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REVIEW ON THE MIRACLE ROLE OF CHIA SEEDS (*SALVIA HISPANICA L.)* NUTRITIONAL AND BIOACTIVE COMPOUNDS IN THE TREATMENT OF CARDIOVASCULAR DISORDER

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Abstract
Chia (Salvia hispanica L.) have growing research interest globally which determined it as functional food which acts as biochemical targets for the treatment of various cardiovascular disorder with reduced toxicological value. It is worldwide popular because of its nutritional, bioactive, and phytochemical compounds value, used as an ingredient in many food industries due to its high dietary fibre content value. Their consumption rate is higher in past years due to the presence of omega-3 fatty acids, proteins, amino acids (essential), and a good source of bioactive peptides. Many researchers focussed on α-linolenic acid which is the effective pioneer of maintenance of functioning of polyunsaturated fatty acids (PUFAs). Chia seed oil is investigated on different screening models either clinically or pre-clinically and demonstrate the levels of the serum lipid profile, diabetic severity changes. The review of the literature highlights the miracle values of the different nutritional composition, antioxidant values, phytochemical constituents, and the role of these in treatment of various cardiovascular disorder such as hypertension, inflammation, atherosclerosis, diabetes. The review highlights antioxidants values, which change the enzyme activities of the liver, blood. There is need to more focussed on the mechanistic approaches on the pharmacological aspects of the chia seeds with respective biological compounds in either clinical trial and animal screening trial before applied to it as a functional food for the therapeutic action in the treatment of diseases.

Keywords: Salvia hispanica L. (Chia), Antioxidants, Biological properties of Salvia hispanica L. (Chia).

Introduction

Over the past decades, there is a substantial change in the human diet, particularly in terms of low fibre, dietary fat and its effect on human health which have become a major socio-economic issue [1]. Various epidemiological and experimental shreds of evidence establish a very strong relationship between dietary fat and the occurrence of coronary heart disease, cancer, diabetes, and depression. Cardiovascular diseases (CVDs) contribute to about 20% of total clinical mortality and morbidity among Americans every year and economically cost around 300 billion annually [2]. And it is assumed that these reports or cases are similar in the world. Newer foods are explored universally, and 'functional foods' have heavy and major attention in recent years and determined as better components of healthy lifestyle changes. As the term "functional" refers to a dietary product that is regularly consumed to provide physiological benefits to the human body with their basic nutritional functions. A typical "functional food" comprises of various bioactive compounds which include different types of essential fatty acids, antioxidants and dietary fibres which shown better and potential effects on human health and it may have major roles in reducing the risk or pathogenesis of chronic degenerative diseases [3,4]. The Phenolic compounds are the major and chief components of many herbal or edible plants which have potent antioxidant properties which can modulate the physiological redox system. As synthetic antioxidants are commonly and widely used, but they possess different toxicological problems when consumed regularly by the human body [5].

Salvia hispanica L. (chia) seeds are the better source of antioxidants due to the presence of various polyphenols, chlorogenic and caffeic acids, myricetin, quercetin, kaempferol as well as essential fatty acids [6,7]. The word chia is derived from the Spanish word *"chian"* which means *"oily"*, as it is oilseed, with a major powerhouse of omega-3 fatty acids, the superior quality of protein, dietary fibre, minerals, vitamins and high range of polyphenolic antioxidants which protect the seeds form any chemical and microbial breakdown [8].

3. Salvia hispanica L. (chia)

It is a herbaceous plant which belongs to the order *Lamiales*, family *Lamiaceae*, subfamily *Nepetoideae*, and genus *Salvia* [9]. The Salvia genus is considered the major numerous in the family *Lamiaceae*. As it consists of approximately 900 species which is widely distributed throughout the different regions of the world, including Southern Africa, Central America, North America, South America and South-East Asia [10]. The chia plant is native to northern Guatemala and southern Mexico and now today cultivated in Australia, Bolivia, Colombia, Guatemala,

Peru, Argentina, and Mexico which is latter being the world's largest producer of chia [11]. The chia seeds have been the part of human nutrition and benefit for the human body since 1500 BC [8,12]. Traditionally the seeds have been used as a food, in a high range of folk medicines, primary cosmetics and also a part of religious rituals in pre-Columbian societies and they used it as regimens [13,14]. Because of its potential and massive nutritional and therapeutic activities, it is widely used in many countries [15].

