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Therapeutic and Pharmacological Properties of Pumpkin Seeds: A Comprehensive Review

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ABSTRACT

A well-known edible plant in the Cucurbitaceae family, the pumpkin has long been utilized as a functional meal or a herbal remedy. Pumpkin seeds are rich in phytoestrogens, vitamin E, and unsaturated fatty acids, which may have medicinal and nutraceutical uses. The use of pumpkins in traditional medicine to treat a wide range of conditions, including inflammation, dyslipidemia, bacterial or fungal infections, malignancies, intestinal parasites, hypertension, arthritis, and hyperglycemia, has drawn attention to the need for additional study on both the fruits and seeds of the pumpkin plant. Proteins, antioxidative phenolic compounds, tocopherols, triterpenes, saponins, phytosterols, lignans, and carotenoids are some of the micro- and macro-constituent compositions that improve pumpkin seeds. Pumpkin seeds have antidepressant properties and are mostly used in the management of benign prostatic hyperplasia (BHP). Regular pumpkin seed eating lowers the risk of Parkinson's and Alzheimer's disease. Since pumpkin seeds are high in tocopherols, they can be extracted for edible oil and then used to formulate other foods at a later time. The pharmacological effects of pumpkin seeds have made them quite popular. Additionally, pumpkin seed oil has numerous health advantages. Pumpkin seeds are mostly composed of unsaturated fatty acids, which have been shown to provide potential health benefits and to prevent disease. Although pumpkin seeds are clearly very useful, their full potential has not yet been discovered.

Keywords- Pumpkin, Seeds, Pharmaceutical, Hyperglycemia, Pharmacological, Prevention.

I. INTRODUCTION

Edible seeds represent a quick, easy, and readily available source of micronutrients and functional compounds that provide numerous health benefits (Chandrasekar and Sivagami, 2021). Cucurbits are one of the major and diverse groups of plant families that are cultivated, as the seeds of these plants exhibit a wide array of therapeutic properties. Pumpkin a fleshy fibrous crop which belongs to *Cucurbitaceae* family is widely cultivated in both tropical and sub-tropical countries (Dotto and Chacha, 2020). Important species of pumpkin include *Cucurbita pepo*, *C. maxima*, *C. moschata*, *C. ficifolia*, and *C. stilbo*. An important part of pumpkin is its low fat, protein rich seeds, packed with different classes of phytochemicals (Lestari and Meiyanto, 2018). The Chinese and the Ayurvedic medicinal system have utilized pumpkin seeds for treating kidney disorders, prostate diseases, and erysipelas skin infections (Dhiman et al., 2012). Results of animal and in vitro experimental studies have demonstrated the antimicrobial, antidiabetic, antihyperlipidemic, anticarcinogenic, antihypertensive, anti-inflammatory, antidepressant, antioxidant, and anthelmintic effects of pumpkin seeds (Roy and Datta, 2015; Syed et al., 2019). Results of randomized control trials signify the role of pumpkin seeds in the treatment of benign prostate hyperplasia (Patel, 2013). This review paper aims to unveil all the nutritional, functional and pharmacological properties of pumpkin seeds.

Pumpkin seeds are rich in phytochemicals, unsaturated fatty acids, essential amino acids, vitamins,

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and minerals (Mondaca et al., 2019; Dowidar et al., 2020; Musaidah et al., 2021; Hagos et al., 2022). Cucurbitacin E contributes to anti-inflammatory and anticancer activities. Cucurbitin, extracted from pumpkin seeds acts as a vasodilator (Chelliah et al., 2018). Tocopherols reduce oxidative damage and render geno-protective effects to the seeds (Yasir et al., 2016). Trigonelline and D-chiro-inositol maintain glycemic control by acting as insulin sensitizers (Adam et al., 2014). Phenols, flavonoid, saponins, and essential fatty acids exhibit anti-hyperlipidemic activity. Rats fed with pumpkin seed extract showed an increase in HDL-C along with decrease in LDL-C and total cholesterol (Sharma et al., 2013). Evidence from human studies is still lacking to substantiate the role of pumpkin seeds in treating metabolic disorders. Previous human studies provided data on the combined beneficial effect of pumpkin, flax, sesame, and black cumin seeds on CVD risk factors (Ristic-Medic et al., 2014; Amin et al., 2015). The nutrient-enriched edible pumpkin seeds which often get discarded habitually may be considered as a functional food.

