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Targeting Prostatic Redox Imbalance: Emerging Phytochemical Antioxidants in the Management of Benign Prostatic Hyperplasia

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ABSTRACT

Benign prostatic hyperplasia (BPH) is a common age-related urological disorder characterized by non-malignant enlargement of the prostate gland, often leading to lower urinary tract symptoms and reduced quality of life in aging men. Mounting evidence implicates oxidative stress and chronic inflammation as pivotal mechanisms in BPH pathogenesis, with increased reactive oxygen species (ROS) generation disrupting cellular homeostasis, promoting stromal proliferation, and impairing apoptosis. In recent years, phytochemical antioxidants have garnered significant attention as promising adjuncts or alternatives to conventional BPH therapies. This review explores the underlying role of redox imbalance in BPH, critically examines the molecular targets of oxidative stress in prostatic tissue, and highlights emerging antioxidant-rich phytochemicals, including flavonoids, polyphenols, carotenoids, and terpenoids. Specific attention is given to curcumin, resveratrol, quercetin, lycopene, and epigallocatechin gallate (EGCG), which demonstrate the capacity to inhibit inflammatory signaling pathways, modulate oxidative enzymes, and restore prostatic redox homeostasis. The pharmacokinetics, safety profiles, and clinical relevance of these agents are discussed in the context of current evidence. This review advocates for integrative strategies that combine antioxidant phytochemicals with standard medical or surgical interventions to holistically target oxidative pathways in BPH, and recommends future directions for translational research and personalized nutraceutical therapy.

Keywords: Benign prostatic hyperplasia, oxidative stress, phytochemicals, antioxidants, inflammation, nutraceuticals

INTRODUCTION

Benign prostatic hyperplasia (BPH) represents a major non-cancerous urological condition that significantly affects the quality of life of aging men worldwide [1]. Characterized by progressive enlargement of the prostate gland, BPH leads to compression of the urethra and resultant lower urinary tract symptoms (LUTS), including urinary hesitancy, nocturia, weak stream, and incomplete bladder emptying [2]. The global burden of BPH is increasing in parallel with the rising aging population, with up to 50 percent of men over 50 years and nearly 90 percent of men over 80 years showing histological evidence of prostatic hyperplasia [1]. While the role of androgens, particularly dihydrotestosterone (DHT), in BPH pathogenesis has been well documented, it is now widely recognized that oxidative stress and chronic inflammation are key contributors to the initiation and progression of prostatic overgrowth [3]. Oxidative stress arises from the accumulation of reactive oxygen species (ROS) that exceed the capacity of the body's intrinsic antioxidant defense systems [4]. These free radicals lead to lipid peroxidation, DNA damage, mitochondrial dysfunction, and alterations in gene expression [4]. The redox imbalance not only disrupts cellular homeostasis but also interacts with hormonal and inflammatory signaling pathways to drive hyperplasia [5].

Standard treatments for BPH include alpha-adrenergic blockers, 5-alpha reductase inhibitors, and surgical interventions such as transurethral resection of the prostate (TURP) [1]. However, these therapies are associated

with significant adverse effects such as sexual dysfunction, hypotension, and retrograde ejaculation, leading many patients to seek safer, non-invasive alternatives. As a result, there is growing interest in the role of plant-based therapeutics, particularly phytochemicals with antioxidant properties, as complementary or alternative approaches to BPH management. Phytochemicals are biologically active compounds derived from plants that exhibit a range of therapeutic effects, including antioxidant, anti-inflammatory, anti-proliferative, and anti-androgenic activities [6]. These include flavonoids, polyphenols, terpenoids, alkaloids, and carotenoids, which have shown promise in preclinical and limited clinical studies in reversing oxidative damage and modulating cellular pathways involved in BPH. By neutralizing ROS, modulating oxidative enzyme activity, and inhibiting inflammatory mediators, these compounds may offer a multi-targeted approach to BPH treatment [7]. This review aims to explore the pathophysiological role of oxidative stress in BPH and highlight the therapeutic potential of phytochemical antioxidants in redressing redox imbalance. The review will examine key classes of phytochemicals, their mechanisms of action, and the evidence supporting their use, while also discussing pharmacokinetic considerations, safety, and clinical relevance.

