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Review Article

Pharmacological Potential and Mechanisms of Action Involved in Oil Species from the Brazilian Amazon: The Case of *Abelmoschus esculentus* L. Moench, *Euterpe oleracea* Martius and *Bixa orellana* Linné

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ABSTRACT

The chemical versatility of vegetable oils, attributed to biological properties, constitutes great value for the economic, technological and nutritional sector, promoting the interest of these Amazonian natural resources. The oils present variations in their chemical composition, regarding the presence of fatty acids with promising biological properties. The species *Abelmoschus esculentus* L. Moench, *Euterpe oleracea* Martius and *Bixa orellana* Linné, have pharmacological activities. Although these species are the subject of many studies, most of the scientific information is not related to the use of their oils. Therefore, this study aimed to review the secondary metabolites of vegetable oils of these species with pharmacological potential, such as antihypercholesterolemic and mechanisms of action involved, aiming to make the use of oil from such species in the field of drug innovation opportune. Therefore, the research was carried out using the following databases: CAPES, PubMed, Science Direct (Elsevier), Springer-Nature, SciELO and Google Scholar journals, using keywords such as *A. esculentus, E. oleracea, B. orellana*, correlated with oils, seeds, secondary metabolites, fatty acids and mechanisms of action. The species showed great bioactive activity attributed to their oils, especially in the anti-hypercholesterolemic activity, which can be explained by several pathways of gene expression mechanisms such as the interaction of peroxisome proliferator-activated receptors (PPARs), hepatic X receptors (LXRs), hepatic nuclear factor-4 (HNF4) receptors and sterol regulatory element binding proteins (SREBPs) that act on lipid modulation. The species have great pharmacological potential, especially in view of the use of their vegetable oils against the modulation of metabolic disorders.

Keywords: Pharmacology, Phytochemistry, Oil, Fruits, Seeds.

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INTRODUCTION

Medicinal plants have been used since the beginning of civilizations because they have numerous benefits to human health, including therapeutic purposes.[1] Knowledge of medicinal species is based on observation and experiences of native peoples.[2] It is from this ethnoknowledge that plant species make up the daily lives of populations, from food to curing diseases.[3]

Knowledge about the medicinal properties of plants in the Amazon Biome contributes significantly to the development of biologically active compounds.[4] The traditional use of plant species with medicinal and functional potential constitutes an important tool for the development of scientific research, as well as for the valorization of natural resources.[5]

The Amazon is home to numerous plant species that produce oilseeds.[4-6] The extraction of vegetable oils is a common practice in Brazilian culture, due to the peculiar physicochemical properties that such oils present in their composition.[7] The variability of oils derived from plant species results in several applicability, as they have biological properties of great value for the economic, technological and nutritional sector, promoting the interest of these Amazonian natural resources.[8]

Due to the numerous possibilities of using these oils, allied to the plant potential of the Amazon region, the demand for bioactive and renewable raw materials from oilseeds has been growing in recent Years.[9] Obtaining vegetable oils from various oilseeds has become conventional to replace animal-derived oils.[10] The interest in the consumption of vegetable oils is due to a number of factors, such as technological development, production cost,

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versatility of the use of these oils in the cosmetics, food and pharmaceuticals industry.[11]

Oils are formed by molecules of triglycerides, derived from a chemical bond of a molecule of glycerol with three molecules of fatty acids, which represent the major components, in addition to exhibiting minor components such as phospholipids, waxes, hydrocarbons, sterols, higher alcohols, pigments and fat-soluble vitamins (A, D, E and K).[12,13] Vegetable oils, obtained from seeds, present variations in their chemical composition, provided according to the degree of unsaturation of each oilseed species.[14] Vegetable oils from seeds contain essential fatty acids, free of trans fats or cholesterol, and fat-soluble vitamins.[14]

Fatty acids have distinct physicochemical properties.[14] In general, saturated fatty acids are solid at room temperature, while mono and polyunsaturated fatty acids have liquid characteristics.[10] The main saturated fatty acids present in the oils are palmitic and stearic, and the unsaturated ones present the oleic, linoleic and linolenic acids.[12]

Essential fatty acids are not synthesized by the human body, such as linoleic and alpha-linolenic acid, so they must be present in the diet so that they can be used by the tissues.[12] Through the action of specific liver enzymes, essential fatty acids give rise to long-chain polyunsaturated fatty acids, which play an important role in health promotion, acting as regulators of several key genes in disease prevention,[15-17] especially for triggering cardioprotective effects, modulating anti-hypercholesterolemic and anti-inflammatory responses.[18-21]

The nutritional value of unconventional oils is a promising alternative for human consumption, as it presents active substances with a significant role due to biological activities.[11-22] Many species are used as bioactive and renewable sources, including *Abelmoschus esculentus* (L.) Moench (okra), a shrub, with fruits in a greenish capsule, containing spherical seeds, with high mucilage when immature, or fibrous as they mature.[23,24]

Okra has excellent bioavailability, low cost and high nutritional and nutritional value.[23-25] It consists of essential nutrients, such as vitamins A, C and E, in addition to providing important mineral compounds for the functioning of the human body.[26,27] The seeds have a high oil content, being a potential non-conventional oilseed source, which can be equated with the composition of oilseeds such as soybeans, peanuts, sesame, among others.[28]

Euterpe oleracea Mart., popular açaizeiro, is a fruit tree of great socioeconomic relevance in the Amazon, due to its potential for full use.[29] With peak production of its fruits, between the months of July and December, it is a species originating from flooded areas and of high natural regeneration.[30] It has smooth globose fruits, violet in color at maturity, known as açaí.[30,31] From the ripe fruit, açaí juice is obtained, commonly consumed by the Amazonian population.[29] It is considered a dietary food supplement due to its high antioxidant content of natural origin,[32] being used as a functional food for health promotion because it has several therapeutic activities.[33]

From the pulp of the fruit, we can obtain an oil, which is characterized as a fluid with a dark green color and a distinct aroma, reminiscent of the açaí berry.[34] Acai oil has 50% total pulp dry matter and has a lipid profile rich in mono- and poly-unsaturated fatty acids.[35] The lipid profile of acai oil is similar to olive oil and avocado oil, which qualifies it as a special edible oil.[36] In addition, acai oil is widely used in folk medicine.[30,31]

Oils obtained from seeds are reported for their medicinal value and functional characteristics, such as *A. esculentus* and *E. oleracea* oils, there is an important plant species with similar functional properties, the species *Bixa orellana* L., known in Brazil as annatto.[37] The species produces a capsular fruit and its interior consists of reddish orange seeds.[37,38] The pigment is due to the bixin component, representing 80% of all carotenoids present in the seeds.[39] *B. orellana* dye is widely used in industry, in the production of dietary supplements, cosmetics, food, textiles, and the manufacture of paints and varnishes.[40,41]

The oil extracted from the seeds of *B. orellana* has significant scientific interest due to its high amount of bioactive compounds.[42] The species has a lipid fraction of fatty acids of great biological importance.[43] The seed oil is composed of tocotrienols, mainly δ-tocotrienol, an advantageous pharmacological compound with antioxidant, anti-inflammatory, anti-dyslipidemic and anti-hyperglycemic effects.[44-46]

In order to understand the potential metabolic effect of these Amazonian vegetable oils, the present review seeks to provide information on the chemical composition, biological properties, especially the anti-hypercholesterolemic activity and its mechanisms involved, of oils obtained from seeds and fruits of *A. esculentus*, *E. oleracea* and *B. orellana*. Bearing in mind that these natural resources are promising sources of functional bioactive substances for development purposes in pharmaceutical innovation. It is of fundamental importance to know research that addresses the chemical characteristics of oils derived from unconventional oilseeds, for the use of these compounds as an alternative treatment or complementary to the conventional treatment of chronic diseases, such as dyslipidemias. The development of new drugs of natural origin associated with the modulation of lipid metabolism against the expression of important transcriptional targets has a fundamental role in the management of metabolic diseases, in order to direct biological tests based on the bioactive action of species of great economic importance.

MATERIALS AND METHODS

This study constitutes an analytical bibliographic study. The present review relates the mapping of secondary metabolites of vegetable oils of the species *A. esculentus*, *E. oleracea* and *B. orellana* and the studies on their pharmacological anti-hypercholesterolemic potential and mechanisms of action involved.

For this, data collection was performed using the following electronic databases: CAPES, PubMed, Science Direct (Elsevier), Springer-Nature, Scielo and Google Scholar journals. The inclusion criteria for this work were: original articles and dissertations exclusive to the species under study, with full text available in Portuguese, English or other languages. As for the search strategy, the descriptive words used in this work were: *Abelmoschus esculentus* (L.) Moench, *Euterpe oleracea* Mart and *Bixa orellana* L.; correlated with oils, seeds, secondary metabolites, fatty acids and gene regulation mechanisms.

