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REVIEW PAPER

Advancements in prevention and treatment of benign prostatic hyperplasia with particular emphasis on fireweed (*Epilobium angustifolium* L.) and nettle (*Urtica dioica* L.). A review

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Summary

Prostate enlargement, medically termed as benign prostatic hyperplasia (BPH), is a prevalent and frequently troublesome issue affecting older men. Research suggests that over 50% of males in their 60s may encounter symptoms associated with BPH. While BPH doesn't pose an immediate threat to life, its implications on urinary function can substantially diminish a man's quality of life. The aetiology of BPH involves complex hormonal and inflammatory mechanisms, leading to prostatic enlargement and obstructive symptoms. Traditional management strategies such as α-blockers and 5-α reductase inhibitors offer symptomatic relief but may cause adverse effects. In recent years, natural compounds have gained attention for their potential efficacy and safety in the management of prostate enlargement. This article reviews recent advancements in prevention and treatment of BPH, with a particular emphasis on the utilisation of herbal remedies, namely fireweed (*Epilobium angustifolium* L.) and nettle *(Urtica dioica* L.*)*. These plants are a rich source of polyphenols, known for their anti-inflammatory properties. Moreover, they seem to positively influence hormonal balance. These two functions appear to be responsible for alleviating LUTS symptoms. The research was conducted using PubMed, Scopus, and Google Scholar databases to gather relevant studies and findings.

Key words: ***BPH, BPO, LUTS, Epilobium angustifolium* L., *Urtica dioica* L.**

Słowa kluczowe: ***łagodny przerost prostaty, objawy z dolnych dróg moczowych, wierzbówka kiprzyca, pokrzywa zwyczajna***

INTRODUCTION

Benign Prostatic Hyperplasia (BPH) is a hot topic in the field of urology and men's health in general. This condition involves the enlargement of the prostate, which surrounds the urethra. Consequently, symptoms such as lower urinary tract symptoms (LUTS) emerge, including incomplete emptying of the bladder, a weak stream, and increased frequency of urination. BPH not only affects physical health but also impacts quality of life. Manifestations of BPH, such as disrupted sleep due to nocturia and the psychological repercussions of managing persistent symptoms are essential for patient care [1–3].

The primary treatment of this condition involves α-blockers and 5-α reductase inhibitors, which are highly effective [4, 5]. However, in some cases, they may lead to various adverse reactions, such as orthostatic hypotension (particularly in older individuals), tachycardia, fatigue, sexual side effects, breast tenderness and enlargement – especially with 5-α reductase inhibitors [6–8].

Research on plant-based treatments of BPH is motivated by the potential efficacy of natural compounds and the desire to reduce numerous adverse effects associated with standard pharmacotherapy [9]. The aim of this work is to review the progress of scientific research from the past 6 years (From January 2019) regarding the use of *Epilobium angustifolium* L. and *Urtica dioica* L. in alleviating symptoms of BPH, and LUTS in general. To achieve this, Pubmed, Scopus, and Google Scholar databases were used to gather relevant studies and findings.

Epilobium angustifolium

Epilobium angustifolium L., synonym *Chamerion*/L./ Holub, also known by names such as perennial fireweed, great willowherb, or French willow, is a medicinal plant belonging to the genus *Epilobium* in the *Onagraceae* family [10]. Fireweed is found in lowlands and mountainous areas of North America and Europe. It is consumed in the form of tea in these regions [11, 12]. Increasing research indicates its potential positive impact on the treatment of dermatological, rheumatology and urological diseases, including BPH [12–16].

