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Natural products for the treatment of urinary incontinence

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ABSTRACT

This review summarises the material covered during a workshop entitled "Natural Products as Treatments for Urinary Incontinence" that was presented at the online ICS (Melbourne) annual conference held in 2021. The clinical and scientific evidence of the effectiveness of naturally sourced treatments such as traditional Chinese medicines, phytoestrogens and saw palmetto for lower urinary tract symptoms are discussed, and also the use of cranberry and D-mannose for the treatment of bacterial infections of the urinary tract. The workshop and this review finish with a look towards the future and a discussion of potential treatments to repair the barrier function of the urothelium, an action that may be useful in conditions such as interstitial cystitis/bladder pain syndrome.

1. Introduction

The workshop was comprised of four presentations covering different aspects of natural products and this review gives a representation of each talk. The use of cranberry and D-mannose to protect against bacterial urinary infection is examined followed by a consideration of the use of traditional Chinese medicines, phytoestrogens and saw palmetto in combatting lower urinary tract symptoms and finally a look at possible ways to protect the bladder by enhancing urothelial barrier function.

[A] Natural products to fight bladder infections

Urinary tract infections (UTIs) are amongst the most common bacterial infections in the world, comprising nearly 25% of all infections, and affecting more than 150 million people annually worldwide [1]. Although UTI are experienced by both men and women, women are more likely to develop UTIs, with half of all women expected to be impacted by a UTI by the time they are aged 30 [2], and one in three women experiencing symptomatic UTI requiring treated with antibiotics by age 24. Unfortunately, 30% of women experiencing a UTI will develop a recurrence of infection within six months regardless of antibiotic treatment and just over 10% will have a third episode within a 12 month period [3]. Recurrent-UTIs typically occur within three months of the first infection, even with complete symptomatic resolution by using first-line antimicrobial therapy (antibiotics). Although acute, uncomplicated UTIs are rarely life threatening, recurrent UTIs will have negative effects on patients' overall quality of life.

Alongside respiratory tract infections, UTIs are the most common reason for antibiotics use in a primary care setting. First line therapy for uncomplicated UTIs include nitrofurantoin or trimethoprim-sulfamethoxazole (TMP-SMX). Globally, antibiotic resistance has significantly increased towards these first-line therapies and the World Health Organisation has declared that resistance to antibiotics is one of the top 10 global public health threats facing humanity. Antibiotic resistance is believed to be driven by long-term and uncontrolled use of antibiotics. The increased risk of antibiotic resistance in UTI patients may last for up to 12 months after the antibiotic prescription has been dispensed [4]. Therefore, one approach that health services in some countries are taking to curb the development of resistant strains has been to tighten antimicrobial stewardship within medical practices limiting availability of antibiotics to patients [5], including those patients with UTIs.

While antibiotics are effective in treating acute UTIs, recently our understanding of the importance of the interactions between the host and the resident bacteria (microbiome) has led to an appreciation of the detrimental effect that antibiotics have on homeostasis within the body. Antibiotic use can lead to negative effects on health via effects on nutrients, metabolism, pathogen resistance and other processes. Antibiotic use can lead to imbalances in gut microbiome which has been associated with the development of disorders such as obesity, allergy, autoimmune diseases, along with various infectious diseases [6].

The increasing antimicrobial stewardship together with our increased understanding of the importance of the host-microbiome relationship has led patients and clinicians to examine new natural

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therapies as treatments of UTI. The non-antibiotic treatments of UTI that are received the most attention are cranberry products and D-mannose. Laboratory studies have indicated that these agents are likely to work by preventing the adhesion of bacteria to the lining of the urinary tract.