BOTANICAL DESCRIPTION

Abelmoschus esculentus (L.) MOENCH

The species *Abelmoschus esculentus* (L.) Moench. was classified in 1737 by Linnaeus as *Hibiscus sculentus* L. and *Hibiscus longifolius* Roxb. Based on the characteristics of the capsule, Medikus (1787) proposed to elevate the previously defined classification to a distinct genus. From 1974 onwards, Terrel and Winters[47] defined it as *Abelmoschus esculentus* (L.) Moench due to the botanical aspects of its peculiar spataceous calyx.[47-49] *Abelmoschus* means source of musk, from the Arabic "abul-lmosk", alluding to the musky aroma produced by its seeds, this odor is used as an ingredient in perfumery.[50-51]

The species belongs to the Kingdom Plantae, Division Magnoliophyta, Class Magnoliopsida, Order Malvales, Family Malvaceae, Genus *Abelmoschus*, Species *A. esculentus*.[47-52] *A. esculentus* has several synonyms, such as *Abelmoschus bammia* Webb, *Abelmoschus longifolius* (Willd.) Kostel., *Abelmoschus officinalis* (DC.) Endl., *Abelmoschus praecox* Sickenb., *Abelmoschus tuberculatus* Pal and Singh, *Hibiscus esculentus* L., *Hibiscus hispidissimus* A. Chev. name Illeg., *Hibiscus longifolius* Willd., *Hibiscus praecox* Forssk.[48-54] As for the region of origin of the species, it is believed that *A. esculentus* was first found in Ethiopia, later on the African continent, and propagated to Western regions, India, Southern Europe, Asia, the Philippines and the Americas.[55,56] Popularly, *A. esculentus* is called "girl's finger", due to the pointed tip of the fruits, which resembles a projection of a long finger.[57] It also receives other popular names, according to the region in which it is found, among them quiabeiro (Portuguese), abelmosco, bâmia, benda, bendé, bend ó, calalu, gobo, gombô, guingombô, kin gombô, quiabeiro-horn-de deer, common okra, quimbombô, quingobó, okra, gumbo and lady finger (English), gombo (French), okra (German and Italian), quimbobó and quimgombó (Spanish), bendi, bhindi, ockro, okra, Vendai (Hindu), Huang-shu-k'uei (Chinese).[52-58]

A. esculentus is traditionally cultivated in tropical, subtropical and warm temperate regions, being widely cultivated in India (the main producer of okra), regions of North America, Southern Europe and Germany.[59-60] In Brazil, the cultivation of okra was introduced through the slave trade, spreading throughout all regions of the country, through culture and eating habits, mainly in the Northeast and Southeast regions.[61] It is a species with high climatic adaptability, fast growth, easy cultivation, high resistance to pests and does not require advanced technology to be cultivated, being economically viable for production.[23-25]

The shrub *A. esculentus* develops annually, reaching an average height of 4m. It has a semi-hardwood main stem, five-lobed alternating polymorphic leaves, hermaphrodite flowers from 5 to 10 cm in diameter, 5 to 8 petals of white or yellow colors, with a red or purple base, similar to hibiscus, dispersed singly in a peduncle of up to 2.5 cm long.[57-62] Fruits with a greenish capsule, slightly curved, in a six-chambered pod and fibrous texture, when immature they have high mucilage, becoming fibrous as they mature.[63,64] The fruit reaches about 10 to 30 cm in length, about 1 to 4 cm in diameter, inside it is full of spherical or ovoid seeds, gray to black in color.[57-64]

Euterpe oleracea martius

The *Euterpe oleracea* Martius palm received the generic epithet in allusion to the goddess Euterpe from Greek mythology, which means elegance of the forest, due to the natural beauty of the species.[65-68] While the term *oleracea,* comes from the aroma and color of the fruits, which resemble wine, both in the pulping process and in the beginning of fermentation of the drink.[69]

The taxonomy of the species is arranged in Kingdom Plantae, Division Magnoliophyta, Class Liliopsida, Subclass Arecidae, Order Arecales, Family Arecaceae, Subfamily Arecoidae, Genus *Euterpe*, Species *Euterpe oleracea* Martius.[70] The species has numerous synonyms in the botanical literature, such as Catis martiana O.F. Cook, *Euterpe badiocarpa* Barb. Rodr., *Euterpe beardii* L.H. Bailey, *Euterpe brasiliana* Oken; *Euterpe cuatrecasana* Dugand.[71,72]

E. oleracea is a tropical palm, typical of the Amazon estuary, popularly known as açaizeiro.[73] It is a spontaneous species from the Brazilian territory, found in the states of Amapá, Maranhão, Mato Grosso, Pará, Tocantins; also in other South American countries, such as Venezuela, Colombia, Ecuador, Suriname and Guyana; and in Central America (Panama).[74] In Brazil, according to the region where it is found, morphological varieties and the communities that use them, the palm tree receives several popular names: açaí de touceira, açaí do Pará, açaí do estuary, açaí do Baixo Amazonas (Northern Region); Juçara (Northeast).[75] Due to its variety of coloration, it is also known as purple, white, sword, ox-blood, una, tinga and chumbinho,[31] being more commercialized, the purple and white açaí.[76]

Açaí is a fruit widely cultivated in the Amazon region and widely consumed because it provides several benefits to human health, such as antioxidant activity.[34] The pulp is consumed daily by the population of several Brazilian states, especially in the northern region of Pará, Maranhão, Amazonas, Amapá, Acre and Rondônia, which are also the main producing and exporting states of açaí.[67-77] The species *E. oleracea* is easy to manage in the Amazon estuary, in lowland soils, located mainly in large regions of Pará and Amapá, which have areas of constant rainfall.[67] It is

a species with high adaptability in periods of flooding and high productivity, due to aerial roots with lenticels and aerenchyma, which allow them to dominate in certain areas.[67,68]

E. oleracea reaches 3 to 20 m in height, has a smooth and cespitose stem of 7 to 18 cm in diameter, gray in color and with lichen spots, it can present shoots from a dispersion unit, forming clumps.[67-76] This stipe can also reach a height of 4 to 30 m. Above the stem, the inflorescences are born and each one of them bears a bunch of hundreds of fruits, ranging from 4 to 8 bunches of fruits per plant. Its leaves are flat pinnate, light green in color, with a petiole of 20 to 40 cm and a total length of 2 to 3.5 meters.[68] The açaizeiro fruits are surrounded by a fibrous tissue, covered by a thin, dry and oily pulp layer; they are drupaceous, globular in shape, rounded with a diameter of 1 to 2 cm, smooth, black-purple;[76] with fibrous mesocarp, thickness of approximately 1 mm.[78] The açaí seed corresponds to 70 - 85% of the fruit size.[76-79]

Bixa orellana linné

The plant species *Bixa orellana* Linné received its scientific name after an expedition carried out in the Northern Amazon region by Francisco Orellana.[41-80] This species originated in the tropical region of the Americas, being native in Brazil, as well as in other regions of South and Central America. It is widely cultivated in tropical countries such as Peru, Mexico, Ecuador, Indonesia, India, Kenya and East Africa.[80,81]

As for its taxonomy, it comprises the division Angiospermae, subdivision Angiosperma, class Dicotiledoneae, order Parietales, suborder Cistianeae, family Bixaceae, genus Bixa and species *Bixa orellana* Linné. The scientific of the species has several synonyms, such as *Bixa americana* Poir., *Bixa purpurea* Sweet, *Bixa upatensis* Ram. Goyena, *Bixa tinctaria* Salisb.[82]

In Brazil it is popularly known as annatto and saffron.[81] The name of the fruit "urucum" means red in the Guarani language "ru-ku".[37] The annatto has different names, such as atole, achiote and bija (Peru, Colombia and Cuba); achiote, bija, onoto (Venezuela); uruku (Paraguay); rocou and rocoyer (Dominican Republic and French Guiana); rocuyer (France); changuaricá, pumacuá and K'uzub, (Mexico); uñañé, eroyá, chagerica, orelana, ranota, annatto and lipstick (USA).[80]

B. orellana L. is a shrub about 6 meters tall, with a coffee brown trunk, alternate heart-shaped, pointed leaves, arranged in a spiral, 8 to 20 cm long and 4 to 15 cm wide are greenish in color on both sides and with extended petioles.[37-83] Its fruits are oval thorny, containing around 30 to 60 seeds per capsule, orange-red in color, 0.3-0.5 cm long and 0.2-0.3 cm in diameter (Figure 1).[37,38]

The main pigment present in the seeds of *B. orellana* L. is bixin, which has a red-yellow color, representing 80% of all carotenoids present in the seeds.[39] Bixin is oil-soluble, being the only natural carotenoid with two carboxylic groups,[84] this substance has important biological activities.[85] This pigment has several applications in the food, chemical, cosmetic and pharmaceutical sectors, presenting great health benefits due to its biological activities.[86,87]

TRADITIONAL USE

Abelmoschus esculentus (L.) Moench

Okra is traditionally used due to its multiple properties, being widely used in cooking and folk medicine.[88] It is widely cultivated in northeastern Brazil and appreciated in several dishes of Brazilian cuisine, being an important ingredient both in food and in folk medicine.[25,89]

Okra has a pleasant taste; provides satiety, refreshness, astringency and high yield; It is also used as an aphrodisiac agent.[25] Consumption occurs mainly as an immature vegetable, having a mucilaginous consistency after cooking.[24] Due to its emollient and demulcent characteristics, a large part of the plant is edible.[52] In traditional medicine, various parts of the okra, such as leaves, buds, flowers, pods, stems and seeds, are used.[88]

