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Pharmacological Properties and Health Benefits of Flaxseed: A Review

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ABSTRACT

Since ancient times, medicinal plants are recognized for their therapeutic effects. Medicinal plants continue to be of paramount importance until the present day. Recently, medicinal plants are gaining much interest due to their utilize for treating different diseases. Experimental scientific investigations on therapeutic roles of many plants have led to the discovery of new valuable drugs. Historically, plant varieties were used for many objectives such as foods, cosmetics and pharmaceutical products. Flax is among the oldest crop plants cultivated for its seed oil and fiber. Flax has become a popular functional food due to its high omega-3 fatty acid content as well as its dietary lignans and fiber. Flaxseed oil is a rich source of nutritive and bioactive compounds. Currently, flaxseed constituents, especially its oil, have gained attention in the area of pharmacological and biomedical research due to its health benefits. In this review, the pharmacological and health benefits properties of flaxseed were demonstrated according to the previous scientific data. Previous literatures indicated the effective role of flaxseed and its chemical constituents for the treatment of many diseases, which makes it as one of the most promising natural products for maintaining the health and integrity of the body's functions.

Keywords: Flaxseed, linseed, *Linum usitatissimum*, phytochemicals, polyunsaturated fatty acids, antioxidants, disease prevention.

1. Introduction

The plant kingdom contains a large number of medical herbs that are used in pharmacy and traditional medicine for the treatment of different diseases. Over the last 30 years, various experimental procedures have been developed for the safety evaluation of medicinal plants (Grujicic *et al*., 2020). Medicinal plants contain a variety of ingredients and bioactive compounds (Chen *et al*., 2019). Nowadays, medicinal plants are reported as attractive plants receiving considerable attentions because of having mild action and no side complications (Dil *et al*., 2020). Sometimes, the extraction of biologically active substances from plants is easier and more convenient than their synthesizing. Consequently, these evidences could justify using medical plants together with the synthetic medicines (Yordanov *et al*., 2009). Flaxseed (*Linum usitatissimum* L., Family: Linaceae), which is produced globally with high yield (Bekhit *et al*., 2018; Suri *et al*., 2020). Flaxseed is one of the oldest crops, having been cultivated since the beginning of civilization (Singh *et al*., 2011). It is grown globally with a total estimated production of 2.65 million tonnes as reported in 2014 (Mandal and Kundu, 2019). Flaxseed, which is also known as linseed, is cultivated in more than 50 countries nowadays, and Canada is

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the largest producer and exporter of flaxseed in the world, other main flaxseed growing countries are India, China, USA and Ethiopia (Singh *et al*., 2011). There is a small difference in using the terms flaxseed and linseed. Flaxseed is used to describe flax when consumed as food by humans while linseed is used to describe flax when it is used in the industry and feed purpose (Morris, 2008). Flaxseed oil is a type of herbal oil obtained from the ripened seeds of the flax plant and widely used for bread, cookies, cakes and other baked foods. Moreover, the traditional utilization of flaxseed has focused on its oil content which can be utilized for paints and coatings, printing inks, soap, core oils, brake linings, and herbicide adjuvant (Carter, 1993; Bekhit *et al*., 2018).

Chemical composition of flaxseed

The main bioactive compounds in flaxseed include 40% lipid, 30% dietary fibre and 20% protein. It is well known that flaxseeds are a source of high content of polyunsaturated fatty acids (PUFAs). The polyunsaturated fatty acids content comprises a bout 53% omega-3, 16% omega-6, 18% monounsaturated fatty acids (MUFAs) and 9% saturated fatty acids (SFAs) (Pradhan *et al*., 2010).

