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CURRENT HEALTH BENEFITS OF PUMPKIN SEEDS (*CUCURBITA* SPP.) AS A NUTRACEUTICAL: A DETAILED LITERATURE REVIEW

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ABSTRACT

Cucurbita species belonging to the *Cucurbitaceae* family are nutraceuticals that have been used in the treatment of various diseases since ancient times. *Cucurbita* spp., which is extremely nutritional, contains many bioactive components. In the current literature, there are many studies on its chemical structure as well as protective and health-improving effects. On the other hand, there are a limited number of studies reporting allergic effects. In addition, in some studies, alternative techniques that can be used for the inclusion of *Cucurbita* spp. in human nutrition more and differences in nutritional characterization caused by pretreatments applied to obtain maximum yield from the product were examined. In this article, recent studies on *Cucurbita* spp. were reviewed in detail.

KEYWORDS: *Cucurbita* spp., Pumpkin, Nutraceuticals.

INTRODUCTION

According to various sources, *Cucurbitaceae* is a very large plant family that includes 118-130 genera and 800-960 species (Kulczyński and Gramza-Michałowska, 2019; Mukherjee et al., 2021; Ozuna and León-Galván, 2017; Rolnik and Olas, 2020). In history, plants belonging to the *Cucurbitaceae* family were used for various purposes, such as containers, bottles, and musical instruments. Therefore, the origin of the word *Cucurbitaceae* comes from the Latin word 'corbis' which means bottle or basket (Rolnik and Olas, 2020). Today, plants belonging to the *Cucurbitaceae* family are grown in temperate climate regions of the world with temperatures between 20-27°C. The pulp, seeds, and flowers of the plants are used primarily in human nutrition and the nutrition of poultry animals and aquatic organisms and have an important place in the pharmaceutical and cosmetic industry (Lemus-Mondaca et al., 2019; Mukherjee et al., 2021; Ozuna and León-Galván, 2017). Plants of the *Cucurbitaceae* family have been used for many years in the Ayurveda system in the traditional medicine and cuisine of many countries, such as India, China, Argentina, Brazil, Mexico, and the USA, with their therapeutic, nutraceutical, and nutritional properties (Amin et al., 2020; Hussain et al., 2021; Mukherjee et al., 2021; Ozuna and León-Galván, 2017; Rolnik and Olas, 2020). The seeds of *Cucurbitaceae* plants generally contain approximately 50% oil (Ozuna and León-Galván, 2017). In some countries, the seeds, which are also rich in protein and bioactive components, are utilized as waste (Amin et al., 2020; Lemus-Mondaca et al., 2019; Ozuna and León-Galván, 2017). United Kingdom, Chile, Bangladesh are some of them (Amin et al., 2020; Li, 2020; Sanzana et al., 2021). Although the *Cucurbita maxima* species is widely consumed in Chile, its seeds are considered agricultural industry waste (Li, 2020; Sanzana et al., 2021).

Cucurbita spp. from the *Cucurbitaceae* family consists of red, orange, green, yellow, and gray pumpkins (Hernández-Pérez et al., 2021). Particularly *Cucurbita maxima* (winter squash), *Cucurbita pepo* (gum squash), *Cucurbita ficifolia* (fig-leaf gourd/black seed squash), *Cucurbita moschata* (pumpkin), and *Cucurbita argyrosperma* (Japanese pie pumpkin) species belonging to the *Cucurbitaceae* genus are extremely valuable economically (Hussain et al., 2021; Mukherjee et al., 2021). However, the most common squash species worldwide are *C. maxima*, *C. pepo*, and *C. moschata* (Hussain et al., 2021). Although the history of squash cultivation is not known exactly, it is thought to have been first grown in present-day Mexico around 5500 BC, and it is grown widely in America, Europe, and Asia today. In recent years, China, India, and Russia have had the largest shares in global squash production (Kulczyński and Gramza-Michałowska, 2019). Other leading countries are Turkey and the USA (Rolnik and Olas, 2020).

Like other genera and species of the *Cucurbitaceae* family, the medicinal and therapeutic uses of *Cucurbita* spp. have been found in many traditional manuscripts, and it has been an important food source since ancient times (Lemus-Mondaca et al., 2019; Tantawy et al., 2018). Pumpkin seeds are still a popular food in many countries today, including Egypt, and flour made from the seeds is used to make cake and bread (Abou-Zeid et al., 2018). The oil extracted from the seeds is used for cooking in some African countries (Rohman, 2020; Rolnik and Olas, 2020). While *C. pepo* is more popular in Western countries, *C. moschata* and *C. maxima* are more popular in Asia (Rolnik and Olas, 2020). They are used in the production of fruit juice, puree, jam, and alcoholic beverages in the food industry worldwide (Lemus-Mondaca et al., 2019; Rohman, 2020). *C. pepo* seeds, which are very rich in tocopherol, are used as vegetables in Pakistan (Saleem et al., 2021).

