

Review Article

PHARMACOLOGICAL PROPERTIES OF *SALVIA HISPANICA* (CHIA) SEEDS: A REVIEW

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Received: 09 Mar 2016 Revised and Accepted: 02 May 2016

ABSTRACT

There is a growing interest worldwide to identify novel functional foods capable of acting on various biochemical targets with limited toxicity. Accordingly, there is a revived interest in *Salvia hispanica* L. (chia) a Mexican herb, as an agriculture crop owing to the nutritional value of the seed oil. Chia seed oil is reported to contain alpha-linolenic acid in abundance besides antioxidant polyphenols. Many researchers have focussed on assessing the possible health benefits of Chia as a dietary supplement and efforts are underway in order to promote it as 'functional food' owing to the presence of α -linolenic acid, an essential precursor fatty acid of physiologically significant polyunsaturated fatty acids. Dietary supplementation of Chia seed oil in rats and humans has demonstrated alleviation of serum lipid profile and diabetic severity. In addition, chia seed oil also acts as an antioxidant *in vivo* and modulates the antioxidant enzyme activities in liver and blood. Here we have reviewed the literature for various therapeutic aspects of Chia seed oil. Dietary Chia provides an array of pharmacological properties, however understanding the nature of bioactive and fatty acids responsible for its biological activity using mechanistic approaches in cell and mammalian models are a prerequisite prior to its usage as a therapeutic agent or functional food.

Keywords: Alpha-linolenic acid, Antioxidant polyphenols, Chia seed oil, *Salvia hispanica*, Pharmacological properties

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INTRODUCTION

Substantial changes in the human diet over the past decades, particularly in terms of dietary fat, low fiber and its effect on human health, have become a major socio-economic interest [1]. Epidemiological and experimental evidence establishes a strong relationship between dietary fat and incidence of coronary heart disease, cancer, diabetes, and depression. Cardiovascular diseases contribute to 20% of total clinical mortality among Americans every year and economically cost around 300 billion annually [2]. It is assumed that the case is similar in rest of the world. Novel foods are being explored universally, and 'functional foods' have received heavy attention in recent years as components of healthy lifestyle changes. The term "functional" refers to a dietary product that is regularly consumed to provide physiological benefits in addition to its basic nutritional functions. A typical "functional food" contains functional bioactive compounds including dietary fiber, oligosaccharides, essential fatty acids, phytochemicals and antioxidants that have beneficial effects on human health and may have potential roles in reducing the risk of chronic degenerative diseases [3, 4]. Phenolic compounds are chief components of many edible plants and have potent antioxidant properties that modulate the physiological redox system. Synthetic antioxidants are widely used for their performance, however, possess different toxicological problems when regularly consumed [5]. The legislation on food safety has gradually become more rigorous, requiring the use of toxicity tests for synthetic antioxidants. There is an emerging interest to identify newer natural sources of functional foods capable of acting on various biochemical targets with limited toxicity.

Salvia hispanica L. (chia) seeds are a promising source of antioxidants due to the presence of polyphenols, chlorogenic and caffeic acids, myricetin, quercetin, kaempferol as well as essential fatty acids [6-7]. *S. hispanica* (chia) an annual herb (Family-Lamiaceae) native to Southern Mexico and Northern Guatemala and has been recently marketed as a crop in South America mainly for the oilseeds [8-9]. *Salvia* genus (fig. 1) has around 900 species growing all around the world, most of which are grown as ornamentals and for oilseeds [10]. Chia grows in tropical to temperate zones from plains to hilly regions. However, recently there is a revived interest in Chia as an agriculture crop owing to nutrition value of the seed oil. Many researchers have focussed on

assessing the possible health benefits of Chia as a dietary supplement and efforts are underway in order to promote it as 'functional food' owing to the presence of α -linolenic acid (ALA), an essential precursor fatty acid of physiologically significant polyunsaturated fatty acids (PUFA).



Fig. 1: *Salvia hispanica* (chia) plant [9]

Increased dietary intake of long-chain fatty acids derived from α -linolenic acid is associated with a reduced risk of cardiovascular diseases [11-12]. PUFAs have been used successfully in rheumatoid arthritis and bronchial asthma [13-14]. Epidemiological studies suggest that dietary fatty acids rich in α -linolenic acid enhanced the childhood teaching and behavior ability [15] and led to decreased the burden of psychiatric illnesses in adults [16]. Plant PUFA synthesized from the α -linolenic acid that are precursors of EPA and DHA appear to share the activity and functional attributes of very long-chain PUFA [17].