Oxidative Stress in BPH Pathophysiology

The prostate gland is particularly vulnerable to oxidative stress due to its high rate of cellular turnover, rich content of polyunsaturated fatty acids (which are prone to lipid peroxidation), and age-associated decline in antioxidant defenses [8]. With advancing age, increased ROS production coupled with impaired detoxification capacity leads to a redox imbalance in prostatic tissues [9]. This imbalance plays a crucial role in the structural and functional changes associated with BPH. ROS such as superoxide anions, hydrogen peroxide, and hydroxyl radicals are generated endogenously through cellular metabolism, particularly via mitochondrial respiration, NADPH oxidase activity, and inflammatory cell infiltration [10]. In BPH, chronic low-grade inflammation mediated by cytokines like IL-6, TNF-α, and IL-8 sustains ROS production, creating a vicious cycle of oxidative damage and inflammatory response [11]. This pro-oxidant environment activates transcription factors such as NF-κB and activator protein-1 (AP-1), which promote the expression of genes involved in inflammation, proliferation, and angiogenesis.

One of the hallmarks of oxidative stress in BPH is lipid peroxidation, where ROS attack unsaturated lipids in cellular membranes, leading to the formation of reactive aldehydes like malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) [4]. These compounds can form adducts with DNA and proteins, further impairing cellular function [12]. Elevated levels of MDA in prostate tissues and plasma of BPH patients have been consistently reported as biomarkers of oxidative damage. Another key mechanism is oxidative DNA damage, evidenced by increased 8-hydroxy-2'-deoxyguanosine (8-OHdG) in prostate epithelial cells [12]. DNA damage promotes genomic instability, alters cell cycle regulation, and inhibits apoptosis, thus favoring hyperplastic growth [13]. In parallel, ROS may suppress the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), further exacerbating the oxidative burden. Additionally, ROS modulates androgen metabolism by enhancing 5-alpha reductase activity, leading to increased conversion of testosterone to DHT, which stimulates prostatic cell proliferation [14]. This mechanistic link underscores the synergistic relationship between hormonal dysregulation and oxidative stress in BPH pathogenesis. Given these insights, redox imbalance represents a valid therapeutic target in BPH, and the restoration of antioxidant capacity could be a promising intervention to halt or reverse disease progression. This has led to considerable interest in phytochemicals with antioxidant capabilities as potential modulators of oxidative pathways in BPH.

Phytochemical Antioxidants in BPH: Mechanistic Insights

Phytochemicals encompass a broad range of secondary metabolites from plants that exhibit potent antioxidant and anti-inflammatory properties [15]. In the context of BPH, several classes of phytochemicals have been studied for their ability to modulate redox homeostasis, inhibit pro-inflammatory mediators, and suppress hyperplastic cell proliferation.

Flavonoids

Flavonoids such as quercetin, kaempferol, apigenin, and luteolin have been shown to scavenge ROS, enhance antioxidant enzyme expression, and inhibit key signaling pathways involved in BPH [16]. Quercetin, found in onions, apples, and berries, reduces MDA levels, increases SOD and CAT activity, and downregulates NF-κB and COX-2 in prostatic tissues [17]. It also induces cell cycle arrest and apoptosis in prostate epithelial cells, thereby limiting hyperplasia.

Polyphenols

Resveratrol, a polyphenol abundant in grapes and red wine, activates sirtuin-1 (SIRT1), which in turn modulates mitochondrial biogenesis and reduces ROS production [18]. It inhibits inflammatory enzymes like COX-2 and iNOS, suppresses TNF-α and IL-6 expression, and enhances Nrf2-mediated antioxidant defense [19]. These effects make resveratrol a dual-action compound that can address both oxidative stress and inflammation in BPH.