Although there is no clear definition of bioactive components in today's literature, they can be defined as active ingredients of animal and plant origin that are safe for health and have the potential to improve organism physiology and metabolism when consumed. These components mostly include polyphenols, carotenoids, tocopherols, sterols, stanols, minerals, vitamins, bioactive proteins, peptides, dietary fiber, prebiotics, and fatty acids (Kulczyński and Gramza-Michałowska, 2019). Functional foods are defined as foods containing biologically active components (Lemus-Mondaca et al., 2019). Pumpkin seeds are a nutraceutical and functional food that contains many bioactive components. Therefore, this study was conducted to provide a comprehensive review of recent research examining the nutritional composition and bioactive, functional, and therapeutic potential of *Cucurbita* spp.

Nutritional Composition and Phenolic and Bioactive Matter Content of *Cucurbita spp.*

The nutritional composition of pumpkin seeds has been investigated in many studies for various species and generally contains around 30-50% protein and around 40% fat. Pumpkin seeds also contain various macro and micronutrients such as carbohydrates, fiber, tocopherol, carotenoid, vitamin B2, vitamin C, phosphorus, zinc, iron, copper, magnesium, potassium, calcium, and selenium. The fatty acid composition of pumpkin seeds mostly consists of palmitic, stearic, oleic, and linoleic acids. In addition, pumpkin seeds contain abundant lignans, such as phospholipids, secoisolariciresinol, and lariciresinol, and phytoestrogens, sterols, flavonoids, anthocyanins, stilbenes, trigonelline, betaine, and phenolic compounds (Amin et al., 2020; Dong et al., 2021; Hussain et al., 2021; Lemus-Mondaca et al., 2019; Lestari et al., 2019; Paul et al., 2020; Ramak and Mahboubi, 2019; Rolnik and Olas, 2020). Also, they contain 'squalene' (89 mg/100 g), a biosynthetic precursor of steroids in plant and animal cells (Hernández-Pérez et al., 2021).

The general nutritional composition of pumpkin seeds and pulp may vary depending on factors such as region, soil structure, climate, cultivation methods, and storage conditions (Kulczyński and Gramza-Michałowska, 2019; Lemus-Mondaca et al., 2019). Kulczyński and Gramza-Michałowska (2019) comparatively investigated the chemical composition of the pulp of different pumpkin species grown in Poland. In the study, they reported that pumpkin pulp contained plenty of b-carotene, lutein, and zeaxanthin. On the other hand, Hernandez-Perez et al. (2021) reported the general nutritional composition of pumpkin seeds as 31.1% total protein, 42% total fat, 8.6% saturated fatty acids, 14.2% MUFA, 20.9% PUFA, 17.81% carbohydrates, and 3.9% total dietary fiber. In another study (Lestari et al., 2019), it was reported that pumpkin seeds generally contained approximately 265 mg of lignan phytoestrogen/100 g and 16 mg of tocopherol/100 g.

When analyzed on a species basis, *C. maxima* is a good source of vitamin A, thiamine, niacin, vitamin B6, vitamin E, and vitamin K (Mukherjee et al., 2021). Montesano et al. (2018) studied the chemical and nutritional characterization of *C. maxima*. In their study, they reported that pumpkin seed oil contained 41.7% MUFA, 37.2% PUFA, 41.4% oleic acid, and 37.0% linoleic acid. In addition, $\Delta^{7,22,25}$-stigmastatrienol, $\Delta^{7,25}$-stigmastadienol, and spinasterol found in the seed composition were reported as the main sterols (Montesano et al., 2018). Specific Δ-sterols found in the seeds of various squashes belong to a separate class of phytosterols that are not part of the standard daily diet. Δ-sterols have different chemical structures due to the position of the double bond in the tetracyclic ring system and their branched lipophilic side chains (Fornara et al., 2020). Hussain et al. (2021) examined the total phenolic substance, flavonoid, carotenoid, and mineral substance contents in the peel, pulp, and seeds of *C. maxima*. In their study, they reported that pumpkin seeds had a higher total phenolic matter and total flavonoids compared to peel and pulp. On the other hand, they reported that there were more K, Na, and Fe in the pulp compared to the seeds and peels (Hussain et al., 2021). The most abundant amino acids in *C. maxima* are glutamic acid and arginine. It also contains an amino acid called 'cucurbitin' (Lemus-Mondaca et al., 2019).

C. pepo, like *C. maxima*, contains vitamins E and K. Its seeds and pulp are a good source of phosphorus, magnesium, calcium, iron, and zinc, especially potassium and sodium (Mukherjee et al., 2021). In a study (Sá et al., 2020), it was reported that the total protein ratio of C. pepo was 36.5%, the fat ratio was 51.0%, the total dietary fiber ratio was 4.43%, and that the ash ratio was 3.21% (21). In addition, it was also reported that its essential amino acid composition included 3.26% histidine, 3.21% isoleucine, 6.49% leucine, 4.17% lysine, 1.88% methionine, 4.47% phenylalanine, 3.30% threonine, 0.86% tryptophan, and 4.71% valine and that it was suitable for the daily essential amino acid requirement, which was shown as a reference in 'WHO/FAO/UNU Expert Advisory Report' (WHO/FAO/UNU, 2007). While the most abundant phenolic matter in *C. pepo* is p-hydroxybenzoic acid, there are also other phenolic compounds, such as caffeic, p-coumaric, ferulic, sinapic, protocatechin, vanillic, syringic acid, and p-hydroxybenzaldehyde (Krimer-Malešević et al., 2011).