Okra leaves are consumed in salads, fresh or cooked, while the seeds can be roasted and ground, for later preparation of decaffeinated coffee.[90] Seed powder is used as a substitute for aluminum salts in water purification.[91] The seeds are a source of oil and protein, with significant amounts of amino acids and unsaturated fatty acids.[28] Other reported uses of the species are the use of fibers from mature fruits and stems of okra in the paper industry.[92]

In the ethnomedicine of different cultures, okra is useful to treat chronic dysentery, diarrhea, gonorrhea and urinary secretions.[93] as well, to promote diuretic effect.[94] Its roots have a demulcent action, the mucilage being used as plasma replacement; the juice of the roots is used topically in dressings of cuts, wounds and boils; they are also used as an infusion in the treatment of syphilis.[52] Fruit infusions treat dysentery and acute diarrhea; inflammation, stomach and intestinal irritation; kidney infections, burning urine, dysuria and gonorrhea.[52-93] The decoction of the fruits has emollient, demulcent and diuretic properties, in addition to being used in spermatorrhea.[62] The seeds are antispasmodic, stimulant and sudorific.[52,93-95]

Okra is considered a plant of great nutritional value, as it contains essential nutrients for the body, such as Vitamins A, C and E; mineral compounds, including sodium, potassium, magnesium and calcium; in addition to trace elements such as zinc, iron and nickel.[26,27] Due to the presence of various substances and polysaccharides, the okra fruit has great benefits for the digestive system, especially for intestinal functioning.[96] For its antioxidant and anti-inflammatory activity, okra is used to treat asthma, abscesses, and bronchitis.[96,97]

Its seeds are rich in minerals, gamma-tocopherols, fat-soluble pigments,[98] polyphenols and flavonoids,[99] they have antibacterial activity and expressive antioxidant effect.[100,101] A quantitative ethnomedicinal survey carried out in India by Esakkimuthu *et al.*[102] showed that *A. esculentus* was one of the plants referred

for the treatment of chronic metabolic diseases, especially type 2 diabetes.

Euterpe oleracea Martius

The açaí, fruit of the açaizeiro, is part of the basic diet consumed by the populations of the northern region of Brazil, it is considered as one of the most nutritious fruits of the Amazon Basin, due to its high energy and nutritional properties.[9] The açaí juice is obtained from a thin layer of pulp, extracted by friction from the fruit peel, manually or mechanically, with the addition of water; resulting in a violet colored drink, which supplies the national and international food market.[103] It is consumed in the form of beverages, supplements and food preparations, as well as in the industrial or artisanal production of juices, ice cream, popsicles and jellies, in addition to medicinal use.[32,104,105]

The active substances responsible for the benefits attributed to the Amazon açaí are related to its chemical composition, such as phenolic compounds, flavonoids and anthocyanins.[106] Its bioactive properties have aroused great interest in the food, cosmetic and pharmaceutical industries,[107-109] due to descriptions reported by popular use in Amazonian communities.[9-29]

Different parts of the plant are traditionally used by Amazonian communities. The leaves are used to cover houses and greenhouses for planting açaí trees.[110,111] In ethnomedicine, they are used for the treatment of snakebites, muscle and chest pain, while the leaves and roots are useful against jaundice and in anti-inflammatory and antimalarial activities.[112,113] Change to Açaí seeds are used for handicrafts as well as organic fertilizer.[32]

The oil extracted from the pulp of the fruit is used as an antidiarrheal and in combination with other medicinal plants, as an antimalarial.[113] Bernaud and Funchal[114] obtained the fixed oil of *Euterpe oleracea*, through the dry pulp of the fruit, which has a rich composition of omega-6, indicated for hydration of dry and aged skin. Another component extracted from this plant species is the palm heart, of great economic and social relevance in the Amazon region.[32]

Açaí is considered a special food because it contains dietary properties, in combination with its lipid composition, bringing numerous health benefits.[9] It has a high content of protein, dietary fiber and antioxidant compounds and low levels of sugars in its composition.[76] In addition to containing large amounts of vitamins A, C and E and minerals such as iron, zinc, copper, potassium.[30] It also has sterols and carotenoids, compounds directly related to the antioxidant, anti-inflammatory, antimicrobial and anticarcinogenic activities of the species.[30,115]

Bixa orellana Linné

The species *Bixa orellana* is a natural source of red dyes from its seeds, the first record of the use of annatto refers to the traditional indigenous use for medicinal and commemorative purposes.[106] The pulp of the seeds of the species is used topically by indigenous peoples to enhance the color of the lips, which gave rise to the nickname of *B. orellana* as the lipstick tree.[116]

In Brazilian cuisine, annatto, popularly called paprika, is used in powder form to enhance the color of food.[117] Annatto is part of the bleaching process for dairy products, in bakery, desserts, dehydrated foods, rice flour, corn starch, oils, fats and beverages; in the textile industry; paint production; in the pharmaceutical sector; cosmetics and perfumery.[118-121]

In traditional medicine, several parts of the species are used, such as seeds, bark, roots, leaves, in addition, the essential oil extracted from the seeds is used for the treatment of various pathologies.[122] The infusion of the leaves has been shown to be effective against bronchitis, sore throat and eye inflammation.[123] The pulp, obtained from annatto seeds, is used in the production of soft drinks and febrifuges;[121,122] are also used as a condiment, laxative, cardiotonic, hypotensive, expectorant and antibiotic. Ethnomedicinal application likely derives from effects such as anti-inflammatory activity (treatment of bruises, wounds and bronchitis) as well as being used for wound healing purposes.[37]

The oil obtained from annatto seeds is used as an astringent, bactericidal, antioxidant compound, as well as in the control of cholesterol levels and reduction of triglyceride levels.[85] The species is also used in bruises, burns, sore throats, as well as asthma, as it has anti-inflammatory and healing properties.[121]

BIOACTIVE METABOLITES OF VEGETABLE OILS AND MAIN PHARMACOLOGICAL ACTIVITIES

Abelmoschus esculentus (L.) Moench

Vegetable oils have a large amount of unsaturated fatty acid chains, without the presence of trans fats and cholesterol.[14] The nutritional value attributed to the seeds of many plant species has provided an alternative source of lipids for human consumption.[23] Among them, the oil from the seeds of *A. esculentus* stands out, which contains substances of paramount importance for human nutrition.[124] Scientific studies have shown that compounds present in *A. esculentus* seed oil induce potential beneficial effects on human health, such as the prevention of chronic diseases.[125,126]

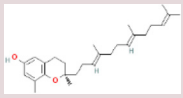
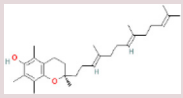
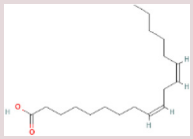
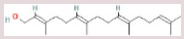
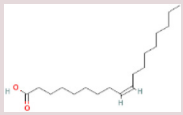
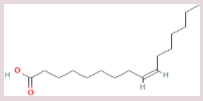
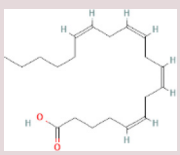
Gemede[125] and Gemede[127] when determining the molar ratios and the bioavailability of *A. esculentus* consumed by indigenous Ethiopians, identified in the composition of the seeds a large amount of high quality proteins, presenting essential amino acids of great importance when compared to others vegetable protein sources. *A. esculentus* seeds are a source of carbohydrates, dietary fiber and minerals, such as potassium, phosphorus, magnesium, calcium and iron;[125] are high in Vitamin E, a powerful natural antioxidant, of great nutritional importance and potential for improving human health.[125] In addition, they have other important antioxidants, such as phenolic compounds, flavonoids, catechins and oligomeric derivatives.[128] They are also sources of triacylglycerides, phytosterols, and phospholipids.[129]

A. esculentus seeds have a high oil content, at a concentration of 20 to 40%, and can be compared to the composition of oilseeds such as soybeans, peanuts, sesame, among others.[27-28,127,130,131] This percentage is certainly related to factors such as seed variety, climatic conditions, temperature and extraction methods used.[23] Oil extraction from *A. esculentus* seeds occurs by several pharmacognostic methods, such as the use of solvents (chemical methods), physical methods or a combination of both. Since chemical extraction generally obtains a greater amount of oil compared to mechanical extraction.[132,133]

Ames and Macleod[134] reported the 148 volatile components of *A. esculentus* oil, with citronylyl esters and pyrroles being the most predominant. Andras[135] obtained a yield between 15.9 and 20.7%, when using supercritical carbon dioxide in the extraction of oil from *A. esculentus*. Dong[136] demonstrated greater efficiency of oil extracted by screw press with greater expression than by extraction of supercritical carbon dioxide and by solvent.

The chemical composition of vegetable oils in relation to the presence of fatty acids can determine the use of these oils for various purposes such as food and/or therapeutics.[23] Depending on the region where it was grown, genotype and extraction medium, the oil from the seeds of *A. esculentus* has different proportions in its constituents,[130] predominating unsaturated fatty acids, mainly polyunsaturated

Table 1: Secondary metabolites of *A. esculentus*, *E. oleracea* and *B. orellana* species and pharmacological activities.

