

Benign prostatic hyperplasia at the environment–biology interface: pathogenesis, natural resources, and sustainable management

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ABSTRACT

Benign prostatic hyperplasia (BPH) is a common age-associated disorder characterized by non-malignant proliferation of prostatic stromal and epithelial cells, particularly within the transition zone of the prostate. Although ageing and androgenic signalling are established determinants of BPH; however, increasing evidence indicates that its development is influenced by complex interactions among environmental exposures, lifestyle factors, metabolic disturbances, inflammation, oxidative stress, genetic susceptibility, and the prostatic microenvironment. This review examines BPH from an integrated biological and environmental perspective, with emphasis on how external and endogenous factors converge on molecular pathways that regulate prostatic growth and tissue remodelling. The roles of androgen receptor signalling, insulin-like growth factor pathways, chronic inflammation, transforming growth factor- β , apoptosis, oxidative stress, microbial stimuli, obesity, metabolic dysfunction, dietary patterns, endocrine-disrupting chemicals, and genetic/epigenetic susceptibility are considered. The review also explains biomarkers that are clinically relevant, current diagnostic and therapeutic approaches “including pharmacological, surgical, lifestyle-based, and emerging non-invasive interventions” against BPH. Moreover, the potential of biological and plant-derived resources bioactive compounds for sustainable prevention and management strategies are also discussed. Although natural products provide chemically diverse molecules with antioxidant, anti-inflammatory, anti-androgenic, and antiproliferative activities; however, their translation to clinical care requires toxicological evaluation, mechanistic validation, rigorous standardization, and well-designed clinical researches. An environmentally informed understanding of BPH may support prevention strategies that integrate healthier lifestyles, reduction of harmful environmental exposures, sustainable utilization of biological resources, and precision-oriented management. Future research is suggested to prioritize interdisciplinary approaches linking environmental health, molecular biology, nutrition, epidemiology, and sustainable bioresource development.

Keywords: Benign prostatic hyperplasia; Biological resources; Enlarged prostate; Environmental exposure; Tissue remodelling

Introduction

Benign prostatic hyperplasia (BPH) is one of the most prevalent urological disorders that affect ageing men worldwide (Zhou *et al.* 2025; Mathey, 2022; Phua, 2021). BPH represents a major cause of lower urinary tract symptoms (LUTS), healthcare utilization, and reduced

quality of life (Zhou *et al.* 2025; Mathey, 2022). This enlargement in the prostate gland may increase bladder outlet resistance by compressing the urethra, and consequently contributing to LUTS, including urinary frequency, urgency, nocturia, hesitancy, weak urinary stream,

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intermittency, straining during micturition, and incomplete bladder emptying (Kaplan, 2025; Mathey, 2022).

Histologically, BPH is characterized by the non-malignant proliferation of epithelial and stromal cells within the transition zone of the prostate, thereby causing progressive enlargement of the prostate gland (Kaplan, 2025). Nevertheless, not all men with histological BPH develop LUTS or bladder outlet obstruction; thus, highlighting that enlargement of prostates only does not determine disease severity. Although BPH is not a malignant disease, its clinical consequences can substantially impair daily functioning and overall quality of life (Zhou *et al.* 2025), particularly when LUTS become persistent or progressive (Zekraoui *et al.* 2025; Zhou *et al.* 2025).

It is reported that chronic inflammation, apoptosis, oxidative stress, tissue remodelling, immune responses, as well as interactions between metabolic and hormonal pathways are collectively associated with prostate enlargement (Kaltsas *et al.* 2025; Mugisha Emmanuel, 2025; Cao *et al.* 2022; Phua, 2021). Oxidative stress has been illustrated as an important mechanism in BPH pathophysiology because excessive reactive oxygen species may promote inflammatory responses, cellular injury, and pathological remodelling of tissues (Feki *et al.* 2025; Kaltsas *et al.* 2025).

Age-related prostatic tissue remodelling, alterations in androgen-related metabolic regulation, and changes in the immune and inflammatory microenvironment are significantly recognized as crucial characteristics of BPH in ageing men (Bossio *et al.* 2026; Cao *et al.* 2022; Phua, 2021). Instead, disease progression reflects a complex interaction among tissue remodelling, inflammation, metabolic dysfunction, hormonal regulation, neural regulation, genetic susceptibility, bladder physiology, and environmental conditions (Daryabari *et al.* 2025; Cao *et al.* 2022; Phua, 2021). Recent evidences by Aghamir *et al.* (2025) and Daryabari *et al.* (2025) suggest that both heritable factors and environmental exposures may contribute to differences in the development and severity of BPH among ageing men.

Environmental and lifestyle factors are reported to modify biological processes (Wang *et al.* 2022), including obesity, metabolic syndrome, diabetes, physical inactivity, and dietary patterns (Jia *et al.* 2024). Biological activities have been associated with systemic inflammation (Russo *et al.* 2021), metabolic dysregulation, oxidative stress, and altered endocrine signalling Jia *et al.* (2024), Blair *et al.* (2022).

Such modulatory events reported by Russo *et al.* (2021), Jia *et al.* (2024) and Blair *et al.* (2022), and Russo *et al.* (2021), are mechanisms that make men develop risk for BPH or related lower urinary tract dysfunction (Ke *et al.* 2026; Russo *et al.* 2021).

Furthermore, exposure to endocrine-disrupting chemicals (EDCs) poses interference on hormonally regulation in the prostate and consequently influences inflammatory and oxidative-stress pathways (De Santana *et al.* 2026). Studies by De Santana *et al.* (2026) and De Falco and Laforgia (2021) reported that exposure to EDCs can influence prostate biology by altering the pathways linked with inflammation and oxidative stress. However, it is important to note that the extent to which specific EDCs (such as bisphenol A, pesticides, phthalates, and persistent organic pollutants) directly influence the development of BPH and progression remains an area requiring further investigation (De Santana *et al.* 2026; De Falco and Laforgia, 2021).

Considering biological resources as complementary approaches for preventing or managing BPH, medicinal plants and other naturally-safe resources comprise bioactive phytochemicals (including flavonoids, polyphenols, terpenoids, alkaloids, carotenoids, phytosterols, and saponins) that confer antioxidant, anti-inflammatory, anti-androgenic, antifibrotic, and antiproliferative activities against BPH-associated pathways (Mbyemeire *et al.* 2026; Singh *et al.* 2026; Ki *et al.* 2024). In agreement with the premise above, recent reviews by Mbyemeire *et al.* (2026) and Singh *et al.* (2026) have illustrated how interest in phytotherapy and herbal medicines as potential complementary approaches to BPH management is increasingly adopted. Nevertheless, despite promising pre-clinical evidences on medicinal plants, and herbal medicines in phytotherapy, most natural products remain insufficiently validated in clinical settings because of variability in phytochemical composition, bioavailability, extraction methods, dosage, standardization, safety evaluation, and the limited availability of high-quality clinical trials (Mbyemeire *et al.* 2026; Singh *et al.* 2026).

Therefore, it is important to mention that a multifactorial model in which endocrine regulation, genetic susceptibility, metabolic disturbances, chronic inflammation, oxidative stress, environmental exposures, and lifestyle behaviours interact can determine BPH susceptibility and progression (Daryabari *et al.* 2025; Jia *et al.*

al. 2024; Cao *et al.* 2022; Phua, 2021). Such an integrated framework is consistent with emerging approaches that consider genetic, environmental, metabolic, inflammatory, and molecular determinants together in understanding prostate disease (Aghamir *et al.* 2025; Daryabari *et al.* 2025). This perspective may facilitate the identification of improved biomarkers, personalized preventive strategies, sustainable therapeutic interventions, and more effective long-term management approaches for ageing male populations (Donath-Miklos *et al.* 2026; Mohammed, 2026; Zhou *et al.* 2025).