To understand the importance of this we need to consider the pathogenesis of UTI and understand the mechanism by which uropathogens, bacteria that cause UTI, gain a foothold in the urinary tract. This has been extensively studied for the gram-negative bacteria *Escherichia coli* (*E. coli*), which is the common causative agent of UTIs, accounting for nearly 80% of all UTIs. Animal models of UTI have revealed that the first step in a UTI is binding of *E. coli* to the urothelium, the cells lining the bladder. This adhesion is followed by invasion and the formation of intracellular bacterial communities, which have been identified in urothelial cells isolated in samples from women and children with UTIs [7]. It is hypothesised that recurrent UTI's occur due to the bacteria contained within the intracellular colony leaving the cell to reinfect the bladder again, and up to 80% of recurrent infections are observed to be caused by the same strain as the initial infection. While the focus of much research in this area has been on E. coli, recent evidence has demonstrated that other bacteria associated with UTIs are also able to invade the host urothelial cells [8].

Cranberry products contain a number of active ingredients, but laboratory based research has suggested that proanthocyanidins (PAC) and fructose are the main active ingredients that prevent bacterial adhesion to the urinary tract [9]. Similarly, D-mannose has been shown to block bacterial adhesion to urothelial cells [10] likely due to its similar structure to the usual bacterial binding site on the urothelium. Hence, laboratory studies have suggested that a high concentration of D-mannose will prevent bacteria binding to the urinary tract [11].

Early studies with cranberry such as that by Takahashi et al. [12] suggested beneficial effects for this natural product and a number of trials followed. Recently a number of reviews have evaluated the effectiveness of cranberry [13,14] and D-mannose [15–17] in preventing or treating UTIs. A recent systematic review of non-antibiotic treatments of UTI [18] concluded that the clinical trial evidence for the efficacy of cranberry in the prevention of UTI was inconclusive, with only 50% of the trials included in the analysis being successful [18]. Although the review reported greater success in clinical trials of D-mannose preventing UTIs, there were only a small number of D-mannose trials identified leading to a conclusions that there was only low level evidence to the effectiveness of D-mannose [18]. Unfortunately, clinical trials of natural remedies such as cranberry and D-mannose were limited by small sample sizes (therefore studies were underpowered), and by poor or inconsistent trial design (eg were unblinded trials, used different definitions of a UTI and differing formulations of cranberry or D-mannose). These factors have led to a lack of real evidence for the effectiveness of these agents in clinical setting.

[B] Phytoestrogens and Saw Palmetto

This section briefly explores oestrogen, phytoestrogens and saw palmetto in managing urinary incontinence and lower urinary tract symptoms associated with menopause (genitourinary symptom of menopause) and bladder outlet obstruction (BOO) associated with benign prostatic hyperplasia (BPH), respectively.

Oestrogen

Dyspareunia and vaginal dryness, recurrent urinary tract infection, and lower urinary tract symptoms are common among postmenopausal women; symptoms that are believed to arise from the declining level of oestrogen and other sex steroids accompanying menopause [1,19,20]. Different forms of estrogen therapy have been studied as a therapeutic option for these symptoms with variable success.

Studies have demonstrated that local estrogen treatment may improve urinary symptoms, while systemic estrogen may worsen them. For example, a 2012 Cochrane review [21] revealed that local estrogen treatment reduced the frequency and urgency of urination. Another pilot study reported that hormonal treatment with estrogen and progesterone, as well as tissue-selective estrogen complex treatment, significantly reduced the prevalence and bother of nocturia, in women with ≥ 2 nocturnal voids [22].

More recently, the use of vaginal prasterone, a precursor to estrogen and androgens, has been studied as a potential treatment for postmenopausal women with genitourinary syndrome of menopause and overactive bladder syndrome. Intravaginal administration of 6.5 mg prasterone was found to be effective in reducing symptoms in these women [23].

In conclusion, estrogen therapy, particularly local estrogen treatment, may be a useful option for postmenopausal women with urinary symptoms. However, the optimal type and dose of estrogen therapy require further research.

