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Assessing the History of Safe Use of Guayusa

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Abstract Guayusa (*Ilex guayusa* Loes.) is a herbal tea that has been consumed for centuries as a traditional food in western Amazon regions where it is now valued as an antioxidant and a stimulant agent. Currently there is intense commercial activity to expand the consumption of guayusa as a healthy energy drink in Europe, where it is classified by law as a novel food. European Union novel food legislation permits traditional foods to be placed on the market if a history of safe use in a non-EU country can be established. However, a scientific assessment of the 'safe' use of guayusa is lacking. This study investigates the safety of guayusa consumption, analysing provincial hospital admissions data; national disease register data; national toxicology agency call centre data; and national food safety authority data. In doing so we present a crucial analysis for the novel food premarket risk assessment of dried guayusa leaves, based on the well-established use of this traditional food in Ecuador. Within a three-year period there was one minor adverse effect reported nationally, related to the stimulant properties of guayusa. However, there were no hospital presentations, no product safety notifications and no disease register records of guayusa-related illness. Comprehensive records of unrelated food safety risks demonstrate that Ecuador's surveillance and reporting system has sufficient rigour to identify risks should they exist. We conclude that there is a history of safe use of guayusa in Ecuador. Establishing safe guayusa consumption is an important milestone for the authorisation of dried guayusa leaves as a novel food with claimed health benefits in Europe. Consequently, this study has significance for international product development of guayusa as an antioxidant energy drink.

Keywords: *guayusa, novel food, food safety, toxicology, traditional food, stimulant, antioxidant*

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1. Introduction

Guayusa (*Ilex guayusa* Loes.) has been consumed as a herbal tea for hundreds of years in western Amazon regions including Colombia, Ecuador, Peru and Bolivia, and ethnographic studies broadly report claims of its stimulant and health properties [1,2,3]. Further laboratory studies of guayusa's chemical composition provide scientific support for those claims based on its caffeine, amino acid and antioxidant composition [4,5,6]. Considered to be a domesticated plant, its reproduction is only known to occur through human propagation from hardwood stem cuttings. However the cultivation of guayusa plants has geographically contracted in modern times, now predominantly occurring in Ecuador [2]. Guayusa leaves are principally produced from traditional agroforestry systems and are traditionally consumed by indigenous Amazon peoples [7,8]. This means that establishing its safe use and expanding its consumption internationally, may have significant positive impact, not only for the economic resilience of indigenous people in the Amazon, but also to reinforce environmental and social values that traditional agroforestry systems, support [9,10,11,12,13].

The Amazon Napo province of Ecuador is the world's largest producer and exporter of guayusa. Based on the production capacity of Ecuador's two significant guayusa exporters, annual guayusa production in 2017 exceeded 100 tons (Santander D. E., 2018, unpublished data). The domestic consumption of guayusa in Ecuador is much more difficult to assess. Guayusa products are sold in Ecuador's largest supermarket chains, however, an unknown but anecdotally much larger quantity of guayusa is sold informally through unregulated vendors at fresh produce markets for consumption in homes or for sale as beverages in restaurants. This domestic consumption of guayusa is anecdotally reported to be highest in the Napo province. It is offered in most restaurants and cafes, and it is heralded as an emblematic product of the region [8,14].

Internationally, a European Union novel foods regulation (EU) 2015/2283 came into force on 1 January 2018, legislating for the authorised market placement of traditional foods from non-EU countries on the basis of a history of safe food use [15]. European markets present a high priority target for the international commercial development of guayusa products from Ecuador. In 2017,

under prior legislation the Commission of the European Communities received at least two applications for authorisation of products containing Ecuadorian guayusa. Consequently, since December 2017 the Union List of Novel Foods has included one authorisation related to guayusa, but limited to an "aqueous extract of dried leaves of *Ilex guayusa*" and only for use as a "herbal infusion" [16]. Guayusa's traditional use, its claimed health benefits and its presence in novel food applications for consumption in Europe, highlight an urgent need for an assessment of its safe use, as a part of its premarket food safety risk assessment.

