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Targeting Oxidative Stress in Urological Complications: Emerging Antioxidant Therapies for Benign Prostatic Hyperplasia and Liver Health Crosstalk

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ABSTRACT

Benign Prostatic Hyperplasia (BPH) is a highly prevalent non-malignant urological disorder characterized by progressive enlargement of the prostate gland, primarily affecting aging males. This pathological growth results in lower urinary tract symptoms (LUTS), including urinary frequency, urgency, nocturia, weak stream, and incomplete bladder emptying, which significantly impair quality of life. While androgenic stimulation has traditionally been implicated in the pathogenesis of BPH, emerging evidence highlights oxidative stress (OS) as a critical driver of disease progression. Oxidative stress promotes cellular damage through excessive generation of reactive oxygen species (ROS), leading to lipid peroxidation, DNA fragmentation, mitochondrial dysfunction, and activation of inflammatory cascades that stimulate stromal and epithelial proliferation within the prostate. Moreover, increasing recognition is being given to the liver-prostate axis, with liver dysfunction — particularly non-alcoholic fatty liver disease (NAFLD) — contributing to systemic oxidative stress and inflammation that may exacerbate BPH pathogenesis. This review comprehensively evaluates the molecular mechanisms linking oxidative stress to BPH and liver dysfunction, while exploring emerging antioxidant therapeutic strategies. Natural phytochemicals, antioxidant vitamins, trace elements, and advanced nano-based delivery systems are critically appraised for their potential to modulate oxidative damage, improve prostate health, and restore liver-prostate homeostasis. Future research directions advocate for personalized antioxidant interventions, redox-based biomarkers, and translational studies to optimize BPH management.

Keywords: Benign Prostatic Hyperplasia; Oxidative Stress; Antioxidant Therapy; Liver-Prostate Crosstalk; Phytochemicals

INTRODUCTION

Benign Prostatic Hyperplasia (BPH) is a non-malignant progressive enlargement of the prostate gland that represents a leading cause of morbidity among aging men worldwide [1]. Epidemiological data indicate that BPH affects over 50% of men above the age of 50 years, with prevalence rising to approximately 80–90% in men older than 80 years [2]. The condition is clinically characterized by lower urinary tract symptoms (LUTS), such as increased urinary frequency, urgency, nocturia, weak urine stream, and incomplete bladder emptying, which significantly affect the quality of life and impose a substantial healthcare burden [1]. Traditionally, the pathogenesis of BPH has been largely attributed to androgenic stimulation, particularly the role of dihydrotestosterone (DHT) in promoting prostatic cell proliferation and hyperplasia [3]. In addition, chronic inflammation within the prostate microenvironment has been recognized as a crucial driver of tissue remodeling, fibrosis, and disease progression [4]. However, accumulating scientific evidence over the past decade has identified oxidative stress (OS) as a pivotal pathogenic factor in BPH development and progression [5]. Oxidative stress arises when there is an imbalance between the generation of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms [6]. Elevated ROS levels within prostatic tissues can trigger lipid peroxidation, DNA fragmentation, mitochondrial dysfunction, and apoptosis, all of which contribute to tissue damage, inflammation, and abnormal cellular proliferation characteristic of BPH [7]. Furthermore, emerging research highlights a critical link between hepatic dysfunction, particularly non-alcoholic fatty liver disease (NAFLD), and BPH, suggesting a complex liver-prostate pathological crosstalk.

NAFLD, a hepatic manifestation of metabolic syndrome, is characterized by excessive fat accumulation in the liver, insulin resistance, and systemic inflammation [8]. This hepatic dysfunction contributes to systemic oxidative stress and inflammatory mediators that may exacerbate BPH development [8]. Therefore, targeting oxidative stress not only offers therapeutic potential for mitigating BPH progression but also provides a novel approach to addressing liver-prostate axis dysfunction in aging males.

Oxidative Stress in the Pathophysiology of BPH

Oxidative stress (OS) plays a central role in the pathogenesis of Benign Prostatic Hyperplasia (BPH), acting as both a trigger and amplifier of prostatic tissue remodeling [5,7]. The prostate gland is highly susceptible to oxidative injury due to its rich content of polyunsaturated fatty acids and high metabolic activity, which favor the generation of reactive oxygen species (ROS) [9]. An imbalance between excessive ROS production and insufficient antioxidant defense mechanisms leads to cellular damage, chronic inflammation, and fibrosis within the prostate [6].

