Biological Activity of Sacha Inchi (Plukenetia volubilis Linneo) and Potential Uses in Human Health: A Review

Running title: State of Art of Sacha Inchi

Denny Miley Cárdenas Sierra¹§, Lyz Jenny Gómez Rave² and Javier Andres Soto¹§*

¹Universidad of Santander, Faculty of Health Sciences, BIOGEN Research Group, Avenida 4 calle 10N-61, 540001 Cúcuta, Colombia
²Institución Universitaria Colegio Mayor de Antioquia, Faculty of Health Sciences, Bioscience Research Group, Tv. 78 #65 - 46, 050001 Medellín, Colombia

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SUMMARY

Sacha inchi (Plukenetia volubilis Linneo) is an ancestral plant originating in the Amazon jungle that has been adopted as a food source due to its high nutritional value, which has gradually been attributed with potential benefits for human health. Diverse prospective studies have evaluated the effect of consuming components from the plant, derivatives from its seeds, leaves and shell on preventing the risk of cardiovascular disease, chronic inflammatory disease, dermatitis and controlling tumor proliferation, especially given its recognized high content of essential fatty acids, phenolic compounds, and vitamin E, showing antioxidant, hypolipemic, immunomodulation, and emollient activity, as well as the capacity to remove heavy metals from aqueous solutions. This review offers a complete description of the information existing on the use and biological activity of P. volubilis L., based on its essentially lipid components and evidenced on its use in the field of human health, in prevention, therapeutic, and nutritional contexts, along with industrial uses, making it a promising bioresource.

*Corresponding author:
E-mail: jav.soto@mail.udes.edu.co
§Both authors contributed equally
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INTRODUCTION

The genus *Plukenetia* has a wide geographical distribution, especially in Central and South America, being present from the Antilles to Bolivia. Sacha inchi (*Plukenetia volubilis Linneo*) is a native plant to the Peruvian jungle that belongs to the Europhorbiaceae family, which encompasses 300 genera and 7500 species (1). It is cultivated at an altitude of 200 to 2000 m.a.s.l (2,3) and its growth is conditioned to different geoclimatic aspects (Fig. 1).

The antiquity of the crops and the importance of this plant are evidenced in the archaeological findings of pre-Inca utensils (4), and throughout history several events have brought to the fore the relevance of this plant on a social and industrial level (Fig. 2). Its common name in the native Quechua language means false (Sacha) peanut (Inchi), given its use as an edible nut initially by the pre-Inca Chanca and Mochica-Chimú indigenous tribes. It is currently cultivated in Asian countries, like Thailand, China, and Vietnam (3,5-8), as well as in Central and South America where, in addition to representing a nutritional alternative, it has become an opportunity of economic development (5).

It is known as mountain peanut, sacha peanut, or Inca nut (6,7,13). Its seed provides polyunsaturated fatty acids, like alpha-linolenic (ALA) and linoleic (LA); bases of omega 3 and 6, respectively (6), gamma and delta tocopherols; natural forms of vitamin E, known for its antioxidant action and antitumor potential (14-19).

To date, positive outcomes have been recognized from consuming the plant or the components present in the seed, shell, and leaves. It is worth highlighting its contribution of energy and proteins, generation of lipid mediators with immunomodulation activity, regulation of cholesterolemia, brain function, and blood pressure (13,21-23), and antioxidant and antitumor potential (24-28). Due to the aforementioned, it is relevant to explore in detail the benefits of this Amazon plant.

The possibility of having access to such benefits is facilitated due to industrial extraction processes, mainly based on treating oily fraction by using pure liquid CO₂, obtaining a sample rich in omega-3 and significant impact on the original composition (29). Bearing in mind the relevance of this promising plant in benefit of human health (30), this review offers a description about the state of the art regarding Sacha inchi, with special emphasis on its biological activity, the characteristics of its components and nutritional usefulness.
COMPOSITION OF THE PLANT

The seed extract is predominantly constituted by lipids (35 %-60 %), represented in polyunsaturated fatty acids (PUFA), like alpha-linolenic acid or ALA (C18:3, ω-3) (47 %-51 %) and linoleic acid or LA (C18:2, ω-6) (34% - 37%) (23), in addition to, monounsaturated fatty acids, like oleic acid (~ 9.5 %); saturated fatty acids, like Palmitic acid (4.4 %) and stearic acid (2.7 %), proteins (25 %-33 %); and other minority compounds, like vitamin E in its α- Tocopherol (50-114 mg/g of oil) and δ-Tocopherol (30-125 mg/g) forms; flavonoids; secoiridoids, lignans, phenols, campesterol, stigmasterol, β-sitosterol, and minerals (6,7,14,15,31-34).