Molecular Formula		Isolated or characterized constituent	Pharmacological activity	*A. esculentus*	*B. orellana*	*E. oleracea*
$C_{27}H_{40}O_2$		δ-tocotrienol	Antidiabetic; Anti-hypercholesterolemic; Anti-inflammatory; Antioxidant[8,169,170]	Fruit	Seed	
$C_{29}H_{44}O_2$		α-tocotrienol	Antidiabetic; Anti-hypercholesterolemic; Anti-inflammatory; Antioxidant[8,169,170]	Fruit	Seed	
$C_{18}H_{32}O_2$		Linoleic Acid	Anti-hypercholesterolemic; Anti-inflammatory; Antioxidant; Chemical mapping[23,28,43,146]	Seed Fruit	Seed	Fruit
$C_{20}H_{34}O$		Geranylgeraniol	Anti-hypercholesterolemic; Anti-inflammatory; Chemical mapping[8,168,171]		Seed	
$C_{18}H_{34}O_2$		Oleic Acid	Anti-hypercholesterolemic; Antioxidant; Chemical mapping[23,42,106]	Fruit Seed	Seed	Fruit
$C_{18}H_{36}O_2$		Stearic Acid	Anti-hypercholesterolemic; Antioxidant; Chemical mapping[43,136,140,146,159]	Fruit	Seed	Fruit
$C_{16}H_{30}O_2$		Palmitoleic Acid	Anti-inflammatory; Antinociceptive; Antioxidant[136,139,140,150]	Seed Fruit		Seed Fruit
$C_{14}H_{28}O_2$		Myristic Acid	Anti-inflammatory; Antinociceptive; Antioxidant[28,139,140]	Seed		Fruit
$C_{16}H_{32}O_2$		Palmitic Acid	Anti-inflammatory; Antinociceptive; Antioxidant[43,137,138,148]	Seed Fruit	Seed	Fruit
$C_{20}H_{32}O_2$		Arachidonic Acid	Anti-inflammatory; Antioxidant[43,139,140,146]		Seed	

Authors 2022.

Figure 1: Species *Abelmoschus esculentus* L. Moench., *Euterpe oleracea* Martius. and *Bixa orellana* Linné. (6x15,81).

fatty acids,[98] in addition to the presence of saturated fatty acids.[28]

Soares[23] showed significant levels of proteins (22.14%), lipids (14.01%) and large amounts of unsaturated lipids (66.32%), especially oleic (20.38%) and linoleic acids (44, 48%), in okra cultivated in northeastern Brazil. Mostly, other studies identified the presence of 33.5% of linoleic acid, 25.2% of palmitic acid and 19.3% of oleic acid, which represent more than 70% of the total fatty acids.[137,138] Anwar,[130] Jarret,[28] Dong,[136] Awolu,[139] and Acikgoz,[140] exhibited similar values in the oil composition of *A. esculentus* seeds, with the presence of acid myristic acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, linolenic acid and behenic acid.

Oleic (omega 9) and linoleic (omega 6) fatty acids, present in *A. esculentus* oil, have great health benefits,[28] such as reducing LDL cholesterol and triglycerides, without decreasing HDL cholesterol levels, in addition to balancing blood pressure.[23] *A. esculentus* seed oil has similarities, in terms of oleic acid content, with some industrially produced oils: corn oil (24.8%); linseed (18.9%); soybean (23.2%) and sunflower seed (17.7%).[141] It was observed in *A. esculentus* seed oil, in hexane extraction, the presence of high content of linoleic acid (44.48%), palmitic acid (28.74%) and oleic acid (20.38%).[23] Similar values were demonstrated in *A. esculentus* oil cultivated in Central America, which revealed a percentage of 42% of linoleic acid, palmitic acid (34%) and oleic acid (18%),[23,142] but the cultivated in India showed different values with low content of linoleic acid (0.1%).[23,143]

Euterpe oleracea Martius

The oil extracted from the pulp of *E. oleracea* is considered a valuable product due to its peculiar sensory characteristics and numerous health benefits.[141-144] The oil represents approximately 50% of the total dry matter of its pulp, it has a lipid profile rich in mono- and poly-unsaturated fatty acids; presents anthocyanins and phytosterols, properties that are similar to olive oil and avocado, qualifying it as a special oil.[35,36] The composition of *E. oleracea* oil consists of 73.9% unsaturated fatty acids and 27.5% saturated fatty acids.[76]

Nascimento[145] showed unsaturated fatty acids (71%), of which 60.81% were monounsaturated and 10.36% were polyunsaturated.

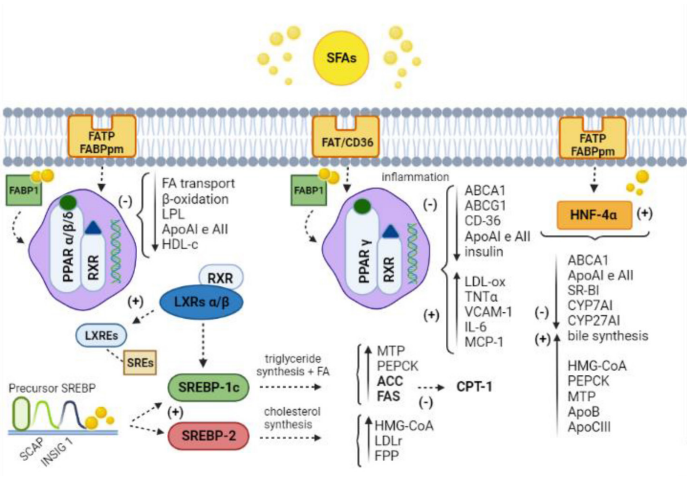


Figure 2: Mechanism of action proposed by SFAs in the gene regulation of cholesterol metabolism.
The proposed mechanism applies mainly to hepatocytes. SFAs are transported by fatty acid transport proteins (FATP), plasma membrane fatty acid binding protein (FABPpm), fatty acid binding protein-1 (FABP1) which is present in hepatocytes, and fatty acid translocase (FAT). /CD36). SFAs act as ligands for peroxisome proliferator-activated receptors (PPARs). PPARs (α,β/δ) form a heterodimer with the retinoid X receptor (RXR), giving rise to the PPAR-RXR complex. The decreased expression of PPARs (α,β/δ) by SFAs in the liver leads to an increase in cholesterol biosynthesis, promotes a reduction in β-oxidation, as well as the expression of lipoprotein lipase receptors (LPLr), blocking cholesterol transport, decreases transcription of ApoAI and ApoAII. PPARγ participate in the regulation of oxidized low-density lipoproteins (ox-LDL) in macrophages, triggering the increase in inflammatory molecules such as tumor necrosis factor-α (TNFα) and vascular adhesion molecules 1 (VCAM-1) and chemoattractant protein 1 of monocytes (MCP 1). SFAs induce SREBP-1c promoter activity, hence genes containing specific response elements (LXREs) or sterol sensitive response elements (SREs). As a result, it increases the (MTP), precursors of LDL, the gluconeogenic enzyme, phosphoenolpyruvate carboxykinase (PEPCK), increases the amount of ACC and FAS, the increased amount of this enzyme decreases the activity of carnitine palmitoyl transferase (CPT-1), resulting in in decreased mitochondrial oxidation. The SREBP2 pathway for cholesterol synthesis and preventing HMGCR degradation, elevates the expression of farnesyl pyrophosphate (FPP) and (LDLr), both with a concentrated effect on cholesterol synthesis. HNF-4α, SFA ligands, act to decrease the expression of ABCA1 and ABCG1, CD-36, as well as ApoAI and Apo AII, class B type I scavenger receptor (SR-BI), decreased biliary synthesis expression, by cytochrome CYP7A1 and CYP27A1. Therefore, increased expression of HMG-CoA, PEPCK, VLDL secretion, involving microsomal transport protein (MTP), ApoB lipoprotein and ApoCIII can be observed. (11,5x16,43).

in *E. oleracea* oil, by enzymatic route, however, by extracting the oil with ether, observed the composition of 68% of unsaturated acids, 60.33% monounsaturated and 7.83% polyunsaturated, demonstrating a difference of these acids according to the extraction method used. It is known that the main unsaturated fatty acids predominant in *E. oleracea* oil are oleic acid (56.2%), linoleic acid (11.5%) and linolenic acid (0.8%), the main saturated fatty acids are palmitic (24.1%) and stearic (1.6%).[146]

E. oleracea oil exhibits a high content of unsaturated fatty acids, with a mitigating effect on the inflammatory process, such as vasoconstriction, chemotaxis, adhesion, diapedesis, activation and cell death.[147] In its phytochemical composition, this oil has a high content of phenols, such as phenolic acids, vanillic acid,

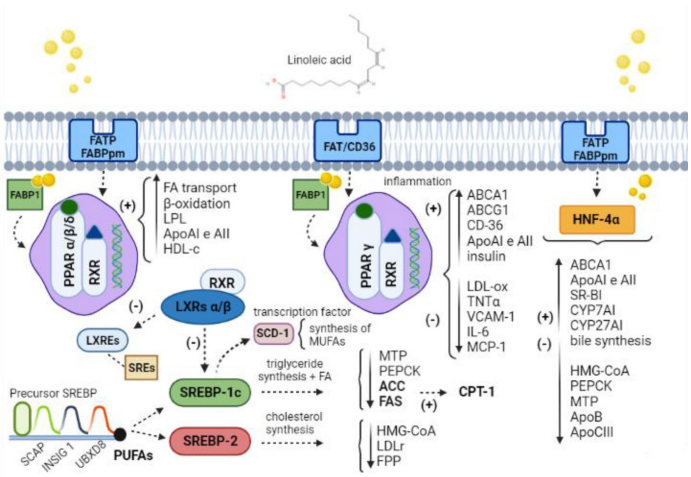


Figure 3: Mechanism of action proposed by PUFAs in the gene regulation of cholesterol metabolism.