Phytoestrogens

Phytoestrogens are plant-derived compounds that are similar in structure to natural estrogen and mimic the actions of estrogen by interacting with estrogen receptors in the body. Phytoestrogens (isoflavones, coumestans, lignans) can be found in different natural sources such as soy, legumes, linseed, grains and vegetables. Phytoestrogens are being explored as natural alternatives to hormone replacement therapy for treating menopausal symptoms like hot flushes and night sweats, as well as for improving bone and cardiovascular health and genitourinary symptoms [24].

Several studies have proposed that phytoestrogens may have a beneficial effect on incontinence symptoms. For example, in one study lignan phytoestrogens were suggested to have a protective effect against self-reported incontinence in postmenopausal women [25]. The authors suggested that prospective clinical and laboratory studies are warranted to investigate the mechanism of this relationship. In a recent systematic review which included a variety of phytoestrogens, in different forms, urogenital disorders improved and women's sexual function also reportedly improved after treatment. The authors concluded that phytoestrogens are a safe, low-risk, accessible treatment compared to hormone therapy and can improve the quality of life for women [26].

In a longitudinal study, where the authors evaluated the relationship between dietary phytoestrogens in mid-life women and the development of urinary incontinence, less evidence was found regarding improvement in symptoms associated with urinary incontinence. The authors concluded that neither high nor low dietary intakes of isoflavones, coumestrol and lignans prevent stress or urge incontinence [27].

While it is tempting to assume that phytoestrogens simply provide estrogen replacement in menopause, their mechanism of action is likely to be more complex since they act as selective estrogen modulators [26] acting as agonists, partial agonists or antagonists in different tissues. Nevertheless, phytoestrogens have been studied for their potential benefits in treating menopausal symptoms and improving genitourinary health. Although evidence regarding the effect of phytoestrogens on incontinence symptoms is mixed, similar to oestrogen, they may have a protective effect against incontinence. However, further research is needed to determine the optimal doses and sources of phytoestrogens for treating incontinence symptoms.

Saw Palmetto

Saw palmetto (Serenoa repens) was first used medicinally by native American Indians to treat urological disorders. Saw palmetto extracts are widely used to treat the urinary symptoms as a result of bladder outlet obstruction associated with benign prostatic hyperplasia (BPH) [28]. The demonstrated mechanisms of action include (i) inhibition of the enzyme 5α-reductase that results in a block of the conversion of testosterone to the more potent dihydrotestosterone (ii) anti-androgen properties (iii) anti-inflammatory effects and (iv) smooth muscle relaxation [28]. One study demonstrated that a fatty acid component of saw palmetto extract causes inhibition of prostatic smooth muscle contractions via a non-specific mechanism [29].

The European Association of Urology recommends a specific saw palmetto extract (hexanic extract) for lower urinary tract symptoms (LUTS) associated with BPH. A study reported that the hexanic extract improved symptoms and quality of life similar to tamsulosin but with fewer adverse effects [30]. In contrast, another study suggested saw palmetto does not result in a clinical benefit for men with lower urinary tract symptoms, but may be effective in combination with other phytotherapy [31]. In support of this notion, a randomised controlled trial (SPRITE) showed saw palmetto plus lycopene and selenium was more effective than PDE5 inhibitors alone for bladder outlet obstruction [32]. However, a Cochrane review reported that *Serenoa repens* provided no improvement in urinary flow measures or prostate size in men with lower urinary tract symptoms associated with BPH [33].

In summary, while saw palmetto has not consistently shown efficacy for BPH, saw palmetto and other natural products may be effective when used appropriately in combination therapy or in specific subgroups. However, variations in product extracts, administration, and population differences make it difficult to draw conclusive comparisons. Therefore, caution and medical consultation are advised for those considering natural products as treatment options.

