



POTENTIAL OF SACHA INCHI (*Plukenetia volubilis* L.) AS AN ANTICANCER : A SYSTEMATIC REVIEW

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Abstrak

Kanker merupakan penyebab kematian utama di seluruh dunia. WHO memperkirakan 20 juta kasus kanker baru dan 9,7 juta kematian pada tahun 2022. Meningkatnya kejadian kanker mendorong pengembangan agen terapeutik baru untuk mencapai kelangsungan hidup pasien yang lebih baik. Terapi alami seperti produk tumbuhan banyak dipelajari, salah satunya ekstrak Sacha Inchi (*Plukenetia volubilis* L.). Sacha Inchi diketahui memiliki kandungan seperti lemak dan protein yang berpotensi sebagai antikanker, namun informasi mengenai efektivitas Sacha Inchi pada neoplasia atau pencegahan tumor masih terbatas. Systematic review ini bertujuan untuk meninjau secara mendalam mengenai penelitian yang berfokus pada potensi antikanker Sacha Inchi. Pencarian dilakukan di 4 database seperti National Library of Medicine (MEDLINE-PubMed), Scopus, Springerlink, dan Sciencedirect. Kata kunci yang digunakan adalah kombinasi dari “sacha inchi”, “plukenetia volubilis”, “anticancer”, “antineoplastic”, “antiproliferative”. Dari pemilihan studi dan ekstraksi data didapatkan 17 artikel yang memberikan informasi tentang ekstrak berbagai bagian tanaman Sacha Inchi dan kandungannya yang berpotensi sebagai antikanker, baik secara *in vitro* maupun *in vivo*. Asam lemak tak jenuh ganda (PUFA) dan senyawa fenolik merupakan senyawa yang paling banyak teridentifikasi. Zat lain seperti tokoferol, peroksida, asam amino, steroid, terpenoid, flavonoid, protein juga diidentifikasi. Studi terinklusi menunjukkan potensi Sacha Inchi sebagai antioksidan dan antikanker.

Keywords : *sacha inchi*, *antineoplastic agent*, *Plukenetia volubilis*

Abstract

Cancer is the leading cause of death worldwide. WHO estimated 20 million new cancer cases and 9.7 million deaths in 2022. The increasing incidence of cancer encourages development of new therapeutic agents for higher patient survival rate. Plant products are widely studied, one of which is Sacha Inchi (*Plukenetia volubilis* L.) extract. Sacha Inchi is known to have contents with anticancer potential, but information regarding its effectiveness is still limited. This systematic review aims to provide in-depth review on studies focus on anticancer potential of Sacha Inchi. The searching process was conducted in 4 databases such as National Library of Medicine (MEDLINE-PubMed), Scopus, Springerlink, and Sciencedirect. Keywords used were combination of “sacha inchi”, “plukenetia volubilis”, “anticancer”, “antineoplastic”, “antiproliferative”. Studies selection and data extraction obtained 17 studies provided information on extracts of Sacha Inchi plants and their anticancer-potential contents, both *in vitro* and *in vivo*. Polyunsaturated fatty acids and phenolic compounds were the most identified compounds. Other identified substances were tocopherols, peroxides, amino acids, steroids, terpenoids, flavonoids, proteins. Included studies showed antioxidant and anticancer potential of Sacha inchi.

Keywords: *sacha inchi*, *antineoplastic agent*, *Plukenetia volubilis*

1. INTRODUCTION

Cancer is a generic term for a large group of diseases that can affect any part of the body and leading cause of death worldwide (WHO, 2022). In 2022, there were an estimated 20 million new cancer cases and 9.7 million deaths. The estimated number of people who were alive within 5 years following a cancer diagnosis was 53.5

million. About 1 in 5 people develop cancer in their lifetime, approximately 1 in 9 men and 1 in 12 women die from the disease. The new estimates available on IARC's Global Cancer Observatory show that 10 types of cancer collectively comprised around two-thirds of new cases and deaths globally in 2022. Data covers 185 countries and 36 cancers. Lung cancer was the most commonly occurring cancer worldwide with 2.5 million new cases accounting for 12.4%

of the total new cases. Female breast cancer ranked second (2.3 million cases, 11.6%), followed by colorectal cancer (1.9 million cases, 9.6%), prostate cancer (1.5 million cases, 7.3%), and stomach cancer (970 000 cases, 4.9%). Lung cancer was the leading cause of cancer death (1.8 million deaths, 18.7% of the total cancer deaths) followed by colorectal cancer (900 000 deaths, 9.3%), liver cancer (760 000 deaths, 7.8%), breast cancer (670 000 deaths, 6.9%) and stomach cancer (660 000 deaths, 6.8%) (WHO, 2024). The increase in the incidence of cancers in the population has multiplied efforts for the development of new therapeutic agents in order to achieve greater patient survival (Mourelle *et al.*, 2023). Natural therapies, such as plant products are being used to treat cancer (Desai *et al.*, 2008).