The proposed mechanism applies mainly to hepatocytes. PUFAs are transported by fatty acid transport proteins (FATP), plasma membrane fatty acid binding protein (FABPpm), as well as fatty acid binding protein-1 (FABP1) that are present in hepatocytes and acid translocase. fatty acids (FAT/CD36). Several fatty acids, especially polyunsaturated fatty acids (PUFAs), act as ligands for peroxisome proliferator-activated receptors (PPARs). PPARs (α,β/δ) form a heterodimer with the retinoid X receptor (RXR), giving rise to the PPAR-RXR complex. Activation of PPARs (α,β/δ) by PUFAs in the liver leads to stimulation of fatty acid catabolism (FA), promotes fatty acid transport and β-oxidation, induces lipoprotein lipase (LPL) expression, increases transcription of the main apolipoproteins, such as ApoAI and ApoAII, present in high-density lipoprotein (HDL). PPARγ can elevate expression of LXRα, ABCA1 and ABCG1 in macrophages, CD-36 scavenger receptors, as well as ApoAI and Apo AII transcription that favors reverse cholesterol transport by HDL-c, as well as increased insulin. PPARγ participate in the regulation of oxidized low-density lipoproteins (ox-LDL) in macrophages, triggering the inhibition of inflammatory molecules such as tumor necrosis factor-α (TNFα) and vascular adhesion molecules 1 (VCAM-1) and chemoattractant protein 1 of monocytes (MCP 1). In addition to reducing the expression of genes involved in the synthesis of fatty acids and cholesterol by binding and inactivating UBXD8, thus inhibiting the proteolytic processing of the sterol regulatory element binding protein (SREBP) 1 that acts as a transcription factor is steril- CoA desaturase 1-(SCD-1), a key enzyme involved in the synthesis of monounsaturated fatty acids. SREBP-1c inhibits the expression of microsomal transfer protein (MTP), a protein necessary for the assembly and secretion of very low density lipoprotein (VLDL), LDL precursors, the gluconeogenic enzyme, phosphoenolpyruvate carboxykinase (PEPCK), as well as reduce the amount of ACC and FAS, the decreased amount of this enzyme elevates the activity of carnitine palmitoyl transferase (CPT-1), resulting in increased mitochondrial oxidation. PUFAs suppress SREBP-1c promoter activity by affecting the LXR-RXR activation pathway to LXREs and SREs. SREBP-2 is suppressed by the PPARα-RXR pathway, which leads to decreased expression of farnesyl pyrophosphate (FPP), HMG-CoA reductase, LDL receptor (LDLr) and reduced synthesis and uptake of cholesterol. HNF-4α acts to increase the expression of ABCA1 and ABCG1, CD-36, as well as the transcription of ApoAI and Apo AII, class B type I scavenger receptor (SR-BI), as well as acting on the expression of biliary synthesis as transcriptional regulator of the cytochrome enzyme gene CYP7A1 and CYP27A1. However, they act to decrease HMG-CoA, PEPCK, VLDL secretion, involving microsomal transport protein (MTP), ApoB lipoprotein and ApoCIII. (11,5x16,43).

syringic acid, protocatechuic acid and ferulic acid, in addition to catechins and procyanidins.[32,108,148] The presence of phytosterols in the oil has also been demonstrated: β-sitosterol, stigmasterol, δ-5-avenasterol, campesterol and cholesterol.[149]

E. oleracea oil has unique sensory properties, offering several health benefits, especially due to its antioxidant activity, due to phenolic compounds.[148] Such oil has α-tocopherol, known as Vitamin E and tocotrienols, compounds that prevent the lipid oxidation of the oil, providing stability for storage.[35-148] Phenolic compounds, especially vanillic acid, influence inflammation, making the oil a promising addition to foods, supplements, cosmetics, and medicines.[34]

Phytochemical studies of *E. oleracea* oil showed, mainly, the following fatty acids: palmitic (20.4%), palmitoleic (3.4%), stearic (1.3%), oleic (63.9%), linoleic (10.3%), linolenic (0.5%) and arachidic (0.05%).[148] Similar results were demonstrated by Dabaja.[150] regarding the composition of the oil, constituted by the majority presence of oleic acid (60%), palmitic acid (22%) and linoleic acid (12%). Demonstrating the rarity and value of *E. oleracea* oil from the Amazon flora, due to the high content of bioactive compounds, which qualify it as an edible oil and a promising natural product in the prevention of chronic and metabolic diseases.[151,152]

Bixa orellana Linné

The oil extracted from the seeds of *Bixa orellana* has been the subject of great interest due to the high amount of active compounds.[153] One of its main constituents is bixin, representing 80% of its composition, it is a carotenoid responsible for the pigmenting characteristic of coloring from yellow to red.[154] Norbixin is also found in large amounts in the oil. The yield of this oil may vary according to the extraction method used.[155,156]

B. orellana oil contains other constituents such as alkaloids, flavonoids, carotenoids, gallic acid, orelin, di, mono and sesquiterpenes, palmitic and linoleic acid, tocophenols and tocotrienols, with significant biological activities.[106,157,158] According to Costa,[106] the fatty acid composition of *B. orellana* oil showed the presence of linoleic acid (19.5%), followed by palmitic acid (15.5%), oleic (8.1%) and stearic (7.1%). While another study reported a higher concentration of palmitic acid (26.9%), linoleic acid (26.1%), oleic acid (17.5%), linolenic acid (15.1%), stearic acid (10.8%) and small amounts of eicosanoic acid (3.6%).[43]

Costa[106] *et al.* identified the presence of arachidonic acid in *B. orellana* oil. It is an important compound, as it is a precursor of prostaglandins and thromboxanes, produced in the inflammatory process.[159] It is also involved in brain and retina development in early life,[160] in addition to playing a key role in cell signaling and division.[161]

The oil from the seeds of *B. orellana* has several phenolic compounds, of significance for human health, related to biological functions, such as reducing the risk of inflammatory, degenerative and cardiovascular diseases.[162] As well, *B. orellana* seed oil is also an important natural source of δ-tocotrienols, antioxidant compounds, anticancer and often associated

with hypocholesterolemic effects, being more effective than tocopherols.[8,106,163] Furthermore, tocotrienols combined with bixin act synergistically to protect polyunsaturated fatty acids from the oxidation process.[164]

A study carried out by Santos[8] characterized annatto seeds, obtaining a concentration of geranylgeraniol above 30% and of tocotrienols around 10%. In addition to these compounds, a large amount of terpenes are found in *B. orellana* seed oil, reaching 57% of the total dry seed, other isoprenoids have been reported such as farnesylacetone, geranylgeranyl octadecanoate and geranylgeraniol.[8,165]

Particularly, in the external part of the seeds of *B. orellana* there is the presence of geranylgeraniol with levels close to 1%.[8,154,155] This compound constitutes an important intermediate in the biosynthesis of substances such as Vitamin K, tocopherols and tocotrienols, hormones and carotenoids,[8,166,167] Silva[168] when extracting and evaluating the concentration of this compound in seeds of *B. orellana* found values around 0.32% to 1.38% of geranylgeraniol (Table 1).

GENE REGULATION MECHANISMS OF FATTY ACIDS

Fatty acids (FA) are carboxylic acids containing only a carboxylate group (-COOH) linked to a hydrocarbon chain that can be saturated, with only single bonds between the carbons of its chains, or unsaturated with double bonds in its carbon chain.[172]

Saturated fatty acids (SFA) are obtained in the diet, mainly from animal and vegetable fats, such as butter, coconut oil and animal fat. Fatty acids can have medium-chain and long-chain classes, for example, myristic (14:0), palmitic (16:0) and stearic (18:0) acids.[173]

Unsaturated fatty acids (UFA) are obtained in the diet through vegetable oils, such as olive, soy, linseed and also fish, including salmon and sardines. They can be classified as monounsaturated (MUFAs), with only one double bond and polyunsaturated (PUFAs), containing two or more double bonds. Unsaturated fatty acids are classified according to the location of the first double bond in the carbon chain, starting from the methyl group, identified by the letter ω.[174] Long-chain SFAs such as palmitic acid (C16:0), myristic acid (C14:0) and lauric acid (C12:0) are known to raise plasma cholesterol. Studies for the modulation of (SFA's)in the plasma cholesterol concentration propose that (SFA's) are able to increase the resources for the biosynthesis of circulating cholesterol.[175]

For the regulation of cholesterol synthesis, cells have two feedback systems. The first concerns the biosynthesis of cholesterol, through the degradation of HMG-CoA reductase (HMGCR), an enzyme involved in the synthesis of cholesterol, from acetyl-CoA, through the mevalonate pathway. The second, at the transcriptional level, corresponds to the activation of the sterol regulatory element binding protein 2 pathway (SREBP2), both sensitive to changes in intracellular cholesterol levels. SFA's reduce intracellular cholesterol, trigger various cellular signaling, which leads to further activation of the cholesterol biosynthetic pathway.[175]