However, PUFA content could be even higher, representing around 93 % of the fatty acids, especially at the expense of essential fatty acids, like ALA and LA, a key fact that differentiates it from other oleaginous plants of great interest, like the olive tree, whose oil contains ω-3 and ω-6 fatty acids in the order of 1 % and 9 %, respectively. This availability seems to vary according to the crop zone, as shown by chromatographic characterization of the oil obtained from certain regions of Ecuador, where the linoleic (C18:2, ω-6) and linolenic (C18:3, alpha isomer, ω-3) acids constitute the majority lipid component, with the latter being even significantly greater than that registered for oil from other plant species, like palm, corn, soy, and sunflower (22). Likewise, the compositional analysis of the Sacha inchi seed cultivated in the department of Putumayo, Colombia, reveals a predominantly lipid content (42.75 %±0.5 %), within the range described for the plant of Peruvian origin, where 83.3 % of such corresponds to polyunsaturated fatty acids, with a very similar content of monounsaturated and saturated fatty acids of 9.4% and 7.3 %, respectively, as well as protein (29.85 %±0.085 %) (21).

The content of unsaturated fatty acids in the lipid component of the seeds also varies inversely with temperature; thus, analysis of plants from Peru and China within a temperature range from 8-35 °C evidenced a significant increase (*P <0.05) in the unsaturation index during the cold season (18.2 °C on average), at the expense of oleic (C18:1, ω-9) and alpha-linolenic (C18:3, ω3) acids or ALA, without variation for the linoleic acid (C18:2, ω-6). Seventeen genes were found responsible for the production and accumulation of unsaturated fatty acids in the seeds during the different development stages of the plants, from the pollinized flower to the mature seed (a process naturally requiring 112 days). Such content was duplicated, going from 41.3 % during week four of development to 92.6 % during the ripe state, where three genes are apparently responsible of this increase, namely SAD-2 (Stearoyl-
acyl-carrier protein desaturase), FAD2-2 (Oleate desaturase), and FAD3 (Linoleate desaturase) (35).

Vašek et al. (3) conducted a research in 2017 looking to characterize the genetic diversity and population structure in 169 samples of *P. volubilis* L. from the Peruvian Amazon, performing 11 combinations of primers and the Amplified Fragment-Length Polymorphism method (AFLP). Although it was not possible to confirm a direct relationship between the plant’s genetic diversity and the geographic location, this work made it possible to demonstrate the presence of nine genetic clusters corresponding to the same number of geographic sites analyzed in the San Martín region; thereby, considering the existence of distinct isolated subpopulations for this plant under the hypothesis of a possible anthropogenic influence modulating such selection (3).

The integrity of the plant’s components is a significant aspect promoting the affordability of Sacha inchi for human use and consumption. Among the preservation strategies to protect the crop from microbiological contamination and pests attack on seeds and fruits there is gamma irradiation (an alternative to chemical or thermal treatment of the plant), with high capacity for penetration city and low affectation of plant’s composition without emitting residues (5,36). Gutiérrez et al (5), researchers from the Food Science and Technology Institute (ICTA) at the Universidad Nacional de Colombia recently analyzed plant properties from oils extracted from Sacha inchi seeds (*P. volubilis* L.) exposed to gamma radiation, like content of fatty acids, tocopherol, peroxide value, acidity and time of oxidation induction, among others, concluding the existence of minimum affectation of these through such intervention, reflected in diminished content of gamma and delta tocopherol by 6.4 % and 5.2 %-6.4 %, respectively, as well as time of oxidation induction (although within that stipulated by the Peruvian norm), observations that support the fact that the moderate use of radiation (between 1 and 5 kGy) would allow the physical-chemical features of the plant to be maintained (5).

Interestingly, the oily composition of the seeds is preserved after industrial fractionation processes, favoring its availability for human consumption (15,29). Implementation of new processes like Time-Domain Nuclear Magnetic Resonance (TD-NMR), offers an optimization of the oily components analysis as alternative to the standard process of continuous extraction with organic solvents (Soxhlet method), without affecting the plant structure and allowing repeated measurements (37). Nuclear Magnetic Resonance analysis highly correlates with other approaches, like gas chromatography with flame ionization detector, which allows an
accurate analysis of the content omega-3 essential fatty acid contents, even in oils enriched with omega-6 ($R^2 = 0.995$ to 0.999) (38).

Likewise, the oxidative stability and concentration of essential fatty acids like omega-3 from the oily plant industrially encapsulated in ovalbumin and polysaccharide biopolymers is maintained from 1 to 1.79 years at room temperature (25 °C), a value that can be doubled with a reduction of only 5 °C (3.29 years at 20 °C) and even up to 17 days at high temperatures like 50 °C (39,40).

**PHYSIOLOGICAL EFFECTS OF THE SACHA INCHI PLANT**

Sacha inchi (*Plukenetia volubilis*) is a plant with a great agroindustrial potential since it contains omega 3, 6 and 9, thus conferring a high nutritional value. This plant is a bioresource that can be positioned in various market segments such as dietary supplements, functional foods, cosmetics and personal care, as well in medicinal approaches, not just for the content of fatty acids but its other bioactive components as it is summarized below.

**Cardioprotective and immunomodulation activities**

Since the early 20th century we have known of the dietary essentiality of fatty acids, like linoleic (ω-6) and alpha-linolenic (ω-3) for humans and other animals (lack of enzymes capable of synthesizing them) (41). Experiments developed by Burr and Wesson in rats (1930 and 1931) (42) revealed the relevance that lies in the physiological functions of fatty acids, like generation of energy, plasma membrane fluidity, signal transduction, and generation of bioactive metabolites, like prostaglandins, thromboxanes, leukotrienes, lipoxins, resolvins, maresins, and neuroprotectins, among others (43-45).