3.1. Botanical description of Salvia hispanica L. (Chia)

The chia plant is about 1 m tall and has simple and opposite leaves which measure up to 4-8 cm long and 3-6 cm wide [16] and have oval-elliptical shape, pubescent and with an acute apex. The flowers are purple and white and sized 3-4 mm and gathered in whorls on top of the shoots. The fruits contain numerous numbers of seeds which is quasi-oval, with a length in between 1-2 mm, and a diameter in between 0.8-1.3 and a width between 0.8-1.4 mm. The seeds are having smooth and shiny peel with mottle-coloured having black, brown, grey, black-spotted and white [17-19]. The optimal development of the plant is continued by the warm climate, heavy rainfall and temperatures about 15-30 ºC [20,21]. The mature seeds of chia have mucilage which was present inside the epidermal cells and when they have come in contact with water it swells and expands which immediately lead to rupturing of the primary cell layer which extends from these epidermal cells thus surrounding the seed, which increases in its sizes and imparts to appear a characteristic gel to chia [22]. The chia plant can produce 500-600 kg seed/acre but under appropriate agronomic conditions and facilities they yield up to 2500 kg/acre has also been reported [8].

Figure 1: *Salvia Hispanica L.* (black and white chia seeds).

3.2. Nutritional Composition and Components of Salvia Hispanica L. (Chia*)*

Nutritional components have high potential due to seed composition and it is depending on the genetic factors and on the ecosystems changes where the plants were grown [23] Chia seeds contain about 16-26% of protein, 31-34% of carbohydrates in total and 23-35% of total dietary fibres. Apart from this, they also have a source of minerals such as calcium, phosphorous, potassium and magnesium, vitamins such as thiamine, riboflavin, niacin, folic acid, ascorbic acid and vitamin A and also having antioxidant compounds such as phenolic compounds which helps in ailments of various adverse conditions [18,19]. The energetic value of chia seeds is about 459-495kcal/100 g [24,25]. Another important characteristic of chia seed is that it does not contain gluten and consumed by persons who are suffered from the celiac disease [26-28]. The seeds of chia composed of total dietary fibre about 47.1-59.8% [29,30] and contain up to 40% of oil with a high content of unsaturated fatty acids such as α-linolenic acid which represents up to 68% [31,32].

3.2.1. Fibres

The dietary fibre which is present in foods, especially in the whole grains, is an important bicomponent due to its potential and high efficacy on health benefits. A large and wide number of research and studies have shown better benefit and effect of fibre consumption which leads to decrease of occurrence of risk of coronary heart disease, diabetes mellitus (Type-II), and several types of cancer diseases, cardiovascular diseases and antioxidant activities [33]. Due to the consumption of various dietary fibre, it can increase in post-meal satiety, and decreasing subsequent hunger. The total consumption of dietary fibre is about 25-30 g/day which shows the positive and potential influence on human health. The content of fibre in chia seeds is about 23-41% in which insoluble content makes about 85% and the soluble content makes about 15% [34,35].

3.2.2. Lipids

The important characteristic of chia is its high content of polyunsaturated fatty acids (PUFAs). The seeds of chia contain about 25-40% which comprises of linolenic acid (ω-3) about 55-60% and linoleic acid (ω-6) about 18-20%. As the human body needs these essential fatty acids for better good health [25,36]. Various epidemiological studies suggest that dietary fatty acids are rich in α-linolenic acid (ALA) which leads to enhance the childhood teaching and behaviour abilities [37] and also led to decrease the risk of psychiatric illnesses in adults [38]. The plant's polyunsaturated fatty acids (PUFAs) synthesized from the α-linolenic acid that are precursors of EPA (Eicosapentaenoic acid) and DHA (Docosahexaenoic acid) which are the functional assets of very long-chain PUFA

[39]. These helped in the ailment of various diseases such as cardiovascular diseases, hypertension, obesity, diabetes and other health-related disorders [40].