II. ANTIOXIDANT PROPERTIES

Phenolic compounds are organic molecules with a benzene ring which is hydroxylated and are present in the form of flavonoids, phenolics, condensed tannins, lignins, stillbene etc. They are considered as the secondary metabolites and are produced both in stress as well as normal condition in plant (Hoed, 2010). Pumpkin seeds are affluent source of many phenolic compounds. Singh and Kumar (2022) identified various phenolic compounds like kaempferol, *p*-coumaric acid, ferulic acid, apigenin, quercetin, vanillic acid, *p*-hydroxybenzoic acid etc. via LCMS profile in pumpkin seeds.

Flavonoid and phenolic compounds possess good antioxidant properties and enhance the immune system by strengthening the defense system of our body (Singh et al., 2017). Flavonoid as well as phenolic compounds act as antioxidants and reported as total phenolic content (TPC) and total flavonoid content (TFC) respectively in the seed extracts. They helped in removing reactive oxygen species (ROS) which results to strengthen the human health. DPPH activity measures the anti-oxidant potential of substances which serves as free radical scavengers or the hydrogen providers. Parry et al. (2008) reported the DPPH activity as 2.2 TE μmol/g in *C. pepo* L.

III. ANTI-NUTRITIONAL PROPERTIES

Plants produce anti-nutritional factors (ANFs) as secondary metabolites. They act as a defensive tool against predators like fungi, insects and bacteria and other animals. The compounds are termed as anti-nutritional because they interfere in the digestion process and affect our health.

ANF's are grouped into nitrogenous toxins (cyanogenic glycosides, toxic amino acids, alkaloids, cumaris, etc.), phenolic compounds (phytoestrogens, tannins, etc.), terpenes (saponins and sequiterpenic lactoses) phytates and oxalates (Betancur-Ancona et al., 2012). Different kinds of anti-nutritional compounds present in pumpkin seeds. Akwaowo et al. (2000) reported several anti-nutritional compounds in various parts (stems, leaves, roots and seeds) of fluted variety of pumpkin (*Telfairia occidentalis* Hook f.).

They found oxalates, cyanides, tannins and phytates as 59, 28.90, 48.20 and 36.40 mg/100 g, respectively. Miteu and Ezeh (2022) also worked on the same variety of pumpkin seeds and reported values of 148.50, 0.50 and 425.10 mg/100 g for oxalate, cyanide and phytate content, respectively. Mohaammed et al. (2014) and Williams et al. (2020) reported 0.43 mg/100 g and 2.92% oxalate content, respectively.

Elinge et al. (2012) worked on *C. pepo* L. and found four anti-nutritional compounds in Nigerian variety of pumpkin. They reported values of cyanide, nitrate, phytate and oxalate as 0.22, 2.27, 35.06 and 0.023 mg/ 100 g, respectively. Badu et al. (2020) also worked on *C. pepo* L. and found two ANF's like phytate and oxalate as 9.67 and 0.21 mg/100 g, respectively. Seeds of another Nigerian species of pumpkin were studied by Nzotta and Onabanjo (2021) who found values of phytates, oxalates, saponins, tannins and trypsin inhibitors as 0.21%, 0.11%, 0.23%, 0.01% and 31.05 mg/g, respectively. Processing of these seeds will help in the reduction of ANF's and thus the nutritional profile can be enhanced along with organoleptic properties (Betancur-Ancona et al., 2012). Karaye et al. (2021) studied few ANF's in seeds of *C. pepo* L.

These ANF's are known for deleterious effect on health but it has been studied that if they are consumed in fewer amounts, they can act as anti-oxidant and anti-cancerous agents and also helps to reduce the glycemic load and minimizes the formation of cavities also (Murevanhema et al., 2013).

IV. PHARMACOLOGICAL PROPERTIES OF PUMPKIN SEEDS

Several bioactive compounds present in pumpkin seeds work upon same or different target sites with the capability to provide many pharmacological benefits by promoting health and reducing the risk of various disorders and diseases. Usually, the combination of active components along with their mutual action mediates the nutraceutical activities of pumpkin seeds (Shalan et al., 2020).