Plukenetia volubilis, commonly known as sacha inchi (SI), has attracted increasing attention in recent years due to the exceptional nutritional composition of the seeds, in particular the lipid fraction (Cardinal-McTeague *et al.*, 2019; Kodahl and Sørensen, 2021). Sacha inchi seeds are the source of healthy lipids and proteins because they are rich in oils (35–60 wt%) and proteins (25–30 wt%) (Gutierrez *et al.*, 2011). The major compositions of sacha inchi oil are polyunsaturated fatty acids (PUFA), about 85–93% of the total. Among these, linolenic acid (omega-3) and linoleic acid (omega-6) are mostly found. Both fatty acids are essential for humans and they could decrease the risk of cancers and other chronic diseases (Jitpinit *et al.*, 2022). Besides the essential fatty acids, tocopherols, carotenes, phytosterols, and polyphenols are also found. These compounds are responsible for the health benefits and bioactivities attributed to sacha inchi (Elgegren *et al.*, 2019). Tocopherols, natural forms of vitamin E, known for its antioxidant activity and antitumor potential. To date, little information is known on how the sacha inchi or its derivatives are related to neoplasia or tumor prevention (Cárdenas *et al.*, 2021), especially from its seeds. This review article aims to provide information and education

about several bioactive of sacha inchi seeds oil which have potential as an anticancer.

2. RESEARCH METHOD

The method used in this review article is a systematic review based on the PRISMA guideline for systematic reviews to find the potential of sacha inchi (*Plukenetia volubilis*) as an anticancer agent.

2.1 Search Strategy and Study Selection

This systematic review study was conducted by searching scientific literature published in 4 databases, namely the National Library of Medicine (MEDLINE-PubMed), Scopus, Springerlink, and Sciencedirect. The search focused on the anticancer effects of Sacha inchi in vivo or in vitro. The search terms used in the MEDLINE-PubMed database were sacha inchi OR "plukenetia volubilis" AND (anticancer OR antineoplastic OR antiproliferative), sacha inchi, and sachainchi. Other databases have customized these search terms with article type and language restrictions.

After the search in all databases was completed, the study selection phase was performed according to the PRISMA 2020 flow chart for new systematic reviews. The first step was to eliminate duplicate articles using spreadsheet software. Next, titles and abstracts were screened to select articles of appropriate scope.

Two independent authors conducted the searching and selection process. All discrepancies were resolved in author board discussion involving the third author.

2.2 Eligibility Criteria

Inclusion criteria for study selection were in vitro or in vivo studies that tested the potential of sacha inchi as an anticancer agent, with publication dates between 2013–2023. Articles must be written in English and the full text is available. Meanwhile, the exclusion criteria are articles irrelevant to the

topic of sacha inchi anticancer effects, studies other than in vitro and in vivo, not written in English, full text not available, duplicate articles, and insufficient data.

2.3 Data Extraction

All eligible articles were then extracted into tables, which included publication title, publication year, author, journal, plant origin, extract type, extraction method, extract yield, identified compound, study design, cell/animal type, assay method, potential anticancer mechanisms, and experimental results.

3. RESULTS

A total of 732 articles were collected from the databases from 2013 until

November 2023. These articles underwent a process of identification for duplication and eligibility, utilizing the limitation features of the databases for publication year, article type, language, and full-text accessibility. Among the articles, 212 were identified as duplicates, while 413 were removed for their irrelevance. Subsequently, 17 articles were selected for further analysis after reading their titles and abstracts and evaluating them for inclusion and exclusion. The identification, screening, and selection process is illustrated in Figure 1. All the included studies were originated from various countries such as Brazil, China, Peru, Taiwan, Columbia, and Thailand which are summarized in Table 1. Potential as anticancer and experimental results are summarized in Table 2.