3.2.3 Protein and amino acids

Protein content in chia seeds is about 16-26%, in which most of them being prolamins about 538 g/kg of crude protein, followed by glutelin about 230 g/kg of crude protein, globulins about 70 g/kg of crude protein and albumins bout 39 g/kg of crude protein [20,17,25]. Globulins are the highest protein content and have significant amounts of aromatic and sulphur amino acids, glutamic acids, and aspartic acids, also with threonine and histidine. So, the isolated globulins from chia seeds contain various essential amino acids for the consumption of human nutrition in which histidine, isoleucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine are present. Chia seed provides a high range of diverse health benefits due to the high amounts of protein and phytochemicals which have better and high concentration of biologically active peptides with antihypertensive and other important functions. There are limited data is present on chia proteins as antihypertensive effects. However, some of the researchers isolated globulin, the high protein fraction, and obtained peptides by using enzymatic hydrolysis to screen antihypertensive peptides which act as natural inhibitors of ACE (Angiotensin-I Converting Enzyme) [41,42]. Chia is a good source of peptides which can play a vital role in the regulation of blood pressure. *Orona-Tamayo et al. in 2015* isolated and hydrolyzed albumin, globulin, prolamin and glutelin protein components with different peptidases such as pepsin, trypsin and chymotrypsin and ultimately tested for inhibition of the angiotensin-I converting enzyme (ACE).

4. Different studies on *Salvia hispanica L.* (Chia)

Some of the studies show the potential and positive effects of the intake of whole or ground chia seeds on the blood pressure levels in human-being. Due to this context, *Vuksan et al. in 2007* screened the diabetic individuals who were suffering from cardiovascular risk to determine the effect of the chia seeds as a supplement in an amount of 37 g/day. These patients showed reduced or decrease in blood pressure by 12 weeks as compared to patients with placebo. And with comparison to the controlled group of patients, the chia supplements reduced SBP (systolic blood pressure) around 6.3 mmHg and they conclude on behalf of this that the long-term consumption of the seeds can have potential to decrease the cardiovascular risk factor [43]. The other study was done by *Toscano et al. in 2014* which show the effects of chia seed supplements on the blood pressure in treated and untreated hypertensive patients or an individual. In this hypertensive subject received supplement with 35 g/day of chia seed flour or placebo for about 12 weeks, and showed a reduction of 5.2 mmHg in blood pressure levels, whereas placebo groups showed no change. So, they concluded that chia flour consumption can decrease blood pressure in hypertensive individuals [44]. However, another study was done when *Nieman et al. in 2009* evaluated an intake of 50 g/day of whole or ground chia seeds in male and female patients for about 12 weeks concerning hypotensive features, manifest no differences in the blood pressure levels in either male or female compared with the controlled groups [45].

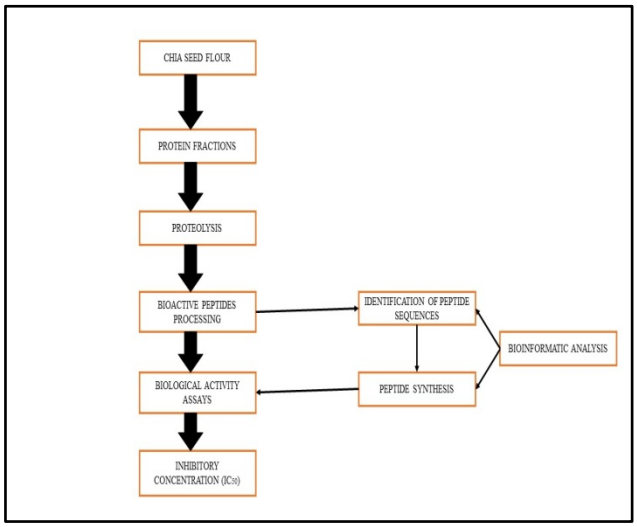

Figure 2: The classical approach to obtain bioactive peptides from chia seeds and identify the various functional and biological activities.

Similar evidence was found by *Neiman et al. in 2012* when they give 25 g/day of whole or ground chia seeds in overweight women for about 10 weeks. They concluded that the ingestion of the chia seeds in an amount of 25-50 g/day did not influence the cardiovascular risk factors. Because of these results, they are controversial and contradictory, as the inhibitory capacity of the food peptides on the angiotensin-converting enzyme is not always related to antihypertensive activities and peptides show high potential inhibitory effects against ACE in vitro but not in vivo evaluations of blood-pressure-lowering effects. As the blood pressure lowering effects depends on the physiological status of an individual and the period of consumption and supplementation as well as the poor absorption of the bioactive peptides [46]. The main chemical composition of *Salvia hispanica L.* seeds includes not only the proteins but also α-linolenic acid and dietary fibre, which are in high concentration and influence high antihypertensive effects. Therefore, the chia components are separately tested in animals and human models with antihypertensive risk factors concerning analysing their inhibitory effects on blood pressure levels.**5. Phytochemical Constituents Of *Salvia Hispanica L.*(Chia)** Total phenolic content in chia seed extracts about 8.8% on the dry basis as shown in

The presence of caffeic acid, chlorogenic acid, and quercetin can be correlated with higher extents of phenolics in chia seeds.