Although the pathophysiology, metabolic and inflammatory determinants, environmental influences, phytotherapy, or clinical management of BPH have been reported. However, these aspects have generally been considered as relatively separate components of the disease. The present review adopts an integrated environment–biology framework in which ageing, metabolic dysfunction, lifestyle, environmental exposures and genetic susceptibility are considered upstream or modifying factors that converge on androgen-related signalling, inflammation, oxidative stress, apoptosis, extracellular-matrix remodelling and other biological processes involved in prostatic enlargement. In addition, rather than presenting biological resources as a broad catalogue of medicinal plants or phytochemicals, this review emphasizes the distinction between resources with direct BPH-related experimental evidence and those supported mainly by indirect biological activities or evidence from other prostate disorders.

A further contribution of this review is its attempt to connect BPH pathobiology with the sustainable development of biological-resource-based interventions. Accordingly, this review will present evidences of natural products not only in terms of their reported antioxidant, anti-inflammatory, anti-androgenic or antiproliferative properties, but also according to the strength of BPH-specific evidence, mechanistic plausibility, standardization, safety, bioavailability and translational potential. These approaches provide a framework for distinguishing established evidence from promising but investigational candidates and highlights research priorities required to move biological resources from preliminary experimental observations toward reproducible and clinically relevant BPH interventions. Hence, this review examines BPH by integrating biological and environmental perspectives, with further discussion on how endogenous and external factors influence molecular pathways involved in tissue remodeling and prostatic growth.

Benign prostatic hyperplasia as an Environment–Biology interface

The prostate is a hormonally responsive organ whose growth and maintenance depend largely on androgen signaling. However, prostate enlargement “a disorder” represents the outcome of interactions among intrinsic biological processes and external environmental influences (Daryabari *et al.* 2025; Phua, 2021). Ageing creates a physiological background in which hormonal regulation, immune function, cellular repair, oxidative balance, and tissue remodelling gradually change (Bossio *et al.* 2026; Cao *et al.* 2022; Phua, 2021). Environmental and lifestyle factors may then modify these processes and influence individual susceptibility to BPH (Daryabari *et al.* 2025; Jia *et al.* 2024; Wang *et al.* 2022).

Ageing and tissue remodeling

Ageing is the strongest and most consistently established risk factor for BPH, although the mechanisms linking chronological ageing to prostatic enlargement are complex and incompletely resolved (Bossio *et al.* 2026; Cao *et al.* 2022; Phua, 2021). Histologically, BPH is characterized by nodular proliferation of epithelial and stromal components, predominantly within the transition and periurethral zones (Phua, 2021). With advancing age, the prostate undergoes progressive changes in cellular composition, stromal architecture, extracellular matrix organization, endocrine signalling, inflammatory activity, and intercellular communication (Cao *et al.* 2022; Ratajczak *et al.* 2022; Phua, 2021). These alterations collectively create a tissue microenvironment that can favour persistent proliferation and remodelling of prostatic tissue (Bossio *et al.* 2026; Cao *et al.* 2022; Phua, 2021).

A fundamental feature of age-associated BPH is the disruption of the balance between cellular proliferation and apoptosis (Phua, 2021). In hyperplastic nodules, particularly within the stromal compartment, increased cellular accumulation may result from enhanced proliferative signalling, altered survival mechanisms, and insufficient compensatory cell death (Mugisha Emmanuel, 2025; Phua, 2021). The development of BPH is increasingly understood as a disorder involving epithelial-stromal interactions and tissue remodelling rather than an isolated abnormality of one cell population (Cao *et al.* 2022; Phua, 2021).

In the ageing prostate, changes in stromal cell phenotype and secretory activity may alter the signals transmitted to adjacent epithelial cells, thereby promoting a pro-proliferative microenvironment (Cao *et al.* 2022; Phua, 2021). Mugisha Emmanuel (2025) suggests that age-related stromal remodelling can alter the extracellular matrix, including changes in matrix organization and mechanical properties, which may influence cell adhesion, mechano-transduction, migration, proliferation, and tissue architecture. These changes may perpetuate a cycle in which stromal activation, extracellular matrix remodelling, inflammation, and cellular proliferation reinforce one another (Kaltsas *et al.* 2025). This is particularly relevant to BPH because progressive stromal remodelling may contribute to prostate enlargement and associated lower urinary tract dysfunction (Kaltsas *et al.* 2025; Phua, 2021).

In addition, ageing is associated with alterations in androgen-related metabolic regulation and changes in the hormonal environment of the prostate (David, 2025; Cao *et al.* 2022). Thus, androgen-related signalling within ageing prostate tissue may interact with inflammatory and metabolic pathways, suggesting that local tissue responses and receptor-mediated signalling are important components of BPH pathophysiology (Cao *et al.* 2022; Phua, 2021). Age-associated changes in the proinflammatory microenvironment may interact with androgen-related metabolic regulation during BPH (Bossio *et al.* 2026; Cao *et al.* 2022). Inflammation and prostatic hyperplasia may therefore form an interconnected relationship in which persistent inflammatory activity and tissue remodelling contribute to cellular and stromal changes associated with disease progression (Ke *et al.* 2026; Kaltsas *et al.* 2025).

Genetic and epigenetic susceptibility

Genetic susceptibility may contribute to inter-individual differences in the development, age of onset, prostate enlargement, and clinical severity of benign prostatic hyperplasia (BPH) (Aghamir *et al.* 2025). Familial clustering of BPH and prostate enlargement suggests that inherited factors contribute to disease susceptibility, although the genetic architecture of BPH is complex and is unlikely to be explained by a single gene (Aghamir *et al.* 2025; Daryabari *et al.* 2025). Variants in genes involved in steroid hormone metabolism, including the SRD5A family, have therefore been investigated as potential modifiers of prostate enlargement and BPH susceptibility (Aghamir *et al.* 2025). However, associations between

individual polymorphisms and BPH have not been entirely consistent across populations, indicating that genetic effects may be modest, population-dependent, and influenced by interactions with age, metabolic status, and environmental exposures (Aghamir *et al.* 2025; Daryabari *et al.* 2025).

In addition to inherited DNA sequence variation, epigenetic regulation provides an important mechanism through which environmental and lifestyle factors may influence BPH susceptibility. Epigenetic processes regulate gene expression without altering the underlying DNA sequence and include DNA methylation, histone modifications, chromatin remodelling, and regulation by non-coding RNAs, including microRNAs and long non-coding RNAs (Aghamir *et al.* 2025). Consequently, genetic differences affecting cytokine signalling, growth-factor activity, extracellular-matrix turnover, or cellular survival may modify the intensity of tissue remodelling following age-related or environmental stimulation (Aghamir *et al.* 2025; Daryabari *et al.* 2025).

On the other hand, environmental endocrine-disrupting chemicals (EDCs) are of particular interest because the prostate is highly responsive to androgenic and oestrogenic signalling (De Santana *et al.* 2026; De Falco and Laforgia, 2021). These environmental effects may also intersect with epigenetic mechanisms involved in prostate biology and disease susceptibility (Aghamir *et al.* 2025). Experimental evidence concerning endocrine-disrupting chemicals indicates that exposure can affect prostate biology, including pathways associated with endocrine signalling, inflammation, and oxidative stress (De Santana *et al.* 2026; De Falco and Laforgia, 2021). Thus, environmental exposures can influence molecular pathways involved in prostate health and disease susceptibility (Corti *et al.* 2022).