As mentioned before, it has been determined that PUFA content like omega-6 (linoleic acid) and omega-3 (α-linoleic acid) in Sacha inchi seeds is above 80%. These biomolecules are involved in the conformation and fluidity of the plasma membrane as well as in immune functions through the genesis of prostaglandins to mediate inflammatory response; also in cholesterolemia, brain function, and blood pressure, according to ALA deficient animal models (13). Additionally, the aging process leads to reduce the activity of desaturase enzymes that along with elongase are responsible for the synthesis of long-chain fatty acids (41), affecting lipid composition and function of the neuronal membrane, whose content of arachidonic and cervonic acid (known as DHA) depend on said hepatic synthesis (46).
It is remarkable the observation between the decrease of the LA/ALA index present in the *P. volubilis* L. oil (lower than one), and the reduced risk of suffering biological events such as cardiovascular disease, neoplasia, severe depression, chronic inflammatory and autoimmune diseases, given the relationship of these pathologies with the presence of proinflammatory cytokines, like IL-1 and leukotrienes like LTB4; the last derived from the consumption of omega 6 fatty acids. The aforementioned stems from the establishment of an optimal range for the rate n-6/n-3 fatty acids from 1:1 to 4:1, recommended for their general equilibrium from the human diet (47,48).

Gonzales *et al.* (49) evaluated the availability of omega-3 fatty acids in 12 healthy human individuals from 20 to 55 years of age (paired by gender) after consuming 10 or 15 mL of Sacha inchi oil, revealing a maximum ALA peak 4 h after intake, which was not detected in individuals consuming another vegetable oil. The maximum plasma concentration post-intake of this fatty acid was significant, at (2.84±0.36) mg/mL in women and 0.94 ± 0.57 mg/mL in men, also observing increased DHA, which reached concentrations of (2.60±0.84) and (1.00±0.38) mg/mL in women and men respectively, findings that contrast with those obtained from individuals who consumed another plant oil (49). Another study conducted during four months with 30 people showed that the permanent consumption of Sacha inchi oil, despite causing incipient nausea that decreased during the course of the study, is safe in terms of side effects at the renal or hepatic level, in addition to its effectiveness, given the 10 % increase in plasma HDL level after its consumption during four consecutive months (50).

Regarding to chronic inflammatory diseases, it has been reported that omega-3 fatty acids exhibit potent immunomodulation activity attributed to the amount and type of eicosanoids derived by its consumption. This potential would fit for *P. volubilis* L. since its composition is based primarily on the content of the PUFAs (21-23). For instance, eicosapentaenoic acid (EPA) (ω-3) competes enzymatically with arachidonic acid (ω-6) for the cyclooxygenase and lipoxygenase paths in the synthesis of prostanoids and leukotrienes, leading to diminished Prostaglandin E2 (PGE₂), Thromboxane A2 (TXA₂) and Leukotriene B4 (LTB₄) levels, involved in the processes of platelet aggregation, vasoconstriction, induction of inflammation, chemotaxis, and leukocyte adhesion.

It has been reported that an optimal equilibrium between omega-6/omega-3 fatty acids in diet should be ranked at or near to 1, as the one naturally found in *P. volubilis* L. It has identified an unbalancing of such index in western countries, reaching 15/1 to 16.7/1, (51); even in the European Union, where the analysis of essential PUFA (LA and ALA) intake
reveals that 52 and 77 % of this countries adequately consume LA and ALA, respectively; however, in some population groups, like lactating women, adolescents, and the elderly, the intake of these essential molecules is considered inadequate (45). Such is the effect of this balance between essential fatty acids that a four-fold reduction in this index (4/1, ω-6/ω-3) reduces - in turn and extraordinarily - mortality associated with cardiovascular diseases by up to 70 %, as well as regulating the proliferation of tumors in patients with colorectal carcinoma when the index falls by almost eight times (2.5/1), in addition to a lower risk of developing other types of neoplasms, such as breast cancer (52,53) as will be discussed ahead.

Likewise, a moderate index below 5/1 between ω-6/ω-3 fatty acids favors the control of inflammation in patients with rheumatoid arthritis and asthma, conferring a determinant role to the balance of PUFA in the human diet in terms of maintenance (or preservation) of the state of health (51), all of which highlights the relevance of the contribution of omega-3 fatty acids from sources like Sacha inchi in the human diet.

Although the protein content of *P. volubilis* L. seeds is approximately half that of lipids, said content has also exhibited anti-inflammatory properties, inhibiting by 78.13 % the denaturation of albumin at 70 °C, with the advantage of its *in vitro* stability after treatment with pepsin and pancreatin (reflecting gastric and duodenal digestion, respectively), resistance that favors the conservation of its biological properties after consumption (54).

**Antioxidant activity**

The composition and the antioxidant potential of the tannin-type polyphenols in the seed and also in the residual cake have been evaluated after extracting the oil by cold pressing in samples of Sacha inchi from the city of Tarapoto in northern Peru. A higher content of total polyphenols and tannins was found in the hydrophilic phase of the cake, consistent with its ability to protect against oxidative damage, as well as a greater inhibition of hydrogen peroxide and a marked reduction in ferric to ferrous ion activity (taken as standard the catenin antioxidant), which was 14 and 29 times higher with respect to the hydrophilic and lipophilic phases of oil, respectively (24).

