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Exploring the Therapeutic Potential of Cucurbita pepo Seed in Modulating Prostatic Biomarkers for Benign Prostatic Hyperplasia (BPH)

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ABSTRACT

Benign prostatic hyperplasia (BPH) is a common, progressive urogenital disorder that affects aging men, leading to a range of urinary and sexual health issues. As the incidence of BPH rises with age, the need for effective treatments without significant side effects has become a priority. Currently, available therapies such as 5-alpha reductase inhibitors, alpha-1 adrenergic antagonists, and antifungal drugs offer relief, but often come with limitations due to adverse effects. In recent years, *Cucurbita pepo* (pumpkin) seed has emerged as a potential natural treatment for BPH, with promising evidence suggesting it can modulate key prostatic biomarkers, reduce inflammation, and improve urinary symptoms. This review explores the therapeutic effects of *Cucurbita pepo* seeds on BPH, focusing on their bioactive compounds such as fatty acids, phytosterols, and antioxidants and their impact on prostatic growth and function. We discuss the molecular mechanisms underlying the beneficial effects of *Cucurbita pepo* seed extracts, clinical studies supporting their use, and the implications for incorporating such natural remedies into BPH management. Additionally, the review highlights the public health potential of *Cucurbita pepo* as a low-cost, sustainable, and patient-friendly option to complement conventional therapies, especially in aging populations.

Keywords: Benign Prostatic Hyperplasia (BPH), *Cucurbita pepo* seed, prostate biomarkers, natural treatments and inflammation

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a progressive urogenital disease, which has an increasing incidence with age and has become a significant health problem. Numerous studies are needed to focus on the search for alternative management for BPH-related symptoms with more efficient drugs [1]. The human prostate is responsible for secreting fluids to nourish the sperm, protect sperm from infection, and prevent urinary tract infections [2]. Unlike other tissues, the growth of the prostate gland tends to increase each year. Typically, men suffer from benign prostatic hyperplasia (BPH), which begins at 25 years old. Common symptoms include pain during urination, difficulty urinating, decreased urine flow, erectile dysfunction, and decreased erectile capability [3]. Prostate cancer still occurs, especially in elderly men. Histologically, BPH increases the cellular flow of the epithelium and the size of the cylindrical glandular duct [4]. The foundation of the prostate swells, causing reticular hyperplasia [5]. Inhibitors of 5-alpha reductase, antifungal drugs, and alpha-1 adrenergic receptor antagonists have been introduced as the most effective therapies for BPH. However, it varies due to numerous unexpected drug side effects. Many investigators have contributed to the foundation of several new medicinal products, typically for natural medications that minimize accidents [6]. Benign prostatic hyperplasia (BPH) and prostate cancer are topical health problems. Currently, prostate cancer is the cancer with the highest proportional percentage of death [7]. In addition to this phenomenon, the potential risk of prostate disease is still increasing.

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Consequently, urologists have mainly studied BPH and prostate cancer [8]. BPH is common in men over 35 years of age and is a chronic and progressive urogenital condition. Age-related alterations lead to diuretic disorders [9]. The number of BPH cases increased by 4 percent, relative to prostate cancer. After 50 and 60, two men are miserable. The incidence of women and boys being admitted has doubled. Overall, around 280 million people are expected to have BPH by 2030. More findings should be carried out to consider the fact that it is not possible to treat BPH with lifetime medications, so many of the BPH therapies are unwanted and brand new [10]. Currently, scientists are concentrating on looking at herbal products reported to have a beneficial effect on age-related induced diseases such as BPH. Cucurbita pepo conforms with all these values, and in terms of their widespread use and content, they drew attention for their high effect on benign prostatic hyperplasia (BPH). The study builds a comprehensive package of curative activities [11].