Li (2020) evaluated the bioactivity and nutritional composition of another species, *C. moschata*, and reported the protein content of *C. moschata* seed as 32.38%, the oil rate as 14.31%, and the moisture content as 28.74%. It was also reported that the seeds of *C. moschata* contained approximately 15.9 mg/100 g of total tocopherol (Rolnik and Olas, 2020). Bouazzaoui and Mulengi (2018) investigated the fatty acid and mineral composition of squash (*C. moschata*) and melon seeds grown in Algeria. In the study, the linoleic acid and oleic acid ratios of *C. moschata* were reported as 50.33% and 30.71%, respectively. In addition, the amounts of potassium, magnesium, and calcium were reported as 394.8, 246.12, and 7.14 mg 100 g^{-1}, respectively.

Current Health Benefits of *Cucurbita spp.*

Oilseeds are the main source of fat-soluble vitamins and are involved in the formation of steroid hormones because they contain squalene. In addition, they have anti-inflammatory, antitumor, antithrombotic, and antimicrobial properties, and they can show biological functions such as immunomodulator and satiety (Hernández-Pérez et al., 2021).

Cucurbita spp. has been used as an anthelmintic, teniacide, and diuretic in the traditional medicine of many cultures (Ramak and Mahboubi, 2019). In addition to these, it has been used in traditional Chinese medicine to treat gallbladder disorders and prostate problems (Hernández-Pérez et al., 2021). Like many other species, *C. maxima* and *C. pepo* seeds have been reported to be anti-inflammatory, antibacterial, antioxidant, antidiabetic, antihyperlipidemic, and immunosuppressive and have a stimulating effect on the central nervous system. In addition, antidiabetic, diuretic, antitumor, anticancer, antihypertensive, antihypercholesterolemic, antiinflammatory, antibacterial, and antiulcer effects of other parts of the plants have been reported (Amin et al., 2020; Mukherjee et al., 2021). It has also been reported that *C. pepo* and *C. maxima* have therapeutic effects on ailments such as obesity and constipation (Mukherjee et al., 2021).

Antidiabetic Effects of Pumpkin Seeds

Recent studies have shown that pumpkin contains pectin, a polysaccharide containing D-Galacturonic acid chains. This compound shows antiinflammatory properties as well as preventing diabetes (Li, 2020). It has been reported that pumpkin seed proteins can lower blood sugar by inhibiting α-amylase and α-glucosidase (Kushawaha et al., 2017; Li, 2020). It has been reported that compounds, such as trigonelline, nicotinic acid (niacin), and D-chiro-inositol, an isomer of inositol, found in pumpkin seeds are also effective in providing glycemic control and maintaining satiety (Hernández-Pérez et al., 2021). It has been reported that *C. pepo* seeds reduce blood sugar levels by increasing insulin secretion and improve glucose tolerance and that their peels lower blood glucose and lipid levels (Mukherjee et al., 2021).

There are many studies in the literature examining the antidiabetic effects of *Cucurbita* spp. Kushawaha et al. (2017) investigated the antidiabetic potential of *C. maxima* seeds in-vivo in healthy and streptozotocin-induced mildly diabetic rats. In the study, it was reported that pumpkin seed extract applied orally in variable doses reduced blood sugar levels in diabetic rat models, and therefore, it could be developed as an antidiabetic agent. In another similar study (Marbun et al., 2018), the antidiabetic effects of ethanolic extracts of the pulp and seeds of *C. moschata* were investigated in streptozotocin-induced rats, and both were reported to provide a significant reduction in blood sugar and to have antidiabetic potential. Liu et al. (2018) reported the alleviating effects of a polysaccharide extract from pumpkin pulp on Type 2 diabetes in rats that were given a high-fat diet and induced by low-dose streptozotocin. It was reported that this mechanism of action might be that pumpkin polysaccharides would increase the production of short-chain fatty acids such as butyric acid in the large intestine of the rat, which in turn would provide glucose homeostasis. Another study (Kalaivani et al., 2018a) examined the efficiency of oral administration of *C. maxima* seed oil for 30 days in rats induced by a high-fat diet. In the study, it was reported that there were significant improvements in body weight gain, glucose, and insulin levels, and lipid profile.