Non-coding RNAs may represent another important interface between genetic susceptibility and environmental regulation. Research on molecular regulation in prostate disease indicates that non-coding RNA-mediated mechanisms can participate in cellular communication and disease-related molecular processes (Aghamir *et al.* 2025). Exosome-associated molecular communication has also emerged as an area of investigation in benign urological disorders, providing a potential mechanism through which regulatory molecules may influence neighbouring cells and tissue responses (Donath-Miklos *et al.* 2026; Hrkač *et al.* 2026).

Environmental and lifestyle factors associated with BPH

Obesity, metabolic syndrome, and diabetes

Obesity and metabolic dysfunction are increasingly recognized as important components of the biological and environmental context in which BPH and LUTS develop (Cao *et al.* 2022). Adipose tissue is an active endocrine and immune-metabolic organ rather than merely an energy-storage depot. Excess adiposity, particularly visceral adiposity, may promote insulin resistance, chronic low-grade inflammation, altered sex-steroid metabolism, oxidative stress, and dysregulated adipokine signaling (Wang *et al.* 2022). These changes were reported by Bossio *et al.* (2026) and Cao *et al.* (2022) to influence the prostate directly or indirectly through effects on androgenic signalling, insulin-related metabolic pathways, vascular function, and the inflammatory microenvironment.

Metabolic syndrome (MetS), generally defined by the clustering of central obesity, impaired glucose regulation, hypertension, hypertriglyceridaemia, and reduced high-density lipoprotein cholesterol, has been linked to BPH (Wang *et al.* 2022). The biological plausibility of this association is supported by the convergence of several pathways relevant to prostatic growth. Hyperinsulinaemia may activate insulin-related growth signalling, while obesity-associated changes in sex-steroid metabolism may alter the hormonal environment of the prostate. Therefore, chronic low-grade inflammation and oxidative stress may promote stromal activation, tissue remodelling, and epithelial–stromal interactions involved in prostate enlargement (Kaltsas *et al.* 2025; Cao *et al.* 2022).

Chronic metabolic disturbances associated with diabetes can contribute to oxidative stress, vascular dysfunction, inflammation, and altered tissue homeostasis, while diabetes-related complications may independently affect urinary tract function (Blair *et al.* 2022). Insulin resistance and compensatory metabolic responses may also influence growth-related signalling and the prostate microenvironment (Cao *et al.* 2022; Wang *et al.* 2022). In addition, diabetes-related urological complications can affect lower urinary tract function independently of prostate size. However, the association between diabetes and BPH-related symptoms should not be interpreted solely as a consequence of prostatic enlargement (Blair *et al.* 2022).

Evidence from Mendelian randomization studies has examined causal relationships between obesity, lifestyle factors, and BPH risk, supporting a potential contribution of

metabolic and lifestyle determinants to BPH susceptibility (Jia *et al.* 2024; Wang *et al.* 2022). These findings suggest that metabolic dysfunction may be related to prostate enlargement and aspects of lower urinary tract dysfunction, although the extent and direction of these relationships require further investigation. Dietary and inflammatory factors may also contribute to this relationship, as recent research has examined the association between dietary inflammatory potential and BPH using both patient data and animal models (Ke *et al.* 2026).

Dietary patterns

Diet represents an important modifiable environmental exposure that may influence BPH through metabolic, inflammatory, oxidative, and hormonal pathways (Ke *et al.* 2026; Russo *et al.* 2021). However, dietary patterns rich in energy-dense foods, saturated fats, refined carbohydrates, and highly processed foods may contribute indirectly to BPH by promoting obesity, insulin resistance, dyslipidaemia, systemic inflammation, and oxidative stress. Thus, the evidence should be interpreted in terms of overall dietary patterns and nutrient composition, rather than attributing BPH risk to a single food or nutrient (Wang *et al.* 2022).

Conversely, dietary patterns characterized by greater consumption of fruits, vegetables, legumes, whole grains, and other plant-derived foods may provide fibre, polyphenols, flavonoids, carotenoids, vitamins, and other bioactive compounds with potential antioxidant and anti-inflammatory effects (Ki *et al.* 2024; Russo *et al.* 2021). Fruits, vegetables, medicinal plants, and other biological resources may provide chemically diverse compounds capable of modulating oxidative stress, inflammatory signalling, cellular proliferation, and hormonal pathways (Mbyemeire *et al.* 2026; Singh *et al.* 2026; Ki *et al.* 2024). Evidence from recent phytotherapy research supports continued investigation of plant-derived interventions for BPH, while experimental work with specific bioactive compounds such as lycopene further illustrates the potential of food-derived constituents in modulating prostatic hyperplasia (Yu *et al.* 2026).

From a sustainable-development perspective, dietary strategies emphasizing diverse, locally available, nutrient-dense plant foods may offer potential advantages by simultaneously supporting metabolic health and reducing reliance on highly processed diets (Aja *et al.* 2025; Russo *et al.* 2021). However, the presence of antioxidant activity in a food or extract does not by itself establish

clinical efficacy against BPH. Bioavailability, metabolism, dose, food matrix, preparation method, standardization, and interactions among dietary components must all be considered (Mbyemeire *et al.* 2026; Singh *et al.* 2026). The development of biological-resource-based interventions should therefore incorporate appropriate standardization, safety assessment, sustainable sourcing, and equitable therapeutic development alongside evidence of biological efficacy.

Endocrine-disrupting chemicals

Endocrine-disrupting chemicals (EDCs) are exogenous substances capable of interfering with hormone synthesis, transport, metabolism, receptor activation, or endocrine feedback mechanisms (Corti *et al.* 2022). Examples of environmental chemicals investigated in relation to endocrine and prostate biology include bisphenols, phthalates, pesticides, organochlorine compounds, and other hormonally active contaminants (Corti *et al.* 2022; De Falco and Laforgia, 2021). Their potential relevance to prostate health arises from the central role of androgenic and oestrogenic signalling in prostate development, maintenance, and tissue remodeling (De Falco and Laforgia, 2021).

Some EDCs may also influence oxidative stress and inflammation, while interactions with broader gene-regulatory mechanisms may contribute to persistent changes in prostate biology (De Santana *et al.* 2026; Corti *et al.* 2022; De Falco and Laforgia, 2021). These mechanisms could theoretically modify the response of prostate tissue to ageing and other environmental stressors (Aghamir *et al.* 2025; Daryabari *et al.* 2025). Developmental exposure to EDCs may theoretically produce persistent alterations in endocrine responsiveness or gene regulation that influence later-life susceptibility to prostate disorders (Aghamir *et al.* 2025; Corti *et al.* 2022). Nevertheless, the extent to which these mechanisms specifically contribute to age-associated BPH remains insufficiently established, and the available evidence should therefore be interpreted cautiously.

A further challenge is that exposure levels of humans to EDCs may vary according to occupation, diet, consumer-product use, geographic location, environmental contamination, and socioeconomic conditions. Thus, it is hypothesized that chemicals may interact with age, metabolic status, genetic susceptibility, and exposures to environmental factors to potentially produce varying biological responses in individuals.

Physical inactivity and lifestyle

Physical inactivity is a potentially modifiable behavioural condition with potential to influence BPH and LUTS based on its association with insulin resistance, obesity, inflammation, metabolic syndrome, and cardiovascular risk (Jia *et al.* 2024; Wang *et al.* 2022). Sedentary behaviour may be a potential risk for adverse metabolic environment that indirectly affects prostate biology (Aja *et al.* 2025), whereas regular physical activity may improve body composition, metabolic health, systemic inflammatory status, and vascular function (Jia *et al.* 2024; Wang *et al.* 2022). Studies examining lifestyle factors have reported relationships between physical activity-related behaviours and BPH, although the observational nature of much of the available evidence means that causal relationships remain difficult to establish (Jia *et al.* 2024; Wang *et al.* 2022).