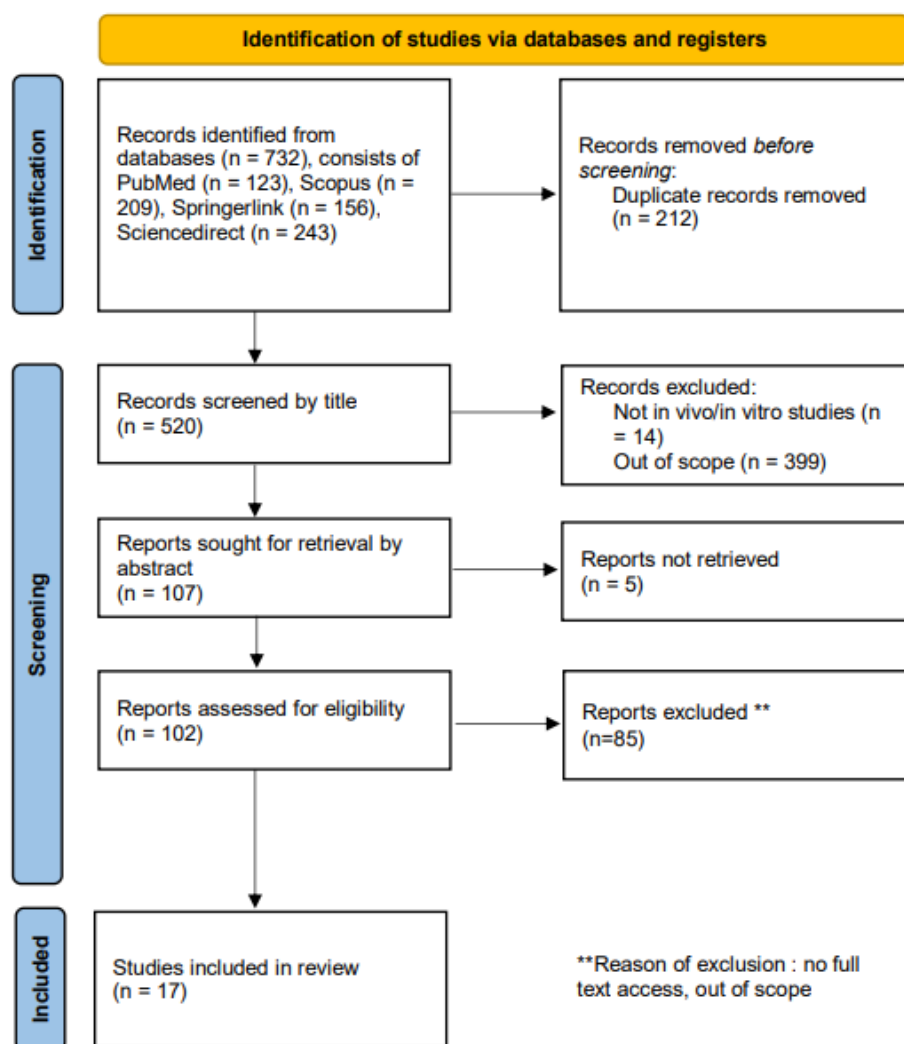


Figure 1. PRISMA Flow Diagram of Articles Identification and Screening (Page et al., 2020)



Table 1. Summarize of Included Studies

No.	Title	Journal	Author	Year	Plant/Root Origin	In Vivo/ In Vitro
1.	Antioxidant and Antiproliferative Activities of Leaf Extracts from <i>Plukenetia volubilis</i> Linneo (Euphorbiaceae)	Evid Based Complement Alternat Med	Nascimento, A. K. L., Melo-Silveira, R. F., Dantas-Santos, N., Fernandes, J. M., Zucolotto, S. M., Rocha, H. A. O., and Scortecci, K. C.	2013	Brazil	In vitro and in vivo
2.	Effects of Maturity and Thermal Treatment on Phenolic Profiles and In Vitro Health-Related Properties of Sacha Inchi Leaves	Plants (Basel)	Kittibunchakul, S., Hudthagosol, C., Sanporkha, P., Sapwarabol, S., Suttisansanee, U., and Sahasakul, Y.	2022	Thailand	In vitro
3.	Determination of hydrophilic-lipophilic balance value and emulsion properties of sachu inchi oil	Asian Pacific Journal of Tropical Biomedicine	Saengsorn, K and Jimtaisong, A.	2017	Thailand	In vitro
4.	Evaluation of Sacha Inchi (<i>Plukenetia volubilis</i> L.) By-Products as Valuable and Sustainable Sources of Health Benefits	Horticulturae	Kittibunchakul, S., Hudthagosol, C., Sanporkha, P., Sapwarabol, S., Temviriyankul, P., and Suttisansanee, U.	2022	Thailand	In vitro
5.	Anti-HMG-CoA reductase and antioxidant activities of Sacha inchi (<i>Plukenetia volubilis</i> L.) nutshell extract	Journal of Associated Medical Sciences	Prasongsu, W., Pimsan, N., Buranapattarachote, C., and Punturee, K.	2021	Thailand	In vitro
6.	Changes in stability, tocopherols, fatty acids and antioxidant capacity of sachu inchi (<i>Plukenetia volubilis</i>) oil during French fries deep-frying	Food Chemistry 340	Rodríguez, G., Squeo, G., Estivi, L., Berru, S. Q., Buleje, D., Caponio, F., Brandolini, A., and Hidalgo, A.	2021	Peru	In vitro
7.	Chemical properties and nutritional factors of pressed-cake from tea and sachu inchi seeds	Food Bioscience 15	Rawdkuen, S., Murdayanti, D., Ketnawa, S., and Phongthai, S.	2016	Thailand	In vitro
8.	Chemical Composition, Oxidative Stability and Antioxidant Capacity of Oil Extracted from Roasted Seeds of Sacha-Inchi (<i>Plukenetia volubilis</i> L.)	Journal of Agricultural and Food Chemistry	Cisneros, F. H., Paredes, D., Arana, A., and Cisneros-Zevallos, L.	2014	Peru	In vitro
9.	In-Vitro Screenings for Biological and Antioxidant Activities of Aqueous Extract from Sacha Inchi (<i>Plukenetia volubilis</i> L.) Husks	Trends In Sciences	Thuanthong et al., 2023	2023	Thailand	In vitro
10.	Microwave-assisted extraction of phenolic compounds from Sacha Inchi shell: Optimization, physicochemical properties and evaluation of their antioxidant activity	Chemical Engineering & Processing: Process Intensification 153	Sanchez-Reinosoa, Z., Mora-Adamesa, W. I., Fuenmayora, C. A., Darghan-Contrerasb, A. E., Gardanac, C., and Gutiérrez, L.	2020	Columbia	In vitro