Regular and adequate dietary supplementation of PUFAs provides considerable visual, neurovascular, cardiovascular, and neurological health benefits. The fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are vital for the homeostatic operation of the cell membrane as it contributes to fluidity across the membrane [18]. The benefits of PUFA supplementation have been reported in various neurological disorders [19-21]. The emergence of processed foods and hydrogenated vegetable fats has reduced the dietary existence of α -linolenic and its derived fatty acids while increasing the consumption of linoleic and its derived fatty acids and saturated fats [22-23]. In this regard, a significant body of evidence indicates that the dietary intake of marine PUFA (fish oil rich in EPA and DHA) appears to play an important role against the adverse effects of the changed dietary habits [24-25]. Long chain PUFA are important structural components of cell membranes and their interactions with phospholipids ensure cell functionality. However, there is a conscious hesitation for marine foods among educated population particularly among western countries owing to the biomagnification of metals and xenobiotic chemicals. Hence, there is a constant search for vegetable sources of PUFA which cross the psychological stigma worldwide.

Chia seeds yield an edible oil which are rich source of polyunsaturated fatty acids (PUFA) along with protein, dietary fiber, minerals and polyphenolic compounds [7, 10, 26]. Chia seeds contain about 25-38% oil and have the highest known percentage (60%) of alpha-linolenic fatty acid (ALA, 18:3) [6]. In addition chia seed oil extraction residue is a good source of dietary fiber and phenolic compounds with antioxidant capacity [7]. ALA plays an important role in health and is fortified in several functional food products and cosmetics. Many studies have provided evidence that regular dietary supplementation with long-chain PUFA brings numerous health benefits, including the prevention of cardiovascular diseases, hypertension and inflammatory diseases [27-28]. Although early studies showed use of fish and fish oil as the source of long-chain fatty acids, recent studies have used vegetable oil or seeds containing α -linolenic fatty acid [29]. ALA is a fatty acid that is converted to long-chain fatty acids EPA and DHA with $\Delta 6$ and $\Delta 5$ desaturase enzymes and, hence, can be substituted for fish oils [23]. Therefore, it is possible that dietary ALA could exert similar physiological effects as in the case of EPA and DHA from dietary fish oil. Accordingly we have made conscious efforts to analyse the available literature carefully in order to mention all the reported pharmacological benefits of *S. hispanica* or chia seeds.

Taxonomical nomenclature

Kingdom: Plantae

Subdivision: Spermatophyta

Order: Lamiales

Family: Lamiaceae

Genus: *Salvia*

Species: *hispanica*

Historical perspective

Chia is an ancient whole grain food that has a favorable nutritional composition compared to commonly consumed grains and seeds and was considered a food and remedy by ancient Aztec and Mayan civilizations [30]. The Aztec capital, Tenochtitlan was reported to receive between 5 and 15 tons of chia seed annually. According to the 16th century Codex Mendoza and Matricula do Los Tributos, most states of Aztec presented the seeds as a tribute to Aztec gods [31]. Though importance of chia as a staple food was not as major as beans/corn but was consumed more frequently than amaranth. Chia seeds were roasted and ground into flour known as chiapinolli which was fortified into tortillas, tamales, or eaten as gruel. The ground chia seeds were used in Chianatoles, an Aztec beverage [32]. Chia seeds were also used for medicinal purposes, uptake of medicines, and treatment of respiratory malaise, kidney problems, eye obstructions and infections (by placing seeds directly under the eyelid). Chia oil served a base in skin emollients, lacquer for

primitive pottery manufacture, craft and body paints too [32]. Spanish manuscripts mention chia as the "running food" due to its consumption by Aztec messengers for endurance during journeys. Influence of Spanish colonization, the cultivation of chia seeds in meso-American society declined gradually but substantially [33].