Regular exercise can improve metabolic health by reducing adiposity, thus abrogating insulin resistance and chronic low-grade inflammation (Wang *et al.* 2022). Metabolic dysfunction, obesity, dietary factors, and inflammation are associated with BPH, physical activity may represent an upstream lifestyle factor capable of modifying several pathways simultaneously (Ke *et al.* 2026; Wang *et al.* 2022), thereby eliciting broader metabolic and inflammatory processes relevant to prostate health (Bossio *et al.* 2026; Jia *et al.* 2024).

A sustainable environmental-health approach to BPH should integrate regular physical activity, healthy dietary patterns, weight management, metabolic disease prevention, and reduction of harmful environmental exposures (Aja *et al.* 2025; Zekraoui *et al.* 2025; Zhou *et al.* 2025). Such an approach is consistent with the concept that BPH and LUTS share biological and behavioural risk factors with other chronic non-communicable diseases (Jia *et al.* 2024; Wang *et al.* 2022). Nevertheless, it should be noted that physical activity is a heterogeneous exposure that varies according to intensity, duration, occupational activity, recreational exercise, sedentary time, age, and comorbidity. Also, it is important to note that LUTS may themselves reduce physical activity, creating the possibility of a sustained BPH.

Molecular mechanisms underlying BPH

Androgen receptor signalling

Androgen signalling is a fundamental regulator of prostate development, differentiation, and tissue homeostasis.

Testosterone can be converted locally to the more potent androgen dihydrotestosterone (DHT) by 5 α -reductase. DHT binds the androgen receptor (AR), a ligand-activated transcription factor expressed in prostate epithelial and stromal compartments. Following ligand activation, AR signalling regulates transcriptional programmes involved in cellular differentiation, secretory function, survival, and tissue maintenance (Ahmed, 2025; David, 2025; Phua, 2021).

Prostatic growth is strongly dependent on androgen signalling, while inhibition of androgen-related pathways represents an established component of pharmacological management for appropriately selected patients with BPH (David, 2025; Zekraoui *et al.* 2025; Phua, 2021). Thus, androgens appear to exert a permissive and regulatory role in BPH pathogenesis. However, the relationship between circulating androgen concentrations and BPH is complex, and serum testosterone or DHT levels alone do not adequately explain the development or severity of the disease (David, 2025; Cao *et al.* 2022).

Androgen-responsive stromal cells can generate paracrine mediators that influence epithelial proliferation (David, 2025), while androgen-related pathways interact with growth factors, extracellular-matrix remodelling, inflammatory mediators, and other tissue-regulatory mechanisms (David, 2025; Cao *et al.* 2022; Phua, 2021). Endocrine-active chemicals may impact steroid hormone-related processes, receptor signalling, and downstream molecular responses. Moreover, disruption of hormone-sensitive pathways provides a biologically plausible mechanism (De Santana *et al.* 2026) through which environmental exposures could modify prostate susceptibility (Daryabari *et al.* 2025; De Falco and Laforgia, 2021).

Insulin-like growth factor signalling

The insulin-like growth factor (IGF) system is an important regulator of cellular proliferation, differentiation, survival, and tissue growth. The system includes IGF-1, IGF-2, their receptors, and IGF-binding proteins, which collectively regulate the availability and biological activity of IGF ligands. IGF signalling can activate intracellular pathways involved in cell survival, proliferation, and tissue remodelling (Zhang *et al.* 2025; Phua, 2021). The IGF axis provides a plausible mechanistic link between metabolic dysfunction and prostate enlargement. Obesity, insulin resistance, and hyperinsulinaemia may alter insulin and IGF-related signalling and may interact with androgen-dependent pathways (Cao *et al.* 2022; Wang *et al.* 2022).

In the prostate, local IGF-related signalling has been implicated in the regulation of stromal and epithelial growth,

and IGF-related mechanisms have been proposed as components of the molecular processes underlying BPH (Zhang *et al.* 2025; Phua, 2021). Therefore, IGF signalling should be regarded as one component of a broader metabolic–endocrine network rather than as an isolated driver of BPH. Its potential relevance to environmental health lies in the possibility that diet, obesity, metabolic dysfunction, and endocrine-related environmental influences may alter insulin- and growth-factor-associated signalling (Cao *et al.* 2022; Wang *et al.* 2022; De Falco and Laforgia, 2021).

Chronic inflammation

Histological and molecular evidence indicates that inflammatory processes are closely associated with benign prostatic enlargement, with immune and inflammatory activity contributing to changes in the local prostatic microenvironment (Kaltsas *et al.* 2025; Cao *et al.* 2022; Phua, 2021). These inflammatory responses may involve immune-cell populations and the release of cytokines, chemokines, reactive oxygen species, and other mediators capable of altering tissue homeostasis and promoting pathological remodelling (Kaltsas *et al.* 2025; Cao *et al.* 2022).

Inflammatory signalling may promote BPH through several interconnected mechanisms. Cytokine- and chemokine-mediated responses can influence stromal and epithelial cell activity, tissue remodelling, and extracellular-matrix dynamics, while inflammatory and oxidative pathways may interact with mechanisms governing cellular survival and proliferation (Kaltsas *et al.* 2025; Phua, 2021). In particular, inflammatory signalling has been proposed as an important component of the pro-inflammatory microenvironment associated with ageing-related BPH, where immune responses may interact with androgen-related metabolic regulation and contribute to persistent tissue remodelling (Bossio *et al.* 2026; Cao *et al.* 2022).

Importantly, inflammation in BPH may arise from infectious stimuli, tissue injury, metabolic dysfunction, immune dysregulation, and other local or systemic inflammatory triggers (Cao *et al.* 2022). The relationship between inflammation and BPH is therefore potentially bidirectional: inflammatory or tissue-remodelling stimuli may initiate or sustain inflammatory responses, while persistent inflammation may further promote stromal activation and pathological tissue remodelling (Ke *et al.* 2026; Cao *et al.* 2022; Phua, 2021). The potential contribution of metabolic and dietary inflammatory influences further supports the view that BPH-associated

inflammation may reflect interactions between local prostate biology and systemic environmental or metabolic conditions (Ke *et al.* 2026).

Inflammatory activity has been linked to processes involved in prostate enlargement and disease progression, while oxidative stress and inflammation may operate as interconnected mechanisms in BPH pathophysiology (Kaltsas *et al.* 2025). Experimental evidence by Feki *et al.* (2025) supports prostate remodelling by illustrating that modulation of oxidative stress and inflammation can influence testosterone-associated prostatic hyperplasia. Similarly, androgen-related metabolic regulation and the pro-inflammatory microenvironment can influence one another during ageing-associated BPH, suggesting that endocrine and immune pathways act in concert rather than independently (Bossio *et al.* 2026; Cao *et al.* 2022). Notably, this interaction may help explain the multifactorial nature of BPH and why targeting a single biological pathway may not completely prevent disease progression.

Oxidative stress

Oxidative stress refers to a disturbance in the balance between the generation of reactive oxygen and nitrogen species and the capacity of endogenous antioxidant systems to neutralize or repair the resulting damage (Feki *et al.* 2025). Excessive reactive species can oxidize lipids, proteins, and nucleic acids and can alter cellular signalling, mitochondrial function, and tissue integrity (Kaltsas *et al.* 2025). In the prostate, oxidative stress may contribute to BPH through several mechanisms. Reactive species can activate redox-sensitive inflammatory pathways, promote cellular injury, influence fibroblast and stromal-cell activity, and modify extracellular-matrix remodelling. Lipid peroxidation and other oxidative processes may also amplify inflammatory responses and tissue injury (Feki *et al.* 2025; Kaltsas *et al.* 2025).