No.	Title	Journal	Author	Year	Plant/Root Origin	In Vivo/ In Vitro
11.	Chemical Composition, Fatty Acid Profile, and Optimization of the Sacha Inchi (<i>Plukenetia volubilis</i> L.) Seed-Roasting Process Using Response Surface Methodology: Assessment of Oxidative Stability and Antioxidant Activity	Foods	Morales, N. B., and Garcia, P. G.	2023	Columbia	In vitro
12.	Sacha inchi (<i>Plukenetia volubilis</i> L.) shell: an alternative source of phenolic compounds and antioxidants	International Journal of Food Science and Technology	Chirinos, R., Necochea, O., Pedreschi, R., and Campos, D.	2016	Peru	In vitro
13.	Screw press extraction of Sacha inchi seeds: Oil yield and its chemical composition and antioxidant properties	J Food Process Preserv	Muangrat, R., Veeraphong, P., and Chantee, N.	2018	Thailand	In vitro
14.	The antioxidant activity of protein fractions from Sacha inchi seeds after a simulated gastrointestinal digestion	LWT - Food Science and Technology 145	Zhan, Q., Wang, Q., Liu, Q., Guo, Y., Gong, F., Hao, L., Wu, H., and Dong, Z	2021	China	In vitro
15.	Antioxidant activities of sacha inchi (<i>Plukenetia volubilis</i> L.) protein isolate and its hydrolysates produced with different proteases	Maejo Int. J. Sci. Technol.	Suwanangul, S., Sangsawad, P., Alashi, M. A., Aluko, R. E., Tochampa, W., Chittrakorn, S., and Ruttartananamongkol, K.	2021	Thailand	In vitro
16.	Characterization of sacha inchi protein hydrolysates produced by crude papain and Calotropis proteases	LWT - Food Science and Technology	Rawdkuen, S., Rodzi, N., and Pinijsuwan, S.	2018	Thailand	In vitro
17.	Peptide fractions from Sacha inchi induced apoptosis in HepG2 cells via P53 activation and a mitochondria-mediated pathway	J Sci Food Agric	He, Z., Lin, J., Peng, D., Zeng, J., Pan, X., Zheng, R., Li, P., and Du, B.	2023	China	In vitro