Table 1: The concentration of phenolic compounds which are present in chia seeds [7, 30, 47]**6.**

Compounds	Bioactive components	Concentration (mg/g seed)
Phenolic acids	Gallic acid	0.0115
	Caffeic acid	0.027-0.086
	Chlorogenic acid	0.013-0.074
	Ferulic acid	Trace
	Rosmarinic acid	0.9267
Esters	Protocatechuic ethyl ester	0.7471
Isoflavones	Daidzin	0.0066
	Glycerin	0.0014
	Genistin	0.0034
	Glycitein	0.0005
	Genistein	0.0051
Flavanols	Quercetin	0.0181-0.209
	Kaempferol	0.0057-0.0435
	Myricetin	0.0095

Antioxidants of *Salvia Hispanica L.* (Chia)

Chia seeds and its oil contain a high range of natural antioxidants such as tocopherols, phytosterols, carotenoids, [48] polyphenolic bioactive compounds which mainly originate from the caffeic acid which is the building block and flavonoids, including flavones such as myricetin, quercetin and kaempferol. These compounds are the main which is responsible for the antioxidant activity of chia seeds due to their ability and potential to scavenge free-radicals to chelate metal ions and to donate hydrogens. The flavones are also responsible for ROS (reactive oxygen species) and RNS (reactive nitrogen species) scavenging activity because due to transfer of a hydrogen and an electron to hydroxyl, peroxyl, and peroxynitrite radicals, which stabilize them and generate stable flavonoid radical [49]. As antioxidant compounds reduce the risk of chronic and deadly diseases including cancer and heart diseases, they show potential efficacy against various disorders such as stroke, atherosclerosis, diabetes, and neurodegenerative disorders such as Alzheimer and Parkinson diseases which leads to damage brain and its parts [50].

7. Biological Properties of *Salvia Hispanica L.* (Chia)

The nutritional and phytochemical constituents such as high content of polyunsaturated fatty acids (PUFAs), dietary fibres, vitamins, minerals and bioactive substances showed the numerous studies on these seeds to prove their therapeutic and pharmacological properties. The chia seeds attributed to various properties such as hypotensive [51], anticancer, laxative, treat cardiovascular system [13] exhibit anti-inflammatory properties as well as control the lipid metabolism [52-54] and have antioxidant properties which can mainly increase the performance level of athletes [55].

7.1. Cardio-Protective Effects of Chia Seeds

Shown by the presence of α-linolenic acid, eicosapentaenoic acids (EPA) played an important role in the formation of various and vital biochemical compounds in the body such as prostaglandins, leukotrienes, and thromboxane which can be encountered to performed various physiological functions [56]. Omega-3 fatty acids have the potential to block the calcium and sodium ion channel dysfunctions, which manifest in the occurrence of hypertension or high blood pressure [57]. Omega-3 fatty acids can improve parasympathetic tone, heart rate variations and protect ventricular arrhythmia conditions.

7.2. Anti-Hyperlipidaemia And Anti-Hypercholesterolemia Activity

Dyslipidemia and visceral adiposity were reduced by chia seed diet in rats [58,59]. The chia seed diet lowers the triacylglycerol levels, increases high-density lipoproteins (HDL) levels cholesterol and linolenic and it derived fatty acids present in rat serum. The mixture of chia seeds and different types of oils are reduced oxidative stress in vivo in obese Wistar rats. Stearoyl-CoA desaturase-1 product was disrupted in the heart, liver and the adipose tissue of chia seed-supplemented rats. In another study, dietary chia seeds prevented the onset of dyslipidemia and insulin resistance in the rats which are fed with the sucrose-rich diet. It also reduced the visceral adiposity [1,60].