Benign prostatic hyperplasia (BPH) is a common urological complication that significantly affects the health of elderly men [12]. The pathology of BPH is characterized by the nonmalignant growth of the prostate gland due to the hyperplasia of stromal cells around the urethra, leading to an enlargement of the gland. As the prostate tissue confines the urethra, instead of excreting urine from the body, the intraorgan pressure significantly accumulates, causing apparent difficulty in urinary excretion and emptying [13]. BPH was the most commonly found among individuals, with severe, moderate, and mild symptoms reported among middle-aged and elderly individuals, with a significant prevalence in older populations. Prostate diseases burden males in another aspect by limiting quality of life and having negative family and socioeconomic impacts that include manpower and a significant increase in medical costs [14]. The risk factors associated with BPH development include advancing age, genetic inheritance, sex hormones, behavioral and environmental influences, hypertension, arteriosclerosis, lifestyle factors, diabetes, and obesity. In general, aging is the main cause of BPH, and it is most common in men over 50 years of age [15]. It is estimated that more than one-third of men over 50 years suffer from BPH, and all men over 80 years of age have apparently enlarged prostates. Statistics show that the risk of BPH will be twice as high if a first or second-degree family member has been diagnosed with the disease. Hormonal changes are also considered a major factor in the development of BPH. Luteinizing hormones can cause an increase in the production of prostate-specific antigen in men, further stimulating the continuous development of BPH [16]. Severe lower urinary tract symptoms have been implicated in reducing the quality of life of nearly one-third of the male population over 40 years of age and are also associated with a significant increase in healthcare costs, a decline in mental and emotional health, and a decrease in sexual function. Therefore, new therapies for treating BPH are urgently needed. The aims of this study were to investigate the anti-inflammatory, anti-cancer, and growth arrest effects of Cucurbita pepo seed.

Current Treatment Options and Limitations

A plethora of treatment options to manage BPH are currently available according to the patient's symptoms and quality of life, i.e., pharmacological interventions, minimally invasive or surgical treatments. Among them, alpha-blockers are recommended as the first-line therapy for BPH patients with moderate to severe symptoms [17]. They act by relaxing the smooth muscle at the bladder neck and the prostate, and the available formulations are tamsulosin, alfuzosin, doxazosin, and terazosin. Their function increases uroflow and relieves the symptoms of BPH. Symptoms are well controlled within 1 to 2 weeks, and patients are motivated as early as three weeks after starting medication. However, the initial rate of efficacy decreases from 60 to 70% to 30 to 40% depending on the duration of taking the alpha-blocker and the severity of LUTS [18]. Moreover, since treatment interruption exacerbates symptoms, patients are recommended to take the medication for a long time. For BPH patients with an enlarged prostate, long-term combination therapy with a 5-alpha-reductase inhibitor is recommended. 5-alpha-reductase inhibitors act by reducing the size of the prostate gland by inhibiting the conversion of testosterone to dihydrotestosterone. They have the best documented role in preventing disease progression by shrinking the prostate, inhibiting prostate cancer risk, and simplifying surgery [19]. After taking combination therapy for at least 1 year, the prevention rate of disease progression requiring surgery is 83%. Although combination therapy reduces the risk of detected prostate cancer, it increases the risk of high-grade and potentially lethal prostate cancer. However, these therapies are currently limited by their adverse effects, the development of prostatic resistance to the medication, and the high cost [20]. A significant proportion of patients experience adverse effects, and treatment discontinuation due to drug-related events at year was twice that for placebo. In the intermittent therapy trial, temporary interruption of tamsulosin in the intervention group due to deteriorating symptoms and quality of life was approximately 20% after 6 months and 40% after 18 months. In the study, discontinuation of combination therapy was approximately 20% after 4 years [21]. Furthermore, the prostatic resistance to the effect of medications was observed in these trials, and the reason could be mainly due to advances in

CNS, surgery, and insufficient efficacy of medication. Therefore, it is necessary to investigate the development of alternative therapies in patients with BPH [22]. According to a survey, 42.5% of men selected from the population reported LUTS, and 44.8% of associated patients sought medical advice, which is similar to other studies. The main reason for not consulting a doctor is that patients believe medications to be useful for LUTS, and many patients have LUTS, so they do not consult clinicians unless they are seriously ill. Therefore, the increased progression of molecular medicine and natural ingredients in the medical field is inevitable to propose a new additional treatment for the limited use of drugs and surgical therapies in BPH. Accordingly, Cucurbita pepo seeds may have potential as a natural extract to affect prostatic biomarkers.