Polyphenols, particularly flavonoids, phenolic acids, and hydrolysable tannins (ellagitannins), are highly prevalent in *Epilobium angustifolium* [17]. Approximately 50 distinct flavonoids and their derivatives have been detected in fireweed extracts. Quercetin-3-O-glucuronide emerges as the predominant and defining flavonoid in *E. angustifolium*, in contrast to myricetin-3-O-rhamnoside (myricitrin), which serves as the primary flavonoid in other *Epilobium* species [18]. Among the phenolic acids found in fireweed, a variety of substances have been identified, including caffeic acid, ellagic acid, ferulic acid, gallic acid, protocatechuic acid, and various isomers of caffeoylquinic acid [19, 20]. In *E. angustifolium*, there is a notable concentration of ellagitannins, constituting approximately 15% of the herb's dry weight [21]. The most abundant ellagitannin found in willowherb is oenothein B, constituting up to 50% of the overall mass of oligomeric ellagitannins present in the extract. The concentration of oenothein B in the raw material fluctuates between 2% and 4.5%, depending on the source plant and the timing of harvest [22]. The products of ellagitannins metabolism in gastrointestinal tract are urolithins (dibenzopyran-6-one derivatives). These compounds possess antiproliferative, anti-inflammatory, and anticancer properties [23]. The precise mechanism of oenothein B transformation into urolithins has not been fully understood yet. Previous suggestions implicated gut microbiota in these processes; however, it was not confirmed in studies [24].

Research has shown that testosterone significantly increases both prostate volume and PSA levels [25]. Studies from the 20th century have demonstrated that oenothein B is efficient against 5α-reductase and aromatase, enzymes acting in the development of BPH. Hence, any substance capable of inhibiting the enzyme 5α-reductase (responsible for metabolizing testosterone into dihydrotestosterone) or aromatase (converting testosterone into 17β-estradiol) are promising in the management of BPH [26]. However, in recent years, another research has emerged that high testosterone levels elevate the risk of BPH [27]. Bo-Wen Xia *et al.* demonstrated that testosterone level was inversely correlated with prostate volume ($P = 0.004$), and both prostate volume and changes in prostate volume in the period longer than four years lowered testosterone levels [28].

Oenothein B, thanks to its wide spectrum of antiproliferative, antioxidant, anti-inflammatory, and anti-androgenic actions, is considered a key component of *Epilobium angustifolium,* responsible for its anti-BPH effects [17].

It's widely acknowledged that polyphenols possess potent anti-inflammatory and antioxidant properties through intricate mechanisms [29]. Polyphenols play a significant role in modulating the NF-κB-related pathway, serving as potent anti-inflammatory agents by inhibiting the synthesis

of cytokines and chemokines associated with inflammation [30]. Additionally, polyphenols exhibit the ability to interact with reactive oxygen species (ROS) and reactive nitrogen species (RNS), effectively halting the cascade of oxidative damage within cells before substantial harm occurs [31]. Numerous researchers have proposed that inflammation is a pivotal factor in the development of prostate ailments, such as benign prostatic hyperplasia and prostate cancer [32, 33].

In addition to polyphenols, the higher portions of *E. angustifolium* possess a lipid-soluble fraction abundant in steroids, terpenoids, and fatty acids, which positively influence hormonal balance (antiandrogenic effect) [13, 17, 24]. As mentioned above, hormonal imbalance contributes significantly to the pathogenesis of BPH [34].

Clinical trial

So far (as of January 2024), only one clinical study has been published confirming the positive impact of *Epilobium* on reducing symptoms of BPH. The study involved 128 men. The treated group took a dietary supplement containing EAE (*Epilobium angustifolium* extract) at a dose of 500 mg, for 6 months. Esposito *et al*., in their randomised double-blinded controlled trial, demonstrated a significant improvement in the quality of life of patients, measured using the International Prostate Specific Score (IPSS) scale. The significant decrease of IPSS (by nearly 2 points) was associated with a reduction in post-void residual (PVR) and, consequently, nocturia. Furthermore, during the study, no adverse effects related to oral intake of the EAE food supplement were noted [35].