V. CANCER AND TUMOR PREVENTION

Pumpkin seeds contain high quality protein, tocopherols and other phytosterols which prevents us from major diseases. In a study, Jayaprakasam et al. (2003) found the anti-proliferative activity of cucurbitacins extracted from *C. andreana* in colon, lung and breast cancer cell lines. Cucurbitacins are tetracyclic triterpenes and highly oxygenated compound and they are comprised of a cucurbitane skeleton made up of 19-(10$\rightarrow$ 9β) abeo-10α-lanost-5-ene. They act as anti-cancerous agents and show COX-2 enzyme inhibition. Ren et al. (2012) also studied a derivative of cucurbitacin, namely, 23, 24-dihydrocucurbitacin F (DHCF) to have significant reduction in proliferative activity on human prostate cancer (PC3) cell lines. This reduction occurs because of actin aggregation and cofilin-actin formation, cytokinesis, cell cycle arrest and apoptosis.

Cucurbitacins induces arrest of cell cycle at G2/M phase and rapidly disrupts cytoskeleton of actin by inciting actin aggregation like human myeloid leukemia cell lines (U937 and HL60), human glioblastoma multiforme cell lines (T98G and U87). Dakeng et al. (2012) also found cucurbitacin from pumpkin seed as anti-cancerous agent. Richter et al. (2013) studied about anti-cancerous effects of seeds of pumpkin by using its extract against human breast cancer cells (MCF7) and chorionic carcinoma cell lines (BeWo and Jeg3) and found cytotoxic effect on the cancerous cells. It also elevated the production of estradiol in concentration dependent manner. Cucurbitacins are regarded as a novel anticancer agent and now as a therapy for benign prostate hyperplasia. Many poly-phenolic compounds present in pumpkin seeds are considered as able to control various inflammatory signals which are associated with cancer stem cells (Sardana et al., 2018).

Amin et al. (2020) stated that the reactive oxygen species (ROS) are responsible for various types of cancers. Food laden with maximum anti-oxidants helps in reducing the chances of cancer. Seeds of pumpkin contain moschatin named novel ribosome-inactivating protein which inhibits the development of melanoma cells M21. Medjakovic et al. (2016) showed that the extracts of pumpkin seeds abdicate the expansion of carcinoma (CT26), hepatocarcinoma (HepG2) with tumor cell lines of colon in human body with approximately 45%–50% inhibition in the growth of cell line. Gutierrez (2016) stated that pumpkin seed extracts have the potential to be developed as a new chemotherapeutic agent who helps in inhibiting the growth of tumors and cancer cells in our body. Chari et al. (2018) showed chemo protective role against the tumor cells. α-Tocopherols present in pumpkin seeds reduces the pro-atherogenic effects caused by the oxidative stress by working as a potential free radical scavenger. It also regulates the expression of genes and CD36 and SR-A receptors which are the receptors of scavengers and are down regulated in the presence of α-tocopherol. The regulation of gene is considered as important for anti- atherogenic effect of vitamin E.

VI. BENIGN PROSTATE HYPERPLASIA (BHP) PREVENTION

Pumpkin seeds are in vogue for the treatment of BHP due to presence of high amount of minerals like zinc and magnesium which helps in regulating prostate growth. Abdel-Rahman (2006) reported that when pumpkin seeds are consumed at about 10%, then it can inhibit the citral induced hyperplasia of the ventral prostate lobe. It will reduce prostate protein binding levels and its weight and improves the testis histology which is favorable for managing BHP. Jiang et al. (2012) found that there was reduction in prostate cancer observed via in vivo as well as in vitro experiments in the group of patients treated by doses of pumpkin seeds. Gazova et al. (2019) stated that pumpkin seeds (*C. pepo*) are approved by European Medicine Agency (EMA/HMPC/136022/ 2010) for treating Benign prostate hyperplasia (BPH), strengthening bladder functions and treats enlarged prostate. They stated that pumpkin seeds help in treating bladder complications by balancing hormones by inhibiting 5α-reductase enzyme, which further results in effects of anabolic and muscle strengthening and direct muscle relaxing effect results in reduced bladder problems. Alhakamy et al. (2019) also stated the importance of pumpkin seeds in treating the condition of benign prostate hyperplasia in men.