Inflammatory activity can increase reactive-species generation, while oxidative stress can further promote inflammatory signalling and tissue injury. This creates a biological feedback loop in which persistent oxidative and inflammatory stress may sustain tissue remodelling (Bossio *et al.* 2026; Kaltsas *et al.* 2025; Cao *et al.* 2022). However, it is proposed that the interpretation of oxidative-stress biomarkers requires caution because measurements may vary according to tissue type, assay methodology, disease stage, diet, metabolic status, and other environmental factors. Therefore, increased malondialdehyde (MDA) level or altered antioxidant enzyme activity should be interpreted as evidence of redox

imbalance rather than definitive proof that oxidative stress independently causes BPH.

The environmental-health relevance of BPH is substantial because oxidative stress may represent a common biological pathway through which environmental pollutants, tobacco smoke, metabolic dysfunction, poor diet, inflammation, and other exposures affect prostate tissue. Experimental evidences by De Santana *et al.* (2026) and Ke *et al.* (2026) indicate that endocrine-disrupting chemicals can influence inflammation and oxidative stress in the prostate, while metabolic and dietary factors may also modify inflammatory and redox-related pathways relevant to BPH. Thus, antioxidant and redox-regulatory systems are potential mechanistic targets for future preventive and therapeutic research against BPH.

Apoptosis and cell survival

Apoptosis (programmed cell death) is essential for maintaining appropriate tissue size and cellular composition because disruption of such system may contribute to the accumulation of epithelial and stromal cells characteristic of BPH (Mugisha Emmanuel, 2025; Phua, 2021). In the hyperplastic prostate, increased tissue mass may reflect enhanced cellular proliferation, altered cell survival and insufficient removal of damaged or excess cells. Signalling pathways that regulate cellular survival and apoptosis may therefore influence prostatic tissue expansion (Mugisha Emmanuel, 2025; Phua, 2021). Cellular stress-response pathways, including those involving heat shock proteins, may also contribute to the regulation of cell survival and tissue homeostasis in BPH (Ratajczak *et al.* 2022). Inflammatory and oxidative pathways may also influence the balance between cell injury, apoptosis, and adaptive cellular responses (Feki *et al.* 2025; Kaltsas *et al.* 2025; Cao *et al.* 2022). Thus, BPH should not be interpreted as a disorder caused solely by increased proliferation. Similarly, apoptosis should be considered in the context of the broader molecular network regulating BPH rather than as an isolated cellular process. Moreover, a complete model should involve dysregulated tissue homeostasis, in which proliferation, survival, apoptosis, inflammation, and tissue remodelling interact over time.

Transforming growth factor- β

Transforming growth factor- β (TGF- β) is a major regulator of tissue homeostasis, cellular differentiation, immune responses, apoptosis, and extracellular-matrix remodeling (Mugisha Emmanuel, 2025). In the prostate, TGF- β

signalling is particularly relevant to stromal biology and tissue remodelling. TGF- β can regulate fibroblast activity and extracellular-matrix production and deposition, including collagen-associated remodeling (Phua, 2021). Persistent or dysregulated TGF- β signalling may therefore contribute to stromal expansion and fibrotic tissue changes, processes that may influence the structural characteristics of BPH (Ke *et al.* 2026; Phua, 2021). However, because TGF- β can exert context-dependent effects, its role should not be described simply as uniformly “pro-proliferative.” Its effects may vary according to cell type, signalling context, disease stage, and the surrounding tissue microenvironment (Ke *et al.* 2026; Phua, 2021). Consequently, TGF- β may represent a potential convergence point through which multiple endogenous and environmental stressors contribute to persistent tissue remodelling (Ke *et al.* 2026; Daryabari *et al.* 2025; Kaltsas *et al.* 2025).

Microbial and infectious influences

Microbial and infectious influences represent an emerging area of BPH research. Historically, the relationship between microorganisms and BPH was often considered primarily in terms of recurrent or persistent bacterial infection. Persistent microbial stimuli may activate innate and adaptive immune responses, leading to inflammatory signalling that can influence prostatic tissue remodelling. However, the presence of microorganisms or microbial DNA does not necessarily demonstrate that a specific pathogen is the direct cause of BPH (Kim and Jung, 2021). Evidences from Cao *et al.* (2022), Kim and Jung (2021) support a stringent model involving immune activation, microbial exposure, dysbiosis, and chronic inflammatory signalling.

The prostate and urinary tract may also be influenced by microbial communities and host–microbe interactions that are not adequately captured by conventional culture-based methods (Kim and Jung, 2021). Recent reviews have highlighted possible relationships between the gut microbiome, urinary microbiome, immune regulation, oxidative stress, and BPH (Kaltsas *et al.* 2025; Kim and Jung, 2021). Dysbiosis may influence systemic inflammatory processes and host metabolic or immune responses, while changes in the urinary microbiome may influence local inflammatory processes (Kim and Jung, 2021). However, microbial influences should currently be regarded as an emerging biological and environmental-health pathway rather than a proven universal cause of BPH.

Clinical Manifestations, Disease Progression, and Complications

BPH-related LUTS may result from a combination of bladder outlet obstruction, increased smooth-muscle tone, structural enlargement of the prostate, and secondary changes in bladder function. Accordingly, prostate enlargement, bladder outlet obstruction, and LUTS should be regarded as related but distinct clinical entities (Kaplan, 2025; Mathey, 2022; Phua, 2021). Storage symptoms include increased daytime urinary frequency, urinary urgency, and nocturia, whereas voiding symptoms include hesitancy, weak or slow urinary stream, intermittency, and straining. Post-micturition symptoms include a sensation of incomplete bladder emptying and post-micturition dribbling.

The International Prostate Symptom Score (IPSS) is widely used to quantify symptom severity and includes both storage and voiding domains together with a quality-of-life assessment. The clinical expression of BPH is influenced by the interaction between prostate enlargement, bladder outlet resistance, detrusor function, age-related changes in bladder physiology, and coexisting conditions (Mohammed, 2026).

Consequently, a relatively large prostate may be associated with modest symptoms in one individual, whereas another patient with a smaller prostate may experience substantial LUTS. This distinction is important because symptom severity cannot be reliably inferred from prostate volume alone (David, 2025; Mathey, 2022; Phua, 2021).

Persistent or severe obstruction of the urethra may contribute to acute or chronic urinary retention, recurrent urinary tract infection, bladder calculi, haematuria, and progressive changes in bladder function (Mathey, 2022). Chronic obstruction may also be associated with upper urinary tract deterioration in severe or complicated cases (Kaplan, 2025). However, it is reported that these complications are not inevitable consequences of BPH and should be interpreted in relation to the severity and duration of obstruction and the presence of other urological conditions (David, 2025; Kaplan, 2025).

LUTS may substantially affect quality of life because nocturia can disrupt sleep, while urgency, frequency, weak urinary flow, and incomplete emptying may interfere with work, travel, social activities, and daily functioning (Kaplan, 2025). The psychological and social burden of LUTS may therefore extend beyond the urinary tract.

Importantly, symptom burden and quality-of-life impairment may be disproportionate to objective measures of prostate enlargement, reinforcing the importance of patient-reported outcomes in clinical evaluation (Mathey, 2022; Kaplan, 2025).

The clinical expression of BPH may also be influenced by systemic metabolic status, obesity, diabetes, physical inactivity, inflammation, and other chronic exposures (Bossio *et al.* 2026; Blair *et al.* 2022). These factors may modify bladder function, prostate biology, and the patient's perception or tolerance of urinary symptoms (Jia *et al.* 2024; Wang *et al.* 2022). Consequently, the clinical phenotype of BPH may reflect the interaction between structural prostate changes and broader biological processes associated with ageing and environmental determinants of health (Bossio *et al.* 2026; Ke *et al.* 2026).