Chia seed oil: extraction

Oil from Chia seeds are extracted employing one of the three methods generally used for any oil seeds, (a) compression method involves pressing the seeds at 4 °C or 25 °C in dark. This result in preservation of antioxidant contents, however, oil recovery is limited [6, 26, 34]. (b) Solvent extraction—involves Soxhlet method using organic solvents like hexane. Though functional characteristics like absorption capacity and emulsifying stability are favored, this method is least preferred as it poses health issues from the use of hexane [6, 26]. (c) Supercritical fluid extraction—is the most preferable method which uses carbon dioxide at 80°C resulting in a better purity of ALA. The oil yield is increased with high pressure [35-36].

Physico-chemical properties of Chia oil

In the aqueous substance, chia seeds tend to exude polysaccharide mucilage (4.5% dry weight) that remains tightly bound to the seed. This polysaccharide is identified to contain D-xylosyl, D-glucosyl and 4-O-methyl- α -D-glucopyranosyluronic acid in ratios of 2:1:1 in a linear tetrasaccharide sequence. A lower content of uronic acid is an indicator of no pectin being associated with this polysaccharide [7]. Chia seed meal (defatted residue) contains nearly 34% dry weight of fibers and 17% dry weight of protein [37]. The primary component of the insoluble deviator fraction is lignin (39-41%) which is thought to protect the unsaturated fats in the chia seed by building a strong and resistant structure. The seed cell wall also contains the general components, cellulose, and hemicellulose [7]. The water-holding capacity, the ability of a moist material to retain water when subjected to an external centrifugal gravitational force or compression of the defatted fiber fraction, was 15.41g/g fiber. It is suggested that the high water-holding capacity is influenced by the polysaccharide mucilages [38]. Contrastingly the oil-holding capacity of chia seeds has a tendency to be low (2.02g/g sample). It is hypothesized that the particle size of the fiber fraction is not small enough to hold higher amounts of oil (since smaller particles present more surface area). The fibrous fraction of the chia seed possesses consistent emulsifying property (a measure of solubilization or dispersion of two immiscible liquids) (53.26 ml/100 ml) which is attributed to the protein fraction because most proteins are strong emulsifiers. Physiologically, these emulsifying properties are significant in regard to the absorption of bile acids, and increasing fecal excretion, which would limit small intestine uptake [38]. The total chia seed phenolic content around 0.9211 \pm 0.008 mg/g (GAE-gallic acid equivalents) and flavonols were found to be in the highest concentrations. The antioxidant activity measured as radical scavenging activity of chia seeds is comparable to Trolox® at 185-210 ppm GAE. Chia seed extracts demonstrated metal-chelating potential against iron and copper-induced free radicals [7].

Possible mechanisms underlying the beneficial effects of Chia seed oil

Alpha-linolenic acid (ALA) metabolism

ALA (C18:3) is the primary fatty acid derived from the lipid fraction of chia seeds. ALA, an essential fatty acid, once inside the human system is converted to EPA and DHA by the sequential activities of $\Delta 6$ and $\Delta 5$ desaturases and carbon chain elongation with an intermediate docosapentaenoic acid (DPA). The primary conversion site is the liver followed by enterocytes [39]. After ALA conversion, very low-density lipoproteins transport newly synthesized EPA/DPA/DHA away from the liver to other parts of the body [39]. During the conversions of ALA, PUFA derived from linoleic, and linolenic fatty acids compete for metabolic enzymes; interestingly this competition exists during esterification into plasma phospholipids and triglycerides [40]. Moreover, an increased concentration of dietary C18:2 caused a decrease in the synthesis of long-chain PUFA derived from ALA (C18:3) and vice versa. Optimal conversion of ALA to EPA/DPA is achieved by the diet low in both linoleic and linolenic and their derived

fatty acids [41]. Interestingly the extent of conversion of EPA to DPA to DHA varies between men and women [42].

Reactive protein interactions

An elevation in plasma C-reactive proteins (CRP) is strongly associated with clinical definitions of atherothrombotic disease [43]. CRP possesses a direct pro-inflammatory effect on human endothelium exhibits synergy with hypercholesterolemia to increase CVD risk. PUFAs suppress pro-inflammatory cytokine production by peripheral blood cells and inhibit lymphocyte proliferation which reduces the chances of initiation of atherothrombosis. Patients with higher CRP levels is associated with a diminished cholesterol lowering response (29%) imposing an overall cardiovascular risk [44]. In patients receiving diabetes therapy, chia seeds reduced systolic blood pressure and CRP concentrations and increased serum ALA/EPA concentrations, however, did not affect body weight [45].