SFA's act by suppressing LDL (rLDL) receptor activity and blocking the transport of cholesterol from the plasma membrane to the endoplasmic reticulum, disrupting the balance between intracellular and extracellular cholesterol. As a result, cholesterol depletion in cells triggers the SREBP2 pathway for cholesterol synthesis and prevents HMGCR degradation, both of which have a concentrated effect on cholesterol synthesis (Figure 2).[176,177]

PUFAs are able to regulate several metabolic pathways through interaction around four transcription factor families: peroxisome proliferator-activated receptor (PPAR) (α, β/δ and γ), hepatic X receptors (LXRs) (α and β), hepatic nuclear factor-4 receptors (HNF4-α) and sterol regulatory element binding proteins (SREBPs) 1 and 2 (Figure 3). These transcription factors play an important role in the hepatic metabolism of carbohydrates, fatty acids, triglycerides, cholesterol, and bile acids.[178-180]

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that regulate genes important in cell differentiation and various metabolic processes, especially lipid and glucose homeostasis. They are heterodimerized with another nuclear receptor, the retinoid X receptor (RXR), in addition, peroxisomal receptors have 3 isoforms: PPARα (NR1C1), PPARβ/δ (NR1C2) and PPARγ (NR1C3).[181]

Gene transcription occurs identically in all three PPAR subtypes. Upon binding with the agonist, the PPARs form a heterodimer with the retinoid X receptor (RXR), giving rise to the PPAR-RXR complex. This complex binds to the peroxisome proliferative response elements in the promoter region of the respective target genes, after the recruitment of transcriptional cofactors, the transcription process begins.[182]

Of all the fatty acid-modulated nuclear receptors, PPARα are the most extensively elucidated. PPARα is a PPAR subtype expressed primarily in liver, muscle and brown adipose tissue. It is considered a central regulator of (FA) metabolism and plays an important role in the transcriptional regulation of metabolic pathways, such as lipid metabolism, adipogenesis and insulin sensitivity.[183-185]

The PPARα target genes are mainly proteins essential in fatty acid uptake and transport and β-oxidation, including fatty acid transport protein (FATP), the plasma membrane fatty acid binding protein (FABPpm), as well as the fatty acid binding-1 (FABP1) which is present in hepatocytes, fatty acid translocase (FAT/CD36), acetyl-coenzyme A long-chain fatty acid synthase (ACSL) and carnitine palmitoyl transferase I (CPT1).[186] Activation of PPARα induces the expression of lipoprotein lipase (LPL), whose function is to hydrolyze triglycerides from lipoproteins (the main source of circulating (FA) and also increases the transcription of

the main apolipoproteins, such as ApoAI and ApoAII, present in high-density lipoprotein. density (HDL).[187,188]

Studies report a wide variety of synthetic and natural lipophilic molecules (called ligands) capable of activating PPAR. Among the natural binders, (UFA's) and PUFAs stand out.[189] The search for plant species that have a high content of these substances has grown, since they represent potential sources for the development of herbal medicines, nutraceuticals and food supplements, which act in the prevention and treatment of hypercholesterolemia.[190]

Studies report that dietary ω-3 polyunsaturated fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are natural activators of PPARα. Other endogenous ligands have also been proposed for PPARα, including unsaturated fatty acids and eicosanoids such as oleic acid (18:1) and linoleic acid (18:2).[191,192] These (UFA's) are present in large amounts in virtually all edible fats and oils, including the fixed oil of *A. esculentus*, *E. oleracea*, and *Bixa orellana*, which have a high content of (UFA's) in the composition of their oils.[28,106,136,150]

When evaluating the binding capacity of (UFA's) to PPARα, a study showed that α-linolenic (18:3), γ-linolenic (18:3), arachidonic (20:4), docosahexaenoic (22:6) and eicosapentaenoic acids (20:5) bound and activated PPARα. However, very long-chain (UFA's) such as erucic (22:1) and nervonic (24:1) acids did not bind or activate PPARα. In the study, optimal binding activity was observed with PUFAs containing 16 to 20 carbons in the chain.[193]

Peroxisomal PPARγ receptors are present in two isoforms (PPARγ1, PPARγ2) that are differentially expressed. PPARγ1 is highly expressed in brown and white adipose tissue, large intestine and immune cells, but is also found in various tissues such as muscle, pancreas, liver, small intestine and kidney, while PPARγ2 is expressed in adipose tissue.[194] PPARγ are key regulators of adipogenesis and insulin sensitivity. These transcription factors, in addition to regulating adipogenesis, also regulate genes related to lipid metabolism, such as LPL, synthesis of acyl-coenzyme A and P2, and glucose control, such as the glucose transporter GLUT4 and phosphoenolpyruvate carboxykinase. (PEPCK).[195]

Inflammation plays an important role in promoting atherosclerosis as it inhibits the efflux of cholesterol, triggering the accumulation of unesterified cholesterol in the foam cells, proliferation of smooth muscle cells in the tunica intima, which leads to inflammation, so inhibiting inflammation is an effective way to attenuate the progression of atherosclerosis.[196]

PPARγ reduction significantly decreases the expression of LXRα, ABCA1 and ABCG1 in macrophages, promoting the reduction of cholesterol efflux. PPARγ also participates in the induction of the expression of CD-36 scavenger receptors, as well as the transcription of ApoAI and Apo AII, which favors the reverse transport of cholesterol by HDL-c to the liver, by the ABCA1 transporter, as well as participates in the uptake of lipoproteins. Oxidized low density (ox LDL) in macrophages, triggering the inhibition of inflammatory molecules such as interleukin-6 (IL-6), tumor necrosis factor-α (TNFα), vascular adhesion molecules 1 (VCAM-1) and protein 1 monocyte chemoattractant (MCP 1). Thus, PPARγ act directly on vascular actions and may promote anti-atherogenic effects.[197]

There are numerous natural PPARγ ligands, these are capable of binding a variety of synthetic lipophilic acids, in particular fatty acids or their derivatives, called eicosanoids, as well as prostaglandins.[193] One study demonstrated that conjugated linoleic acids (CLA) are also able to activate PPARγ. In addition, nitro-fatty acids such as nitrolinoleic acid have been shown to be a potent activator of PPARγ.[198] However, it is still unclear how PUFAs act in direct activation as a PPARγ ligand, possibly their mechanism is related to promoting the conversion of incoming fatty acids to TGs and thus stimulating the general storage capacity of TG, thereby protecting against lipotoxicity.[199]

PPAR-β/δ is a transcription factor that profoundly influences important cellular functions that regulate metabolism and inflammation. Despite being expressed in most tissues, its expression level varies according to cell type and disease state.[200] This receptor has the ability to act as a metabolic switch, shifting cellular energy utilization from glycolysis to fatty acid oxidation and thereby improving systemic glycemic control and lipid metabolism, making it an attractive target for prevention. or treatment of diseases related to the metabolic syndrome (eg, obesity, dyslipidemia, diabetes).[201]

In skeletal muscle cells, PPAR-β/δ activation by fatty acids increases fatty acid absorption and catabolism through β-oxidation. In addition to its effects on fatty acid oxidation, PPAR-β/δ leads to improved blood glucose homeostasis through a number of mechanisms. PPAR-δ is strongly expressed in pancreatic islet beta cells, promoting insulin secretion.[202,203] The PPAR-β/δ receptor is activated by long-chain, saturated or unsaturated fatty acids, and by prostacillin.[177]

The sterol regulatory element binding protein (SREBP) family is composed of two members: SREBP-1 and SREBP-2. However, there are two isoforms of SREBP-1 (SREBP-1a and SREBP-1c). SREBP-1 is a regulator of fatty acid and triglyceride synthesis, while SREBP-2 regulates cholesterol synthesis. SREBP-1c is the predominant subtype of SREBP-1 expressed in liver, white adipose tissue, adrenal gland, rodent and human brain.[204,205] SREBP-1c has been implicated in the human development of the pathophysiology of metabolic syndromes such as obesity, type 2 diabetes, dyslipidemia, atherosclerosis, and lipodystrophy.[205]

SREBP-1c inhibits the expression of microsomal transfer protein (MTP), a protein necessary for the assembly and secretion of very low density lipoprotein (VLDL), as well as the gluconeogenic enzyme, phosphoenolpyruvate carboxykinase (PEPCK).[206] Similar effects are seen in animals expressing SREBP-1c, whereas animals expressing SREBP-2 exhibit increased expression of genes involved in cholesterol synthesis.[203,204]

Studies have shown that the target of PUFAs has been identified as UBXD8, a protein bound to the endoplasmic reticulum (ER) membrane that facilitates the degradation of insulin-induced gene 1 (INSIG-1) that normally sequesters the SCAP-SREBP complex in the ER and prevents its activation. Thus, PUFAs have been shown to inhibit UBXD8 activity, causing the SCAP-SREBP complex to remain in the ER.[207]

