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Liver Function as a Determinant of Antioxidant Therapeutic Efficacy in Benign Prostatic Hyperplasia: A Systems Biology Perspective

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ABSTRACT

Benign Prostatic Hyperplasia (BPH) is a non-malignant enlargement of the prostate gland predominantly affecting aging males. While oxidative stress (OS) is recognized as a key pathogenic driver in BPH, emerging evidence highlights the liver's critical role in modulating systemic redox homeostasis and influencing antioxidant therapeutic responses. Liver function not only governs the bioavailability, metabolism, and clearance of antioxidant compounds but also contributes to systemic inflammation and metabolic alterations that exacerbate BPH pathophysiology. This review adopts a systems biology approach to explore the complex liver-prostate axis, emphasizing how liver health determines the pharmacokinetics, pharmacodynamics, and therapeutic efficacy of antioxidant interventions in BPH management. We discuss the molecular mechanisms underpinning hepatic regulation of antioxidant bioactivity, the impact of liver dysfunction on BPH progression, and emerging therapeutic strategies aimed at restoring liver-prostate homeostasis. Future research directions advocate for precision antioxidant therapy guided by liver function biomarkers, systems biology modeling, and integrative metabolic profiling.

Keywords: Benign Prostatic Hyperplasia; Liver Function; Antioxidant Therapy; Oxidative Stress; Systems Biology

INTRODUCTION

Benign Prostatic Hyperplasia (BPH) is a non-malignant enlargement of the prostate gland that occurs predominantly in aging males and remains one of the most common urological conditions worldwide [1]. Epidemiological data suggest that more than 50% of men over 50 years and up to 90% of men over 80 years develop histological features of BPH [2]. Clinically, the condition is characterized by lower urinary tract symptoms (LUTS), including urinary frequency, urgency, nocturia, weak urinary stream, and incomplete bladder emptying, which significantly compromise the quality of life and increase healthcare utilization [3]. Historically, the pathophysiology of BPH has been attributed to age-related hormonal imbalances, particularly elevated dihydrotestosterone (DHT) levels, as well as to chronic inflammation within the prostate microenvironment [1]. However, growing evidence supports the pivotal role of oxidative stress (OS) as a core driver of prostatic enlargement and symptom progression [4]. Oxidative stress is defined as a disturbance in the balance between reactive oxygen species (ROS) production and the body's antioxidant defense mechanisms [5]. In the prostate, excessive ROS generation contributes to a cascade of detrimental cellular events, including DNA damage, mitochondrial dysfunction, protein oxidation, and lipid peroxidation [4,6]. These events amplify inflammatory signaling, promote fibroblast activation, and accelerate stromal and epithelial hyperplasia [6]. Importantly, the liver plays a central role in regulating systemic redox homeostasis through its functions in detoxification, metabolism, and biosynthesis of endogenous antioxidants such as glutathione [7]. The liver also mediates the biotransformation of exogenous antioxidant compounds, including dietary phytochemicals, vitamins, and pharmacological agents [8]. In individuals with hepatic dysfunction—particularly those with non-alcoholic fatty liver disease (NAFLD),

non-alcoholic steatohepatitis (NASH), or other manifestations of metabolic syndrome—the antioxidant capacity is often impaired [9]. This impairment not only reduces the bioavailability and efficacy of antioxidant therapies but also contributes to a systemic pro-inflammatory, pro-oxidant state that may exacerbate BPH progression [10]. This review adopts a systems biology perspective to explore the interplay between liver function and the therapeutic efficacy of antioxidants in BPH. By integrating insights from molecular biology, pharmacokinetics, and network medicine, we aim to highlight how liver health determines both the metabolism and the clinical effectiveness of antioxidant-based interventions. The review also discusses the potential for personalized antioxidant strategies in BPH patients with comorbid hepatic dysfunction and outlines directions for future translational research focused on the liver-prostate axis.

Oxidative Stress in BPH: Pathogenic Mechanisms

Oxidative stress has emerged as a fundamental contributor to the pathogenesis of BPH [4,6]. Under normal physiological conditions, the production of reactive oxygen species (ROS)—including superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH)—is tightly regulated by endogenous antioxidant systems such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) [11]. In aging men, however, increased ROS production and a decline in antioxidant defense mechanisms lead to oxidative imbalance, contributing to cellular damage and tissue dysfunction [12].