Specific biological properties of Chia oil

Owing to the presence of ALA at higher concentrations and antioxidants many researchers have assessed the protective properties of Chia seed and its oil against different ailments employing rodent and cell models (fig. 2). A few reports have been mentioned as follows.

Anti-Hyperlipidemia and anti-hypercholesterolemia

Chia seed diet in rats, reduced dyslipidemia and visceral adiposity [30, 46]. The chia diet caused lower triacylglycerol levels, increased HDL cholesterol and linolenic and it derived fatty acids in rat serum. The blending of chia seeds and different types of oils are reduced oxidative stress *in vivo* in obese wistar rats. In addition, stearoyl-CoA desaturase-1 products were depleted in the heart, liver and the adipose tissue of chia seed-supplemented rats [1, 47]. In a separate study, dietary chia seeds prevented the onset of dyslipidemia and insulin resistance (IR) in the rats fed with the sucrose-rich diet. Dietary chia seed also reduced the visceral adiposity [46]. In addition, Chia oil also reduced adipocyte hypertrophy, lipolysis and the anti-lipolytic action of insulin among high sucrose rats [48-49]. Interestingly, chia fed pigs and rabbits resulted in an increase of PUFA in meat fats as well as aroma and flavor [49-51]. The combination of different seeds mixtures has shown to increase PUFA levels in plasma and liver of experimental animals in addition to the anti-atherogenic, hypolipidemic and immune modulator effects which may attribute to antioxidant potential of unsaturated fatty acids especially ALA present in the seed mixture [52-54].

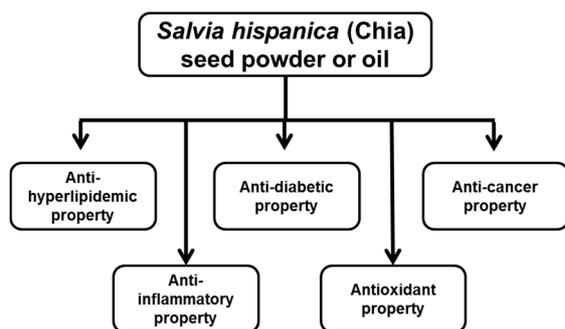


Fig. 2: Biological activities of *Salvia hispanica* (chia) seeds

Anti-diabetic activity

A few reports demonstrated the potentially beneficial physiological effects of Chia against the risk factors for Type 2 diabetes in experimental animals [55]. In a 6-month crossover study type, 2 diabetic subjects consuming Chia on a daily basis (37g/d) demonstrated lower blood pressure, lower pro-inflammatory markers and coagulation factors [46]. In another study, there was a significant reduction in waist circumference in healthy individuals after a month of Chia supplementation, however; there was no change in body weight suggesting the specific loss of fat mass. In a

chronic treatment regime, dietary chia seed reduced the visceral adiposity and insulin resistance among sucrose-induced diabetic rats suggesting its role in lipid and glucose homeostasis [46,56]. In a separate study, Chia enriched diet modulated dyslipidemia, liver TAG, fatty acid oxidase, acetyl-coA carboxylase and glucose-6-phosphate dehydrogenase. Protein levels of PPAR α increased, and the increased mature form of SREBP-1 (Sterol regulatory element binding protein-1) levels in the sucrose-rich diet (SRD) was normalized by chia. This study attributed some key mechanisms to the biological effects of dietary chia seed in preventing and normalizing/improving dyslipidemia and liver steatosis in an insulin-resistant rat model [57].