The effect of dietary consumption of essential fatty acids ω-3 has been carefully evaluated in a murine model in terms of generation of new long-chain PUFA molecules, the activity and expression of liver desaturations and in the control of oxidative stress. In this work, male Wistar rats consuming oils from five plants with differential alpha-linolenic acid content, as the only source of lipids in the diet, were studied. Animals fed with Sacha inchi oil showed
a notable reduction of the \( \omega-6/\omega-3 \) LCPUFA radius from (9.24±0.6) (control group) to (0.29±0.03) as well as a lower expression and activity of \( \Delta-5 \) and \( \Delta-6 \) desaturases, thus requiring less biosynthesis of endogenous PUFA (given the exogenous source) (25).

Consumption of ALA in the diet shows a directly proportional relationship with a greater union from the Peroxisome proliferator-activated receptor alpha (PPAR-\( \alpha \)) transcription factor to the DNA, both in signal of a cyto-protector effect as well a possible immunomodulation, given that this molecule forms a non-functional complex with the p65 subunit of Nuclear Factor \( \kappa B \) (NF-\( \kappa B \)) blocking its proinflammatory effect (55).

In addition, antioxidant potential linked to the increased level of Glutathione (GSH) in plasma and diminished reduced/oxidized (GSH/GSSH) radius has been evidenced. GSH is considered one of the most important antioxidant molecules, like Glutathione peroxidase coenzyme (56), an enzyme that in this very study increased its hepatic activity, like superoxide dismutase, Glutathione reductase and catalase, leading to the conclusion that ALA consumption, as shown after the diet with Sacha inchi, constitutes a protection mechanism against hepatic oxidative stress (25).

Although the information available regarding the antioxidant potential of \( P. \ volubilis \) L. bio components derives principally from seeds, it is worth highlighting that the analysis of diverse extracts obtained from leaves has demonstrated such antioxidant potential. Various extracts like aqueous, methanolic, ethanolic, in chloroform and in hexane have evidenced the capacity to reduce the Mo\(^{6+} \) ion to Mo\(^{5+} \) from ammonium molybdate in acid medium and in presence of 250 \( \mu \)g/ml of the aforementioned extracts (generating green phosphate complex/Mo). Total antioxidant capacity was registered at 83.42 EAA/g, 89.21 EAA/g, and 97.76 EAA/g (equivalents of ascorbic acid/g) compared with ascorbic acid as referent, for the fractions in hexane, chloroform, and methanol, respectively (27).

It is considered that the antioxidant potential of a plant depends on the content of its antioxidant compounds. For \( P. \ volubilis \) L., flavonoids have shown their capacity to prevent and eliminate free radicals from oxygen (57,58). These compounds have been identified from the hydroalcoholic extract of \( P. \ volubilis \) L. leaf (Tarapoto, Peru), along with tannins and in sync with the demonstration of a significant in-vitro inhibitor effect of the lipid peroxidation (measured as formation of malonaldehyde) induced by ferric ion/ascorbate in hepatic tissue of rats (\( Rattus rattus albinus \) variety) after concomitant treatment of hepatocyte homogenate with a dosage of 70 and 140 mg/L of the extract (**p<0.001), without statistical difference
between dosages as such (59). Likewise, the nutshell has exhibited high content of alpha-tocopherol, a molecule considered as the main active metabolite of vitamin E (60) and responsible for its antioxidant activity in biological systems, protecting the unsaturated fatty acids from oxidation (61).

Overall, the total tocopherol content in *P. volubilis* L. described by Pereira in shell and seeds (average of 3.06 and 8.99 mg/100 g, respectively) (62) is higher than that of other oleaginous plants, like rye (0.1 mg/100 g), adding α, β, and γ-tocopherol (63), and similar to that of diverse legumes (10 mg/100 g), although in these no β-tocopherol has been detected (64). It should be stressed that said value (62) is even lower than the total value of vitamin E determined in other studies of oil from Sacha inchi seed, as already stated (14,15,31), sharing in all cases the plant origin (Peruvian Amazon jungle).

*Anti-proliferative and antitumoral activity*

To date, little information is known on the possible effects of Sacha inchi or its derivatives in the context of neoplasia in terms of tumor prevention. Recently, a group of researchers from Peru performed experiments based on *in vivo* colon cancer model implementing a murine model (28 Holtzman male albino rats) and 1,2-dimethylhydrazine, a recognized inducer of colorectal carcinoma (65) of broad experimental use with diverse rat strains (26,66-68), given that its hepatic metabolites azoxymethane and methylazoxymethanol are, in turn, transformed by the intestinal epithelial cells or by resident bacteria in carbon and methyl ions, with the consequential generation of mutations through methylation in the tissue itself (69). This study found a 12.5 % increase in the number of individuals protected against tumor induction (without injury) in the group of rats exposed to the carcinogen and consuming Sacha inchi seed oil (at a dosage of 150 µl/kg/day), compared with the control group, although there were no significant differences that would reveal the association between consumption of *P. volubilis* L. oil and prevention in terms of the genesis of neoplastic lesions (26).