Several key molecular pathways have been implicated in OS-mediated prostatic remodeling: Activation of NF-κB and other redox-sensitive transcription factors: ROS can activate nuclear factor-kappa B (NF-κB), which induces the transcription of multiple pro-inflammatory cytokines, chemokines, and adhesion molecules [13]. This initiates a chronic inflammatory response that perpetuates tissue injury and fibrosis in the prostate [13].

Upregulation of pro-inflammatory cytokines (e.g., IL-6, TNF-α): These cytokines contribute to a paracrine and autocrine feedback loop that stimulates stromal and epithelial proliferation, angiogenesis, and recruitment of immune cells, further amplifying oxidative and inflammatory damage [14].

Enhanced TGF-β signaling: Transforming growth factor-beta (TGF-β) is a key mediator of fibrosis and is upregulated in response to oxidative stress. TGF-β activation promotes fibroblast-to-myofibroblast differentiation, extracellular matrix (ECM) accumulation, and tissue stiffness—all hallmark features of BPH [15].

Cyclooxygenase-2 (COX-2) induction: COX-2 is an enzyme responsible for prostaglandin synthesis and is induced under oxidative stress conditions [16]. Elevated COX-2 activity contributes to inflammation, hyperplasia, and LUTS in BPH patients [16]. Collectively, these molecular events result in prostatic tissue remodeling, characterized by epithelial and stromal hyperplasia, increased smooth muscle tone, and impaired urinary flow. Understanding these redox-regulated mechanisms not only underscores the importance of oxidative stress in BPH progression but also supports the rationale for antioxidant-based therapeutic interventions. Furthermore, given the liver's influence on antioxidant metabolism and systemic oxidative balance, liver function becomes a crucial determinant of treatment efficacy in BPH patients [17].

Liver Function: Central Modulator of Antioxidant Efficacy

The liver plays a fundamental role in determining the systemic bioavailability, distribution, and therapeutic action of antioxidant compounds used in the management of Benign Prostatic Hyperplasia (BPH) [7,8]. As the body's primary metabolic hub, the liver orchestrates a wide array of biochemical processes that govern the detoxification and biotransformation of both endogenous and exogenous antioxidants [9,10].

Hepatic Metabolism of Antioxidants

Most antioxidant agents, including phytochemicals, vitamins, and pharmacological antioxidants, undergo hepatic metabolism through phase I and phase II enzymatic reactions [18]. Phase I reactions are primarily mediated by the cytochrome P450 (CYP450) enzyme family, which introduces reactive or polar groups to antioxidant molecules, preparing them for further metabolism [19]. Subsequently, phase II reactions involve conjugation processes such as glucuronidation, sulfation, or methylation, facilitating their solubilization and excretion [19]. Additionally, the liver regulates the biosynthesis and activity of endogenous antioxidant enzymes like

superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). These enzymes are crucial in maintaining intracellular redox balance and neutralizing reactive oxygen species (ROS) [20]. However, liver dysfunction—especially in the context of non-alcoholic fatty liver disease (NAFLD), steatohepatits, or cirrhosis—disrupts these metabolic pathways [21]. Impaired liver function may lead to reduced bioactivation or premature clearance of antioxidants, diminishing their therapeutic efficacy in target tissues such as the prostate [22]. Furthermore, hepatic injury may compromise the synthesis of endogenous antioxidants, exacerbating systemic oxidative stress [8].

Liver-Derived Mediators in BPH Progression

Liver damage has systemic ramifications beyond impaired antioxidant metabolism. Hepatic injury is associated with elevated systemic oxidative stress markers, including malondialdehyde (MDA) and 8-hydroxy-2'-deoxyguanosine (8-OHdG), which can exacerbate oxidative damage in distant organs, including the prostate [23]. Moreover, inflammatory cytokines produced by the injured liver, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), enter systemic circulation and can contribute to the inflammatory microenvironment within the prostate, promoting hyperplasia and fibrosis [24].

Disturbance in bile acid metabolism, a frequent consequence of liver dysfunction, has also been shown to modulate androgen receptor signaling pathways in prostatic cells, influencing cellular proliferation and tissue remodeling [25]. These mechanisms collectively demonstrate how compromised liver health can aggravate BPH pathogenesis through systemic metabolic and inflammatory pathways.