Rationale for Investigating Cucurbita pepo Seed

The rationale for investigating the therapeutic potential of the seed of Cucurbita pepo arises from its nutritional composition and bioactive compounds, such as unsaturated fatty acids, carotenoids, tocochromanols, phytosterols, squalene, and enzyme-inhibiting anthocyanins [23]. Prostatic zinc, which is linked to the dietary intake of squalene and vitamin E, and free fatty acids, which are generally reduced alongside undetectable serum squalene levels in obese men, play a part in the genesis of benign prostatic hyperplasia. Linoleic acid and alpha-linolenic acid seem to reduce inflammation through the biosynthesis of anti-inflammatory lipid mediators and reduction of possible compounds that would escalate inflammation, i.e., arachidonic acid and sterols. Similar to squalene, the main metabolic pathway of phytosterols leads to the biosynthesis of sterol hormones, particularly prostate-derived dihydrotestosterone and its diol analog; yet phytosterols' serum, and not prostate, levels show an inverse relationship with prostate gland size and function [24]. A multitude of scientific papers, both in vivo and double-blind placebo-controlled randomized trials, supplied the results of the seed's therapeutic potential against prostatitis, prostadynia, chronic pelvic pain syndrome, and BPH-related LUTS. The positive in vivo animal evidence recommended the seed's capability to reduce BPH-related LUTS in men alone or in addition to alpha-1 blockers, 5-alpha reductase inhibitors, and/or antibiotics [3]. Consequently, Cucurbita pepo seed could prolong intervals between treatment settings, diminish dosages, and/or cut down side effects or drug costs. Despite the numerous multi-center double-blind trials underway, the extent provides a basis for use in younger males who do not wish for any form of hormonal treatment, suffer from adverse experiences of such therapy, or plan to father children. Emphasis is placed on a trend of frequent, irregular, and unexplained urological diseases; a rising consciousness of consumers' preventive or complementary choices that embrace alternative treatments based on seeds; and the restricted efficacy of present drugs. Perceiving such marketing prospects, herbal supplements could diversify the overactive bladder pharmaceuticals market.

Bioactive Compounds in Cucurbita pepo Seed

Cucurbita pepo is known to be a bioactive-rich plant source that contains compounds having therapeutic potential to manage BPH symptoms [20]. The anti-inflammatory, antioxidant, and apoptosis induction abilities of its compounds are based on their capability to act biochemically via different mechanisms and magnitudes. Age-old phytotherapeutic wisdom suggests the use of pumpkin seeds to manage prostatic problems, although scientific explanations have not been established [21]. The present study aimed to determine the potential active compounds present in Cucurbita pepo seeds that are responsible for its prostatic beneficial effects [22]. Therapeutic components responsible for BPH management are primarily phytochemicals, which are secondary phytoconstituents analyzed through chromatographic or spectrophotometric assessments of antioxidant, anti-inflammatory, or therapeutic potentials. Phytochemicals mainly consist of nitrogen-free compounds present in significant levels among bioactive compounds, including various classes of compounds [24]. Further, carbohydrates, cellulose, and lignin are major phytocompounds in Cucurbita pepo seeds. The major phytosterolic component compounds, present at the highest level in the dried intact seed, include lanosterol, sitosterol, zeaxanthin, lanolin alcohol, and compesterol. Bioactive compounds such as phytosterols found in plants and their extracts possess cholesterol-lowering potential and can manage prostatic health [5]. Fatty acids assessed at different levels possess an anti-inflammatory effect on cellular health. Vitamin E, vitamin K, and minerals such as zinc, vital for prostate health, have also been quantified. Many bioactive compounds found in seeds have the potential to manage BPH symptoms. Inhibition of 5-reductase, antioxidant activities, and antiandrogenic activities associated with phytocompounds have been well recognized, suggesting the scientific basis of the therapeutic activity of pumpkin seed in managing BPH problems.

Phytosterols

Sterols are cholesterol-like molecules found in all plants, animals, and fungi [3]. The sterol found in plants is called phytosterols (PSs), which are structurally similar to cholesterol except that they have one or more double carbon–carbon bonds in the aliphatic side chain and a trans configuration with a methyl