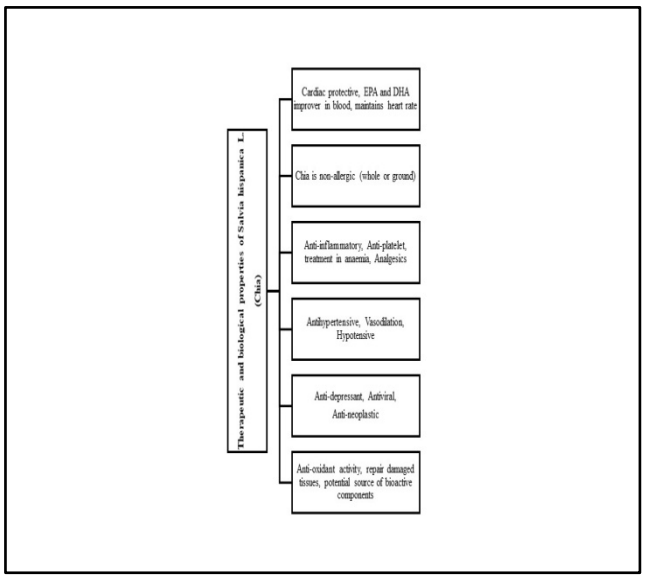

Figure 3: Shows the various therapeutic and pharmacological properties which are present in the *Salvia hispanica L.* (Chia)

With these properties, chia oil also reduced adipocyte hypertrophy, lipolysis and anti-lipolytic action of insulin in high sucrose rats. The combination of different seeds mixtures increases polyunsaturated fatty acids (PUFA) [61] levels in the plasma and liver of experimental animals besides with anti-atherogenic, hypolipidemic and immune modulator effects which contribute to the antioxidant potential of unsaturated fatty acids especially ALA present in the seed mixtures [62-64].

7.3. Anti-diabetic activity

Various reports determined the potential and beneficial physiological effects and role of chia against the risk factors for Type 2 diabetes in an experimental animal [65]. In a crossover design study of about 6-months in which Type 2 diabetic subjects consuming chia daily about 35 g/day and demonstrated the activity of lower blood pressure, lower pro-inflammatory markers and coagulation factors [66]. High levels of glycemia in the blood can activate the pathways related to the overproduction of ROS (reactive oxygen species) that induce a biochemical cascade which ultimately resulting in increased inflammation and endothelial dysfunction. As these conditions are associated with the development of diseases such as diabetes and risk factors and related cardiovascular problems [67]. In a separate study, chia enriched diet modulated dyslipidemia, liver triacylglycerol (TAG), fatty acid oxidase, acetyl-CoA carboxylase and glucose-6 phosphate dehydrogenase. The protein levels of PPARα increases and the increased mature form of sterol regulatory element-binding protein-1 (SREBP-1) levels in the sucrose-rich diet (SRD) was decreased and normalized by chia. This study shows and attributed some key mechanisms which have biological effects of dietary chia seed in preventing and normalizing/improving dyslipidemia and liver steatosis in an insulin-resistant rat model [68].

7.4. Effective role of chia on the immune system

The effect of chia seed on the immune system of male Wistar rats of about 23 days old, in which the concentrations of thymus and serum IgE were used as an indicator of immunity. That trial was conducted for about one month, rats were divided into 3 groups in which one group was fed with chia seeds about 150 g/kg diet, the second group was fed with chia oil about 50 g/kg diet, and while the third group was kept control. The diet of both groups was formulated in such a way that they had a similar concentration of α-linolenic acid and energy. The body weight of all the three groups was measured after 4 hours of fasting and the termination of the feed period, blood was analysed for serum IgE when chia is administered in seed or oil form. It was estimated that the concentration of IgE was considerably higher in both the groups as compared to control group. The inclusion of chia in any form did not induce any symptoms such as abnormal behaviour, diarrhoea, dermatitis, supplementation of diets with other sources of ω-3 fatty acids such as flaxseed or marine products usually which results in allergy, fishy flavour, disruption and problems of the gastrointestinal tract [69].

7.5. Anti-inflammatory activity

The inflammatory disorder is associated with pain, redness, swelling and severity of which it leads to loss of major and vital functions in the body. The inflammatory molecules released leukocytes which is an interdependent chain of reactions and the inflammatory mediators inclusive of linoleic acid and its derivatives eicosanoids, prostaglandins E2 and leukotriene B4 are derived from arachidonic acid. However, the lower risks of pro-inflammatory reactions are demonstrated with chia seed oil diet. The n-3 PUFA (polyunsaturated fatty acids) in chia seed oil has a strong suggestion to compete with arachidonic acid for the incorporation into the membrane. Therefore, it generates slightly modified prostaglandins and eicosanoids such as LTE5, LTB5 AND PGE3 which induce lesser extent of inflammation via induction of cyclooxygenase enzyme-2 (COX-2). Anticoagulant and anti-inflammatory effect of chia seeds may help in preventing strokes and heart attacks in type-2 diabetic patients.