Biomarkers and diagnostic approaches

The evaluation of men with suspected BPH or male LUTS should begin with a structured clinical assessment rather than with a single diagnostic test. The initial evaluation generally includes a detailed medical history, assessment of symptom severity using a validated questionnaire, physical examination including digital rectal examination (DRE), urinalysis, and measurement of post-void residual (PVR) urine.

The IPSS is a validated symptom assessment tool used to quantify the severity of urinary symptoms and evaluate their effect on quality of life (Mohammed, 2026). Although the score is clinically useful, it does not identify the underlying cause of LUTS and should therefore be interpreted together with clinical history and objective evaluation. DRE may provide information regarding prostate size, consistency, and the presence of abnormalities requiring further evaluation (Mohammed, 2026; Borikappakul, 2025). However, DRE is reported to be less perfect for measuring prostate volume and should not be wholly considered when accurate volumetric assessment/imaging is clinically necessary (Mathey, 2022).

Urinalysis is also a vital component of the initial evaluation of prostate status because urinary infection, haematuria, and other abnormalities may contribute to urinary symptoms or even suggest alternative diagnoses (Kim and Jung, 2021). PVR measurement provides information about bladder emptying but should be interpreted cautiously because an elevated residual volume may reflect bladder outlet obstruction, impaired detrusor contractility, or other causes of incomplete emptying (Mathey, 2022; Kim and Jung, 2021).

Uroflowmetry provides a non-invasive assessment of urinary flow by measuring maximum urinary flow rate (Qmax), voided volume, flow pattern, and PVR. The parameters determined by uroflowmetry may provide useful information regarding voiding dysfunction (Song *et al.* 2025a). However, a decrease in urinary flow is not specifically linked for bladder outlet obstruction because it may also result from impaired detrusor contractility or inadequate bladder filling.

Serum prostate-specific antigen (PSA) may provide clinically useful information in men with LUTS, but it is not specific for BPH (Mohammed, 2026; Borikappakul, 2025). PSA concentrations may also be influenced by prostate cancer, prostatitis, infection, prostate manipulation, and other factors. In the context of BPH evaluation, PSA may assist in estimating prostate volume and predicting the risk of disease progression or urinary retention (Borikappakul, 2025). However, PSA testing should be undertaken when the result is expected to influence clinical decision-making, particularly where prostate cancer assessment is relevant.

Ultrasonography may be used to assess prostate volume, bladder morphology, bladder-wall changes, upper urinary tract abnormalities, and PVR. Trans-abdominal ultrasound is commonly used for non-invasive assessment, whereas transrectal ultrasound may provide more detailed evaluation of prostate anatomy when clinically indicated (Mohammed, 2026). Cystoscopy is not required routinely for all men with LUTS but may be considered when there is suspected urethral stricture, bladder pathology, haematuria, or another specific clinical indication (Borikappakul, 2025).

Emerging biomarkers and precision diagnostic approaches

Conventional clinical assessment remains the foundation of BPH diagnosis, but substantial research is focused on identifying molecular biomarkers that could improve disease phenotyping and patient stratification (Donath-Miklos *et al.* 2026). Candidate biomarkers have been investigated in blood, urine, prostatic secretions, tissue, and extracellular vesicles. These include inflammatory mediators, growth factors, microRNAs, long non-coding RNAs, metabolites, proteins, and other molecular signatures (Donath-Miklos *et al.* 2026; Mohammed, 2026; Borikappakul, 2025).

MicroRNAs have been recently investigated because they potentially regulate post-transcriptional gene expression and influence pathways involved in cellular proliferation, apoptosis, inflammation, androgen signalling, and

extracellular-matrix remodeling (Song *et al.* 2025b). Current guideline literature recognizes microRNA-based approaches as an emerging area of BPH research, although these biomarkers have not yet replaced conventional clinical evaluation in routine practice (Donath-Miklos *et al.* 2026; Mohammed, 2026).

Metabolomics and proteomics may provide complementary information regarding the biological phenotype of BPH (Aghamir *et al.* 2025). Metabolomic approaches can identify changes in metabolic pathways associated with oxidative stress, inflammation, energy metabolism, and endocrine regulation, whereas proteomic approaches may identify disease-associated proteins involved in growth-factor signalling, tissue remodelling, and immune responses (Borikappakul, 2025). Transcriptomic and epigenomic approaches may similarly reveal molecular signatures associated with disease heterogeneity (Mohammed, 2026).

However, many proposed biomarkers have been evaluated in small cohorts, with heterogeneous populations, variable assay platforms, and limited external validation. A biomarker should therefore not be considered clinically useful solely because it is statistically associated with BPH (Donath-Miklos *et al.* 2026). Clinical translation requires independent validation, reproducibility, demonstration of incremental value beyond established clinical variables, and evidence that biomarker-guided decision-making improves patient outcomes (Mohammed, 2026).

Current management strategies for benign prostatic hyperplasia

Management of BPH-associated LUTS should be individualized according to symptom severity, degree of bother, prostate characteristics, risk of disease progression, bladder function, comorbidities, treatment-related risks, patient preference, and local availability of therapeutic options (Zhou *et al.* 2025). Importantly, the presence of LUTS does not necessarily require immediate pharmacological or surgical intervention. Management may range from conservative monitoring to pharmacotherapy, minimally invasive procedures, or surgery depending on the clinical context (Zekraoui *et al.* 2025). Therefore, management approaches is advised to follow a risk- and symptom-oriented approach rather than a one-size-fits-all model (Zhou *et al.* 2025). Patients with mild or minimally bothersome symptoms may be managed conservatively, whereas those with persistent bothersome symptoms, progressive disease, recurrent complications, or treatment

failure may require pharmacological or procedural intervention (Zekraoui *et al.* 2025). The European Association of Urology (EAU) guidelines recognize pharmacological treatment and surgical intervention as complementary components of LUTS/BPO management, with treatment selection guided by clinical characteristics and patient preference (Zekraoui *et al.* 2025; Zhou *et al.* 2025).

Lifestyle and behavioural modification

Lifestyle and behavioural interventions may be appropriate as initial or adjunctive strategies, particularly in men with mild or moderately bothersome LUTS (Jia *et al.* 2024). Measures may include moderation of excessive fluid intake, particularly before bedtime or situations in which urinary frequency is inconvenient; reduction of individual bladder irritants where relevant; optimization of voiding habits; management of constipation; maintenance of physical activity; and optimization of metabolic health (Aja *et al.* 2025; Zhou *et al.* 2025).

These interventions may reduce symptom burden and improve general health, but evidence that they independently prevent prostate enlargement or halt the biological progression of BPH remains limited (Zekraoui *et al.* 2025). Their value is therefore best understood as part of a broader strategy for improving urinary symptoms, reducing modifiable contributors to LUTS, and managing comorbid conditions (Aja *et al.* 2025; Zekraoui *et al.* 2025).

Physical activity and metabolic-health interventions may be particularly relevant because obesity, insulin resistance, diabetes, and systemic inflammation have been associated with BPH and LUTS (Bossio *et al.* 2026). Improvement of metabolic health may therefore influence several biological pathways implicated in disease, including insulin/IGF signalling, inflammatory activity, oxidative stress, and endocrine dysregulation (Ke *et al.* 2026). Nevertheless, the effects of lifestyle modification on BPH-specific outcomes should not be overstated (Jia *et al.* 2024; Blair *et al.* 2022; Wang *et al.* 2022).

Conservative management may offer an important low-resource approach to symptom management (Wang *et al.* 2022). Preventive measures that improve physical activity, metabolic health, diet, and general well-being may potentially produce benefits across several non-communicable diseases while avoiding unnecessary medical interventions (Zhou *et al.* 2025). However, this should not be interpreted to mean that lifestyle modification can replace evidence-based treatment in patients with severe

symptoms or complications (Aja *et al.* 2025; Jia *et al.* 2024; Wang *et al.* 2022).