In addition to studies examining the efficiency of *Cucurbita* spp. alone against diabetes, there are also studies examining the synergistic effects with different functional foods. Candido et al. (2018) investigated the effects of pumpkin seeds and flaxseed on food intake, postmeal glycemia, and appetitive responses in healthy normoglycemic adults in a randomized single-blind placebo-controlled study. In the study, it was reported that acute consumption of 65 grams of pumpkin seeds significantly reduced postprandial glycemia up to the 2nd hour after the meal compared to the control group. Dowidar et al. (2010) comparatively investigated the effectiveness of pumpkin seeds, vildagliptin, and gum arabic on 70 diabetic male albino rats. In the study, it was reported that the combination of these three factors could alleviate the severity of hyperglycemia, insulin resistance, and dyslipidemia and suppress glucagon secretion. Similarly, Arzoo et al. (2018) investigated the synergistic effect of salep root and pumpkin seed powder against diabetes in streptozotocin-induced rats. In the study, it was reported that the combination of pumpkin seeds and salep root significantly improved various biochemical parameters such as DNA damage in the blood cells of rats.

Effects of Pumpkin Seeds on Obesity and Nutritional Status

It has been reported that the bioactive components in oilseeds can function in weight loss. The explanation of the mechanism of this function is that these components are enzyme inhibitors in the digestion and absorption stages of foods, they are inhibitors of adipogenesis factors, and they are appetite suppressants (Hernández-Pérez et al., 2021). The efficiency of pumpkin seeds on obesity and nutritional status has been examined in many studies, either alone or in combination. For example, Avila-Nava et al. (2017) studied the effect of a 3-month pre-Hispanic Mexican diet intervention on anomalies caused by a high-fat diet enriched with sucrose for 6 months in rats. In the study, the pre-Hispanic Mexican diet included traditional foods such as dried corn, beans, tomatoes, chia, and pumpkin seeds. After obesity induction, rats that were given a pre-Hispanic Mexican diet showed improvement in glucose intolerance, body weight, serum and liver triglycerides, and leptin levels. In addition, it was reported that this diet decreased adipocyte size and increased the levels of UCP-1 (uncoupling protein-1), PPAR-a (peroxisome proliferator-activated receptor), PGC1 (peroxisome proliferator-activated receptor coactivator), Tbx-1 (T-box protein 1) in white adipose tissue. Also, this diet significantly reduced reactive oxygen species (ROS), oxidized proteins, and the GSSH/GSH ratio. The authors reported that the pre-Hispanic Mexican diet containing pumpkin seeds was effective in preventing anomalies caused by obesity by increasing fatty acid oxidation, reducing oxidative stress, and changing the gut microbiota.

Syam et al. (2020a) studied the effects of *C. moschata* seed flour on body weight and serum zinc levels in malnourished Wistar rats. In the study, it was reported that pumpkin seed flour significantly increased body weight and serum zinc levels but that more studies were needed to better understand the effective dose. In another study on the same topic (Syam et al., 2020b), the effects of biscuits made from pumpkin seed flour on body weight and serum zinc levels in malnourished Wistar rats were investigated. In the study, it was reported that the intervention was effective in gaining bodyweight but did not cause a significant change in serum zinc levels.

Effects of Pumpkin Seeds on Cardiovascular Health

The high level of carotenoids found in pumpkins has important functions in maintaining heart health (Li, 2020). The pumpkin plant lowers blood pressure and cholesterol (Paul et al., 2020). As is known, angiotensin-1-converting enzyme (ACE) plays a key role in blood pressure homeostasis, and ACE inhibitors are important in this sense (Park et al., 2019). According to a study (Liang et al., 2021), pumpkin seed proteins have ACE inhibitory potential, and thus they are promising in the treatment of hypertension. In addition, Park et al. (2019) reported that when fruit juices with low ACE inhibitory potential were consumed in combination with some oilseeds, the inhibitory potential increased. In addition, it was reported in the same study that hemp seeds and pumpkin seeds added to fruit juice were the best combination in terms of synergistic effect. Majid et al. (2020) studied the effects of 1000 mg of pumpkin seed oil daily on total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and systolic (SBP) and diastolic (DBP) blood pressure. This randomized controlled study on 127 participants aged 39-63 with one or more disorders, such as dyslipidemia, hypertension, diabetes, or obesity, lasted 90 days. In the study, it was reported that pumpkin seed oil provided a significant increase in HDL cholesterol and a decrease in LDL cholesterol and that the specified dose of pumpkin seed oil was antihypertensive and hypolipidemic. In addition, no toxic effects of the intervention were reported. In another study (Wong et al., 2019), the therapeutic effect of pumpkin seed oil was studied on 22 postmenopausal women with hypertension aged 48-64 years. In the study, it was reported that 1 g of pumpkin seed oil taken 3 times a day for 6 weeks reduced the augmentation index, brachial-central blood pressure, and the risk for cardiovascular diseases. However, no difference was observed in arterial stiffness and heart rate variability. Kalaivani et al. (2018b) reported that oral intake of *C. maxima* seed oil (100 mg/kg) for 30 days in rats induced by a high-fat diet improved parameters, such as LDL, HDL, triglycerides, total cholesterol, adiponectin, leptin, amylase, and lipase. It was also reported in the study that this intervention enabled the activation of enzymes, such as fatty acid synthase, acetyl CoA carboxylase, carnitine palmitoyl transferase-1, and HMG CoA reductase and changed the activities of proinflammatory cytokines, such as IL-6 and TNF-A. Therefore, it was reported that it could improve lipid metabolism and obesity. In another study (Sanzana et al., 2021), it was stated that *C. maxima* seed extract inhibited thrombin receptor activator peptide-6 (TRAP-6), adenosine diphosphate, and platelet aggregation induced by collagen. In addition, it was reported in the study that pumpkin seed extract had high antiplatelet potential and might be effective in preventing thrombotic events.