Flaxseed health benefits

Flaxseed oil was used to treat various health complaints in ancient Greece and Rome and was described in ancient Ayurvedic and Egyptian sources. In the last two decades, flaxseed has been the focus of increased interest in the field of diet and disease research due to the potential health benefits associated with some of its biologically active components (Goyal *et al*., 2014; Zhou *et al*., 2020). Flaxseeds were also incorporated into food with other nutraceuticals or food ingredients to improve the nutritional quality of food (Dong *et al*., 2015; de Moura *et al*., 2016). Many nutritional, physiological, biochemical and pharmacological researches focused on the effects of flaxseed extracts due to the health properties of flaxseed constituents (Abdel-Moneim *et al*., 2010; Akpolat *et al*., 2011; Khan *et al*., 2012; Rizwan *et al*., 2014; Jangale *et al*., 2016; Yari *et al*., 2016). Recently, a concern was raised about the presence of components in flaxseed that may have undesirable effects that could affect the bioavailability and bioaccessibility of essential nutrients (Dzuvor *et al*., 2018). These include the presence of protease inhibitors, phytic acid, linatine and cynogenic glycosides in flaxseed. However, there no deleterious effects reported of these components in human studies. The concentrations of these components delivered through dietary flaxseed may be below that needed to induce any biological actions (Parikh *et al*., 2019).

Flaxseed and cardiovascular disease

Flaxseed oil gained much attention because of its unique nutrient components and potential effect on the prevention of cardiovascular disease such as hypertension and hyperlipidemia (Prasad, 1997; Lucas *et al*., 2004; Haghighatsiar *et al*., 2019). It is associated with lowering of serum lipids and decreasing oxidative stress and so it may prevent cardiovascular diseases (Prasad, 2009; Xu *et al*., 2012). Because it have some health effect in reducing lactate dehydrogenase (LDH) responsible for heart disease (Cunnane *et al*., 1993; Jenkins *et al*., 1999). Dietary flaxseed may offer protection against ischemic heart disease by improving vascular relaxation responses and by inhibiting the incidence of ventricular fibrillation (Jennifer *et al*., 2010). In animal models of heart disease, dietary flaxseed has decreased the progression of atherosclerosis induced by high dietary cholesterol or high dietary trans fat content (Dupasquier *et al*., 2010; Bassett *et al*., 2011). Flaxseed can also lower circulating trans fats levels (Bassett *et al*., 2011). In humans exhibiting symptoms of cardiovascular disease, dietary flaxseed has displayed powerfully protective effects. The most impressive involves the decrease in both systolic and diastolic blood pressure in patients with peripheral arterial disease (Rodriguez-Leyva *et al*., 2013). Alpha-linolenic acid (ALA) from flaxseed decreased the production of reactive oxygen species (ROS) and increased the levels of cardiac antioxidant enzymes (Xie *et al*., 2011). Numerous studies have shown the ability of increased omega 3 fatty acid intake to help regulate and reduce blood pressure in persons who have been diagnosed with hypertension. Furthermore, a diet low in saturated fats and rich in monounsaturated and polyunsaturated fats,

including omega-3 fatty acids from flaxseed, can reduce heart disease (Bernacchia *et al*., 2014). Rodriguez-Leyva *et al*. (2010) analysing epidemiological investigations and experimental studies suggested that ALA intake from flaxseed has been demonstrated to combat cardiovascular disease.

Flaxseed and diabetes

Flaxseed oil may impacts another major disease that is growing in incidence across the globe: diabetes by regulation of blood glucose (Haghighatsiar *et al*., 2019). Bhardwaj *et al*. (2015) suggested that adding flaxseed oil to the diet may decrease insulin resistance in diabetics and pre-diabetics and help in reducing the risk of developing type 2 as well as type 1 diabetes. Evidence suggested that omega-3 fatty acid in flaxseed oil is generally protective for diabetes risk. Based on the results of clinical trials, epidemiological investigations and experimental studies, ingestion of flaxseed oil has been suggested to have a positive impact on diabetics as well as pre-diabetics. Several small studies using a fasting glucose tolerance approach have found a reduction in postprandial blood glucose levels of women consuming flaxseed (Cunnane *et al*., 1993; Cunnane *et al*., 1995). Similar results has also been reported by Nazni *et al*. (2006) who conducted a study on 25 diabetic subjects and supplemented flaxseed powder in bread form for 90 days and reported a significant reduction in blood glucose levels after supplementation. Utilization of flaxseed for glycemic control may also be associated to the decrease in risk of obesity and dyslipidemia, since these are risk factors for the development of diabetes and resistance to insulin (Morisset *et al*., 2009; Wu *et al*., 2010).