Preclinical trials

Evidence of significant therapeutic potential of fireweed in combating BPH is provided by the work of Deng *et al*., where the therapeutic effects of ethyl acetate extracts (EAE) and *n*-butanol extracts (BUE) from *Chamerion angustifolium (Epilobium angustifolium)* were investigated. *In vitro,* both extracts demonstrated anti-BPH activity by influencing the inhibition of proliferation in BHP-1 cells (cell viability 37.21±9.51% and 56.91±8.08%, respectively) and suppressing prostate-specific antigen (PSA) in androgen-sensitive human prostate adenocarcinoma cells (LNCap cells). The relative level of PSA secretion decreased to 36.12±3.65% (P<0.01). Further *in vivo* studies on rats confirmed the therapeutic effect of BUE. It was demonstrated that the administration of BUE *in vivo* led to a decrease in androgen levels, inhibited the expression of nuclear factor kappa B (NF-κB), and alleviated inflammatory responses and oxidative stress [36]. Last year's research on the anti-proliferative effect of ethanolic extract of *E. angustifolium* (EAE) provides interesting data against selected cell lines of 5 chosen types of cancer. Bacterial cellulose (BC) membranes were employed in the study as matrices. The research revealed that the HT-29 cell line (colorectal cancer cells) exhibited the highest sensitivity to the tested plant extract. The study did not encompass cell lines of prostate cancer [16]. Subsequent research should broaden its scope to include prostate cancer, given the evidenced heightened risk of colorectal cancer in patients with prostate cancer, as indicated by a large clinical study [37]. Although it is not entirely clear whether BPH increases the risk of prostate cancer, the symptoms of these two conditions are very similar, and in both the treatment is aimed at reducing lower urinary tract symptoms (LUTS) [38, 39]. In addition to ethanolic extracts, the freeze-dried infusion of *E. angustifolium* is also a valuable source of polyphenols. In the study by Szwajgier *et al.* 2021, it was demonstrated that this infusion is particularly rich in gallic acid (407.02 ± 7.10 mg GAE/g of raw material) [40]. Other studies confirm the inhibitory effect of gallic acid (GAE) on the development of prostate cancer by inhibiting the expression of histone deacetylase 1 and 2 (HDAC1 and 2). They also suggest a potential cytotoxic effect by blocking the growth of DU145 cells at G2/M phases through the activation of Chk1 and Chk2 (checkpoint kinase 1 and 2) and the inhibition of Cdc25C (cell division cycle 25C) and Cdc2 (cyclin-dependent kinase 2) activities [41, 42].

In vitro studies from the beginning of 2024 confirm the antioxidant effect of *Epilobium angustifolium*. Yukset *et al*. examined 14 different parts from 6 plants, including *Epilobium,* in their research. Analyses revealed that among these plants, fireweed, especially its floral part, exhibited the highest antioxidative capacity [43].

Interestingly, other studies from the last months have confirmed the thermal stability of the antioxidant properties of Rosebay Willowherb (*Chamerion angustifolium*) dried at 60°C and 150°C. Fireweed extract is suggested to enhance the ARA (antiradical activity) between 1.6 and 4.9 times in low-ARA foods, such as bread or other extensively processed foods. Additionally, incorporating polyphenolic plant components from these extracts into diet is recommended as a preventive measure against free-radical pathologies such as BPH [44].

Urtica dioica L.

Stinging Nettle (*Urtica dioica* L.), also known as Ortiga and common nettle, belongs to the *Urticaceae* family. Nettle is an herbaceous perennial plant that grows in Eurasia, North Africa, and North America, particularly in humid soils and grasslands. It is a popular multi-purpose species rich in valuable active compounds that have the potential to alleviate many disorders. The use of phytoallergic plants such as nettle has increased recently due to their exceptional chemical composition and favourable association with human health [45–47].

Urtica dioica exhibits a diverse chemical profile, influenced by its variety, genotype, climate, soil conditions, vegetative stage, and time of harvest, all of which contributing to variations in its nutritional content. The leaves of this plant are rich in flavonoids – compounds with anti-inflammatory and antioxidant properties, as mentioned above. The predominant phenolic compounds found in nettles include rutin, quercetin, 5-O-caffeoylquinic acid, and isoquercetin. The quantity of phenolic compounds present in nettle leaves may range between 150 and 1941 mg GAE g−1 (DM). They are also a source of minerals (mainly calcium, magnesium, iron, and silicon), salicylic acid, and tannins [48–52]. In addition to culinary use, the leaves of this plant are used in numerous inflammatory conditions, including rheumatologic and urologic diseases. They help treat conditions related not only to inflammatory components but also to hormonal imbalance, especially in endocrinology, aiding in alleviating symptoms of polycystic ovarian syndrome (PCOS) and often accompanying acne vulgaris [53–56].