Pharmacological treatment

Pharmacological treatment is selected according to symptom profile, prostate characteristics, disease progression risk, comorbidities, and potential adverse effects (Zekraoui *et al.* 2025; Zhou *et al.* 2025).

α_1 -Adrenergic receptor antagonists

α_1 -Adrenergic receptor antagonists reduce smooth-muscle tone in the prostate and bladder neck by inhibiting α_1 -adrenergic signalling. This can reduce the dynamic component of bladder outlet resistance and improve urinary symptoms and flow (Gborgsong *et al.* 2025). These agents generally act relatively rapidly and may be useful in men with bothersome moderate-to-severe LUTS. However, α_1 -blockers do not substantially reduce prostate volume and should not be considered disease-modifying therapies for long-term prostate enlargement (Zekraoui *et al.* 2025). Thus, treatment-related adverse effects from α_1 -Adrenergic receptor antagonists may include dizziness, orthostatic hypotension, fatigue, and ejaculatory disturbances, with the risk profile varying between agents (Zekraoui *et al.* 2025; Zhou *et al.* 2025).

5 α -Reductase inhibitors

5 α -Reductase inhibitors reduce the conversion of testosterone to DHT and thereby reduce androgenic stimulation of prostatic tissue (David, 2025). They are particularly relevant in men with demonstrable prostate enlargement or an increased risk of disease progression. Unlike α_1 -blockers, the therapeutic effects of 5 α -Reductase inhibitors develop more gradually but may include reduction in prostate volume and reduction in the risk of acute urinary retention and the need for BPH-related surgery in appropriate patients (Zekraoui *et al.* 2025; Zhou *et al.* 2025). However, the use of 5 α -Reductase inhibitors may be associated with sexual adverse effects and changes in serum PSA interpretation, which must be considered during clinical monitoring (David, 2025; Zhou *et al.* 2025).

Phosphodiesterase-5 inhibitors

Phosphodiesterase-5 (PDE-5) inhibitors may improve LUTS through effects on smooth-muscle tone, cyclic guanosine monophosphate signalling, pelvic vascular function, and potentially bladder and prostate tissue signalling. Their use may be particularly relevant in men with coexisting erectile dysfunction

(Zekraoui *et al.* 2025; Zhou *et al.* 2025). The improvement in LUTS with PDE-5 inhibition does not necessarily result from a reduction in prostate volume. Therefore, these agents represent a different therapeutic strategy from 5 α -reductase inhibitors and may be selected according to the patient's symptom profile and comorbidities (Zekraoui *et al.* 2025; Zhou *et al.* 2025).

Surgical and minimally invasive treatment

Procedural treatment is an important component of BPH management for patients with persistent bothersome symptoms despite conservative or pharmacological treatment, those who prefer procedural intervention, or those who develop complications attributable to bladder outlet obstruction (Zekraoui *et al.* 2025; Zhou *et al.* 2025). Surgical approaches include resection, enucleation, vaporization, simple prostatectomy in selected cases, and other procedures adapted to prostate size and anatomy (Zekraoui *et al.* 2025; Song *et al.* 2025a).

Trans-urethral resection of the prostate has historically served as a reference procedure, while newer approaches have expanded the range of available surgical techniques. Current EAU guidance organizes surgical management according to approaches including resection and enucleation, reflecting the increasing diversity of treatment options (Zhou *et al.* 2025). Minimally invasive surgical therapies may offer advantages in selected patients by reducing invasiveness, shortening recovery time, or preserving particular aspects of sexual or urinary function. However, their effectiveness, durability, eligibility criteria, and resource requirements vary substantially between technologies (Zekraoui *et al.* 2025; Zhou *et al.* 2025).

From a sustainability perspective, minimally invasive procedures should not automatically be regarded as environmentally superior to conventional surgery. A meaningful sustainability assessment would require consideration of the entire treatment pathway, including disposable equipment, energy use, operating-room requirements, hospital stay, repeat-procedure rates, and long-term treatment effectiveness. Thus, the environmental sustainability of BPH treatment remains an important area for health-system research.

Biological resources with evidence relevant to BPH

Growing interest in biological resources for benign prostatic hyperplasia (BPH) has been driven by the multifactorial nature of the disorder, which involves androgen signaling (Zekraoui *et al.* 2025), chronic inflammation (Kaltsas *et al.* 2025),

oxidative stress (Jia *et al.* 2024), altered cellular proliferation and apoptosis (Phua, 2021). Consequently, natural products containing polyphenols, flavonoids, terpenoids, carotenoids, phytosterols and other bioactive constituents have been investigated as potential modulators of pathways involved in BPH development and progression (Mbyemeire *et al.* 2026; Singh *et al.* 2026; Kaltsas *et al.* 2025). However, the evidence is heterogeneous, and biological activity observed in chemical assays or non-BPH experimental models should not be interpreted as direct evidence of therapeutic efficacy against BPH (Mbyemeire *et al.* 2026; Gborsong *et al.* 2025).

Natural resources with direct evidence against BPH

Among recently investigated medicinal plants, *Thymelaea hirsuta* provides direct experimental evidence relevant to BPH. Feki *et al.* (2025) investigated an extract of *Thymelaea hirsuta* in testosterone-induced BPH in rats and evaluated oxidative stress, inflammation and apoptosis. The study is particularly relevant because it used an established experimental model of prostatic hyperplasia and examined biological processes directly implicated in BPH pathophysiology. The findings support further investigation of *Thymelaea hirsuta* as a potential source of bioactive constituents targeting the interconnected oxidative, inflammatory and apoptotic pathways involved in prostatic remodelling (Feki *et al.* 2025). However, the evidence remains preclinical and should not be extrapolated directly to clinical efficacy in men with BPH (Feki *et al.* 2025).

Lycopene represents another food-derived biological resource that has been investigated in relation to prostatic hyperplasia (Mbyemeire *et al.* 2026; Yu *et al.* 2026). Mbyemeire *et al.* (2026) examined lycopene either alone or in combination with other botanical interventions, although the available clinical evidence has been limited and heterogeneous. More recently, Yu *et al.* (2026) investigated lycopene-loaded pickering emulsions stabilized with chitosan/zein, examining their physicochemical characteristics, bioaccessibility and effects on prostatic hyperplasia. The research by Yu *et al.* (2026) moved beyond simply demonstrating the presence of a bioactive compound and addresses formulation and bioaccessibility, which are major determinants of the translational potential of food-derived compounds. Nevertheless, the formulation-based evidence remains experimental and requires independent validation before clinical application can be established.

In addition, *Serenoa repens* (saw palmetto) has been among the most extensively investigated botanical interventions for BPH-related urinary symptoms (Schwartzmann *et al.* 2026; Tacklind *et al.* 2024; Jung *et al.* 2021) reported potential improvements in symptom severity with some *Serenoa repens* preparations, particularly hexanic lipidosterolic extracts and β -sitosterol-enriched preparations, while emphasizing substantial heterogeneity in formulations, dosing and study design. Thus, *Serenoa repens* illustrates both the potential and the limitations of phytotherapy for BPH indicating that substantial clinical investigation exists, but therapeutic conclusions depend strongly on the specific preparation and study design (Schwartzmann *et al.* 2026).

Other traditionally used phytotherapeutic resources include *Pygeum africanum*, *Urtica dioica*, *Cucurbita pepo* and *Secale cereal* which have been investigated for BPH-related symptoms and urinary-flow outcomes, but the amount and quality of evidence differ substantially among individual preparations (Mbyemeire *et al.* 2026; Bent *et al.* 2006). Although possible improvements of benign issues were suggested for *Pygeum africanum* and *Secale cereale*, whereas evidence for *Urtica dioica* and *Cucurbita pepo* as isolated interventions against BPH was more limited (Bent *et al.* 2006). Mbyemeire *et al.* (2026) emphasized considerable heterogeneity in study design, preparation, dosage and outcome assessment of the traditionally used phytotherapeutic resources on prostate enlargement. These findings on natural resources with direct evidence against BPH indicate that traditional use and repeated investigation provide a rationale for further research but do not establish equivalent efficacy among different botanical preparations.