Hepatoprotective Effects of Pumpkin Seeds

Due to the presence of bioactive components in pumpkin seed oil, it has protective potential against liver damage (Radić et al., 2021). Since pumpkin seeds contain $\Delta^{5,6,7,8}$-sterols, as well as phenolic compounds, such as phenylethanoid, vanillic acid, vanillin, luteolin, and sinapic acid, their consumption decreases markers of inflammation, increases lymphocyte count, increases phagocytic activity, and prevents the progression of fatty liver to steatohepatitis (Lemus-Mondaca et al., 2019; Radić et al., 2021; Tantawy et al., 2018). Al-Okbi et al. (2017) reported that adding pumpkin seed oil to oral nanoemulsions was effective in improving bioavailability and therapeutic effect and inhibited the progression of non-alcoholic fatty liver disease to steatohepatitis. On the other hand, Radic et al. (2021) studied the hepatoprotective effects of *C. pepo* in adult male Wistar rats exposed to chronic alcohol intake for 6 weeks. In the study, it was reported that 2 ml/kg pumpkin seed oil for 42 days had a therapeutic function in a rat model through general protective molecular mechanisms.

Effects of Pumpkin Seeds on Erectile Function and Reproductive Performance

Pumpkin seed oil is an antioxidant that can provide a scavenging effect on reactive oxygen species produced during gametogenesis (Bakeer et al., 2021). The pharmacological mechanism of action of the pumpkin seed oil is the inhibition of the 5-a-reductase enzyme, which is responsible for the conversion of testosterone to dihydrotestosterone (DHT) and is effective in androgen and estrogen metabolism. It contains beta-sitosterol, which is an inhibitor of the *C. pepo* 5-a reductase enzyme. It is reported that linoleic acid found in pumpkin seeds is also a 5-a reductase inhibitor (Hajhashemi et al., 2019). For these reasons, pumpkin seeds have positive effects on erectile function and reproductive performance (Tantawy et al., 2018).

Lotfi et al. (2021) investigated the effects of pumpkin seeds, sunflower seeds, and vitamin E on the reproductive performance of a 45-week-old 30 Ross breeding rooster for 60 days. In the study, it was reported that the combination of pumpkin seed oil and vitamin E was the most effective in features, such as concentration, viability, membrane integrity, total motility, and progressive motility in rooster sperm. Akomolafe et al. (2021) studied the effects of raw and roasted pumpkin seeds (*C. pepo*) on some key markers of erectile function in male rats. In the study, it was reported that raw and roasted pumpkin seeds modulated the enzymes involved in erectile function and had a therapeutic role in this area. In addition, it was emphasized that roasted pumpkin seeds were more effective. On the other hand, no significant difference was observed in acetylcholine esterase activities in rat groups fed with raw and roasted pumpkin seeds.

Effects of Pumpkin Seeds on Urinary Function

Pumpkin seed oil is very effective in the treatment of benign prostatic hyperplasia, overactive bladder, androgenic alopecia, and prostate cancer. The effectiveness of the oil comes from the phytoestrogens and unsaturated fatty acids it contains. Δ-phytosterols, which are found free and bound to sugar molecules in pumpkin seeds, have an inhibitory effect on 5-a reductase in cultured human prostate fibroblasts (Tantawy et al., 2018). Pumpkin seeds inhibit DHT, which binds to the cytoplasmic androgen receptor. This may reduce the formation of DHT receptor complexes that stimulate prostate enlargement (Fornara et al., 2020). Pumpkin seeds may also have anti-inflammatory effects, scavenge free radicals, and relax the bladder sphincter (Ramak and Mahboubi, 2019; Tantawy et al., 2018). In traditional medicine, it has been reported that *C. maxima* seeds prevent the formation of kidney stones by increasing the functioning of the urinary bladder and are used in the treatment of digestive disorders (Mukherjee et al., 2021). *C. pepo* seed oil is frequently used as an alternative treatment for overactive bladder and prostate enlargement problems in Europe (Tantawy et al., 2018).