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group at C-10 [5]. The types of PSs vary between plants; however, the well-characterized PSs that have been extensively studied include β-sitosterol, campesterol, stigmasterol, brassicasterol, avenasterol, and ergostanol. Avenasterol is a major PS in Cucurbita pepo seeds, followed by β-sitosterol and Δ-5-avenasterol [6]. β-sitosterol consists of up to 78% of the overall PS content in Cucurbita pepo seeds [8]. Apart from having a similar structure to cholesterol, PSs are also identical to some food and steroid hormones, thus they have potential therapeutic benefits. The physiological functions reported include protecting cellular health, antioxidant activity, antithrombotic effects, anti-atherosclerosis, anti-nephrotic properties, and anticancer effects [10]. The ability to reduce cholesterol absorption, due to sterol/cholesterol competition for intestinal transporters, leads to lower cholesterol blood levels and decreases the risk of developing coronary heart disease and carcinoma [11]. Aside from their health properties in general, the role of PSs in males significantly targets prostate health. The prostate has long been recognized as being sensitive to dietary and endogenous compositions of fats and sterols. Anti-inflammatory effects from PSs have been recognized as a significant target in managing the prostate, as explained by the lower prostaglandin E2 levels in BPH men supplemented with PSs [12]. Epidemiological evidence and clinical studies have provided some indication of the effectiveness of PSs in the treatment of men, especially in the management of benign prostatic hyperplasia (BPH). As an important bioactive component in Cucurbita pepo seeds, PSs have a promising future as therapeutic agents for the management of BPH in aging men. Previous evidence revealed that the major PS, β-sitosterol, in 12-month-old Cucurbita pepo seeds showed preventive potential against DHT-induced proliferation at both transcriptional levels of the androgen-regulated gene and the synthesis of extracellular matrix metalloproteinases. DHT, being one of the androgens, is believed to be involved in the onset and progression of BPH. Furthermore, the levels of PSs in the blood serum after supplying BPH volunteers with randomized PSs for a 6-month period showed that the extent of the reduction in DHT excess is proportional to the efficacy of PSs [14].

Fatty Acids

Fatty acids are the key major components of Cucurbita pepo seeds. According to their functionality, fatty acids are classified into two categories: (1) saturated fatty acids (SFAs), such as palmitic acid and stearic acid, which have been reported as arterial thrombosis inducers increasing the incidence of coronary heart diseases, and (2) unsaturated fatty acids (UFAs), which include both mono-unsaturated fatty acids (MUFAs), like oleic acid, and poly-unsaturated fatty acids (PUFAs), such as linoleic acid and alpha-linolenic acid [5]. From a biochemical viewpoint, the polyene structure of a fatty acid functionally behaves as an electron donor, transferring its electrons to molecular dissolved oxygen, which affects the corresponding molecular change and/or interacts with other biological macromolecules [7]. Fatty acids, mainly PUFAs, have been reported to demonstrate subsequent interactions with specific peripheral cytosolic androgen receptor assays, while they have also been demonstrated to directly interrupt the androgen synthesis pathways. Moreover, the consumption of oleic acid by hypercholesterolemic men has led to significantly reduced levels of low-density lipoproteins-cholesterol [8]. Lipids, particularly fatty acids, have been studied to assess their functionalities towards prostate diseases. For instance, they alleviate the prostate limitation clinical profiles on one hand by alleviating the symptoms of mild to moderate benign prostatic hyperplasia and, on the other hand, towards blocking malignancy. High levels of inflammatory biomarkers are related to benign prostatic hyperplasia [9]. Recent reports have shown that prostaglandins, as a representation of inflammatory biomarkers in prostate cancer aetiology, have been decreased by the anti-inflammatory phytoconstituents extracted from berries of two Cucurbita pepo cultivars. In this study, we included the only form of the two Cucurbita pepo, pumpkin seed, which is classified as medicinal. By profoundly reviewing assays, nine phytosterols and a series of fatty acids were observed in the pumpkin seed. In light of these data, further proven confirmation is warranted to evaluate the degree to which the fruit or seeds can be used in the prevention of prostate diseases [10].

Minerals and Vitamins

In an experimental model, C. pepo seeds were shown to have 0.94% and 26% mineral and fatty acid content, respectively. The mineral content of C. pepo seeds includes several essential minerals such as K, Ca, P, Na, Zn, Fe, and Mg. Copper, manganese, chromium, and iodine were present in trace amounts, and physiological levels are required for improvement, particularly with reference to BPH [11]. Many vitamins and minerals such as zinc, selenium, and vitamins A, C, and E are recognized as stimulating prostate growth, the degeneracy of abnormal tissue, and playing a pivotal role in patient recovery. C. pepo seed is a source of zinc that is present in chelated form and is recognized to alleviate prostate problems. In an in vivo rat study, the application of zinc as support in BPH management did not have the equivalent impact as pumpkin seed oil supplementation, unlike selenium. Vitamins are useful in redox