Flaxseed and inflammatory diseases

Flaxseed consumption is common in many countries and is considered safe and beneficial because of its antioxidative and anti-inflammatory effects (Cohen *et al*., 2005; Lee *et al*., 2009; Hajiahmadi *et al*., 2020). Bernacchia *et al*. (2014) reported that the healthy properties of flaxseed oil are related to anti-inflammatory and antioxidant. It has been reported that inflammatory response are attenuated by antioxidants (Chun *et al*., 2008; Vinayaga-Moorthi *et al*., 2006; Hajiahmadi *et al*., 2020). Consumption of ground flaxseed for 4 wk reduced proinflammatory oxylipins in the plasma of older adults (Caligiuri *et al*., 2014). The clinical significance of omega fatty acids lies primarily in the role they play in inflammatory events in the body. Indeed, omega-3 fatty acid derived from flaxseed has anti-inflammatory actions and significant cardiovascular benefits attributable to increasing ones consumption of omega-3 fatty acid (Kapoor and Huang, 2006).

Flaxseed and lipid profile

Flaxseed has received increasing attention for their potential role in preventing lipid disorders (Abdel-Moneim *et al*., 2010; Abdel-Moneim *et al*., 2011). Shadmani and Karami (2013) showed that flaxseed supplementation for 3 months could improve lipid profile levels. Previous animal studies suggested that flaxseed reduces both total and low density lipoprotein cholesterol (LDL-C) (Prasad, 1997; Lucas *et al*., 2004). In human studies, flaxseed administered was associated with reduction in serum triglycerides and LDL-C without any alteration of high density lipoprotein cholesterol (HDL) (Bierenbaum *et al*., 1993). Consumption of flaxseed oil can prevent against alcoholic hepatic steatosis by ameliorating lipid homeostasis at the adipose tissue-liver axis in mice (Wang *et al*., 2016), improve the lipid profile in people (Mirfatahi *et al*., 2016), and relax both constipation and diarrhea (Palla and Gilani, 2015). Overall, flaxseed supplementation was associated with a decrease in blood total and LDL cholesterol concentrations but did not substantially affect HDL-C and triglycerides (Pan *et al*., 2009). Several animal studies have shown variable effects of flaxseed on serum lipid profile. The majority of human studies have reported that flaxseed reduces total cholesterol by 6–11% and LDL-C by 9–18% in normolipidemic subjects (Cunnane *et al*., 1993; Clark *et al*., 1995; Cunnane *et al*., 1995) and total cholesterol by 5–17% and LDL-C by 4–10% in hypercholesterolemic patients (Jenkins *et al*., 1999; Mandasescu *et al*., 2005; Patade *et al*., 2008). Ground flaxseed 38–40 g/day in food, can also reduce the levels of atherogenic lipoproteins (a) [Lp(a)] and apolipoproteins A-1 and B after 12 weeks of dietary intervention

(Lucas *et al*., 2002; Bloedon *et al*., 2008). Most animal studies have demonstrated no changes in serum HDL-cholesterol and triglyceride levels (Lucas *et al*., 2004; Alexander *et al*., 2007).

Flaxseed and immune system

Flaxseed oil contains abundant of healthy components which are very important in the prevention and treatment of chronic disease and in supporting the immune system (Morshedzadeh *et al*., 2019). It has been reported to enhance immune system, promote the growth and productive performance (Sekine *et al*., 2008). Flaxseed oil plays a role for improving immune function because bioactive compounds have demonstrated a beneficial impact by affecting immune cells and immune response mediators. Flaxseed may play an important role in the clinical management of autoimmune diseases and certain hormone and prostate. The lignans and ALA in flaxseed help prevent inflammation that affects the body's immune system. Flaxseed in the diet may be useful in the treatment of such immune disorders as rheumatoid arthritis, psoriasis and lupus (Tripathi *et al*., 2013).