Leibbrand et al. (2019) investigated the effectiveness of oil-free hydroethanolic pumpkin seed (*C. pepo*) extract on benign prostatic hyperplasia. In a single-center study of 60 men with benign prostatic hyperplasia, participants consumed oil-free hydroethanolic pumpkin seed extract once a day at bedtime for 12 weeks. At the end of the study, the International Prostate Symptom Score of individuals decreased by an average of 30%. In addition, residual urine volume after nocturia and urination significantly decreased. On the other hand, Tantawy et al. (2018) examined the efficacy of pumpkin seed oil (*C. pepo*) phonophoresis on 60 participants with chronic non-bacterial prostatitis. In the study, it was reported that the combination of pumpkin seed oil with ultrasound increased the effectiveness in terms of urine amount, urine flow rate, white blood cell in prostate secretion (WBC), and chronic prostate symptom index (NIH-CPSI).

In another study (Gažová et al., 2019), the effectiveness of CELcomplex containing *C. pepo* seed extract, flax, and casuarina in the treatment of stress urinary incontinence in women was examined. It was reported that CELcomplex, which was administered to 86 women with stress urinary incontinence for 12 weeks, was significantly effective in alleviating the symptoms of the disease. Similarly, Palacios et al. (2020) investigated the effectiveness of a formulation called Femaxeen, obtained by purification of pollen, pumpkin seeds, and vitamin E, on 81 women aged 18-74 years with moderate, severe, and very severe urinary incontinence. In this randomized controlled study, it was reported that Femaxeen provided a statistically significant decrease in the incontinence severity index from the beginning to the 90th day and that it was effective in urinary incontinence as a result.

Anti-Inflammatory Effects of Pumpkin Seeds

Many studies in the literature report the anti-inflammatory effects of *Cucurbita* spp. For example, Dong et al. (2021) studied the composition and anti-inflammatory properties of pumpkin seeds. In the study, it was reported that pumpkin seeds involve fatty acids such as hydroxyoleic acid, which has an anti-inflammatory function. Arslanbaş et al. (2020) comparatively investigated the anti-inflammatory effects of pumpkin seed oil of Turkey origin at doses of 40 mg/kg and 100 mg/kg on 42 4-month-old Wistar albino rats. In the study, it was reported that especially high dose (100 mg/kg) application of pumpkin seed oil showed a significant anti-inflammatory effect and did not have any biogenic effect. In the study, the mechanism of action of pumpkin seed oil was explained as destroying free radicals, stimulating antioxidant enzyme activities, and inhibiting lipid peroxidation. In another study (Bardaa et al., 2020), the effectiveness of pumpkin seed

(*C. pepo*), flaxseed, and prickly pear seed oils on acute inflammation and oxidative stress was investigated on 36 adults male Wistar rats. In the study, it was reported that all three seed oils were effective in acute inflammation and reduced the clinical signs of inflammation, infiltration of inflammatory cells, vascular occlusion, and adverse biochemical markers. Wahid et al. (2021) compared the analgesic and anti-inflammatory effects of seed oil extracts of *C. maxima* and *Cucumis sativus* to aspirin and brufen in rats. In the study, it was reported that seed extracts had fewer side effects and were safe for up to 30 days compared to aspirin and brufen but that more clinical studies were needed to recommend their use in humans. In another study conducted on male rats (Abou-Zeid et al., 2018), it was reported that pumpkin seed oil (*C. pepo*) was effective in reducing adverse effects such as oxidative stress and apoptosis caused by Emamectin, which is used as a pesticide. Paul et al. (2020) examined the effect of *C. maxima* seed oil in rats against major organ damage caused by formaldehyde, a very dangerous chemical. In the study, the intervention reduced formaldehyde-induced organ damage in rats by inhibiting oxidative damage and lipid peroxidation. Zhao et al. (2017) studied the effect of pumpkin seed oil on metabolic disease in Wistar rats. In the study, it was reported that pumpkin seed oil supplementation reduced endoplasmic reticulum stress and unfolded protein response in rats. In addition, Cvetkovic et al. (2021) reported that *C. pepo* could be an alternative to synthetic antioxidants in the food and pharmaceutical industry, as it is a good source of phytochemicals.

Anti-cancer Effects of Pumpkin Seeds

With its rich polyphenol and bioactive components, pumpkin seed is a chemopreventive agent against many types of cancer, especially breast, colorectal, and lung cancer (Nomikos et al., 2021; Rohman, 2020). In addition, it has been reported that especially *C. pepo* is effective in the development of both innate and adaptive immunity (Mukherjee et al., 2021). Russo et al. (2017) reported that carotenoid extract from *C. moschata* delayed proliferation in cancer cells but could not kill them directly. The explanation of this mechanism was that carotenoid extract caused changes in intracellular energy metabolism and induced autophagy. Similarly, Moccia et al. (2020) reported in their study on cells with chronic lymphocytic leukemia that the carotenoid extract obtained from *C. moschata* could delay cell growth in the leukemic cell line and that it was, therefore, a potential chemopreventive agent. In another study (Nomikos et al., 2021), it was reported that pumpkin seed extract induced autophagy by inhibiting proliferation in PC-3 prostate cancer cells.