Moreover, nettle root extract is recommended primarily for patients with BPH to alleviate symptoms of this disease. The roots of nettle also contain a significant abundance of phenolic compounds. The concentration of phenolic compounds in nettle roots ranges widely, from 20 to 1020 mg GAE g−1 (DM). However, the primary active constituents of lipid fractions in nettle root are phytosterols. The average total sterol content ranges from 0.80 to 0.86 g kg^{-1} dry weight. Among these, a group of phytosterols crucial for LUTS/BPH therapy are the widespread Δ5-phytosterols, with β-sitosterol as their main representative [48, 57]. Triterpenes represent an additional category of bioactive compounds present in nettle root. This group encompasses a diverse array of molecules and serves as secondary plant metabolites. Pentacyclic triterpenes exhibit varied pharmacological effects, including anti-inflammatory, antioxidant, hypoglycaemic, anticancer, and antibacterial properties [57, 58]. Stinging nettle is a source of lectins and polysaccharides, including glucans, arabinogalactan acid, and glucogalacturonans. Research has demonstrated their ability to inhibit cellular metabolism and growth in the prostate gland [52]. Furthermore, *Urtica* possesses the ability to inhibit the conversion of testosterone to dihydrotestosterone (DHT), interact with sex hormone-binding globulin (SHBG), and impede the conversion of androgens into oestrogens. Likely attributed to the presence of β-sitosterol, this effect entails the inhibition of 5α-reductase [59]. Clinical investigations comparing β-sitosterol to a placebo revealed enhancements in maximum urine flow rate, yet did not induce a reduction in prostate size [60]. Research suggests that the lignans found in stinging nettle display a notable attraction to SHBG. Additionally, the extract demonstrates effectiveness in curbing the proliferation of prostate cell receptors [55].

Clinical trials

The association between elevated serum PSA levels and increased risk of BPH and prostate cancer has been well established [61, 62]. Elevated levels of this marker along with deviations in physical examination are indications for prostate biopsy [63]. However, it turns out that a significant portion of biopsies are unnecessary and expose patients to complications [64]. Cai *et al.* investigated the effects of two herbal preparations on PSA levels. In the group of patients administered with product composed of *Urtica dioica*, a significant decrease in PSA levels was observed in over 75% of the subjects (p<0.001). This resulted in a reduction in the frequency of prostate biopsies based on changes in PSA values and mpMRI results in the group taking the nettle-based preparation. The conclusions of this study suggest that herbal therapy may play a significant role in reducing the number of unnecessary biopsies. Currently (January 2024), this is the only research examining such a relationship. Due to the short observation period (3-month therapy) and small study group, further research should be conducted [65].

On the other hand, another randomized study from 2022 did not confirm the beneficial effect of nettle on reducing PSA levels. It has been demonstrated that supplementation with nettle root extract at a dose of 600 mg per day for 8 weeks has a significant impact on reducing bothersome

Table 1.

Literature overview investigating the impact of *Epilobium angustifolium* and *Urtica dioica* products in the prevention and treatment of BPH.