Anti-cancer property

Nutrition has a significant role in the initiation and progression of cancer [58]. Dietary PUFAs have been shown to play an important alleviating role in various forms of human cancers [59]. Several studies demonstrate the cytotoxic ability of PUFAs against different types of cancer cells and may act synergistically with current chemotherapeutic drugs [60]. Arachidonic acid (20:4, n-6) derived from ALA induces apoptosis of tumor cells by converting sphingomyelin to ceramide that triggers the release of pro-apoptotic proteins [61]. In addition, eicosanoids derived from AA act as active carcinogens or tumor promoters in view of their pro-inflammatory actions and thus participate in cancer development [62]. Moreover, peanut oil rich in linoleic/oleic and their derive PUFAs protects against murine mammary cancer development by modulating tumor membrane fatty acids composition, lipoxygenases (LOX) and cyclooxygenase (COX) enzyme [63]. Hence, it is hypothesized that chia seed oil as it contains all the derived of α -linolenic, linoleic/oleic in good balance may produce the same effect.

Anti-inflammatory property

The inflammatory disorder is associated with pain, redness, and swelling, severity of which leads to loss of vital functions. An interdependent chain of reactions are mediated by inflammatory molecules released from leukocytes. The key inflammatory mediators inclusive of linoleic and it derive eicosanoids, prostaglandin E₂ and leukotriene B₄, are derived from arachidonic acid (fig. 3). However, lower risks of pro-inflammatory reactions are demonstrated with Chia seed oil diet [63-65]. The n3 PUFA in Chia seed oil are suggested to compete with arachidonic acid for the incorporation into the membrane. Hence, generate slightly modified prostaglandins and eicosanoids viz., LTE₅, LTB₅, and PGE₃ which induce lesser extent of inflammation via reduced induction of COX-2 [65].

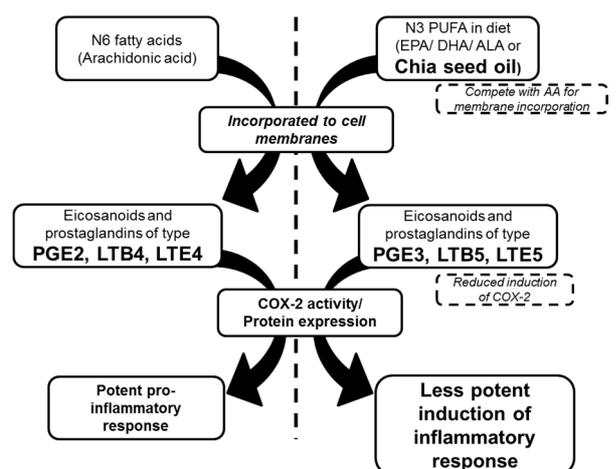


Fig. 3: Schematic representation of anti-inflammatory mechanism of Chia seed oil

Anti-oxidants activity

Chia seed and oil is an excellent source of antioxidants such as tocopherols, phytosterol, carotenoids and phenolic compounds,

chlorogenic acid, caffeic acid, myricetin, quercetin and kaempferol [6-7, 26, 65]. Several reports demonstrate potent antioxidant property of chia seeds among *in vitro* assays [66]. Among obesity model of rats, dietary chia oil induced the expression of HSP70 and HSP25 in skeletal muscle and restored superoxide dismutase and glutathione peroxidase expression [56]. In addition, extended treatment with chia seed and short treatment with chia oil restored peroxisome proliferator activated receptor- γ coactivator-1 α (PGC-1 α) expression.

CONCLUSION

The worldwide increase in the awareness about public health has necessitated the search for functional food with multiple health benefits. The use of medicinal food derived from folk and tribal diet to prevent degenerative diseases is relevant at the present scenario. Accordingly, seeds of *Salvia hispanica* L. (Chia), a traditional food in central and southern America, is currently consumed for various health benefits. Owing to the abundance of PUFA fatty acids derived from ALA and antioxidants, Chia seeds possess significant anti-inflammatory and antioxidant properties *in vivo*. Epidemiological and experimental reports mention the medicinal use (oral supplements) of *Chia*, however protocols regarding extraction and effective dose, should be standardized in order to suit the human consumption on a large scale, supported by sound scientific data. In this review, we have thoroughly analyzed the available literature on the various therapeutic aspects of Chia. Dietary Chia provides an array of pharmacological properties, however understanding the nature of bioactive and fatty acids responsible for its biological activity using mechanistic approaches in cell and mammal models are a prerequisite prior to its therapeutic usage.

ACKNOWLEDGEMENT

The author Ramzi Abdulrashed thanks IBB University, Yemen for the financial assistance.

CONFLICT OF INTERESTS

The authors declare no competing financial interests

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