Table 2. Summarize of Potential Sacha Inchi as an Anticancer

Parts and Type of Extract	Extraction Method	Yield of Extract	Identified Substances	Cell/Animal Type	Assay Method	Potential Anticancer & Mechanism	Experimental Result	Citation
Leaf extracted in methanol, ethanol, chloroform, hexane, and water respectively, and resuspended with DMSO.	Maceration	10% w/v	phenolic compounds, steroids, and/or terpenoids	3T3, CHO, HeLa, A549 cells	TAC assay, DPPH assay, cell proliferation on analysis, flowcytometer	Antioxidant, antiproliferative (apoptotic mechanism)	TAC assays values ranged from 59.31 to 97.76 EAA/g. DPPH assay values ranged from 62.8% to 88.3%. The cell viability assay showed that the extracts were able to reduce the viability of cancer cells such as HeLa and A549 cells. The extracts MEL and HEL (250 µg/mL) were able to reduce the proliferation of HeLa cells up to 54.3% and 48.5%, respectively. The flowcytometer results showed that these extracts induce cell death via the apoptosis pathway. These extracts were also able to induce proliferation of fibroblast cells, 3T3 cells.	Nascimento et al., 2013
High-temperature combination with enzymatic hydrolysis treatment from the SI pressed cake.	Enzymatic hydrolysis	1% w/v	peptides	HepG2 cells	Flowcytometry and Western blot assays	Anti-hepatoma (suppress the cell cycle and facilitate cell apoptosis)	Treatment with Sacha inchi peptides (SPs) significantly reduced the proliferation of HepG2 cells by inducing apoptosis and arresting the cell cycle at the G0/G1 phase. SPs also induced HepG2 cell apoptosis by increasing the levels of proteins such as Bax, Caspase-3 and P53.	He et al., 2023
Sacha inchi oil	Kernels pressing	NA	Phenols, tocopherol and fatty acid	NA	DPPH assay	Antioxidant	Roasting partially of Sacha-inchi (<i>Plukenetia volubilis</i> L.) seeds increased oil oxidation and its antioxidant capacity, slightly decreased tocopherol content, and did not affect the fatty acid profile.	Cisneros et al., 2014
Sacha inchi oil	NA	NA	Peroxide, acid, omega-3, omega-6 and omega-9, vitamin E	NA	DPPH Assay	Antioxidant	Sacha inchi oil (67 and 167 ppm) and its emulsion showed 65%, 85% and 89% DPPH inhibition.	Saengsorn and Jintaisong, 2017
Sacha inchi oil	Cold pressing	NA	α-linolenic, linoleic acid and tocopherols	NA	ABTS and DPPH assay	Antioxidant	In the hexane extracts, antioxidant capacity of sacha inchi (SI) is higher compared to soybean oil (SO).	Rodriguez et al., 2021
Sacha inchi oil	Cold pressing	6,6% w/v	Fatty acid, amino acids	NA	ABTS method	Antioxidant	Roasting partially increased the indicators of lipid oxidation in the oil extracted from roasted seeds, as well as the antioxidant activity of the seeds.	Morales and Garcia, 2023



Parts and Type of Extract	Extraction Method	Yield of Extract	Identified Substances	Cell/Animal Type	Assay Method	Potential Anticancer & Mechanism	Experimental Result	Citation
Powdered sample of SI pressed-cake extracted with extraction solvent (acetone and water)	Infusion	10% w/v	carbohydrates, protein, essential amino acids, essential fatty acids, dietary fiber, and mineral	NA	DPPH and FRAP assay	Antioxidant	Both DPPH radical scavenging activity and FRAP values of sachu inchi pressed-cake (32.43% dan 732.67 mmol FeSO ₄ /L) showed that sachu inchi pressed-cakes is good sources for bioactive compounds with high antioxidant activities.	Rawdkuen et al., 2016
SI shell dissolved with six different solvents with different composition of methanol/ethanol/water/acetic acid/acetone	Infusion	10% w/v	Phenolic compounds	NA	ABTS, FRAP and ORAC assay	Antioxidant	ABTS, FRAP and ORAC AOXC were within the range of 34.1 and 93.9; 45.0 and 114.0 and, 92.5 and 192.6 l/mol TE g ⁻¹ , respectively. This study highlights the potential use of SI shell as a novel and alternative source of PC antioxidants for the nutraceutical and/or functional food industries.	Chirinos et al., 2016
Sachu inchi shell extracted using aqueous ethanol	Infusion	10% w/v	Phenolic compounds	NA	FRAP and TEAC assay	Antioxidant	Under the optimal extraction conditions (1500 W, E63.0 %, and 110 s) the FRAP and TEAC values were 374.39 ± 1.81 and 384.50 ± 3.55 µmol Trolox/g SI-shell. These results indicate that SI-shell is a promissory source of natural compounds with antioxidant activity	Sanchez-Reinoso et al., 2020
Screw-pressed sachu inchi seed extracted with different solvents (hexane, propanol, ethanol)	Single screw press & infusion	16,6% w/v	Polyunsaturated fatty acids, phenolic compounds	NA	DPPH and ABTS assay	Antioxidant	Sachu inchi oil was more effective at scavenging ABTS radicals than DPPH radicals, with IC ₅₀ values of 215.48 and 317.33 mg/mL, respectively.	Muangrat et al., 2017
Defatted Sachu inchi seed flour extracted with distilled water (albumin), NaCl (globulin) and NaOH (glutelin)	Infusion	10% w/v	protein fractions (albumin, globulin and glutelin)	NA	ABTS and ORAC assay	Antioxidant	SGID promoted the release of smaller bioactive peptides from protein fractions from Sachu inchi seeds (PFFSIS) evidenced by the increased soluble peptide content, DH and low MW distribution. Besides, the extracellular antioxidant capacity of PFFSIS were significantly increased after the SGID due to potential antioxidant mechanisms inside and outside the cell. The glutelin fraction showed the highest antioxidant activity after the SGID, followed by albumin and globulin fractions.	Zhan et al., 2021