The SREBP-1c protein also acts by activating fatty acid and triglyceride synthesis enzymes in the liver, such as acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). ACC catalyzes the carboxylation of acetyl-CoA to form malonyl-CoA, which is a key molecule in the control of intracellular fatty acid metabolism, as ACC phosphorylation renders it inactive.[208] FAS is responsible for the synthesis of fatty acids, being one of the main lipogenic enzymes, it acts by catalyzing all steps of the reaction, in the conversion of acetyl-CoA and malonyl-CoA to palmitate. The action of these enzymes leads to the accumulation of malonyl-CoA content, which inhibits the activity of carnitine palmitoyl transferase (CPT-1), resulting in decreased mitochondrial oxidation.[209]

Another important enzyme that SREBP-1c acts as a transcription factor is steryl-CoA desaturase 1-(SCD-1), a key enzyme involved in the synthesis of monounsaturated fatty acids, which catalyzes the insertion of a double bond between carbons 9 and 1. 10, in the long saturated fatty acid chain,[210] playing a crucial role in lipid metabolism and body weight control, so overexpression of SCD-1 in humans may be involved in the development of hypertriglyceridemia, atherosclerosis, and diabetes.[211] The nuclear SREBP-2 protein is reduced by the activation of PPARα, due to the upregulation of INSIGs, which in turn leads to a decrease in gene expression of targets such as farnesyl pyrophosphate (FPP), HMG-CoA reductase, LDL receptor and reduced synthesis and uptake of cholesterol.[212,213]

The conversion of insoluble cholesterol to soluble bile acids is the main pathway, allowing the excretion of these lipids. Nuclear receptors are ligand-activated transcription factors that regulate various physiological processes, as well as cholesterol metabolism, synthesis and conjugation of bile acids, regulated by hepatic nuclear factor-4 (HNF-4α) receptors.[214]

HNF-4α are mainly expressed in the liver, but can be found at lower levels in some organs, such as the kidney, intestine, colon and pancreatic β cells, contributing to their specificities.[204] Studies indicate that fatty acyl-CoAs are able to bind directly to HNF-4α, at physiological concentrations, so saturated fatty acids can act as ligands, such as palmitoyl CoA (16:0) and myristoyl-CoA (14: 0), resulting in the activation of HNF-4α. While the binding of unsaturated fatty acids, such as α-linolenic acid (18:3n3), icosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6, n6), results in the inhibition of HNF-4α.[177,204]

HNF-4α are proteins that act as nuclear receptors, belonging to the NR2A subfamily, play an important role in the maintenance of hepatic lipid homeostasis, through the regulation of the transcription of genes involved in the lipolysis of hepatic triglycerides, oxidation of fatty acids, mediated by phosphorylation of protein kinase C (PKC), secretion of VLDL, such as apolipoprotein B (ApoB) and (ApoCIII).[215]

Thus, hepatic deficiency of HNF-4α results in reduced expression of genes involved in cholesterol biosynthesis, by HMG-CoA reductase, VLDL secretion, involving microsomal transport protein (MTP) and apolipoprotein B (ApoB), as well as in HDL biogenesis, by ABCA1, responsible for 80% of plasma HDL and ApoAI and ApoAII, necessary in the maintenance of HDL. HNF-4α receptors can also upregulate the expression of the scavenger class B type I receptor (SR-BI), an HDL receptor that selectively uptakes cholesteryl esters from plasma HDL.[214,216]

HNF-4α deficiency in pancreatic cells reduces glucose-stimulated insulin secretion, aggravating glucose intolerance and insulin insensitivity.[214] In addition to acting in the regulation of metabolism and conjugation of bile acids in the liver, as a transcriptional regulator of the enzymatic gene cytochrome P450 7A1 (CYP7A1) and P450 27A1 (CYP27A1), which act in the modification of the steroid ring, through classical and alternative pathways., synthesizing cholic acid (CA), xenodeoxycholic acid (CDCA), for conjugation of acids in hepatocytes with glycine and taurine before they are secreted again.[217]

The liver X receptor (LXR-α) is a nuclear receptor protein encoded by the NR1H3 gene, and the LXR-β receptor by the NR1H2 gene, both mediate the regulation of genes involved in cholesterol, lipid and bile acid metabolism. LXRs (α and β) bind to oxysterols such as 22(R)-hydroxycholesterol and 24,25-epoxycholesterol, which directly regulate the expression of genes involved in the synthesis of hepatic bile acids, such as 7a-hydroxylase (CYP7A) and indirectly lipogenic genes through the transcriptional regulation of the SREBP1c gene. Lu 2001[218] LXRα is mainly expressed in the liver, kidneys, intestine, adipose and adrenal glands, while LXRβ can be expressed in several organs.[219]

LXRs bind with direct nucleotide repeats (DR4) as a heterodimer with RXRα, called specific response elements (LXREs), in promoter regions of target genes.[180] PUFAs inhibit the prolipogenic actions of LXRs through several mechanisms. One of the mechanisms of action is the competitive binding of PUFAs to LXRs, preventing the binding of oxysterol, antagonizing the induction of target genes such as SREBP1c and, consequently, genes containing specific response elements (LXREs) or sterol-sensitive response elements (SREs).[220]

Another suggested mechanism is through the inhibition of LXRs by PUFAs, through the activation of PPARα and PPARγ. PUFAs are potent activators of PPARα and PPARγ and their overexpression inhibits the SREBP-1c promoter, dose-dependent activity.[221] According to Yoshikawa[220] unsaturated fatty acids promoted a decrease in the activity of the SREBP-1c promoter,

effectively through arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, linoleic acid.

ANTI-HYPERCHOLESTEROLEMIC ACTIVITY AND MECHANISMS INVOLVED

Dyslipidemias (hyperlipidemia) are defined as changes in lipid metabolism, directly affecting abnormal levels of lipids in the blood. In dyslipidemia, changes in the lipid profile can include high total cholesterol (TC), high triglycerides (TG), low high-density lipoprotein cholesterol (HDL-c), and high levels of low-density lipoprotein cholesterol (LDL-c).[222]

Hyperlipidemia is considered one of the main determinants of the occurrence of cardiovascular (CVD) and cerebrovascular diseases, including atherosclerosis, acute myocardial infarction, ischemic heart disease. According to the type of alteration in serum lipid levels, dyslipidemia is classified as: isolated hypercholesterolemia, isolated hypertriglyceridemia, mixed hyperlipidemia and low HDL-C.[223]

Cholesterol is an element that performs vital constitutive and metabolic functions for the human body, makes up cell membranes and is a precursor of bile acids, vitamin D and steroid hormones.[224] However, its accumulation in the bloodstream has been studied for decades with regard to its atherogenic potential, which may trigger cardiovascular disease.[6]

The plant species *A. esculentus*, *E. oleracea*, *B. orellana* have great relevance due to their nutritional composition and pharmacological properties, providing several health effects. The oils obtained from the seeds of these species show variations in their chemical composition, these substances have shown regulatory activity of several key genes of lipid metabolism, acting in the control and prevention of diseases, especially in the metabolic syndrome, in the development of dyslipidemia.[225-227]

Among the food components identified as inhibitors of cholesterol absorption is stearic acid (18:0), an 18-carbon saturated fatty acid present in virtually all edible fats and oils,[228] including the fixed oil of *A. esculentus*, *E. oleracea*, *B. orellana*. This compound has a high content in the oil composition of these species.[106,140,148]

The increase in blood cholesterol levels is mainly observed in the ingestion of palmitic acid (C16:0) and myristic acid (C14:0), however stearic acid does not promote hypercholesterolemia, this is due to the dehydrogenation of this fatty acid being faster than that chain elongation, causing it to be converted more quickly to oleic acid (monounsaturated fatty acid) in the liver, through desaturases, thus requiring prior peroxisomal β-oxidation to shorten the fatty acid chain before entry into mitochondria.[173]

A possible mechanism of action of stearic acid would be its ability to interfere with the formation of micelles, through incorporation into hepatic and biliary phospholipids, resulting in a decrease in cholesterol solubility.[229] In addition, unlike most dietary components that inhibit cholesterol absorption, such as phytosterols and soluble fiber, stearic acid has good tissue absorption.[230]

The study carried out by Khan,[126] with the oil from the seeds of *A. esculentus*, demonstrated a significant effect in the reduction of triglycerides, LDL, however, observed the increase of HDL in the test carried out with animals. This anti-hypercholesterolemic effect is based precisely on the ability of fatty acids, such as stearic acid and linoleic acid, to reallocate cholesterol towards bile acid. It is known that these fatty acids are important natural activators of PPARα, inducing the expression of lipoprotein lipase (LPL), increasing the transcription of the main apolipoproteins of HDL, they can also act by interacting with the HNF-4α, the main responsible for the metabolism and regulation of bile acids.[231,232]

It was also observed in a Sabitha study[233] that the level of high-density lipoprotein (HDL) increased significantly in diabetes-induced rats after receiving a treatment from *A. esculentus* seeds, in addition to reducing levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL).