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equilibrium and block the creation of oxidative damage [16]. Specifically, the water-soluble vitamin C and the fat-soluble antioxidant vitamins such as A and E provide synergistic effects, avoiding free cholesterol peroxide synthesis and equilibrium degradation. The antioxidant functions of carotenoids, particularly beta-carotene, as well as vitamins A, C, and E, were investigated in another experimental process. For a period of 11 weeks, rats were fed dietary zinc supplements concurrently with vitamins, and it was concluded that the prevention of prostatic complications was feasible [17]. Vitamins have immunomodulatory and lymphocyte-regulating characteristics; thus, they might contribute to protection against complicated impure process alteration and the restoration of damaged tissues in a BPH patient. Beta-carotene can be converted to a trace of zinc-based copper-zinc superoxide dismutase, improving protection against tissue degradation. Low-dose vitamin E can alleviate slow reactive oxygen species output and down-regulate gene expression in the nuclear protein NF-kB [20]. It can be deduced that individually available minerals and vitamins, combined with omega-3, -7, and -9 MUFA and PUFA in C. pepo seed as patient dietary supplements, might manage BPH immunologically, retard prostate hyperplasia via 5α-reductase blockage, decrease male-stimulating hormone output via male hormone receptor blocking, down-regulate gene expression buildup, hold in check the release and expiry of normal cells, and retain prostatic cell proliferation. In addition, our human foods nowadays are often absorbable with low minerals and vitamins and have an unrealistically high ratio of omega-6 fatty acids versus omega-3. When compared to other seeds, low fatty acid pumpkin seed has a ratio of omega-6 versus omega-3 linoleic acid.

Mechanisms of Action in BPH

Several possible mechanisms of action for which Cucurbita pepo seeds may exert a beneficial effect on the management of BPH have been postulated due to the seeds' anti-inflammatory and antioxidant properties. Experimental results have confirmed these activities in the seeds' action [19]. Firstly, they could possess anti-inflammatory properties. This would result in reducing swelling and the pain associated with the enlargement of the prostate, which are common symptoms of BPH. The potential of seeds to reduce clinical symptoms was demonstrated in an in vivo study and in clinical trials, which reflects the usefulness of using the extract of the seeds in the management of BPH. New aspects of the seeds' beneficial action in BPH are related to potential hormonal action modifying prostate functions [20]. For instance, the results regarding the anti-inflammatory action of Cucurbita pepo extracts provide the scientific background for undertaking clinical trials for BPH management and improved BPH symptoms, while the hormonal action is probably responsible for modifying the multimodal activity of prostatic ingredients [21]. The seeds' constituents could also possess potentially anti-proliferative effects due to their capacity to inhibit abnormal growth of prostate cells. In the reproductive tract, zinc protects against diverse prostatic and testicular pathological states associated with impaired testis, gamete, and sperm functions. The increased prostatic blood flow may therefore also help explain the observed reduction in urinary discomfort and improvement in the urinary flow rate, largely as a result of an anti-inflammatory action. Modulation of active testosterone is important in the treatment of an abnormal testosterone/estradiol ratio in the diseases of the prostate and for inducing the regression of BPH in men.

Anti-inflammatory Properties

Inflammation is one of the main factors that contribute to the pathophysiology of BPH, leading to the disruption of cellular proliferation and apoptosis in the prostate gland. Histologically, inflammation could lead to changes in the morphology of prostate glands such as hyperplasia, inflammation, and fibrosis [18]. The presence of inflammatory morphology in prostatitis is associated with an increased number of apoptotic cells and factors that block cell proliferation. In the animal model, administration of carrageenan, which leads to inflammation in the rat, resulted in BPH symptoms such as increased prostatic index, hormone dihydrotestosterone, and epithelial cell numbers in the rat ventral prostate. Several studies suggest the potential of Cucurbita pepo L. seed to reduce inflammatory markers including COX-2, NFkB, IL-6, TNF-α, and PGE2 in prostate tissue [19]. Proteomic analysis of protein expression in urogenital organs demonstrated that cucurbitin, as one of the bioactive compounds of Cucurbita pepo L. seed, was shown to reduce the activity of inflammation, enhance the activity of apoptosis, and reduce the process of angiogenesis, hence preventing prostate cancer. Combinations of phytosterol and α-linolenic acid could suppress 5α-reductase expression and reduce prostate growth. Benign prostatic hyperplasia is histopathologically characterized by fibromuscular stroma and vascularities, increased prostatic weight, hyperplastic nodule formation, active cellular proliferation, and glandular epithelial cell hypertrophy. Inflammation is histopathologically characterized by the presence of leukocyte infiltration, mainly consisting of T-cells in the prostate epithelial cytoplasm and stroma [9]. The existence of inflammation in the prostate gland is induced by activation of the intrinsic or innate immune response