Type of product	Used dose	Experimental model	Mechanism of action	Impact on BPH	Reference
Food supplement based on *E. angustifolium* ethyl acetate extract (standardized to contain ≥ 15% oenothein B)	Oral administration of EAE 500mg 1x1 for 6 months	Clinical trial	The anti-inflammatory action is attributed to the presence of oenothein A and B, which undergo conversion by gut fermentation into urolithin	Reduction in International Prostate Symptom Score (IPSS), decreased Post-Void Residual (PVR), and nocturia attenuation.	[35]
E. angustifolium ethyl acetate and *n*-butanol extracts	*In vivo*: oral administration of BUE at 100, 200 and 400 mg/kg for 28 days	Preclinical trial *(In vitro, in vivo)*	*In vivo:* Anti-androgenic and anti-proliferative effects by reducing DHT levels and 5AR activity, while also suppressing NF-κB expression, easing inflammation and oxidative stress.	Reducing PSA secretion	[36]
Prostaflog® (Dietary supplement with plant extracts of turmeric, Boswellia, nettle, pine and with soy lecithin)	Oral administration: 2 tablets (containing 240 mg of *Urtica dioica* extract) per day for 3 months	Clinical trial	The anti-inflammatory effect is achieved by influencing the IL-8 level.	Reducing PSA secretion	[65]
Urtica dioica root extract	Oral administration: 300 mg of nettle root extract, twice a day for 8 weeks.	Clinical trial	Anti-proliferative action. Nettle root extract, containing lignans, blocks SHBG, inhibits aromatase, and hinders prostate cell growth.	Decreased frequency of urination, urinary urgency, and nocturia. PSA level unaffected.	[66]
Urtica dioica root extract	Oral administration: 450 mg of nettle root extract, per day for 12 weeks	Clinical trial	Anti-inflammatory action measured by MDA and SOD.	Reduction in International Prostate Symptom Score (IPSS). PSA level unaffected.	[67]
Combined preparation of *Serenoa repens* and *Urtica dioica* extracts (SR/UD) (aqueous ethanolic extract from roots of *U. dioica)*	–	Preclinical trial *(in vitro)*	SR/UD decreases ROS, inhibits NF-κB translocation, and suppresses IL-6 and IL-8 production.	Antioxidant and the anti-inflammatory effects of SR/UD in an *in vitro* human model of BPH.	[72]

symptoms associated with LUTS including nocturia and urinary frequency. However, it was not observed that supplementation with nettle alone, without standard pharmacological therapy, reduces PSA levels in the subjects. Furthermore, no improvement in the quality of life was observed in the study group [66].

Similar conclusions were drawn from the study by Mirhashemi *et al.*, where no significant decrease in PSA was also observed in the study group. However, these studies demonstrated that 12 weeks of supplementation with *Urtica dioica* root extract (UDE) reduced inflammatory response measured by hs-CRP (p-value 0.013) and oxidative stress measured by malondialdehyde (MDA) level (p-value <0.001) and superoxide dismutase (SOD) activity (p-value <0.001) [67]. MDA and SOD are commonly used markers of oxidative stress in BPH research [68–70].

Preclinical trials

In recent years, there have not been many new *in vivo* and *in vitro* studies investigating the impact of stinging nettle on the treatment and prevention of BPH. As mentioned above, chronic inflammation plays a pivotal role in the development of BPH, with numerous studies confirming the significant involvement of pro-inflammatory cytokines and chemokines in the process [71]. Saponaro *et al.* investigated the antioxidant potential of combined preparation of *Serenoa repens* and *Urtica dioica* (SR/UD) in a human *in vitro* model of BPH. The findings validated the antioxidant and anti-inflammatory properties of SR/UD. Specifically, SR/UD was shown to significantly decrease the generation of reactive oxygen species (ROS), inhibit the translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) into the nucleus, and subsequently suppress the production of interleukin 6 (IL-6) and interleukin 8 (IL-8) concurrently by 50% [72].

CONCLUSIONS

In conclusion, based on current research, both fireweed and nettle exhibit promising therapeutic potential in the management of BPH. These botanicals, rich in bioactive compounds like ellagitannins, flavonoids, and sterols, demonstrate anti-inflammatory, antioxidant, and anti-proliferative properties, which could alleviate BPH symptoms. Clinical trials support the efficacy of these herbs in improving quality of life and reducing urinary symptoms associated with BPH. However, despite the encouraging findings, it's important to note that the current body of clinical evidence remains limited, with only a few studies conducted thus far. Before considering their inclusion in urology guidelines, it is necessary to conduct more clinical trials to assess the effectiveness and safety of standardised preparations based on fireweed and nettle**.** Additionally, ongoing preclinical research underscores the potential of these herbs in targeting key pathways involved in BPH pathogenesis, providing further avenues for exploration and development of novel therapeutic interventions [62].

Ethical approval: The research conducted is not related to either human or animal use.

Conflict of interest: Authors declare no conflict of interest.

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