Flaxseed and antioxidative effects

Oxidative stress has been shown to play a role in the pathogenesis of many diseases. It was reported the usage of natural antioxidant additives decrease oxidative stress level and chronic disease (Işık *et al*., 2015). Flaxseed as a dietary supplement could enhance the antioxidant capacity in liver of rats exposed to carbon tetrachloride (CCl_4) and in mammary gland of Cows (Cortes *et al*., 2012). Flaxseed oil also produces a protective effect against sodium nitroprusside induced nephrotoxicity and oxidative damage in male rats (Khan *et al*., 2012). Antioxidant property of flaxseed chutney was evident from lowered lipid peroxidation (TBARS) and predictor enzyme γ-glutamyl transpeptidase (GGT) profile in azoxymethane treated rats (Hernandez-Salazar *et al*., 2013).

Flaxseed and nephropathy

Flaxseed oil supplementation was observed as reducing renal inflammation and fibrosis in animal models (Baggio *et al*., 2005). Gopinath *et al*. (2011) showed that increased dietary intake of long-chain omega-3 fatty acid was inversely associated with the prevalence of chronic kidney disease. El-Sayed *et al*. (2014) investigated the effect supplemented diets with different doses of flaxseed on some biological, biochemical and histopathology alterations in rats suffering from nephropathy. The results indicated that the diet of flaxseed (3, 5 and 7g/100g) treated groups get better in body weight gain%, kidney functions (serum urea, uric acid and creatinine), glutathione (GSH) and malondialdehyde (MDA) renal tissue ameliorated especially in renal failure rats fed on diet containing 5% and 7% flaxseed.

Flaxseed and hepatopathy

Ahmad *et al*. (2019) studied the effects of flaxseed oil on hypercholesterolemia induced hepatotoxicity in male rabbits. Serum parameters of total cholesterol, LDL-C, HDL-C and triglycerides were evaluated. Flaxseed has beneficial effects in hypercholesterolemia-induced hepatotoxicity as well as in diseases that have risk factors for the development of the disease. Ume Salma *et al*. (2019) investigated the hepatoprotective effect of flaxseed and its protein on ethanol-induced hepatotoxicity in adult Wistar rats. The flaxseed and its protein significantly prevented the elevation of plasma markers of hepatic damage, lowered lipid peroxidation, mitigated changes in antioxidant enzymes, and suppressed histopathological signs of hepatic damage. These findings implicated the ameliorative effect of flaxseed and its protein on ethanol-induced hepatotoxicity.

Flaxseed and cancer

Flaxseed is already used extensively in animal studies to treat a variety of cancers (Mason and Thompson, 2014). Flaxseed oil is widely recognized for its exceptional nutritional value, high concentration of fiber based lignans and large amounts of omega-3 fatty acids. It is one of a generic group of functional foods that is often taken by cancer patients as a potential treatment (Buckner *et al*., 2019). The beneficial properties of consuming flaxseeds are protecting against

various cancers like prostate cancer, breast cancer and colon cancer (Steven and Ehlrich, 2013). Flaxseed has been shown to reduce the early risk markers for and incidence of mammary and colonic carcinogenesis in animal models (Thompson *et al*., 1996). Improved symptoms and survival, and was associated with improved mental health among breast cancer patients. Flaxseed have been shown to reduce mammary tumor size by >50% and tumor number by 37% in carcinogen-treated rats (Thompson *et al*., 1996). Phipps *et al*. (1993) demonstrated that the ingestion of 10 g of flaxseed per day elicited several hormonal changes associated with reduced breast cancer risk. Moreover, Flower *et al*. (2014) indicated that the regular consumption of flax decreased breast cancer risk.