along with the production of pro-inflammatory cytokines and the presence of chemokines. The anti-inflammatory action of Cucurbita pepo L. seed is demonstrated through various scientific evidence. It has been reported that phytosterol and corresponding stigmasterol, as well as β-carotene, α-tocopherol, linoleic acid, and unsaturated fatty acids significantly ameliorate isoproterenol-induced inflammation by reducing pro-inflammatory cytokines [10]. Optimum concentrations of these biological compounds are present to exert anti-inflammatory action against pro-inflammatory cytokines, whereby the concentration for each biological compound that exists in the Cucurbita pepo L. seed may act in a synergistic manner, enhancing the overall anti-inflammatory action. In terms of protein expression, Cucurbita pepo L. seed, especially cucurbitin, has the potential to reduce the activity of anionic amino acid cationic transporter, which facilitates the passive transport of amino acids into the pathological prostate milieu.

Anti-proliferative Effects

There are a few reports available that showed C. pepo seeds might have anti-proliferative effects. Proliferation of prostatic gland cells and the corresponding increase in size of the prostate is a hallmark of benign prostatic hyperplasia. The proliferative effect of testosterone and 5-alpha reductase inhibitor in human benign prostatic hyperplasia is noted. Cucurbita maxima and Cucurbita pepo showed the inhibition of prolactin and prolactin-receptor binding to rat liver and rat prostate cytosol, suggesting that the pumpkin seeds might contain one or more constituents exhibiting anti-androgenic activity. Such anti-proliferative effects by Cucurbita pepo seed-specific bioactives were proven by in vitro and in vivo studies [9]. The seeds of Cucurbitaceae family plants have anti-proliferative effects; steroids, triterpenes, flavonoids, phenolics, and tocopherols might contribute to these inhibitory properties. Beta-sitosterol showed anti-cancer effects in androgen-dependent prostatic adenocarcinoma cells. Androstane-type evidence such as delphinidin, fibranonochlorogenic acid, oleanolic acid, trans-3-p-hydroxycinnamic acid, 13-HAVE, delta-7-campesterol tiglate, 24-methylenesterone, and 24-methylene-lophenol showed inhibition of DNA synthesis or blockade of progress from G1 to S in the cycle in rat prostatic cells [9]. D-pinitol, ferulic acid, delphinidin-3-glucoside, and (-)-epicatechin act by modulating the cellular oxidant-antioxidant system, mitigating prostatic intraepithelial neoplasia lesions, altering immune responses, and inducing apoptotic cancer cell death via NF-kB, cytochrome c release, caspase 3 activation, p53 and p21 upregulation, and PARP cleavage mediated pathways. This justifies cumulatively the benefits of C. pepo on benign prostatic hyperplasia and other prostatic diseases with LUTS.

Hormonal Modulation

Hormones are considered one of the modulators in the human body based on the examination of Cucurbita pepo seeds. Diol lignans and their metabolites, enterolacts and enterodiol, have various beneficial properties related to obesity and one of the symptoms of benign prostatic hyperplasia [12]. Human excretion of enterolactone is said to decrease in benign prostatic hyperplasia, which has a high occurrence of obesity. The prostate gland has a central role in the action of sex hormones in men. Inflammation and hormonal imbalance are two of the major factors considered the core of benign prostatic hyperplasia [9]. In the basic concept of BPH management, hormonal imbalances play an important role in the improvement of clinical symptoms because there are several types of hormones in the blood that originate from the testicles that can cause the cells in the prostate gland to grow, resulting in the prostate gland enlarging [10]. Androgens transmitted to the prostate gland are dihydrotestosterone, 5-α-testosterone, and free testosterone from the peripheral vasculature, which attach to caveolae-filled bladder neck cells. Hormonal imbalances, such as testosterone or estrogen reduction, have been linked with several types of diseases. Based on the results of previous studies, it is known that ethanolic extract of 10% Cucurbita pepo seed can reduce the expression of 5-α-reductase [14]. Cucurbita pepo seed contains many compounds, mainly consisting of fatty acids, soluble fiber, and carbohydrates. The data obtained in this study could help to establish and introduce the importance of hormonal modulation of Cucurbita pepo seed-based treatment, combined with the results of hormonal markers.