Emerging BPH-specific experimental evidence

Qianlong Shutong Formula (QLSTF), a traditional Chinese medicine preparation, has recently been investigated using an integrated network-pharmacology and experimental approach. Zhang *et al.* (2025) identified multiple candidate bioactive constituents and potential targets and subsequently used in vitro and in vivo experiments to investigate its effects in BPH. The study associated QLSTF activity with inhibition of cellular proliferation and modulation of the PI3K/AKT signalling pathway, providing a mechanistic basis for its further investigation as a BPH-related intervention (Zhang *et al.* 2025). Nevertheless, network-pharmacology predictions and molecular docking should be interpreted as

hypothesis-generating approaches and require experimental and clinical confirmation (Zhang *et al.* 2025).

Croton membranaceus is another biologically derived intervention of particular relevance to BPH research. Gborsong *et al.* (2025) investigated the safety of combining *Croton membranaceus* with tamsulosin in a self-prescribed treatment context for BPH. The study by Gborsong *et al.* (2025) highlights an issue that is sometimes overlooked in discussions of herbal medicine, which is the need to evaluate safety and potential interactions when biological resources are used alongside conventional pharmacological treatment (Gborsong *et al.* 2025). However, safety evidence should not be interpreted as evidence of independent therapeutic efficacy; consequently, controlled studies evaluating standardized *Croton membranaceus* preparations and clinically relevant BPH outcomes remain necessary (Gborsong *et al.* 2025).

Evaluated herbal medicines using outcomes including prostate index, prostate-specific antigen, dihydrotestosterone and testosterone, highlighting the expanding preclinical literature while also emphasizing that the efficacy of herbal medicine for BPH remains incompletely established. This evidence supports continued experimental investigation but also reinforces the importance of distinguishing animal evidence from clinically demonstrated benefit.

Natural compounds and mechanisms relevant to BPH

The biological plausibility of natural products in BPH arises from their potential to influence several interconnected pathological processes rather than a single molecular target (Singh *et al.* 2026; Kaltsas *et al.* 2025). Oxidative stress and chronic inflammation are closely associated with BPH pathophysiology, and experimental evidence indicates that modulation of these pathways can influence testosterone-associated prostatic hyperplasia (Feki *et al.* 2025; Kaltsas *et al.* 2025). Consequently, compounds with antioxidant and anti-inflammatory properties have been investigated as potential modulators of BPH-associated tissue remodelling (Kaltsas *et al.* 2025; Singh *et al.* 2026).

Androgen-related signalling represents another important therapeutic pathway because testosterone and its conversion to dihydrotestosterone influence prostate growth and tissue homeostasis (Phua, 2021; Izumi *et al.* 2013). Natural compounds capable of influencing androgen metabolism, androgen-receptor-associated signalling or downstream

proliferative pathways may therefore have potential relevance to BPH, although mechanistic plausibility alone does not demonstrate clinical efficacy (Mbyemeire *et al.* 2026; Singh *et al.* 2026).

From promising biological resource to clinically relevant BPH intervention

The major challenge in translating biological resources into BPH therapeutics is the gap between biological activity and clinically meaningful outcomes. A plant extract may demonstrate antioxidant activity, inhibit inflammatory mediators or reduce cellular proliferation in vitro while failing to produce equivalent effects in vivo because of poor absorption, rapid metabolism, inadequate target-tissue exposure or toxicity (Mbyemeire *et al.* 2026; Singh *et al.* 2026). Similarly, substantial variation in species authentication, geographical origin, cultivation conditions, extraction procedures, phytochemical composition and dosage can make findings obtained with one preparation difficult to reproduce with another (Mbyemeire *et al.* 2026; Zhang *et al.* 2025).

Standardization is therefore essential for the development of credible BPH-related phytotherapeutic interventions. Future investigations should provide appropriate botanical authentication, chemical characterization, standardized extraction procedures, identification or quantification of relevant marker compounds, batch-to-batch reproducibility, dose-response relationships, toxicological evaluation and pharmacokinetic information (Mbyemeire *et al.* 2026; Singh *et al.* 2026). Where combination preparations are investigated, their individual constituents and potential synergistic or antagonistic interactions should also be considered (Zhang *et al.* 2025).

Importantly, evidence should be interpreted according to its proximity to clinically relevant BPH outcomes. Human randomized clinical studies provide stronger translational evidence than animal BPH models, while validated animal models provide stronger disease-specific evidence than general antioxidant assays or experiments conducted in unrelated disease models. Evidence from prostate cancer studies or general inflammatory models may provide mechanistic rationale but should not be presented as direct evidence that a natural product treats BPH (Mbyemeire *et al.* 2026). Similarly, improvement in antioxidant biomarkers alone cannot establish an effect on prostate enlargement, urinary symptoms, prostate volume or bladder outlet obstruction.

Sustainable development of BPH-related biological resources

The environmental dimension remains relevant to the development of biological-resource-based interventions, particularly where medicinal plants are obtained from biodiversity-rich environments. Sustainable cultivation, appropriate harvesting practices, species conservation, traceability and responsible processing can reduce pressure on biological resources while supporting their continued investigation (Mbyemeire *et al.* 2026; Aja *et al.* 2025). Agricultural and food-processing by-products may also represent potential sources of bioactive compounds, provided that their composition, safety, efficacy and environmental implications are independently demonstrated rather than inferred from the edible or primary plant material (Mbyemeire *et al.* 2026; Yu *et al.* 2026).

Therefore, sustainability should be considered an important component of biological-resource development, but it should remain secondary to demonstrated biological efficacy and safety. A sustainable source of a natural product does not necessarily constitute an effective BPH treatment. The future development of BPH-related biological resources should consequently integrate BPH-specific efficacy, mechanistic validation, chemical standardization, toxicological safety, pharmacokinetics, clinical evaluation and environmental sustainability within the same translational framework (Mbyemeire *et al.* 2026; Singh *et al.* 2026).

Future directions

The precise association between risk factors (environmental exposures, endocrine disruption, inflammation, oxidative stress, metabolic disease) and BPH require further investigation by adopting relevant research methodologies. Also, the molecular mechanisms linking environmental factors with androgen receptor signalling and prostatic tissue remodelling are suggested to be further investigated. Similarly, research on natural biological resources should move beyond preliminary antioxidant assays as future studies should include chemical standardization, mechanistic experiments, toxicological assessment, pharmacokinetic studies, and controlled clinical trials.

Conclusion

The traditional view of prostate enlargement/Benign Prostatic Hyperplasia (BPH) as an exclusively age- and hormone-dependent disorder is incomplete. Thus, BPH is a multifactorial disorder that develops through

multi-complex interactions among ageing, inflammation, oxidative stress, hormonal regulation, metabolic dysfunction, genetic susceptibility, environmental exposures, and lifestyle factors. An integrated environment–biology perspective provides a broader framework for understanding prostate enlargement/BPH. Environmental and lifestyle factors may influence biological pathways that regulate prostatic growth, inflammation, oxidative balance, and tissue remodelling. However, biological resources offer promising opportunities for the development of sustainable preventive and therapeutic strategies. Thus, it is proposed that future interdisciplinary research on BPH should link environmental health, molecular biology, nutrition, medicine, and sustainable bioresource development. Thus, there is call for action regarding more effective prevention, improved BPH management, and responsible utilization of natural resources for prostate health.

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