Parts and Type of Extract	Extraction Method	Yield of Extract	Identified Substances	Cell/Animal Type	Assay Method	Potential Anticancer & Mechanism	Experimental Result	Citation
Sacha inchi meal (oil product)	Protein hydrolysis	7% w/v	amino acids, protein	NA	DPPH and FRAP assay	Antioxidant	The antioxidant properties, such as DPPH scavenging and FRAP showed a rising protein concentrate (PH) when increasing the hydrolysates (DH) of sachu inchi.	Rawdkuen et al., 2018
sacha inchi meal dispersed in deionised water	Infusion	10% w/v	protein, alanine, valine and proline, phenylalanine	NA	DPPH, FRAP and Fe ²⁺ chelation methods	Antioxidant	Sacha inchi protein hydrolysates with pepsin (SPHPe) shows the highest antioxidant activities by DPPH (55.7%), FRAP (0.167 mmol Fe ²⁺ /g) and metal ion chelation (55.4%) assays while the sachu inchi protein isolate shows the highest hydroxyl radical scavenging activity (73.3%).	Suwanangul et al., 2021
Hot water extracts of 3 different parts of Sacha inchi (nutshell, baby nut and leaf) and Sacha inchi nut oil	Infusion	10% w/v	Phenolic compounds, steroids, and/or terpenoids	NA	ABTS and DPPH assay	Antioxidant	Sacha inchi nutshell extract showed the highest antioxidant activity. Antioxidant activity was correlated to total phenolic content.	Prasongsut et al., 2021
Freeze-dried and oven-dried young and mature leaves extracted in water	Infusion	1% w/v	Phenolic, flavonoid	NA	DPPH, FRAP, ORAC assay	Antioxidant	Mature sachu inchi leaves exhibited higher antioxidant potential than young leaves after freeze-drying.	Kittibunchakul et al., 2022
Powdery sample of husk and shell poured in aqueous ethanol	Infusion	0,2% w/v	protein, carbohydrates, total dietary fiber, fat, energy, phenolics	NA	FRAP, ORAC and DPPH radical scavenging assay	Antioxidant	Total phenolic content was 1.6-fold greater in the shell than in the husk of sachu inchi, leading to 1.8–2.7-fold higher antioxidant activity.	Kittibunchakul et al., 2022
Sacha inchi husk powder extracted with distilled water	Infusion	6,6% w/v	Total phenolic, total flavonoid	NA	DPPH, ABTS, FRAP and metal chelating assay	Antioxidant	The aqueous extracts from Sachu inchi husks powder obtained at the extraction temperature of 80 °C showed the highest antioxidant activities (1,055.81, 53.60 and 1.59 µmol TE/g dry extract for DPPH, ABTS and FRAP assays, respectively, and 413.32 µmol EE/g dry extract for metal chelating assay).	Thuanthong et al., 2023

Fifteen studies explored antioxidant activity of Sacha inchi extract *in vitro*, while only two studies focused on anticancer activity in cancer cell lines (He *et al.*, 2023; Nascimento *et al.*, 2013). Treatment of HeLa cell lines with Sacha inchi leaf extract can inhibit cell growth, reduce oxidative stress, and induce apoptosis (Nascimento *et al.*, 2023). Meanwhile, peptides obtained by enzymatic hydrolysis of Sacha inchi pressed cake product induced apoptosis and inhibited cell cycle of HepG2 cell lines (He *et al.*, 2023).