VII. ALZHEIMER'S AND PARKINSON'S DISEASE PREVENTION

Performance of memory is very much affected by production of new hippocampus neurons and strength of the synaptic connection between neurons. Diet and physical activity are the external factors which protects existing neurons from various damaging factors like stress hormones and oxidative stress. It facilitates the process of neurogenesis and brain derived neurotropic factors (BDNF) that are responsible for neuron proliferation, differentiation and survival. The functioning of BDNF is regulated by glutamate (Shalan etal, 2020). The gluco-corticoid receptors in brain are widely present in the hippocampus, prefrontal cortex and amygdala. Gluco-corticoid receptor activity is related with the impairment of memory because it has been found to cause the damage of hippocampus neurons through neuroinflammation (Zhang et al., 2017), reduction of the level of hippocampus BDNF (Makini et al., 2010) and hyperphosphorylation of Tau in the

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hippocampus (Chen et al., 2017). Supplementing black mulberry fruit extract along with sunflower and pumpkin seeds and exercise helps in reducing the serum gluco corticoid receptor-*α* levels (Pinheiro et al., 2016) further reducing the chances of Alzheimer's and other memory related diseases. Tucker and Townseed (2005) also stated that pumpkin seeds help in preventing Alzheimer's disease. Kumar et al. (2016) stated that phenolic compounds are having potential to prevent from various diseases and helps in reducing the chances of Parkinson's disease.

VIII. HYPERCHOLESTEROLEMIA AND HYPERLIPIDEMIA PREVENTION

Hyperlipidemia, including hypercholesterolemia and hypertriglyceridemia, is a major risk factor for the development of cardiovascular diseases. If a diet is hypercholesterolemic, it affects the liver which is the primary organ to metabolize cholesterol ingested in excess amount affected by oxidation stress. It is a result of imbalance between production of free radicals and effectiveness of antioxidant defense system (Lum and Roebuck, 2001). The condition of atherosclerosis develops when endogenous pro-oxidant conditions are affected in liver cells (Napolitano et al.,2001). In a study, Makni et al. (2008) showed that pumpkin seeds and flax seeds mixture is abundant in PUFAs which has strong hypocholesterolemic and hypotriglyceridemic effects in the liver and plama of rats with reduction of low density lipoprotein (LDL) and increase in high density lipoprotein (HDL) levels. HDL levels contribute to its anti-atherogenic properties and inhibit LDL oxidation and protect the endothelial cells from cytotoxic effects [106]. Pumpkin seed showed anti-atherogenic as well as hepato-protective effect in rats suffering from hypercholesterolemia (Makni et al., 2010). In another study, Makni et al. (2011) showed that when diabetic rats were fed with certain amount of pumpkin seeds, there was improvement in the condition of hyperlipidemia and increase in anti-oxidant activity was also observed.

IX. DIABETES AND HYPERGLYCEMIA PREVENTION

Pumpkin seeds have considerable amounts of phenolic antioxidant compounds, among these: trigonelline, D-chiro-inositol, and nicotinic acid, those are considered to be insulin action mediators or insulin sensitizers. Their potential mechanisms affect pancreatic β-cell qualification, insulin release and activities of enzymes associated with glucose metabolism (Adams et al., 2014). D-chiro-inositol included in the seeds assumed to be an intracellular insulin action mediator via stimulating the glycogen synthase dephosphorylation, pyruvate dehydrogenase and the rate-limiting enzymes of both the oxidative and non-oxidative glucose uptake pathways (Larner, 2002). Trigonelline, a plant alkaloid included in pumpkin seeds, can ameliorate hyperglycemia and hyperlipidemia. The previous study informed that trigonelline and nicotinic acid in pumpkin seeds can boost the capacity of enzymes related to the metabolism pathway of glucose; glucokinase and glucose-6-phosphatase. The further study proposed that the rich content of protein constituents with wide molecular weight range (3-60 kDa) in pumpkin seeds may consolidate blood insulin level and blood glucose tolerance (Yoshinari et al., 2009).

Diabetes is the most common disease spread worldwide and pumpkin seeds have shown good response against diabetic rats in several studies. In a study, Adams et al. (2011) showed improvement in diabetes and hyperglycemia condition due to use of pumpkin seeds. Bharti et al. (2013) studied dose dependent effect of tocopherols extracted from pumpkin seeds on diabetes mellitus in in-vivo study in rats. Significant reduction in glucose levels were seen in diabetic rats by feeding them with higher dose of pumpkin seed extracts evaluated by docking (HOMA-IR). Tocopherols extracted from seeds of pumpkin regulated hyperglycemia, hypertriglyceridemia and lipogenesis. Kushawaha et al. (2016) reported *α*–amylase and *β*–glucosidase inhibitory activity in the extract of *C. maxima* seed which functions as an antidiabetic.