Chari et al. (2018) studied the prophylactic efficiency of pumpkin seed oil in 54 male Wistar rats with 1,2-dimethylhydrazine-induced colon cancer. In the study, it was reported that the consumption of pumpkin seeds was effective in preventing colon cancer (Fawzy et al., 2018). Another study examined the effectiveness of pumpkin seed oil (*C. pepo*) against the negative effects of bisphenol-a (BPA) in male rats. In the study, it was reported that pumpkin seed oil alleviated the negative effects of BPA in rats and that it could, therefore, be used as a therapeutic agent in humans. In addition, Endo et al. (2019) reported that red pumpkin seed extract suppressed ROS-induced melanosome transfer after ultraviolet exposure.

Neurological and Cognitive Performance Effects of Pumpkin Seeds

Many positive effects of pumpkin seeds on cognitive performance, memory, and neural activation have been reported. For example, Shalan et al. (2020) investigated the effects of mulberry fruit extract, sunflower seeds, and pumpkin seeds in combination with exercise on memory function and neural activation biomarkers in healthy adults. In the study, which included 40 women aged 19-24 years who expressed themselves as sedentary, it was reported that consumption of 100 mg/kg black mulberry extract, 50 mg/kg sunflower seeds, 50 mg/kg pumpkin seeds twice a day for 60 days increased memory performance in young adults, independent of the exercise factor. In another similar study (Shalan et al., 2021), the effect of combining black mulberry fruit, sunflower seed, and pumpkin seed supplements with exercise on cognitive performance in sedentary university students was investigated. In the study, it was reported that these supplements increased perception, attention, and executive function independent of exercise.

Saleem et al. (2021) investigated the anti-Parkinson’s activity of methanolic extract of *C. pepo* seeds in the treatment of rats with haloperidol-induced Parkinson's. In the study, improvement in motor functions, dose-related increase in catalase, superoxide dismutase, glutathione, and acetylcholine esterase levels, and dose-related decrease in malondialdehyde and nitrite levels were reported. Therefore, it was reported that *C. pepo* seeds could be used in the treatment of Parkinson's disease.

Anthelmintic Effects of Pumpkin Seeds

C. moschata, *C. maxima*, and *C. pepo* seeds show moderate anthelmintic activity thanks to the cucurbitin they contain and are a natural vermifuge used worldwide (Acorda et al., 2019). It has been reported that *C. pepo* seed is traditionally used in the treatment of intestinal parasites and worms in Asian and South American countries. Similarly, it has been reported that *C. pepo* seed is used in kidney and bladder disorders as well as tapeworm treatments in Africa (Mukherjee et al., 2021).

Maldonado et al. (2018) tested the antiparasitic activity of *C. maxima* seeds on *Strongyloides venezuelensis* larvae in vitro. In the study, it was reported that low-dose pumpkin seed extract showed anthelmintic properties against *S. venezuelensis* larvae. In their study on 90 Philippine Jolo domestic chickens, Acorda et al. (2019) reported that pumpkin seeds had an alternative anthelmintic potential for chickens.

Other Beneficial Effects of Pumpkin Seeds

The protective or healing potential of pumpkin seeds against many ailments has been reported. Kassab et al. (2020) studied the protective effect of pumpkin seed oil on orlistat-induced tongue mucosal damage in adult male Wistar rats. In a study conducted on 50 adult male rats, it was reported that pumpkin seed oil alleviated the negative effects of orlistat and maintained the tongue mucosal structure. In another study (Ahmed et al., 2020), the therapeutic effects of pumpkin seed oil on peptic ulcers in Wistar rats were examined, and it was reported that pumpkin seed oil was protective in the treatment of gastric ulcers.

Oyetayo et al. (2020) studied the effect of raw and roasted pumpkin seeds (*C. pepo*) on cisplatin-induced nephrotoxicity in rats. Significant improvement in renal biomarkers caused by cisplatin intoxication was observed in both groups (with roasted pumpkin seeds being more effective) over 14 days. Therefore, it was reported that pumpkin seeds can be used as an adjuvant in the treatment of nephrotoxic disorders.

Lestari et al. (2019) studied the effect of pumpkin seeds on postmenopausal syndromes caused by estrogen deficiency. In the study, it was reported that pumpkin seed oil (*C. moschata*) extract increased HDL and decreased LDL, improved the uterus and mammary glands, and increased bone density. Pumpkin seeds, which contain a high concentration of lignan phytoestrogen, have the potential to be developed as an antidegenerative agent to protect against estrogen deficiency, especially in women. In another study (Hamdi and Hassan, 2021), the protective effect of pumpkin seed oil on maternal and developmental toxicity caused by nano alumina application used in various fields of the industry was investigated. The harmful effects of nano alumina application in pregnancy, such as fetal growth retardation, morphological anomalies, hepatic and neural DNA damage, and histopathological changes in hepatic and neural tissues in mother and fetus are known. In a study conducted on healthy 7-9 week old female and male Wistar rats, it was reported that cold-pressed pumpkin seed oil healed DNA damage, preserved histopathological changes, improved fetal growth parameters, and significantly decreased malondialdehyde level.