The analysis of the effect of consumption of a Sacha inchi fatty acid supplement (constituted by a mixture of fatty acids, principally alpha-linoleic acid, ω-3 at 54.5 %), in the context of antineoplastic control has yielded interesting results, as shown by the reduction of up to 2.3 and 3.0 fold the tumor mass and the proliferation of Walker 256 cells in a murine model of breast cancer, respectively, consistent with the data obtained after the diet with fish oil, along with the decrease of TNF-α, IL-6, and triacylglycerides by 65 %, 62.5 %, and 50 % in plasma, respectively (28); findings that call on the need to explore the antitumor biological
activity of ALA in humans, as important component of the *P. volubilis* L. seeds. Additionally, antitumor potential has been recorded from *P. volubilis* L. leaf extracts obtained evidenced in the decreased viability of A549 cells (human pulmonary carcinoma) and HeLa cells (human cervical carcinoma), along with a significant reduction of 48.5 % and 54.3 % of their proliferation, after 48 h of treatment with 250 µg/mL of the fractions in methanol and hexane, respectively, table 2. These fractions also induced early apoptosis by 10.2 % and 13.3 % of the HeLa cells, an effect that was higher for the aqueous fraction (17.2 %) (27).

This activity registered for Sacha inchi leaf extracts turns out interesting considering that such material – contain 5.34 % to 10.85 % of polyphenols (specially from the plant’s leaf extract obtained with chloroform) (27), compounds present in plants from the Europhorbiaceae family, like *Euphorbia* (70), with a background of *in-vitro* anti-proliferative activity in digestive tract, although well-known for their antioxidant activity upon acting as reducing agents and even metal chelators. It is considered that this same property, related to the inhibition of lipid peroxidation, protects against the onset of cancer, taking into account that within the two most important classes of polyphenols, flavonoids are the main ones found in *P. volubilis* L. (71) (*Table 1* shows the compendium of the main biological activity referred to Sacha inchi parts in the health context).

TECHNOLOGY AND SACHA INCHI

Currently, some technological tools are known that facilitate the use of the useful components of Sacha inchi, such as nanoparticles and microencapsulation, to which it is important to refer. One of the new therapeutic trends in the field of cancer, for example, is related to the use of tiny particles with special features in terms of specificity and biological safety. The peculiarity of these molecules (nanoparticles) is mainly based on their small size and the versatility to act as transporters of any type of element and to interact with biomolecules present in different cellular locations, with properties such as a size of less than 100nm, as well as a contrast between rigidity and flexibility, giving them use in medicine, among other areas (76,77).

The nanoparticles have been proven as alternatives in the distribution of drugs in the treatment of cancer, and among the most evaluated ones are gold, silver and iron nanoparticles due to their outstanding properties (78). It has been observed that these molecules exhibit stability and easy entry into the cell, in addition to an acceptable biocompatibility. But the main scientific attraction is that they are biologically inert and non-toxic and can also be synthesized through two mechanisms, chemically, a process that
involves the use of toxic chemical agents, prolonged synthesis protocols and physical processes that affect the stability of the nanoparticles; and through the use of plants (79,80), a process known as green chemistry, which is cost-effective, environmentally friendly and scalable, especially for low-income countries.

There are several approaches focused on demonstrating the effectiveness of nanoparticles synthesized from plant extracts, revealing both their microbicidal and tumoricidal capacities. Ezhilarasi et al. (81), used nickel oxide nanoparticles prepared from extracts of Moringa oleifera, demonstrating the inhibitory effect of in vitro proliferation on HT-29 colon tumor cells, postulating in this way the potentiality of this green technology in biomedical treatments. An interesting finding regarding biosecurity was observed in the performance of gold nanoparticles conjugated with extracts also obtained from this plant, one of the most studied in this regard. This assay demonstrated the absence of cytotoxicity of the nanoparticles towards blood mononuclear cells, but in turn showed proliferative inhibitory effects in A459 and SNO tumor lines through the induction of apoptotic mechanisms (82), demonstrating the selectivity of the phytonanoparticles. As for the synthesis of phytonanoparticles using Sacha inchi, the conjugation of these extracts with silver particles has been achieved, which have shown antioxidant effects (Table 1) (73).

Similarly, the generation of cuprous oxide (Cu2O) nanoparticles from copper (Cu) using Plukenetia volubilis L. leaves (due to their polyphenol, alkaloid and sugar content) has been recently described as a promising low-cost and environmentally friendly technology for the catalytic treatment of methane blue (due to its polyphenol, alkaloid and sugar content) has recently been described as a promising low-cost and environmentally friendly technology for the catalytic treatment of methylene blue as a water pollutant (83), which in turn could represent an interesting indirect use of the plant and also for the benefit of human health, if it is taken into account that this compound is recognized as having potential in antimicrobial and antitumor treatment and as an antioxidant (77,84,85), among other industrial uses.