Different parts of the sacha inchi plant such as leaves, shell, husk and especially seeds have antioxidant properties with identified substances such as PUFA, tocopherol, peroxide, amino acid, steroids, terpenoids, flavonoid, protein, and phenolic (Chirinos *et al.*, 2016; Cisneros *et al.*, 2014; Kittibunchakul *et al.*, 2022; Kittibunchakul *et al.*, 2022 (b); Morales and Garcia, 2023; Muangrat *et al.*, 2017; Nascimento *et al.*, 2013; Prasongsub *et al.*, 2021; Rawdkuen *et al.*, 2016; Rawdkuen *et al.*, 2018; Rodriguez *et al.*, 2021; Sanchez-Reinoso *et al.*, 2020; Saengsorn and Jimtaisong, 2017; Suwanangul *et al.*, 2021; Thuanthong *et al.*, 2023; Zhan *et al.*, 2021). PUFA and phenolic were the most identified compounds. High antioxidant content is shown by various methods such as DPPH, ABTS, FRAP, TEAC, ORAC assays and Fe²⁺ chelation methods. Muangrat *et al.*, 2017 demonstrated that sacha inchi oil was more effective in scavenging ABTS radicals than DPPH radicals. Its antioxidant activity was also correlated to total phenolic content in the nutshell extract (Prasongsub *et al.*, 2021). In addition, total phenolic content in the shell was higher than in the husk of sacha inchi (Kittibunchakul *et al.*, 2022).

4. DISCUSSION

Sacha inchi is a well-known indigenous plant for routine diet and traditional remedy to treat various diseases. The main identified bioactive compounds are fatty acids and proteins which potentially act as antioxidant. This has led to Sacha

inchi's research approach to explore its antioxidant activity, including the search for anticancer mechanisms (Rodzi and Lee, 2022).

Polyunsaturated fatty acids (PUFAs) are essential fatty acids that include omega-3 and omega-6 (Iizuka, 2019). Naturally occurring PUFAs play an important role in cell growth and are used as biochemical precursors and energy sources. As tumor cells grow rapidly, they voraciously consume nutrients for proliferation. Therefore, PUFAs are preferentially taken up by tumor cells. In fact, PUFAs are easily incorporated into the lipid bilayer of cells due to their lipophilic nature, and this will disrupt the membrane structure and fluidity of active cells (Wang *et al.*, 2012).

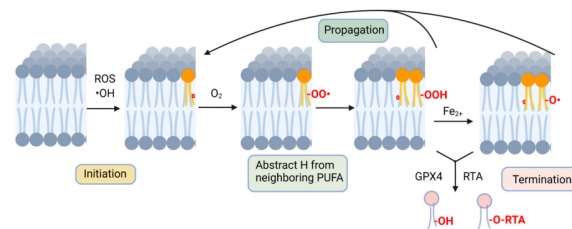


Figure 2. Non-enzymatic lipid peroxidation of PUFA (Mortensen *et al.*, 2023).

One of the proposed mechanisms for the anticancer effects of PUFA is the induction of lipid peroxidation (Ding and Lind, 2007). PUFA effects on membrane structure, peroxidation of highly unsaturated fatty acids has been associated with cytotoxicity in neoplastic cells. In response to oxidative stress, PUFAs undergo free radical chain reaction degradation, resulting in the formation of fatty acid hydroperoxides and hydroxides as immediate products and aldehydes, among other end products. Either in cultured tumor cells or in tumor-bearing animals, PUFA supplementation caused a decrease in cell proliferation or tumor growth that correlated with a concomitant increase in the level of cellular lipid peroxidation. These observations suggest that PUFAs interfere with tumor cell proliferation *in vitro* and *in vivo* through the formation of oxidation products. A number of lipid hydroperoxides and aldehydes

derived from lipid peroxidation have been implicated as causative agents in cytotoxic processes in neoplastic cells (Germain *et al.*, 1998).

Other notable substances of *Sacha inchi* plant is phenolic. Phenolic compounds are known to possess anticancer properties, with their antioxidant activity being the primary factor contributing to this effect. They act as strong radical scavengers, metal chelators, modifiers of endogenous defense mechanisms such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidases (GPx), enhancers of glutathione (GSH) redox status. Additionally, they regulate diverse proteins and transcription factors such as nuclear factor erythroid related factor (NRF2) (Chander, 2018). Moreover, their anticarcinogenic effects are associated with their ability to inhibit cell proliferation (extracellular signal-regulated kinase (Erk)1/2, D-type cyclins, and cyclin-dependent kinases (CDKs)), angiogenesis (vascular endothelial growth factor (VEGF) and MIC-1), as well as to suppress oncogenic signaling cascades (phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt)), induce apoptosis, and prevent cellular migration and metastasis (Abotaleb *et al.*, 2020).