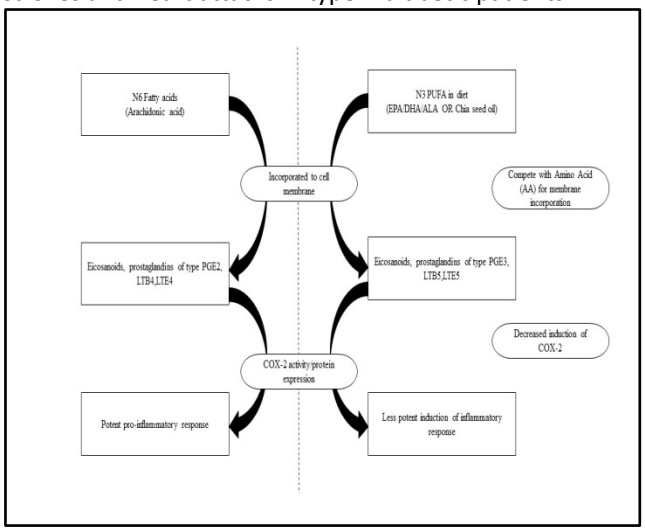

Figure 4: Depicts the schematic representation of the mechanism of action of the *Salvia hispanica L.* (chia) seed oil.

7.6. Anti-oxidant activity

Chia seeds and its oil contain a high range of natural antioxidants such as tocopherols, phytosterols, carotenoids, polyphenolic compounds which are mainly constructed from the caffeic acid which is the building block and flavonoids, including flavones myricetin, quercetin and kaempferol. This class of compounds is the main responsible for the antioxidant activity of chia seeds due to their ability to scavenge free-radicals, to chelate

metal ions and to donate hydrogens. Flavones is the major responsible of ROS and RNS scavenging activity because of the transfer of hydrogen and an electron to hydroxyl, peroxyl, and peroxynitrite radicals which stabilize them giving rise to a relatively stable flavonoid radical.

Antioxidant compounds reduce the risk of chronic diseases such as cancer and heart diseases, they give protection against some disorders such as atherosclerosis, stroke, diabetes and neurodegenerative diseases such as Alzheimer and Parkinson [58,60].

Numerous reports demonstrate the potent antioxidant property of chia seeds among in vitro assays. Among obesity model of rats, dietary chia oil-induced the HSP70 expression and HSP25 in skeletal muscle and restored the superoxide dismutase and glutathione peroxidase expression. Besides, extended treatment with chia seed and short treatment with chia oil which restored peroxisome proliferator-activated receptor-γ-coactivator-1α (PGC-1α) expression [70].

8. Conclusion and future perspective

As per the paper, it was concluded that Salvia hispanica L. is a plant known since ancient times whose seeds used as a portion of basic food in the diet of Mayan and Aztec populations. As the worldwide increase in the awareness about public health so this was searched and used as a functional food which has multiple health and biological benefits on humankind. Chia seeds are the good source of nutraceuticals and a numerous report which shown their beneficial effects on human health due to their chemical and bioactive composition and components. As they are rich in a wide range of PUFA (polyunsaturated fatty acids), especially linolenic acid. As they also contain a high range of polyphenols including caffeic and chlorogenic acids, myricetin, quercetin and kaempferol which give rise to the high value of antioxidant value and activity. Chia seeds have significant anti-inflammatory and antioxidant properties in vivo. Various epidemiological and experimental reports mention the medicinal properties and usage of chia as oral supplements. Review highlights the 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 by using mechanistic approaches in cell and mammal models are prerequisite before its therapeutic usage. The future perspective is done on new investigations that focussed on chia proteins and their bioactive compounds and peptides which are necessary to demonstrate especially the mechanisms of action that contribute to the observed health benefits. The various technologies such as advancement of “omics techniques” include metabolomics (metabolites study), genomics (genes study), proteomics (proteins study), transcriptomics (mRNA study), toxicogenomic (toxicity study) applied with specific biological samples and provide a better efficacious potential therapeutic category which interprets the molecular level mechanisms and also determined the better pharmacological medicinal properties of *Salvinia hispanica L.* (Chia seeds). As their bioactive compounds used as a functional food supplement, nutritional supplement, and used in treatment as herbal remedies for various cardiovascular disorder in today as well as in future also.

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