It has also been possible to develop an even more ecological and cost-effective method of synthesis, using sunlight as the source of energy, which catalyzes the formation of gold particles together with the oil extract of Sacha inchi (86). So far there is no evidence of the application of nanoparticles based on Sacha inchi in studies of basic experimentation regarding their behavior as an element with antitumoral properties, opening a potential exploratory market for this purpose.
On the other hand, microencapsulation technology has favored the food industry through the enrichment of foods with PUFAs such as omega 3 and 6 from Sacha inchi, while preserving the characteristics of these essential fatty acids, improving their oxidative stability, as mentioned previously in this review (39,40), also by generating emulsions and combining spray drying and spay chilling methods, with materials such as skimmed milk powder, acacia gum, mixture grape juice-acacia gum and hydrogenated palm oil as a wall, with acceptable organoleptic properties (87).

The microencapsulation method by spray drying continues to show recently high efficiency and oxidative protection of Plukenetia volubilis L oil, among other plant species, in the field of functional foods, especially when using modified starch (Hi-Cap) as wall material, with an encapsulation efficiency of 93.3 % with respect to the range of 61.1-73.0 % obtained with other wall materials such as maltodextrin, arabic gum, Whey Protein Concentrate or a mixture of these; likewise, a lower humidity and a notably higher half-life of 144.3 days at 25 °C with respect to an average of 79.9-84.1 days for the other materials (88).

In the plant seed oil microencapsulation technology, other wall materials such as ovalbumin (protein) and sodium alginate (polysaccharide) have been used jointly as biopolymers by complex coacervation process, providing resistance to high temperatures (approximately 190 °C) and gastric digestion (given its pH=3. 8 and the polysaccharide wall), also with an efficiency close to 95 % in the encapsulation process and a higher bioavailability of the oil for its intestinal absorption (90).

Very recently, this last microencapsulation process has been optimized by adding a third component (tannic acid) to the protein-polysaccharide wall (ovalbumin-pectin), with a contrasting effect since the nutritional value of the capsules seems to be increased, although the encapsulation efficiency does not exceed 80 % (91). The use of this acid not only replaces the use of other compounds considered toxic such as glutaraldehyde and formaldehyde to facilitate the interaction between ovalbumin biopolymers and polysaccharides (92), but because it is constituted by high molecular weight polyphenols it provides an additional contribution as a result of its antioxidant value (93,94).

POTENTIAL FOR RESEARCH

Besides the biological activity described for Sacha inchi components, the antimicrobial effect, emollient activity, and absorption of heavy metals have been reported recently. In the first case, the effect of the oil from the plant’s seeds has been explored on the adherence of
skin commensal bacteria, *Staphylococcus aureus*, starting from the traditional recognized use (empirical) of the plant to treat cutaneous wounds, besides humectation and scarring.

The bactericide potential of Amazonian of Sacha inchi extra virgin oil has been assessed (with standard content of PUFAs of 84 %, 48 % of ALA and 35 % of LA) through inhibition of bacterial growth after treatment of 10-million UFC with the oil during 24 h and at corporal temperature conditions, with respect to the control group in medium without the oil and phenol as positive control; however, such effect was not observed, since a survival of approximately 90% of the microorganisms was evidenced in the experiment. In contrast, protective or preventive (39.2± 3.4 %) and curative (33.9± 1.8 %) outcomes were found against adherence of *S. aureus* based on the oil treatment of human keratinocytes and skin explants in the presence of the microorganism; an effect possibly attributed to the content of ω-3 and ω-6 fatty acids of this oil, discarding its possible direct damage (cytotoxicity) to the epithelial cells (95).

Due to the scarce information available, it is important to explore in depth the possible antimicrobial potential of *P. volubilis* L., since it is not yet catalogued within the group of 221 medicinal plants with known antifungal, antiparasitic, antiviral or bacteriostatic activity since it is extremely important to find biological alternatives, in this case of plant origin, to counteract the current increase in bacterial resistance, which represents a need, as well as a clear opportunity for social welfare.

The bioremediation effect of Sacha inchi shells has been exemplified in the bio-absorbent potential for the Pb^{2+} and Cu^{2+} ions. Treatment of aqueous solutions containing heavy metals with biomass based on the triturate of seed shells at conditions of acid pH and 323 K°, revealed increments of 15.72 % in the weight corresponding to Pb^{2+} and of 6.33 % for Cu^{2+} in the treating biomass, as evidence of the bioremediation effect (96). This biological activity recently attributed to *P. volubilis* L. components represents a potential use and benefit, given that the process used to obtain them is simple and cost-effective given the vast availability of the plant’s waste products.

The properties of Sacha inchi as emollient and saponin have been assessed in a study that recruited infants from 4 to 8 years of age with atopic dermatitis. This study sought to favor the reestablishment of the affected skin given the known imbalance of fatty acids, a key feature in this pathology, finding a significant improvement of the inflammation and pruritus observed in the group treated during two months with the plant oil ($p = 0.0004$), with respect to the control group (placebo), an effect that remained stable over time one month after suspending
the treatment (p=0.002) (97). These observations generate an encouraging sight to treat this chronic event without known cure, as well as a panorama of constant inquiry of the still unknown benefits on the Amazonian plant.