Carotenoids

Lycopene, a red pigment found in tomatoes, exerts strong singlet oxygen quenching ability. Lycopene reduces prostatic DHT levels, downregulates insulin-like growth factor (IGF) signaling, and inhibits cell cycle progression [20]. Clinical studies have demonstrated that lycopene supplementation can reduce prostate volume and improve LUTS in men with BPH, likely through its antioxidative and anti-inflammatory effects [21].

Curcuminoids

Curcumin, derived from the turmeric plant, modulates multiple redox-sensitive pathways. It inhibits NF-κB, reduces iNOS and COX-2 expression, and activates the Nrf2/HO-1 axis, enhancing the cellular antioxidant response [22]. It also modulates apoptotic proteins, shifting the balance towards cell death in hyperplastic prostate cells [23]. Its anti-fibrotic and anti-angiogenic effects further contribute to prostatic tissue normalization [24].

Catechins

Epigallocatechin-3-gallate (EGCG), the most abundant catechin in green tea, exhibits powerful antioxidant and anti-androgenic properties. It suppresses 5-alpha reductase activity, reducing DHT synthesis, and inhibits ROS generation via NADPH oxidase inhibition [25]. EGCG also promotes DNA repair, reduces pro-inflammatory cytokines, and induces apoptosis in prostatic cells [26]. These compounds collectively exert a pleiotropic effect on BPH-related oxidative and inflammatory pathways. Their ability to simultaneously modulate multiple molecular targets positions them as attractive agents in integrated BPH therapy, particularly for patients seeking non-hormonal, natural alternatives.

Clinical and Preclinical Evidence

A growing body of experimental and clinical evidence supports the efficacy of phytochemical antioxidants in the prevention and management of benign prostatic hyperplasia (BPH). Preclinical studies using animal models of hormone-induced prostatic hyperplasia have demonstrated the capacity of phytochemicals to suppress prostate enlargement, modulate oxidative biomarkers, and restore tissue architecture. For instance, in testosterone-induced BPH rat models, treatment with lycopene led to a significant reduction in prostate weight and prostatic index, accompanied by decreased lipid peroxidation and improved antioxidant enzyme activity [27]. Similarly, administration of quercetin to rats with induced BPH reversed histological features of hyperplasia, reduced serum DHT levels, and normalized activities of catalase and superoxide dismutase in prostate tissues [28]. Green tea extract rich in epigallocatechin gallate (EGCG) has been shown to attenuate testosterone-induced prostatic enlargement in rodents by suppressing oxidative DNA damage and inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [29]. These changes correlated with improved urinary function and lower prostate-specific antigen (PSA) levels, highlighting both functional and biochemical benefits.

Curcumin has demonstrated protective effects against estrogen and testosterone-induced BPH in rats by modulating the NF-κB signaling pathway and enhancing Nrf2-mediated antioxidant responses [30]. These effects were accompanied by reduced epithelial hyperplasia, suppressed COX-2 expression, and decreased nitric oxide production. In clinical settings, although fewer studies have been conducted, emerging results are promising. A randomized controlled trial involving 40 men with moderate BPH symptoms showed that supplementation with lycopene (15 mg/day) for six months significantly reduced prostate volume and improved the International Prostate Symptom Score (IPSS) compared to placebo [31]. Another study involving a combination of quercetin and saw palmetto extract resulted in marked improvement in urinary flow rate, reduced post-void residual volume, and lower oxidative stress markers [32]. Despite these encouraging findings, clinical trials often face limitations such as small sample sizes, short duration, lack of standardized extract concentrations, and variability in patient populations. Moreover, inter-individual differences in phytochemical metabolism and absorption complicate the translation of results. Nonetheless, the accumulated evidence supports the potential of phytochemical antioxidants as viable adjuncts in the management of BPH, particularly in early stages or in patients unfit for pharmacological or surgical therapy. Future clinical trials should adopt standardized formulations, ensure adequate sample sizes, and incorporate validated biomarkers of oxidative stress and inflammation to confirm efficacy and guide clinical recommendations.