Prommoban et al. (2021) studied the fatty acid composition, antioxidant activity, and pharmacological activity of aqueous enzymatic extraction of *C. moschata* seed oil. High antioxidant, anti-skin aging, and skin whitening potential were reported in the study. Hajhashemi et al. (2019) studied the hair-growing effect of pumpkin seed (*C. pepo*) oil in male Swedish rats. In the study, it was reported that components, such as free fatty acids, phytoestrogens, and vitamin E in pumpkin seed oil promoted hair growth in rats. In addition, since *C. maxima* core is a good source of magnesium, which acts as an n-methyl-d-aspartate (NMDA) receptor blocker, it was reported to be effective in reducing acute or chronic pain and neural pain (Wahid et al., 2021).

DISCUSSION

Many health benefits of *Cucurbita* spp. are reported in the current literature. It is important to understand the effects of pre-consumption pre-treatments on food to get the maximum benefit from the pumpkin plant, which is very popular and widely consumed around the world. A few studies in the available literature have examined the effects of these pretreatments. For example, Petkova and Antova (2019) investigated the quality parameters of pumpkin, melon, and sunflower seed oils after conventional and microwave heating. In the study, it was reported that pumpkin, melon, and sunflower seed oils were oxidized in direct proportion to the processing time and intensity in both types of processing. It was also reported that conventional heating caused the acceleration of lipid oxidation and that pumpkin seeds were more stable compared to microwave heating. On the other hand, microwave heating reduced the tocopherol content less than conventional heating. In another study (Peng et al., 2021), the effects of roasting on antioxidant activity, phenolic compounds, and nutritional values in *C. pepo* seeds were investigated. Pumpkin seed samples were roasted at 120, 160, and 200 °C for 10 minutes. In the study, it was reported that as the roasting temperature increased, total phenolic compounds, total flavonoids, and total antioxidant capacity increased, as well. In addition, it was reported that there was no significant difference in the fatty acid composition according to temperature. Also, Maillard reaction products and lipid peroxidation products increased in direct proportion to the temperature. In the study, the optimum roasting temperature was reported as 160 °C. Akomolafe (2021) investigated the effect of roasting on the phenolic phytochemicals and antioxidant activity of pumpkin seeds (*C. pepo*). In the study, it was reported that the functional properties of pumpkin seeds increased due to the release of phenolic phytochemicals after roasting.

It is extremely necessary that *Cucurbita* spp., whose many benefits have been reported, should be included in the human diet more. Pumpkin seed flour may cease to be industrial waste and increase the functional potential of wheat flour, which has a great place in our daily life. Apostrol et al. (2018) reported that the oil-free seed pulp, which becomes waste during the production of pumpkin seed oil, may contribute to increasing the functional potential of existing wheat flour due to its nutritional values and physicochemical properties. Miedzianka et al. (2021) investigated the nutritional properties of some oilseed flours, such as pumpkin seeds, evening primrose, peanuts, and almonds, which are evaluated as waste in the cold press oil industry. The authors suggested the use of these gluten-free raw materials, which are rich in PUFA and have a high antioxidant capacity and polyphenol composition, instead of wheat flour.

On the other hand, it has also been reported that pumpkin seeds can have an allergic effect and cause life-threatening anaphylaxis, albeit rare. Gawryjołek et al. (2021) reported that a 2-year-old child who could tolerate pumpkin pulp satisfactorily developed anaphylaxis against pumpkin seeds. The authors emphasized that pumpkin pulp and pumpkin seeds might show different allergenic effects. Despite all the known health benefits of *Cucurbita* spp., awareness of its allergic effects is extremely important for conscious consumption.

Apart from all these, more studies, especially on humans, are needed to better understand the amount and frequency of consumption of *Cucurbita* spp.

CONCLUSION

In this review, the nutritional composition, bioactive, functional, and therapeutic potential, and current health benefits of *Cucurbita* spp. were investigated. In the current literature, many protective antidiabetic, antiobesogenic, hepatoprotective, anti-inflammatory, anticancer, and anthelmintic effects of *Cucurbita* spp. have been reported. In addition, significant health benefits have been reported on cardiovascular health, erectile function and reproductive performance, urinary function, and neurological and cognitive performance. It is extremely important to include *Cucurbita* spp., which is highly nutritionally valuable and characterized as a nutraceutical, in human nutrition more. However, it should be kept in mind that although rare, it may cause allergic reactions. More studies are needed to understand how much and how often it should be consumed.

Authors' Contribution

The design, data collection, analysis and interpretation of this study was done by ŞK. The drafting of the article and the approval of the final version of the article were done by PFT.

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Availability of Data and Materials

Data is available from the corresponding author upon request.

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