Given the benefit to human health attributed to the consumption of omega-3 fatty acids, Peru is currently projecting an extension of the food sources containing them, favoring its dietary intake through strategies like feeding guinea pigs, poultry, and chickens with a combination of Sacha inchi oils and fish, which enrich their meat with these lipids (13). Such types of alternatives could impact positively in the maintenance of human health upon recognizing that fish oil is a source of omega-3 fatty acids, like EPA and DHA, relevant due to their higher degree of unsaturation with respect to ALA, contributing through its incorporation, to the regulation of the inflammatory immune response, blood pressure (which has been lower in individuals who consume it with respect to the control group without consumption) (98), reduction of triacylglyceride levels in the circulation, prevention of neurodegenerative and neuropsychiatric disorder, maintenance of memory and visual function (99-101). However, the high content of essential fatty acids (EFA) from the P. volubilis L seed oil, especially at the expense of ALA, will permit – as such – the production of other LCPUFAs, like EPA and DHA, in the organism (its metabolites) with all its benefits attributed, as mentioned before (41,102,103).

Sources of high daily impact are represented by milk and dairy products, like yoghurt, already supplemented with sources rich in linoleic fatty acid through fish and sunflower oils, canola, and soy, showing a moderate increase of such unsaturated fatty acid content (104-106). For yoghurt, supplementing this lactic ferment with Sacha inchi seeds has been studied recently, revealing an increase of 25 and 50 fold the levels of ALA and LA respectively, going from an average PUFA content of 3.60 % to 81.51 %, in the modified product with respect to the control, concomitant with reduced contents of saturated fatty acids (palmitic and stearic) from 76 % to 84 %, added to sensory acceptance >70 % in consumers (volunteers) (107).

CONCLUSIONS AND RECOMMENDATIONS

P. volubilis L. is part of a select list of the most promising plants in Peruvian traditional medicine, attributed to the place where it has been described ancestrally, jointly with Smallanthus sonchifolius (yacon root), Croton lehleri (dragon’s blood), Uncaria tomentosa/U. guianensis (cat’s claw), Lepidium meyenii (maca root), Physalis peruviana (cape gooseberry), Minthostachys mollis (muña), Notholaena nivea (cuti-cuti), Maytenus macrocarpa (chuchuhuasi), Dracontium loretense (jergon sacha), Gentianella nitida (hercampuri), and Zea
mays (purple corn) (33), highlighting, among other features, the high nutritional value and antioxidant potential of the phenolic components of its seeds (mostly tannin type, 93.1%) (23). The presence of polyphenols from this plant has been also reported in its leaves (24,27).

It is considered that fatty acid content with higher proportion of PUFA in Sacha inchi constitutes a benefit to human health due to its antiatherogenic, antithrombogenic, and hypocholesterolemic effects (62), besides having a high nutritional value from components, like seed oil, pie, and leaf, projecting it as a promising crop with potential for cost-effective production that will allow to contemplate alternatives to substitute illegal crops in the Putumayo region in Colombia for example, increasing the social impact of this plant (21,27).

Precisely, regarding the usefulness of its components, there is evidence related with antitumor activity from seed oils and from Sacha inchi leaf aqueous and organic extracts, to which we add the finding of the stimulant effect of the latter on the proliferation of normal cells, as noted by the increase by approximately 175 % of the 3T3 cells (mouse fibroblasts) (27), opening the doors for a deeply search of other potential uses of this plant, for example, in tissue regeneration, requiring the use of human cells.

The genetic and population diversity has been described for P. volubilis L. dependent on the geographic region of origin, as reported, implying the need to study the biological properties of the plant, bearing in mind the region from which it is obtained, as a constant research activity in favor of recognizing its potential and new evidence of usefulness to benefit human health.

List of abbreviations:
The authors approved the consent for publishing the manuscript.

**Competing interests**

The authors declare that they have no competing interests. The Editor may ask for further information relating to competing interests.

**Ethical statement and consent to participate**

This article does not contain studies by any of the authors on humans and animals. All associated authors are listed within the manuscript, and no other person satisfied the criteria for authorship.

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**AUTHORS’ CONTRIBUTION**

DC has contributed significantly to the search for bibliographic sources as well as to the writing of the manuscript and proposal of the subject of this revision. JS contributed complementing the information collected previously, reviewing the writing in the foreign language and designing the tables and figures. LG has reviewed the document providing ideas on the distribution of items within the manuscript. The authors have given final approval of the version to be published. All authors read and approved the final manuscript.

**ORCID ID**

D.M. Cárdenas Sierra [https://orcid.org/0000-0002-2881-8504](https://orcid.org/0000-0002-2881-8504)

L.J. Gómez Rave [https://orcid.org/0000-0001-7055-4103](https://orcid.org/0000-0001-7055-4103)

J.A. Soto [https://orcid.org/0000-0002-4786-3431](https://orcid.org/0000-0002-4786-3431)

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Fig 1. Geographic distribution of the *Plukenetia* genus in Latin America and crop features of the *volubilis* specie. Brasil, Venezuela and Colombia are the countries that more genus of the plant host due to the extension of the Amazon jungle and therefore to the biodiversity of this region. One of the most striking characteristics of this type of plant is its ability to grow in different types of soils, although it is also true that requires certain conditions for proper growth, one of them being the constant availability of water sources. Adapted from *(9)*, *(10)*, *(11)*, *(12)*.
Fig. 2. Timeline of historical events of the *Sacha Inchi* plant. It is a crop planted by ancient pre-Inca cultures such as the Mochica and Chimu civilizations (20), whose main physical and organoleptic characteristics were first described by de la Vega, and which Linne later called *Plukenetia volubilis*. In the 1970s, a former Peruvian minister for agriculture screened the potential of the Amazonian region for new types of food crops, thus rediscovering *Sacha Inchi*, describing its chemical and nutritional attributes. Various publications have contributed to complementing the knowledge about this plant, among them those referring to its potential as a source of food between tribes, as a novel food, and the whole plant as drug Generally Regarded As Safe (GRAS) by the US Food and Drug Administration.
Please note that this is an unedited version of the manuscript that has been accepted for publication. This version will undergo copyediting and typesetting before its final form for publication. We are providing this version as a service to our readers. The published version will differ from this one as a result of linguistic and technical corrections and layout editing.