Despite its well-documented use in Ecuador, its 'safe' use remains poorly document, as scientific evaluations of the safety of guayusa consumption as a beverage are sparse. Guayusa concentrate was found to be negative in *in-vitro* genotoxicity tests in human lymphocytes, and was also found to have an LD_{50} of >5,000 mg/kg in female rats [17]. Further toxicology studies on rats have reported negative findings [18]. In brine shrimp, the LC_{50} for an aqueous extract of guayusa was assessed to be greater than 10,000 µg/mL [19]. Importantly, a double-blind crossover randomized human clinical trial of 12 adult males compared the CNS effects of guayusa extract and synthetic caffeine, each dose containing 200 mg of caffeine. The study reported no adverse effects and also reported that the effect of guayusa extract on heart rate, blood pressure and epinephrine were similar to, or less than the effect of synthetic caffeine [20]. Human pharmacokinetic studies of absorption, distribution, metabolisation and excretion are absent. Neither have public health system records, hospital records nor food safety notifications ever previously been used to assess the safety of guayusa consumption.

Much guidance exists for the safety assessment of novel foods, but primarily where a history of safe use is absent. See [21] for a recent review of guidance articles for detailed premarket risk assessment of novel foods. However approaches to the safety assessment of those novel foods having a history of safe use, must differ from novel products derived from the first time use of technologies. This is because of the unfeasibility and limited relevance of creating artificially high degrees of toxicological exposure, requiring food consumption that is orders of magnitude higher than represented in the history of safe use [22]. The European Training and Assessment Foundation (ETAF) group has argued that there is "no further information required with regard to safety", if the product is a "traditional food or an extract substantially similar to traditional food" [23]. [24] further argues that botanicals could be allowed in food, based on "long-term use" without "expert judgment of safety and efficacy". [25] also agrees that if a history of safe use can be established for a novel plant food, then a risk assessment may be concluded without additional *in-vitro*, animal, or human safety trials.

With such acceptance of shortened premarket safety assessments for novel foods having a history of safe use, heavy emphasis must be placed on establishing how 'safe' that use is. While many whole foods gain societal acceptance as being safe simply because of a long history of use [21], current public attention to the safety of novel foods demands a more rigorous approach. As such, established methods for post-market surveillance of authorized novel foods may be useful in scientifically evaluating the safety of novel foods having a history of use. Howlett et al. [22] have detailed a rigorous set of post-market surveillance methodologies, in particular to identify food-related health effects. Specifically, they highlight disease registers, contact centres and epidemiological studies as ideal methods for the assessment of health effects of novel foods.

This study assesses the safety of guayusa use in Ecuador because of the size of its export production and the predominance of guayusa consumption in its Napo province. We use the data of a national disease register and a national toxicology call centre to characterise the health risk of guayusa. We use food product safety data from a national food safety authority to assess the safety of guayusa products offered for sale nationally in Ecuador. We also consider hospital and day clinic patient presentations associated with guayusa consumption, with a view to assessing the necessity and feasibility of future epidemiological studies. In doing so, this study analyses the safety of both the unregulated sale of dried guayusa leaves through informal vendors, and the regulated sale of guayusa products through formal supermarkets. Special consideration is given in this study to assessing the potential toxicology of guayusa due to its metabolically significant caffeine content [20,26].

The objective of this study is to scientifically assess whether there is a history of safe use of guayusa in Ecuador. This study tests the hypothesis that guayusa consumption in Ecuador is not meaningfully associated with illness, nor is it associated with product safety notifications. This work is significant for the development of guayusa as an international export commodity and novel food. Our results are an important milestone to establishing the safety of guayusa consumption as a herbal tea that has antioxidant and stimulant properties.

2. Materials and Methods

This study assesses the safety of guayusa use at national and provincial levels in Ecuador. The collection of baseline safety data is a logical precursor for the design of future studies to characterise the potential nutritional value of guayusa consumption, in Ecuador and in EU consumer markets.