Vitamin E (alpha-tocopherol), also found in the *Sacha inchi* plant, is an essential micronutrient and fat-soluble antioxidant with a proposed role in protecting tissues from uncontrolled lipid peroxidation (Galli *et al.*, 2022). A number of potential mechanisms have been proposed to explain how vitamin E compounds might exert beneficial protective effects against cancer. These include the following: the inhibition of cancer formation by the quenching of free radicals; direct effects on tumor cells, such as the control of tumor growth through the induction of differentiation; the inhibition or induction of the cell cycle; and the elimination of tumor cells by increased efficacy of antitumor actions by the immune system (Kline *et al.*, 2001).

Several studies showed flavonoid content in *Sacha inchi* leaves and husk as antioxidant (Kittibunchakul *et al.*, 2022;

Thuanthong *et al.*, 2023). Almost every group of flavonoids has a capacity to act as antioxidants (Panche *et al.*, 2016). The best characterized mechanism of antioxidant action of flavonoids is due to their ability to interact with ROS by scavenging or reducing them (Speisky *et al.*, 2022). A second mechanism of the antioxidant action of flavonoids, in which the oxidation of its phenolic moieties is also involved, is an "indirect mechanism" where these compounds do not directly interact with ROS but with certain proteins that, via the regulation of gene expression, ultimately upregulate the cell's endogenous antioxidant capacity (Erlank *et al.*, 2011; Dinkova-Kostova and Talalay, 2008). In this mechanism, the oxidation of some of the flavonoid's phenolic moieties would constitute a step needed to subsequently exert its antioxidant action (Speisky *et al.*, 2022).

Some studies have demonstrated the antioxidant properties of *Sacha inchi* leaves and husk, with flavonoids identified as a key component (Kittibunchakul *et al.*, 2022; Thuanthong *et al.*, 2023). It is notable that almost every group of flavonoids has the capacity to act as antioxidants (Panche *et al.*, 2016). The most thoroughly researched mechanism of the antioxidant action of flavonoids is their capacity to interact with ROS by scavenging or reducing them (Speisky *et al.*, 2022). A second mechanism of the antioxidant action of flavonoids, in which the oxidation of its phenolic moieties is also involved, is an "indirect mechanism." In this mechanism, these compounds do not directly interact with ROS but with certain proteins that, via the regulation of gene expression, ultimately upregulate the cell's endogenous antioxidant capacity (Erlank *et al.*, 2011; Dinkova-Kostova and Talalay, 2008). In this mechanism, the oxidation of some of the flavonoids' phenolic moieties constitutes a necessary step for the subsequent exertion of their antioxidant action (Speisky *et al.*, 2022).

In addition to studies demonstrating the antioxidant activity of *Sacha inchi* extracts, two studies were identified that

examined the anticancer effects of plant extracts on cancer cells. These studies revealed the presence of additional mechanisms beyond antioxidants, including apoptosis induction and cell cycle arrest (He et al., 2023; Nascimento et al., 2013). This represents a preliminary investigation into the potential mechanisms underlying the numerous beneficial effects of Sacha inchi. This review indicates that Sacha inchi has the potential to be an anticancer agent, as it has been shown to suppress oxidative stress, induce apoptosis, and arrest tumor cell growth. However, further research is necessary to develop this agent into a viable anticancer treatment. In particular, the cellular pathways involved in these effects must be elucidated.

This study represents the first systematic review to discuss the potential of Sacha inchi as an anticancer agent. The review study has been conducted as comprehensively as possible, with a wide range of search studies and databases, in order to explain the potential of Sacha inchi to fight cancer in in vitro and in vivo studies. This study serves as a foundation for further research on Sacha inchi. However, it is important to note that this study is not without limitations, including the absence of quality assessment and the inherent limitations of the researchers involved.

5. CONCLUSION AND SUGGESTION

The Sacha inchi plant contains numerous compounds with antioxidant and anticancer properties. The most prevalent compounds identified were polyunsaturated fatty acids (PUFAs) and phenolic compounds. Other substances, including tocopherol, peroxide, amino acids, steroids, terpenoids, flavonoids, and proteins, were also identified. PUFAs are essential fatty acids, including omega-3 and omega-6, which can induce the formation of lipid peroxidation derivatives such as lipid hydroperoxides and aldehydes, which disrupt the structure and fluidity of cancer cell membranes, thereby inhibiting tumor proliferation. Phenolic compounds exhibit

anticancer activity, primarily due to their antioxidant properties, which can inhibit free radicals. Other

Additional in vivo research will be needed to substantiate these findings, allowing for a more comprehensive exploration of the benefits associated with sacha inchi content. This information can then be used as the basis for further clinical studies, which can be conducted in a real-world setting.

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