Table 1. Biological spectrum of Sacha inchi

<table>
<thead>
<tr>
<th>Biological effect</th>
<th>Plant part</th>
<th>Country</th>
<th>Assay outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antioxidative</strong></td>
<td>Seed</td>
<td>Peru</td>
<td>Seeds of 16 cultivars were assessed searching for different phytochemicals, finding a high variability in the content of the evaluated compounds. The hydrophilic and lipophilic antioxidant capacities were correlated with total phenolic and total carotenoid contents, respectively. This study positions the seed as source of polyunsaturated fatty acids, tocopherols, phytosterols, phenolic compounds with antioxidant capacity</td>
<td>(7)</td>
</tr>
<tr>
<td></td>
<td>Seed (oil)</td>
<td>Peru</td>
<td>The antioxidant activity of the lipophilic and hydrophilic extracts of the oil were measured <em>in vitro</em> by ABTS assay for lipophilic antioxidants and DPPH for hydrophilics. Lipophilic extract showed greater antioxidant activity using the DPPH assay compared to hydrophilic extract of the oil, which showed greater activity using the ABTS method.</td>
<td>(34)</td>
</tr>
<tr>
<td></td>
<td>Seed (Raw and honey-coated)</td>
<td>Peru</td>
<td>Several approaches were applied onto kernels in order to assess the variations on the content of total phenolic content (open boiling, pressure boiling, low and high temperature roasting and honey roasting). The DPPH outcome was influenced by process temperature and water activity of seeds.</td>
<td>(72)</td>
</tr>
<tr>
<td></td>
<td>Leaf (leaf extract and leaf extract based silver nanoparticles)</td>
<td>Ecuador</td>
<td>The antioxidant efficacy of AgNPs (silver nanoparticles) was higher than leaf extracts against the DPPH assay. Radical scavenging activities were found to be maximum of 22.5 % in 0.6 mL for AgNPs whereas 19 % in 1.0 mL for leaf extracts.</td>
<td>(73)</td>
</tr>
<tr>
<td><strong>Antidyslipidemic</strong></td>
<td>Seed (roasted)</td>
<td>Peru</td>
<td>The effect of the intake of 30 g of <em>sacha inchi</em> seeds per day for 6 weeks was assessed on</td>
<td>(74)</td>
</tr>
</tbody>
</table>
28 volunteers. The control group received 30 g of confit wheat (*Triticum aestivum*). A reduction in cholesterol, triglycerides, and LDL levels was observed, as well as an increase in HDL levels.

This experimental work sought to know the effect, effective dose and side effects of Sacha inchi oil (*Plukenetia volubilis L*) in the lipid profile of 24 patients with hypercholesterolemia. The participants were randomized to receive 5 mL or 10 mL of an oil suspension for four months. Intake of the oil resulted in a drop in mean TC (total cholesterol) and non-esterified fatty acids (NSAIDs) values with c-HDL elevation in both groups.

<table>
<thead>
<tr>
<th>Seed (oil)</th>
<th>Peru</th>
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<tr>
<td>28 volunteers. The control group received 30 g of confit wheat (<em>Triticum aestivum</em>). A reduction in cholesterol, triglycerides, and LDL levels was observed, as well as an increase in HDL levels.</td>
<td>(75)</td>
</tr>
</tbody>
</table>

HeLa (cervix) and A549 (lung) tumor cell lines were treated with several leaf extracts. The methanol and hexane compounds were able to reduce the proliferation of HeLa cells up to 54.3 % and 48.5 %, respectively.

Seed oil was shown to have potential anticancer activity in Walker 256 tumor-bearing rats. A Sacha inchi oil based diet (1 g/kg body weight, daily, for 4 weeks) reduced tumor mass and proliferation of Walker 256 tumor cells *ex vivo*. This assay also identified an increased lipoperoxidation in Walker 256 tumor tissues as well a reduction of the glycemia, triglycerides and inflammatory cytokines plasma levels.

<table>
<thead>
<tr>
<th>Leaf (leaf extracts)</th>
<th>Brazil</th>
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</tbody>
</table>

This table summarizes experimental trials focused on evidencing three clinical or biological applications related to certain parts of the Sacha inchi plant. In relation to the origin of the crop, it is evident that most of the studies come from South America, specifically from Peru. ABTS [2,2’-azinobis-(3-ethylbenzothiazoline-6-sulfonate)] Assay, DPPH [(2,2-diphenyl-1-picryl-hydrazyl-hydrate) Assay