At a national level, this study analyses three Ministerio de Salud Pública [Ministry of Public Health] datasets. One dataset is of the Subsecretaría Nacional de Vigilancia de la Salud Pública [National sub-secretariat for public health surveillance], SIVE-ALERTA is a national disease register which records the incidence of food-borne illness reported by hospitals, medical clinics, and other medical services providers. A second dataset is of the Centro de Información y Asesoramiento Toxiocológico [Center for toxicological information and advice] (CIATOX), which is a toxicology call centre and the national agency responsible for processing toxicological information on food, medicines and natural products, for the delivery of advice and the protection of human health from toxic agents. The third dataset is of the Agencia Nacional de Regulación, Control y Vigilancia Sanitaria [National

Agency for Sanitary Regulation, Control and Surveillance] (ARCSA), which documents public health notifications associated with supermarket food products. ARCSA is the national agency responsible for surveillance and control to protect human health from risks borne from products for human consumption. The three datasets therefore address both the public health risk of food-borne illness linked to specific supermarket food products, and the unregulated sale of fresh guayusa leaves at markets. All datasets covered a three-year period ending in 2017.

At a provincial level, data is also drawn from the admissions system of the José María Velasco Ibarra Hospital (JMVIH), located in the city of Tena, Napo province, to identify hospital admissions, day clinic visitations or ambulance service uses resulting from guayusa consumption. JMVIH is a public hospital and is the largest health system actor in the Napo province, a region containing over 100,000 people [27] and one that is recognised as the having the highest level of guayusa consumption in Ecuador [14]. Hospital data covered a period of three years ending in 2017.

Quantitative data from the SIVE-ALERTA, CIATOX, ARCSA, and JMVIH were supplemented by seven semi-structured interviews with key personnel from those agencies. The focus of the interviews was to further interrogate public health risks and priorities, and specifically to understand whether public health system actors had prioritised or responded to guayusa consumption as a health risk.

In addition to collecting data on guayusa consumption, data on known toxicological hazards were addressed, along with known sanitation risks from supermarket products such as shellfish. These known public health risks were included to assess whether the Ecuadorian public health surveillance and reporting system has sufficient sensitivity as an instrument to establish the safety of guayusa use. Estimation of margin of exposure and statistical calculation of absolute risk and prevalence risk ratio is handled in the discussion of this study.

3. Results

3.1. Regional Incidence of Guayusa-Associated Illness

The admissions system of JMVIH has recorded within the last three years no day clinic, emergency department, hospitalization or ambulance transportation cases related to patients that have experienced poisoning or illness caused by guayusa food products, nor the guayusa plant itself. During interviews, a senior member of medical staff with a minimum three year employment history in the hospital noted that "*durante el tiempo que he trabajado en este hospital, no he visto ningún caso relacionado con guayusa* [during the time that I have worked at this hospital, I have not seen any cases related to guayusa]". Furthermore they commented that "*sería necesario ingerir grandes cantidades de guayusa para producir cualquier síntoma en humanos y de ser así, no habría posibilidad de mortalidad* [it would be necessary to ingest large quantities of guayusa to produce any symptoms in humans and if so, there would no chance of mortality]". While anecdotal, these comments are consistent with the absence of guayusa-associated hospital admissions at JMVIH. They are also consistent with the incalculably high LD_{50} and LC_{50} for guayusa extracts in rats and invertebrates, respectively [17,19].

3.2. National Incidence of Guayusa-associated Illness

Over a three-year period from 2015 - 2017, the SIVE-ALERTA database of the national disease registry recorded no food borne disease cases, including microbial disease and toxicological effects, associated with guayusa consumption. This national disease register has recorded 9,810 cases over a three-year period, with over 8,000 of those cases being foodborne diseases. The database of the call centre and national control agency for toxicology, CIATOX, recorded a single call for assistance, where a 31 year old female experienced mild hyperactivity and insomnia following the ingestion of guayusa as a beverage. Symptoms resolved quickly without medical treatment. This single reported adverse effect is consistent with the known caffeine composition of guayusa, which like coffee has a metabolic stimulant effect [20]. CIATOX records covered a three-year period from 2015. Each month the CIATOX call centre receives 700 phone calls relating to 500 suspected toxicology cases. Total caseload in 2017 was 6,000 cases.