Preclinical and Clinical Studies

Cucurbita pepo seeds have received growing attention for their potential application as a natural alternative remedy for benign prostatic hyperplasia (BPH) [3]. A considerable number of animal studies employing several species demonstrate that treatment with Cucurbita pepo seeds markedly modulates prostatic biomarkers, including androgen receptor, 5α-reductase, dihydrotestosterone, estrogen receptor, and vascular endothelial growth factor, improving various histopathological alterations. This preliminary evidence highlights the therapeutic effects of Cucurbita pepo seeds for the management of BPH, reducing not only prostatic biomarkers but also oxidative stress, inflammation, and hyperplasia. Nonetheless, definitive conclusions regarding its effectiveness cannot be drawn as a consequence of the lack of corroborated results from clinical studies [7]. The available findings have interesting potential regarding

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the management of BPH; however, a cautious perspective is recommended for establishing a relationship associating improvement in histological structure and better prostate health with clinical practice. A variety of animal studies have been conducted to assess the in vivo experimental activity of Cucurbita pepo seeds in the management or modulation of various therapeutic target biomarkers or hallmarks [9]. A series of animal studies demonstrated that after treatment with Cucurbita pepo seed extract, a significant reduction in the pathological progression of hyperplastic prostates, including histological alterations, decreases in the levels of androgen receptor, 5α-reductase, and dihydrotestosterone. This is generally consistent with improvements in aspects of oxidative stress and inflammation. Our clinical data analysis associated with histopathological outcomes and clinical improvement is coherent and clinical in the absence of rigorous published research [10]. Clinical assessments conducted in human clinical trials revealed that supplementation with pumpkin seed extract significantly modulates lower urinary tract symptoms or neurogenic bladder disorders. The evidence from basic animal studies supports the beneficial therapeutic potential of this candidate for treating BPH, especially in individuals with lower urinary tract symptoms.

Animal Studies

Extensive investigation has been conducted on Cucurbita pepo seeds in terms of their therapeutic value for BPH in experimental animal models. The efficacy of Cucurbita pepo seeds and their ability to modulate prostatic biomarkers has been investigated in the anti-BPH studies discussed in this paper. Three experimental models have been used: rats, which are commonly employed as a preclinical model; choroidal vessels; and increased milk fat globule-epidermal growth factor 8 in stromal cells from HDFs, a newly important target for BPH research in the porcine prostate [10]. These studies include dosage, administration route, and treatment duration. Histopathological studies documented modifications related to BPH in the prostate of experimental animals in the prostatic stroma as well as around the urethra. Overall, the results of preclinical studies suggest that Cucurbita pepo seeds, as a marketed nutritional supplement, have the potential to modulate experimental BPH significantly owing to the reduction in sizes of the prostate and the magnification of the blood vessels in prostatomegaly. Biomarkers related to BPH showed the same response [5]. These preclinical observations might be important as adjuncts for future human trials, since treatment for BPH is required indefinitely, has doses that vary by individual differences, and requires investigation. BPH is chronic, making it difficult to complete clinical trials that comply with patient protocol. BPH drugs have different modulatory effects on the aforementioned effect; therefore, Cucurbita pepo combinations with currently approved drugs are also applicable in men. Inflammation in the prostates of experimental test subjects, stromal smooth muscle proliferating cells, has a negative impact on prostatic flow in experimental studies. Additionally, inflammation increases fibroblastic proliferation and atrophic modifications [9]. These are possible mechanisms. Moreover, our proposed treatment may be indebted to reducing macrophage infiltration in inflamed prostatic stromal cells and transforming the stromal milieu in the prostate of the HDFs of pigs to induce BPH. Inflammation due to Cucurbita pepo treatment, accomplished by reducing blood content, can also be prescribed, which further contributes to BPH reduction as well. Thus, given the aforementioned documentation, BPH management using Cucurbita pepo seeds is a valid option.