The study carried out by Farias and Souza[227] obtained the reduction of total cholesterol and LDL-cholesterol treated with *E. oleracea* oil, in rats with hyperlipidemia induction by saturated fat, it was possible to observe in the study, anti-hypercholesterolemic and antiatherogenic, that is, the species has in its composition mostly monounsaturated fatty acids (MUFAs), suggesting that *E. oleracea* oil has important bioactivities in the metabolic syndrome. These fatty acids are potent activators of PPARs and their overexpression can inhibit the SREBP-1c promoter and the steryl-CoA desaturase 1-(SCD-1) enzyme, both involved in lipid metabolism and body weight control.[211] In another study, vasodilator activity was demonstrated via the NO-GMPC pathway, indicating the use of acai oil as a promising source in the treatment of cardiovascular diseases.[151]

Vitamin E is composed of two classes of compounds: tocopherols and tocotrienols. α-Tocopherol compounds and tocotrienols are important cholesterol-lowering agents. The micromolar portion of tocotrienol cancels the activity of HMG-CoA reductase, the hepatic enzyme attributed to the synthesis of cholesterol via the mevalonate pathway.[234] In an *in silico* study, tocotrienols also showed significant values for lipid peroxidase inhibition, antioxidant activity, anti-inflammatory activity, antihypercholesterolemic activity, inhibition of cholesterol synthesis.[171]

A double-blind, placebo-controlled clinical study of human volunteers with high blood cholesterol levels (> 200mg/dl) using 120mg/kg of tocotrienol over eight weeks showed that tocotrienols reduced triglyceride levels by 28% when compared to the placebo group. A decrease in mass, average weight and percentage of body fat was also observed in those participants who received tocotrienol.[233]

In this context, the species *B. orellana*, a potent source of tocotrienols, as well as having greater bioavailability compared to alpha tocopherol,[236] emerges with significant significance, due to studies that report tocotrienols as effective antioxidant, anti-inflammatory agents. inflammatory, anti-dyslipidemic and anti-hyperglycemic.[44,46]

Wong[170] evaluated the potential of tocotrienol extracted from *B. orellana* against the metabolic syndrome and osteoporosis in rats with a high-fat diet, the study showed that after the administration of 60 mg/kg of tocotrienol for 5 months, the compound was able to prevent the rise in blood pressure, blood glucose, triglycerides and total cholesterol levels. In a similar study by Zaiden[235] it was shown that after one month administration of γ and δ-tocotrienol, there was a significant reduction in serum cholesterol, triglycerides and LDL levels in hyperlipidemic mice, however body weight did not diverge. between the experimental groups. Surprisingly, tocotrienols have been found to be effective in preventing most medical complications associated with metabolic syndrome.[170]

A study carried out with tocotrienol fractions showed induction of the expression of LXRα and apolipoproteins, increasing the activities of PPARα, PPARγ and PPARδ, in addition to suppressing the production of inflammatory signal-inducible nitric oxide in macrophages, thus functioning as an inflammatory modulator, playing a fundamental role in the prevention of atherosclerosis and in the regulation of energy metabolism.[196]

Tocotrienols are important negative regulators of the peroxisome proliferator-activated receptor γ (PPARγ), the critical transcription factor in adipocyte differentiation.[237] In addition to preventing activation of nuclear factor-κB (NF-κB), thereby stopping tissue inflammation.[238] Thus, these compounds act in diverse biological activities related to protection from metabolic, cardiovascular pathologies, such as in the development of atherosclerosis, and in the management of conditions of diabetes mellitus.[239]

Studies with tocotrienols, especially γ and δ, showed satisfactory results in glycemic control in several *in vitro* models and in animal-induced obesity models.[240-242] *In vitro* studies observed that γ-tocotrienol restored glucose uptake, insulin sensitivity, and B-Akt protein kinase signaling in primary mouse adipocytes.[240]

In addition to these compounds, others also have therapeutic potential such as geranylgeraniol, a 20-carbon isoprenoid found in edible oils such as olive oil, linseed and sunflower, which has favorable metabolic effects. Geranylgeraniol is present in high amounts in the species *B. orellana*.[154,155] thus attributing anti-hypercholesterolemic and anti-inflammatory activities to the species.

Geranylgeraniol (GGOH) is an intermediate product in the mevalonate pathway and acts as a precursor to geranylgeranylpyrophosphate (GGPP), necessary for membrane anchoring of intracellular proteins, especially small proteins that are involved in various cell signaling pathways.[243]

In a study, treatment with GGPP led to an increase in PPARγ expression, thus acting as an agonist, by inhibiting the isoprenoid biosynthetic pathway, which may be involved in the occurrence of insulin resistance and type 2 diabetes. GGOH counteracts the effect of statin (a lipid-lowering agent that inhibits HMGCoA, involved in cholesterol biosynthesis and adipogenesis) on PPARγ, suggesting potential in the prevention or treatment of statin-induced diabetes without interfering with the reduction of plasma cholesterol.[244]

In an *in silico* study, another mechanism of action of geranylgeraniol was evidenced, in addition to the negative regulation of the activity of 3-hydroxy-3-methylglutaryl-CoA (HMG-Coa) reductase, this compound can act by inhibiting lanosterol synthase (oxidosqualene cyclase- OSC) a membrane-bound protein responsible for steroid synthesis in mammals and monooxygenase (squalene epoxidase-SQLE), a second limiting enzyme in cholesterol biosynthesis, contributing to the regulation of lipid metabolism.[171]

The bioactive compounds present in vegetable oils, especially the species *A.esculentus, E. oleracea*, *B. orellana*, present several natural ligands of great pharmacological and economic interest in the development of phytotherapics, nutraceuticals and food supplements that act as expression modulators. gene, at transcriptional levels, in order to help and prevent several pathologies, such as dyslipidemia.

CONCLUSION

The Amazonian species *A. esculentus*, *E. oleracea* and *B. orellana* have a wide variety of traditional uses, especially in the use of unconventional vegetable oils, these oils are rich in chemical compounds, which make them relevant for their bioactive actions of pharmacological interest. The biological activities promoted by *A. esculentus, E. oleracea and B. orellana* oil are mainly due to the presence of monounsaturated and polyunsaturated fatty acids in their compositions, as well as to substances found in a restricted number of species. vegetables, such as carotenoids, tocotrienols, geranylgeraniol with effective therapeutic effects. These substances are natural ligands of important targets in the modulation of lipid metabolism, such as peroxisome proliferator-activated receptor (PPAR) transcription factors (α, β and γ), hepatic X receptors (LXRs) (α and β), hepatic receptors nuclear factor-4 (HNF4-α) and sterol regulatory element binding proteins (SREBPs) 1 and 2. In this context, this review presents perspectives that encourage the exploration of new sources of unconventional vegetable oils, associated with the versatility of use of these oils in pharmaceutical innovation, in order to direct new research on gene expression pathways in the management of chronic diseases, such as dyslipidemias.

ABBREVIATIONS

ACC: Acetyl-CoA carboxylase; **FA:** Fatty acids; **UFA:** Unsaturated fatty acids; **MUFA:** Monounsaturated fatty acids; **PUFA:** Polyunsaturated fatty acids; **SFA:** Saturated fatty acids; **ApoAI:** Apolipoprotein AI; **ApoAII:** Apolipoprotein AII; **ApoB:** Apolipoprotein B; **CPT1:** Carnitine palmitoyltransferase 1; **CDCA:** Chenodeoxycholic acid; **CLA:** Conjugated linoleic acids; **TC:** Total cholesterol; **CYP7A:** 7 Alpha-hydroxylase; **CVD:** Cardiovascular diseases; **DHA:** Docosahexaenoic acid; **DNR:** Direct nucleotide repeats; **EPA:** Eicosapentaenoic acid; **FABP1:** Fatty acid binding protein-1; **FABPpm:** Plasma membrane fatty acid binding protein; **FAS:** Fatty acid synthase; **FATP:** Fatty acid transport protein; **FPP:** Farnesyl pyrophosphate; **GGOH:** Geranylgeraniol; **GGPP:** Geranylgeranyl pyrophosphate; **GLUT4:** Glucose transporter type 4; **HDL:** High density lipoprotein; **HMG-Coa:** 3-hydroxy-3-methylglutaryl coenzyme A; **HMGCR:** 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; **HNF4-α**: Nuclear receptor hepatocyte nuclear factor 4-alpha; **IL-6:** Interleukin-6; **INSIG-1:** Insulin-induced gene 1; **LDL:** Low density lipoprotein; **LDL-ox:** Oxidized low density lipoproteins; **LPL:** Lipoprotein lipase; **LXRs:** Liver X receptor; **LXR-α:** Liver X receptor alpha; **MCP1:** Monocyte chemoattractant protein 1; **MTP:** Microsomal transfer protein; **NF-Kb:** Nuclear factor kappa B; **NR2A:** Subunit type glutamate receptors; **OSC:** Oxidosqualene cyclase; **PEPCK:** Phosphoenolpyruvate carboxykinase; **PKC:** Protein kinase C; **PPAR:** Peroxisome proliferator-activated receptor**; rLDL:** Low density lipoproteins receptor; **RXR:** Retinoid X receptor; **SCD-1:** Stearoyl-CoA desaturase-1; **SQLE:** Squalene epoxidase; **SR-BI:** Receptor scavenger receptor class B type I; **SREs**: Sterol Regulatory Element-Binding Protein; **SREBPs:** Steroid regulatory element binding protein; **SREBP1-c:** Sterol regulatory element binding protein-1c; **SREBP2:** Sterol regulatory element-binding protein-2; **TG:** Triglycerides; **TNFα:** Tumor necrosis factor-α; **VCAM-1:** Vascular adhesion molecules 1; **VLDL:** Very low density lipoprotein.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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