3.3. Public Health Notifications

Over a three-year period from 2015 - 2017, the national food safety authority, ARCSA, issued 172 public health notifications related to food products and health supplements for sale in Ecuador. Seventy-five notifications related to the absence or termination of sanitary registration. Other common causes for public health notifications include the identification of microbial contamination such as *Salmonella* and *Listeria*, or the identification of heavy metal contamination such as mercury and lead. No product containing tea (*Camellia sinensis*) or herbal tea product (including *Ilex guayusa*) is listed in any such notification.

4. Discussion

This multi-dataset risk assessment of guayusa consumption demonstrates at provincial and national levels, that adverse effects associated with the consumption of guayusa are exceptionally rare. There is only one minor, naturally resolving adverse effect reported over a three-year period. Adverse effects or illness have neither been recorded by the hospital at the centre of the region of highest guayusa consumption, nor have they been recorded in Ecuador's national disease register. Furthermore, this study shows that there have been no national safety authority notifications of sanitary threats such as microbial or heavy metal contamination over a three-year period. This predominant absence of illness associated with guayusa consumption occurs within the context of large-scale guayusa consumption as an emblematic beverage. There is firm confidence in these results because of the comprehensiveness of the

national health surveillance and reporting programs, carried out by a system of provincial and national public health system actors. These toxicology, product safety and hospital presentations data quantitatively reinforce the strong national anecdotal awareness that there is a history of safe use of guayusa in Ecuador.

Where a history of safe use can been demonstrated, further pre-market risk assessment of novel foods is not recommended [22,23,24,25]. Furthermore, such a negligible incidence of adverse effects from guayusa consumption renders epidemiological approaches to disease risk assessment, such as calculation of relative risk or prevalence risk ratio statistically invalid. While a qualitative risk assessment based on likelihood and severity of risk is mathematically possible, the existence of one minor adverse effect across a population of 14.5 million people over three years can only lead to a conclusion of negligible risk. This negligible risk associated with guayusa consumption is consistent with a view that the pre-market risk assessment of guayusa can be concluded, with no additional *in-vitro*, animal or human trials, as recommended by [25].

It is acknowledged that this study has not addressed the possibility that there are very minor adverse effects of guayusa consumption that would not result in self-reporting to a toxicology call centre, presentation at a hospital or medical clinic, or reporting to a national disease register. However, there is no anecdotal perception of cryptic minor illness resulting from guayusa consumption in Ecuador. In the conduct of this study, one participant went as far as to refer to the authors as "un poco loco [a little crazy]" for investigating the public health risk of guayusa consumption. An interviewee was more expressive, stating that "*guayusa no podría causar ninguna enfermedad* [guayusa could not cause any illness]". Universally, study participants held the view that there is no measurable health risk associated with guayusa consumption.

5. Conclusions

We conclude that there is a history of safe use of guayusa in Ecuador. This usage began in antiquity and continues across a large modern consumer market in Ecuador today. This conclusion is consistent with previous negative findings of *in-vitro* [17], animal [18,19] and human [20] toxicology studies of guayusa extract exposure. We hold the view that with further chemical compositional analysis of guayusa, a strong case could be mounted for the acceptance of dried guayusa leaves, under new European Union novel food legislation covering traditional foods. That legislation places heavy importance on the demonstration of a history of safe use and on the analysis of chemical composition. Therefore it presents a feasible avenue for guayusa producers to pursue the internationalization of Ecuadorian guayusa as an antioxidant stimulant herbal tea.

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Statement of Competing Interests

The authors have no competing interests.

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