implicated in chronic periodontitis. Both Tuquinga Usca (2013)[57] and Contero et al. (2015)[58] reported an estrogenic effect of guayusa in albino rats, both in terms of significantly increased estradiol levels and weight of reproductive organs.

Sequeda-Castañeda et al. (2016)[33] summarized a number of investigations of the safety of guayusa preparations and attest an excellent safety profile. No signs of hepatotoxicity were found in an in vivo hepatotoxicity model using Wistar rats. No acute toxicity was shown at 1,000, 500, 250, and 125 mg/kg ethanol extract in animals. Repeat doses were also found to be safe. Due to the high caffeine content, however, large quantities can affect the nervous system. Bussmann et al. (2011)[59] demonstrated a LC_{50} > 10,000 µg/mL for an aqueous extract and 300 µg/mL for an ethanol extract of guayusa leaves in the brine shrimp lethality assay. Kapp et al. (2016)[60] found guayusa concentrate to be negative in in vitro genotoxicity tests, including the Ames test and a chromosome aberration study in human lymphocytes. This confirmed previous results finding an LD_{50} > 5,000 mg/kg for female rats. A 90-day sub-chronic study at 1,200, 2,500, and 5,000 mg/kg/d of guayusa concentrate administered to male and female rats found effects comparable to those of caffeine, including weight loss, reductions in food efficiency and triglycerides values, increases in serum alanine aminotransferase, serum aspartate aminotransferase, and cholesterol, as well as adaptive salivary gland hypertrophy. Overall, no harmful effects specific to guayusa or its components were observed in any of the tested models.

Tea being made from guayusa (*Ilex guayusa*)
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ADULTERATION

Although adulteration with other related plants, such as yerba maté, is conceivable, adulteration of guayusa products is, so far, not known to occur. While there is a *European Pharmacopoeia* monograph for testing of yerba maté (Mate Folium PhEur 10.0),[61] which provides macroscopic, microscopic, thin-layer-chromatography (TLC), and high-performance-liquid-chromatography (HPLC) tests for confirming composition, identity, quality, and strength, no known monographs are available for guayusa or yaupon that provide identification methods for differentiating or ruling out admixing among the three related species.

SUSTAINABILITY AND FUTURE OUTLOOK

The International Union for Conservation of Nature (IUCN) assigns wild *I. guayusa* to the conservation category of least concern (LC), meaning that the species is not considered to be threatened. According to the 2019 IUCN report, "this species has a very wide distribution, large population, is not currently experiencing any major threats, and no significant future threats have been identified."[4]