Pharmacokinetics and Safety Considerations

Although phytochemical antioxidants have demonstrated substantial therapeutic potential in preclinical and early clinical settings, their pharmacokinetic limitations represent a major barrier to effective clinical translation. Most phytochemicals suffer from poor oral bioavailability due to low aqueous solubility, rapid metabolism, and limited gastrointestinal absorption [33]. For example, curcumin undergoes extensive first-pass metabolism in the liver and intestinal wall, resulting in low systemic bioavailability [34]. Similar limitations apply to resveratrol and quercetin, which are rapidly conjugated to inactive glucuronides and sulfates [35]. These pharmacokinetic shortcomings restrict their accumulation in target tissues such as the prostate and thus limit therapeutic efficacy. To overcome these challenges, several strategies have been developed. Nanoformulations, including liposomes, solid lipid nanoparticles, and polymeric micelles, enhance solubility and protect phytochemicals from degradation [36]. Phytosomes, which are complexes of phytochemicals with phospholipids, improve membrane permeability and

systemic absorption [37]. Piperine, an alkaloid found in black pepper, is also co-administered with curcumin to inhibit glucuronidation and increase systemic availability [38]. Safety profiles of phytochemical antioxidants are generally favorable, especially when derived from dietary sources. Most compounds such as lycopene, quercetin, and EGCG are well tolerated at moderate doses, with minimal adverse effects. However, high doses or prolonged use may pose safety risks. For instance, excessive intake of EGCG has been associated with hepatotoxicity, and high concentrations of polyphenols may exert pro-oxidant effects under certain conditions, especially in iron-rich tissues [39]. Drug interactions also represent a concern. Quercetin and resveratrol, for instance, can inhibit cytochrome P450 enzymes, potentially affecting the metabolism of concomitant medications [40]. Therefore, clinicians and patients should exercise caution when using phytochemicals alongside conventional pharmacotherapies, especially in elderly patients with polypharmacy.

Future Directions and Integrative Therapeutic Strategies

The management of benign prostatic hyperplasia is progressively shifting toward integrative and personalized approaches that address the multifactorial nature of the disease. While conventional therapies such as alpha-blockers and 5-alpha reductase inhibitors remain effective, their side effects and contraindications have spurred interest in complementary options such as phytochemical antioxidants.

Future therapeutic strategies should consider combining phytochemical agents with standard pharmacological or minimally invasive surgical interventions. For example, concurrent use of EGCG or lycopene with alpha-blockers may reduce the required drug dose, thereby minimizing side effects while maintaining therapeutic efficacy. Combination therapy may also target different pathogenic mechanisms, such as hormonal, oxidative, and inflammatory, offering a more holistic intervention.

Advances in systems biology and bioinformatics can support the identification of patients who would benefit most from antioxidant-based interventions, based on their genetic, metabolic, and inflammatory profiles. Biomarker-guided therapy may optimize outcomes and avoid unnecessary exposure to ineffective treatments. Further, the design of large-scale, double-blind, placebo-controlled clinical trials using standardized phytochemical preparations is critical to validate efficacy and safety. These studies should evaluate both subjective (symptom score, quality of life) and objective (prostate volume, PSA, oxidative stress markers) endpoints to provide comprehensive clinical evidence. On a translational level, the development of prostate-targeted drug delivery systems, including nanoparticles, implantable depots, and hydrogels, may improve therapeutic concentrations of phytochemicals within the prostate while reducing systemic exposure. Lastly, public health initiatives promoting diets rich in antioxidant-containing fruits and vegetables may have a preventive role in populations at risk for BPH. Nutritional counseling integrated into urology clinics could enhance patient engagement and long-term adherence to phytochemical-rich interventions.

CONCLUSION

Oxidative stress plays a critical role in the pathogenesis and progression of BPH. Phytochemical antioxidants offer a promising avenue to modulate redox pathways, reduce inflammation, and attenuate prostate enlargement. While preclinical findings are robust, clinical evidence remains nascent. Strategic integration of phytochemicals into multimodal BPH treatment regimens may offer safer and more effective outcomes for aging men. Ongoing research into their pharmacokinetics, molecular targets, and synergistic interactions will further refine their role in precision urological care.

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