Flaxseed and nervous system

Flaxseed oil effectively treats some cases of depression, improves the mental function of old people. Flaxseed oil is beneficial in the treatment of and often improves the symptoms of multiple sclerosis (Tripathi *et al*., 2013). The omega-3 fatty acid, in flaxseed oil makes about 55–60% of total fatty acids (Oomah, 2001; Bozan and Temelli, 2002). Indeed omega-3 fatty acids found in flaxseed is good for maintaining brain health as about 60% of the brain consists of lipids which make up the lining, or cell membrane, of every brain cell (Anis *et al*., 2016). When mothers of rats were fed flaxseed during pregnancy, the brains of newborn pups were heavier and contained significantly greater amounts of ALA (Lenzi Almeida *et al*., 2011). In pups given milled flaxseed or flaxseed oil soon after birth, these pups showed higher brain mass, demonstrating the value of milled flaxseed particularly in contributing to early postnatal brain development (Pessanha *et al*., 2015). Li *et al*. (2012) investigated the neuroprotective actions of flaxseed against N-methyl-d-aspartate (NMDA) in primary cultured cortical neurons. The results suggested that the flaxseed protected cortical neurons by inhibiting the expression of GluN2B-containing NMDA receptor and regulating the Bcl-2 family. Supplementations to the flaxseed have shown anti-depressant-like effects in mice subjected to chronic stress (Ma *et al*., 2013).

Flaxseed and bone health

The omega-3 fat found in flaxseed promotes bone health by helping to prevent excessive bone turnover. Flaxseed oil shortens the time being necessary for tired muscles to recover after exertion. It is alleviates the symptoms of rheumatoid arthritis. This oil accelerates the healing of sprains (Griel *et al*., 2007). Maíra *et al*. (2018) evaluated the effects of flaxseed flour diet on bone health in adult Wistar male rats. They found that a diet containing flaxseed flour contributed to bone mineral density and femur resistance at 180 day. Chen *et al*. (2019) studied the effect of flaxseed oil on bone damage induced by a high fat diet (HFD) and to explore the possible mechanism in Male Sprague Dawley rats. The results showed that flaxseed oil alleviated bone loss in HFD rats, probably by promoting osteoblastic β-catenin/RUNX2/osterix gene and protein expression and restoring palmitic acid (PA)-induced alkaline phosphatase (ALP) activity decreases. These findings indicated that the flaxseed oil might be a potential therapeutic agent for high fat diet-induced bone loss, most likely by promoting osteogenesis. Additionally, Ragheb *et al*. (2019) investigated the possible protective effect of flaxseed powder on glucocorticoid (GCD)-induced osteoporosis in female rats. The alleviating roles of this plant on some other side effects of glucocorticoid therapy were also studied. The results indicated that feeding GCD resulted in a significant decline in bone mineral concentration (BMC), bone mineral density (BMD) and the concentrations of calcium and phosphorus in both sera and left femur bones which was supported by histopathological findings. Feed intake, body weight gains and hence feed efficiency ratio were also significantly reduced. Conversely, the activities of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were significantly increased revealing a marked liver injury. Supplementation of GCD with the studied plant alleviated the marked lesion noticed in bone tissue and increased its mineralization and density. Feed intake and liver functions were improved in flaxseed-fed groups. The results suggested that the dietary supplementation with flaxseed powder is recommended to prevent GCD-induced Osteoporosis and some other side effects. The supplementation was more potent in elevating bone mineral density.

Conclusion

There are growing scientific evidences supporting the beneficial influences of plant products on human health. Scientific studies shown that the consumption of natural plants products is strongly associated with reduction of different diseases. Flaxseed is considered to be one of the most healthy dietary plant oils. In this review, flaxseed and its chemical constituents have interesting therapeutic effects against many diseases and physiological disturbances such as cardiovascular disease, diabetes, dyslipidemia, immune disorders, oxidative stress, nephropathy, hepatopathy, cancer, neuropathy and bone diseases. However, many of these effects have been evaluated in experimental animals and it is necessary to perform investigations with human beings to confirm the benefits attributed to flaxseed and its chemical constituents.

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