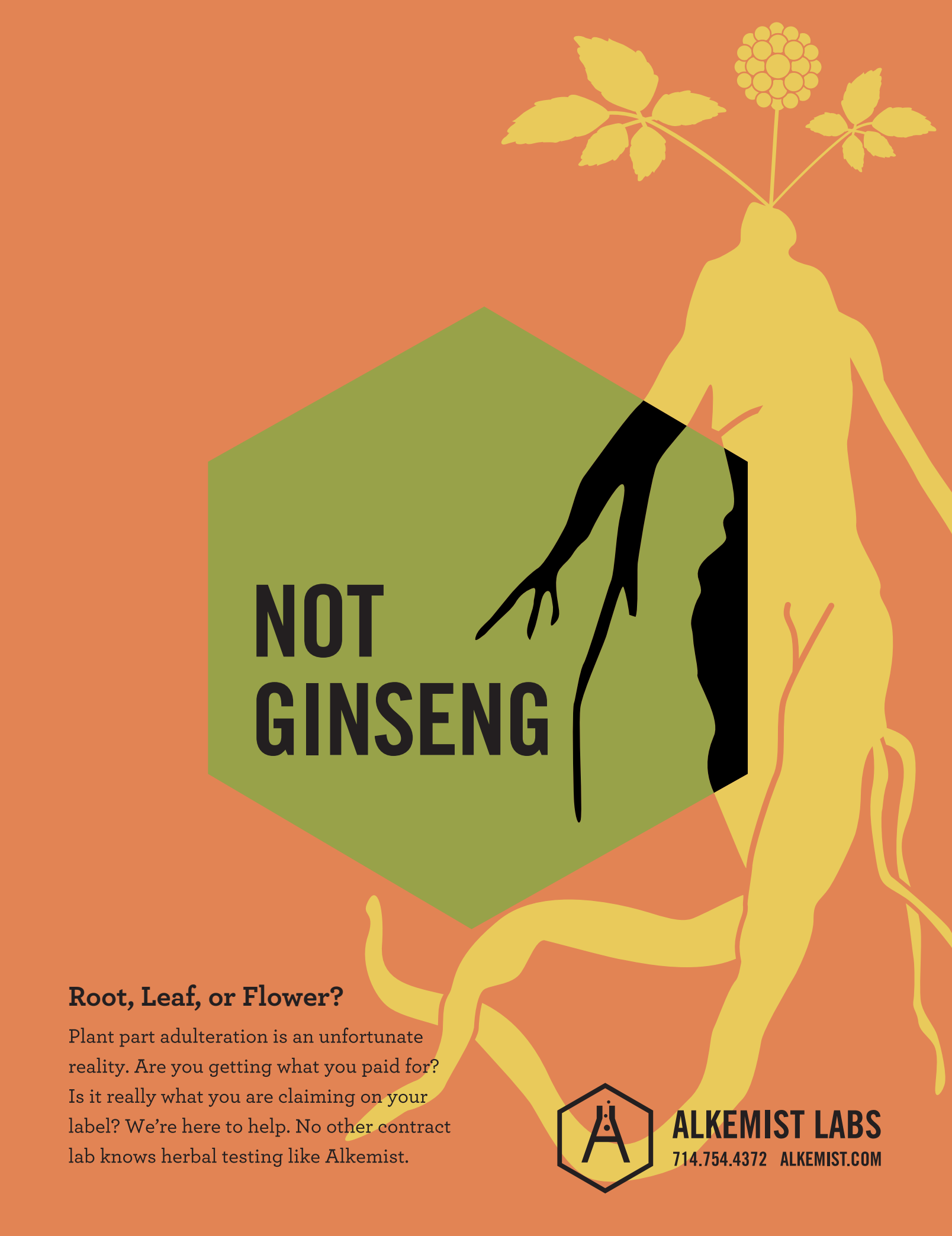
In 2009, the company RUNA (Brooklyn, New York) began to commercialize guayusa in Ecuador and, by 2017, had 477 hectares of cultivation area under US Department of Agriculture (USDA) National Organic Program (NOP) certification.[6] Today, NOP-certified guayusa operations in Ecuador include Asociación de Caficultores el Pangui, Fundación Chankuap "Recursos Para el Futuro," Greenmattersecuador CIA LTDA, Jumandipro S.A., Productos SKS Farms CIA LTDA, Rareeats S.A., Runatarpuna Exportadora S.A., and Tryskelwork Soluciones S.A.[62] One of these organic guayusa operations has also achieved economic and social sustainability certification through implementation of the Fair Trade USA standards: Runatarpuna Exportadora S.A. (Quito, Pichincha, Ecuador), which exports organic- and fair trade-certified guayusa to their North American counterpart, RUNA. Runatarpuna's guayusa farmers are situated primarily in Napo Province in the Ecuadorian Amazonian rainforest, and cultivate it within a multi-crop traditional agroforestry system along with cacao (*Theobroma cacao*, Malvaceae), coffee (*Coffea arabica*, Rubiaceae), and yuca (*Manihot esculenta*, Euphorbiaceae).[63] As opposed to mono-cropping, these traditional agroforestry practices are believed to mitigate some of the local effects of climate change and increase food security for smallholder farmers.[6]

RUNA is also a Certified B Corporation, audited under a certification standard that measures a company's social and environmental performance, public transparency, and legal accountability.[64] In 2018, RUNA's nonprofit arm, Runa Foundation, merged with PlanJunto Ltda to form a new organization called Aliados, whose mission is "to build resilient community business based on biodiversity in the Andes and the Amazon — and connect them to markets across the globe." A current Aliados venture involves a partnership with Ally Guayusa, an indigenous-owned guayusa export association composed of 140 farming families operating 40 hectares of organic guayusa production.[65]

Before RUNA was founded in 2009, the use of guayusa leaf was relatively unknown outside of the Amazon. The socially conscious and responsible manner in which RUNA has sought to bring guayusa to the world is admirable. In collaboration with the local farming communities, RUNA has invested in building the foundation for a guayusa market that is ecologically, economically, and socially sustainable. However, Krause and Ness (2017) caution that guayusa production is still a niche agroforestry experiment and that the sustainability initiatives, such as fair trade and organic standards and certifications, so far "only provide partial solutions for protecting ecosystem services in the Ecuadorian Amazon." Growing popularity and success of guayusa in the global market may present the risk of its becoming a new monoculture cash crop that could displace diverse agroforestry systems.[6] HG

Declaration of Interest

The authors declare that they have no conflict of interest and no affiliation with the Runa organizations.



Root, Leaf, or Flower?

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