Molecular Mechanisms

At the molecular level, oxidative stress activates several redox-sensitive transcription factors and signaling pathways that drive BPH development. Excess ROS in prostatic tissues triggers the activation of nuclear factor-kappa B (NF-κB), a key regulator of inflammatory responses, leading to the upregulation of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [10]. These cytokines create a pro-inflammatory microenvironment that promotes cellular proliferation and inhibits apoptosis [11]. Furthermore, oxidative stress induces transforming growth factor-beta (TGF-β) signaling, which facilitates fibroblast activation, extracellular matrix deposition, and tissue fibrosis — critical processes in prostatic remodeling [12]. Additionally, cyclooxygenase-2 (COX-2), another redox-sensitive enzyme, is upregulated under oxidative stress conditions, leading to the synthesis of prostaglandins that perpetuate inflammation and hyperplasia [13].

Impact on Prostatic Remodeling

The cumulative effects of oxidative stress result in abnormal cellular proliferation of epithelial and stromal cells, increased extracellular matrix production, and stromal hypertrophy, all of which contribute to the narrowing of the prostatic urethra and the manifestation of lower urinary tract symptoms (LUTS) [14]. The degree of oxidative damage correlates with BPH severity, underscoring the critical role of oxidative stress in disease progression [10].

Liver-Prostate Crosstalk: A Redox-Based Perspective

Recent advances in molecular medicine have elucidated a complex and dynamic bidirectional communication network between the liver and prostate, with oxidative stress (OS) emerging as a central mediator of this liver-prostate axis. This redox-based crosstalk is increasingly recognized as a crucial determinant in the pathogenesis of benign prostatic hyperplasia (BPH), particularly in patients with concurrent metabolic disorders such as non-alcoholic fatty liver disease (NAFLD) [15]. Both BPH and NAFLD share common risk factors including aging, obesity, metabolic syndrome, insulin resistance, and systemic inflammation, which converge through oxidative stress-driven pathways [16].

The liver, as a central metabolic organ, influences distant tissues, including the prostate, through the secretion of inflammatory cytokines, metabolic hormones, and oxidative stress biomarkers [17]. In patients with NAFLD, hepatic steatosis and fibrosis are associated with increased production of reactive oxygen species (ROS), leading to systemic oxidative stress that can exacerbate prostatic cellular dysfunction [18]. Elevated serum oxidative stress markers such as malondialdehyde (MDA), 8-hydroxy-2'-deoxyguanosine (8-OHdG), and reduced antioxidant enzyme activity are frequently observed in patients with NAFLD and correlate with the severity of BPH [19].

Mechanisms Linking NAFLD and BPH

Several mechanisms underpin the liver-prostate interplay. Altered bile acid metabolism secondary to hepatic dysfunction can influence androgen receptor signaling in prostatic tissues, contributing to abnormal cellular proliferation, stromal remodeling, and hypertrophy [20]. Furthermore, NAFLD-induced hepatic insulin resistance leads to hyperinsulinemia, which enhances insulin-like growth factor-1 (IGF-1) activity — a known driver of prostatic hyperplasia [21]. Additionally, inflammatory mediators produced by the liver, such as TNF-α, IL-6, and C-reactive protein (CRP), can reach the prostate via systemic circulation, promoting a pro-inflammatory and pro-oxidant microenvironment conducive to BPH progression [22]. Therefore, liver dysfunction plays a pivotal role in modulating prostate health, with oxidative stress serving as a mechanistic bridge linking metabolic liver disease and urological complications. Targeting this liver-prostate redox crosstalk presents a novel therapeutic approach in the integrated management of BPH.

Therapeutic Implications for Liver Health and Prostate Homeostasis

The emerging role of oxidative stress in the pathogenesis of benign prostatic hyperplasia (BPH) and its systemic interactions, particularly with liver dysfunction, underscores the importance of antioxidant therapies as a dual-targeted strategy. Antioxidant interventions not only alleviate the hallmark lower urinary tract symptoms (LUTS) associated with BPH but also offer hepatoprotective benefits that address underlying metabolic dysfunctions [23].