X. ANEMIA PREVENTION

Iron deficiency anemia (IDA) is well established nutritional disorder all over the world and a major problem in developing countries like India. In a study, Naghii and Mahmood [88] reported that pumpkin seeds and the iron fortified cereal were given to 8 healthy females and their blood samples were taken after some days. There was a significant increase in iron levels of those females. Pumpkin seeds can be utilized for alleviating today's most prevalent deficiency disease. Pumpkin seed possess higher iron content and is regarded as beneficial in treating the deficiency of iron (Białek et al., 2016).

XI. ANTI-OXIDANT ACTIVITY

Pumpkin seeds are composed of *β*-carotene which makes it nutritionally as well as pharmacologically important ingredient. *β*-Carotene, tocopherols and other carotene components in pumpkin seeds shows anti-oxidant activities that protects cells against the damage caused by reactive oxygen species and other free radicals (Ceclu and Nistor, 2020). Yasir et al. (2016) also found that extracts obtained from pumpkin seeds exhibited antioxidant as well as geno-protective effects. Muchirah et al. (2018) reported higher

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anti-oxidant activity of ethanolic extract of pumpkin seeds.

XII. ANTI-DEPRESSANT ACTIVITY

Depression in very common mental disorder and is affecting approx. 45.7 Million people in India. Pumpkin seeds act as a natural source of anti-depressant and are gaining pharmacological importance. Pumpkin seeds show an antidepressant food score of 47% which is due to presence of 5-hydroxytryptophan which is a tryptophan intermediate helping in formation of serotonin (a neurotransmitter) (LaChance and Ramsey, 2018). Eleiwa et al. (2014) also studied anti-depressant activity in rats. They injected aqueous methanolic extract of pumpkin seeds in rats and found significant decrease in the depression rate. Pumpkin seeds are remarkable source of zinc which helps our brain to convert tryptophan into serotonin which imparts feelings of wellbeing (Al Zuhair et al., 2000).

XIII. ANTIBACTERIAL AND ANTHELMINTIC ACTIVITY

Pumpkin seeds possess good anti-bacterial and anti-microbial activities which are important for maintaining good health. Seeds of pumpkin show good anthelmintic activity and helps in maintaining good gut health. In a review, Caili et al. (2006) showed that pumpkin seeds possess good anti-bacterial activity. A peptide extracted from pumpkin seeds having molecular weight (MW) 8 kDa was known to inhibit *F. oxysporum*, *M. arachidicola, B.cinerea* by taking a particular dose of 375 µg. Further, two more proteins were identified from pumpkin seeds as α- and β-moschin (MW: 12 kDa) and they showed translation inhibiting activity with anti-oxidant activity of 17 µM and 300 nM, respectively. Mainly, three basic proteins of pumpkin seeds: MAP2 (MW: 2249D), MAP4 (4650D) and MAP11 (11696D), inhibits the growth of yeast cells. Brogan and Mossialos. (2016) showed that pumpkin seeds help in preventing from infection of various microbes and pumpkin seeds also possess anthelmintic properties (Alhawiti et al., 2019).

XIV. NUTRACEUTICAL POTENTIAL AND FUTURE PROSPECTIVE

In the recent years, pumpkin seeds have a large range of application as a food or herbal medicine. Those waste streams are valuable and can be utilized for food products and/or nutraceutical products. They can be consumed as a snack, salads or breakfast cereal in the roasted form (salted or not). In addition, they could be used in baking as the excellent ingredients of bread or cakes. Moreover, their oil is excellent and could gain acceptance as edible oil and additive component in food, pharmaceutical and cosmetic industries. Pumpkin seeds oil is useful for frying, cooking, baking and salad dressing. Supplement from pumpkin seeds could be developed in the form of a soft capsule. In cosmetic industries, they usually use for skin care products such as anti-aging, free-radical scavenging, skin protection and hair care products such as hair growth stimulants and emollients. The consumption of pumpkin seeds in the oil form or roasted pumpkin seeds is proved to exhibit several positive health effects (Lestari and Meiyanto, 2018).

XV. CONCLUSIONS

The general conclusion of this literature study is that pumpkin seeds have emerging bioactive compositions that promote health and human life. All of these findings bring us to the new idea in developing and innovating neutraceuticals, pharmaceuticals, and therapeutic products from pumpkin seeds for the large range application.

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