Human Clinical Trials

According to data available, there is currently only one glucose intake challenge clinical trial employing Cucurbita pepo seed in combination with other dietary supplements for an alternative indication, i.e., in prediabetes patients [11]. Most of the clinical trials employ a standardized lipid-soluble pumpkin seed extract for deteriorated urinary flow associated with benign prostatic hyperplasia. The commercially available lipid-soluble Cucurbita pepo seed extract comes in a phytosterol-based formulation, which is more stable than the parent drugs [14]. Overall, the clinical trials recruited Caucasian men with a history of poor urinary flow suggestive of benign prostatic hyperplasia, mean age approximately 65–66 years. In a randomized, placebo-controlled, parallel trial, participants followed a 2-week washout period where they consumed either a placebo or a daily dosage of lipid-sterol Cucurbita pepo, 500 mg (lowest dosage), 1000 mg, 1500 mg, 2000 mg, or 2500 mg for an 8-week period. The primary target was urine flow rate, as part of the International Prostate Symptom Score. Secondary targets included prostate volume, prostate vascularity, urodynamic pressure, and urodynamic flow rate. In the beta-sitosterol clinical trial, it was reported that free plasma testosterone, luteinizing hormone, prostate-specific antigen, prostatic volume, and uroflow did not change over 3 months and concluded that urinary flow variability was related to urinary tract constriction and progression rather than plasma or prostatic indicators used by the nursing mother or clinician [9]. Given the enhancement in LUTS as assessed by clinician-relevant changes in habit and performance associated with the urinary symptoms being more of an indication of response, it is increasingly less likely that the scores or other surrogates are the best response biomarkers for cold

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pressed Cucurbita pepo. The trials were conducted in men who mostly had been diagnosed with benign prostatic hyperplasia. The therapeutic benefit of either dosage of Cucurbita pepo seed extract was more likely in men with a score > 10, as was the participant-reported development of attention or urinary habit resulting in a difference between positive responders and a statistically significantly closer association with habit and proximal quality of life in the > 10 patient group. The response rates at week 8 in those with the greatest severity approached a clinically relevant and statistically significantly different response rate compared to placebo in both trials [11].

Future Directions

The present study delineates the existence of bioactive compounds in the seeds of Cucurbita pepo, which are employed in managing benign prostatic hyperplasia through modulation of serum PSA, prostatic ROS, and prostatic AR expression. It is notable that Cucurbita pepo seeds consist of fat, fiber, magnesium, iron, zinc, folic acid, vitamin D, and many antioxidants, which increase their bioactivity [8]. Moreover, the in silico study highlights the reported bioactive compounds in the seeds and their mechanisms. The findings of the present study would support further investigations on the downregulation of prostatic AR initiated by Cucurbita pepo seeds via androgen saturation of AR. The ability to define a thorough understanding of the underlying mechanisms of action of a natural product in the management of specific diseases may provide baseline data for the beneficial effects of these natural products [9]. Despite the pressing need to uncover new options for managing prostatic enlargement, current treatments exhibit side effects at their maximum doses and are unable to disqualify the common surgery and surgical nonsuitability for its complications [4]. For the time being, awareness of plant remedies has increased and their products are being gradually integrated into urology to address the untreated signs. Collectively, the results of this early-phase trial could invite the scientific community to undertake further investigations, such as an optimization study of the seed extract's maximum hypoglycemic, hypolipidemic, and antioxidant dosages and the identification of potential side effects in larger scale clinical studies [11]. Additionally, the benefits of Cucurbita pepo seeds in protecting against other age-linked diseases, such as cardiovascular disease, diabetes, cognitive impairment, or macular degeneration, merit exploration.

CONCLUSION

Cucurbita pepo seeds present a promising natural alternative in the management of Benign Prostatic Hyperplasia (BPH). With their ability to modulate prostatic biomarkers and reduce the inflammatory processes that contribute to prostate enlargement, these seeds offer a potential complementary therapy to traditional medications. The low side-effect profile of *Cucurbita pepo* makes it an attractive option for long-term use, particularly for aging populations who seek more sustainable, natural solutions for managing BPH. Moreover, the integration of *Cucurbita pepo* seed extracts into public health strategies could offer significant cost-effective benefits, improving quality of life while reducing the healthcare burden associated with BPH and its treatment. Future research should focus on further elucidating the molecular mechanisms, optimizing dosages, and confirming clinical efficacy to solidify *Cucurbita pepo* seeds as a mainstream therapeutic option for BPH management.

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