One of the primary therapeutic implications of antioxidant therapy is the reduction of systemic inflammation. Oxidative stress perpetuates a cycle of chronic inflammation through the activation of redox-sensitive transcription factors like NF-κB, which regulates the expression of inflammatory cytokines [23]. By scavenging reactive oxygen species (ROS) and modulating inflammatory pathways, antioxidants can suppress the release of pro-inflammatory mediators, thus reducing inflammation within both the prostate and liver tissues [24]. Furthermore, antioxidants play a significant role in improving lipid metabolism, which is often dysregulated in patients with non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome-conditions commonly associated with BPH [25]. Phytochemicals such as resveratrol and curcumin have demonstrated lipid-lowering effects, enhancing hepatic lipid clearance and reducing hepatic steatosis, thereby indirectly improving prostate health through the liver-prostate axis [26]. Mitochondrial dysfunction, another consequence of oxidative stress, contributes to energy imbalance and cellular damage within both the prostate and liver [27]. Antioxidants enhance mitochondrial biogenesis and protect mitochondrial membranes from lipid peroxidation, restoring normal energy metabolism [28]. These hepatoprotective effects not only preserve liver function but also help maintain systemic metabolic balance, ultimately benefiting prostatic tissue homeostasis. Therefore, antioxidant therapy provides a promising integrative approach in managing BPH patients, particularly those with comorbid liver dysfunction, emphasizing the interconnectedness of organ systems and the importance of systemic therapeutic strategies.

Future Perspectives and Research Directions

Although substantial progress has been made in elucidating the role of oxidative stress (OS) in the pathogenesis of benign prostatic hyperplasia (BPH) and its systemic interplay with liver dysfunction, several research gaps persist that require focused attention. The future of BPH management hinges on integrative strategies that combine antioxidant therapy with personalized medicine, novel biomarkers, and translational interventions targeting the liver-prostate axis.

Development of Biomarkers to Assess Redox Status in BPH

There is a critical need to develop sensitive, specific, and reliable biomarkers capable of objectively assessing oxidative stress levels in patients with BPH. Potential biomarkers may include oxidative DNA damage products (e.g., 8-hydroxy-2'-deoxyguanosine), lipid peroxidation markers (e.g., malondialdehyde), protein carbonyl content, and antioxidant enzyme activities (e.g., superoxide dismutase, glutathione peroxidase). These biomarkers will facilitate early detection, patient risk stratification, therapeutic monitoring, and evaluation of antioxidant treatment efficacy.

Clinical Trials Evaluating Combination Antioxidant Therapies

Given the multifactorial nature of BPH pathogenesis, future clinical trials should explore combination antioxidant therapies that target multiple redox-sensitive pathways simultaneously. Synergistic formulations of phytochemicals (e.g., lycopene, curcumin, resveratrol) with micronutrients (vitamins C and E, selenium, zinc) could offer superior therapeutic benefits compared to monotherapies. These trials should also evaluate safety profiles, optimal dosing regimens, and long-term outcomes in diverse patient populations.

Exploration of Gut Microbiota-Mediated Antioxidant Modulation

Emerging evidence suggests a significant role of gut microbiota in regulating systemic oxidative stress and inflammation. Modulation of gut microbiota through probiotics, prebiotics, synbiotics, or dietary interventions may enhance endogenous antioxidant defenses, thereby offering an innovative therapeutic strategy in BPH management.

Translational Research into Liver-Prostate Axis Targeting Agents

Future research should prioritize the development of pharmacological agents, nutraceuticals, or functional foods specifically designed to modulate the liver-prostate axis. Targeting shared oxidative stress and inflammatory pathways between the liver and prostate may provide a holistic approach to treating BPH, particularly in patients with comorbid metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), or other hepatic disorders. Integration of multi-omics technologies, bioinformatics, and precision medicine frameworks will be crucial in driving this translational research forward.

CONCLUSION

Oxidative stress has emerged as a pivotal factor in the pathogenesis of benign prostatic hyperplasia and its systemic complications, particularly liver dysfunction. The intricate liver-prostate axis highlights the importance of addressing oxidative damage not only within the prostate but also at the systemic level. Antioxidant therapies — especially those derived from natural phytochemicals and enhanced by advanced delivery systems such as nanotechnology — hold significant potential in restoring redox homeostasis, reducing inflammation, and improving metabolic health. Moving forward, personalized antioxidant strategies guided by molecular profiling, redox biomarkers, and patient-specific risk factors could revolutionize the management of BPH, offering integrated therapeutic approaches that simultaneously target urological complications and liver health. Collaborative translational research and well-designed clinical trials will be essential in advancing these therapeutic innovations from bench to bedside.

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