Systems Biology Perspective on the Liver-Prostate Axis

Systems biology provides a comprehensive framework for understanding the complex, multi-organ interactions that underlie the liver-prostate axis in BPH [26,27]. This approach integrates computational modeling, network biology, and multi-omics data (including genomics, metabolomics, and proteomics) to elucidate how molecular pathways intersect across different tissues [28].

Applying systems biology to the liver-prostate axis allows for:

Detailed mapping of metabolic and signaling pathways that link liver function with prostatic health, particularly those involving oxidative stress, inflammation, and hormonal regulation [29]. Identification of critical molecular nodes or network hubs that may serve as targets for therapeutic intervention, such as transcription factors (e.g., NF-κB), antioxidant response elements (AREs), or key enzymes in ROS detoxification pathways [30]. Prediction of patient-specific responses to antioxidant therapies based on individual variations in liver function, genetic polymorphisms in metabolic enzymes, or differences in gut microbiota composition [31]. This systems-level perspective facilitates precision medicine approaches, enabling the tailoring of antioxidant therapy regimens to the metabolic and hepatic profile of each BPH patient.

Therapeutic Implications and Strategies

Personalized Antioxidant Therapy

Stratifying BPH patients based on liver function biomarkers—including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and liver fibrosis scores—can guide the selection, dosing, and monitoring of antioxidant therapies. This personalized approach ensures optimal therapeutic efficacy while minimizing potential adverse effects related to hepatic metabolism [32].

Liver-Targeted Interventions

Given the liver's central role in regulating antioxidant bioavailability and systemic oxidative stress, interventions aimed at improving liver health are essential in the integrated management of BPH. These may include:

Hepatoprotective phytochemicals such as silymarin (milk thistle extract), curcumin, and green tea polyphenols, which enhance liver detoxification pathways and antioxidant defenses [33].

Lifestyle interventions focusing on weight management, reduction of dietary saturated fats, and increased consumption of antioxidant-rich foods to reduce hepatic fat accumulation and inflammation [34].

Gut microbiota-targeted therapies, including probiotics and prebiotics, which improve hepatic antioxidant capacity by modulating gut-liver axis interactions [35].

Combination Therapies

Combining antioxidants with metabolic modulators offers a synergistic approach to BPH management in patients with comorbid liver dysfunction. For instance, integrating antioxidant agents with statins

(which possess anti-inflammatory and antioxidant properties) or insulin sensitizers (e.g., metformin) may enhance therapeutic outcomes by targeting both metabolic and redox-related pathways [36]. Such combination therapies not only address prostate-specific oxidative stress but also correct systemic metabolic derangements that contribute to BPH progression, reflecting the holistic therapeutic paradigm supported by systems biology.

Future Research Directions

Future research should focus on advancing a more integrative and personalized approach to the management of benign prostatic hyperplasia (BPH), particularly in patients with comorbid liver dysfunction. One of the critical areas of exploration is the development of liver-prostate axis-specific antioxidant formulations. These novel therapeutics should be designed to optimize bioavailability, overcome hepatic metabolic barriers, and target both hepatic and prostatic oxidative stress pathways simultaneously. Additionally, future clinical trials evaluating antioxidant therapies for BPH should incorporate routine liver function assessments. Stratifying patients based on liver health biomarkers, including liver enzyme levels and fibrosis scores, will provide valuable insights into therapeutic responses and safety profiles, facilitating personalized antioxidant therapy.

Systems pharmacology modeling represents another promising area, utilizing computational tools to predict therapeutic outcomes based on individual metabolic profiles, drug-liver interactions, and prostatic redox status. This will enable more accurate dosing, reduced adverse effects, and maximized efficacy. Furthermore, expanding research into the gut-liver-prostate microbiome axis is essential. The gut microbiota plays a vital role in modulating systemic inflammation, oxidative stress, and liver metabolism. Exploring how alterations in gut microbial composition affect the liver-prostate axis and antioxidant responses could unveil innovative therapeutic avenues, such as microbiome-targeted interventions, in the integrated management of BPH.

CONCLUSION

Liver function is a crucial determinant of antioxidant therapeutic efficacy in the management of benign prostatic hyperplasia. The systems biology perspective highlights the need for integrative approaches that consider hepatic metabolism, systemic oxidative stress, and liver-derived inflammatory mediators in designing personalized antioxidant strategies. Future therapeutic interventions targeting the liver-prostate axis hold promise in improving patient outcomes and addressing the metabolic complexity of BPH.

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