[C] Chinese Herbal Formulations for Overactive Bladder

Chinese herbal formulations have traditionally been used for centuries to treat urinary disorders and recently have gained increasing attention as a potential alternative or complementary therapy for overactive bladder (OAB) [34]. Traditional Chinese Medicine (TCM) is a holistic healthcare system that originated in China thousands of years ago. It is based on the concept of Qi (pronounced "chee"), which is believed to be the vital energy that flows through the body and is responsible for maintaining health and well-being. TCM utilises various modalities, including herbal medicine, acupuncture, dietary therapy, massage, and movement exercises, to balance and harmonise the flow of Qi in the body [35]. While single-herb medicine is used, TCM more commonly combines single herbs with other herbs to design customised herbal formulations for each patient that create a synergistic effect and allow for a more tailored and comprehensive approach to treatment [36]. The focus of this section is to review the current evidence for the use of Chinese herbal formulations in OAB management.

Ba-Wei-Di-Huang-Wan (BWDHW)

Ba-Wei-Di-Huang-Wan (BWDHW) is a traditional Chinese herbal formula composed of eight herbs and has been used for centuries to regulate various bodily functions, including the kidneys and bladder. BWDHW is commonly used to treat traditional conditions related to "Kidney Yin" deficiency, which can manifest as urinary symptoms common in OAB, such as frequency, urgency, and nocturia. Despite this traditional use, a randomised, double-blind, placebo-controlled trial of 186 women with OAB found that an 8-week BWDHW intervention did not significantly improve overall OAB symptoms [4]. However, the study did report specific reductions in urinary frequency and urgency indicating BWDHW actions were more than simply placebo effects [37]. Gosha-jinki-gan (GJG) is a variation of BWDHW, composed of ten herbs, mainly used to manage lower urinary tract symptoms, diabetic neuropathy, and nocturia. GJG has been found to significantly reduce urinary frequency, improve quality of life, and have a low incidence of adverse effects in females with overactive bladder [38,39]. GJG in combination with α1-adrenoceptor blockers or antimuscarinic drugs has also been shown to improve LUTS and cold sensitivity in patients that were unresponsive to α1-blockers or antimuscarinic drugs, but it did not change maximal urinary flow rate or post-void residual urine [40]. A study comparing furosemide and GJG for treating nocturnal polyuria found both treatments improved the nocturia score, but furosemide was more effective in reducing nocturnal frequency and urine volume [41]. A trial investigated the efficacy of two other formulas, Bu-Zhong-Yi-Qi-Tang and Sang-Piao-Xiao-San, in treating patients with overactive bladder found significant improvement in the frequency of voiding, urgency, and urge incontinence, with few side effects (dry mouth) [42]. While some of these clinical trials show promising results for TCM herbal formulas in treating overactive bladder and related symptoms, it is essential to note that the efficacy of these treatments can vary and may not be reliable. Out of all the trials discussed above, the only one that was explicitly reported as a randomised, double-blind, and placebo-controlled trial is the one investigating BWDHW treatment which showed no significant improvement to overall OAB symptoms. It is also difficult to generalise the findings to other populations, as most of these studies have, as expected, been performed in Asian countries that practise TCM more commonly.

Laboratory studies of mechanisms of action

Several lab-based studies using rats have shown that these herbal formulations or extracts from them could improve OAB symptoms by increasing the sensitivity and expression of β_3-adrenoceptors, attenuation of TRPV1 expression, inhibiting signalling via Ca^{2+} and the rho kinase pathway (calcium sensitisation), enhancement of nitric oxide, and promotion of potassium channel expression [43]. For instance, THC-002, an extract of BWDHW, was shown to inhibit the expression of tachykinins, P2X3 and TRPV1 receptors and reduce ATP-induced detrusor overactivity in spontaneously hypertensive rats [44]. BWDHW treatment in the same species ameliorates cyclophosphamide-induced persistent detrusor overactivity by suppressing the overexpression of $P2X_2$, $P2X_3$, M_2 and M_3 receptors in the mucosa and M_2 and M_3 receptors in the detrusor [45]. Furthermore, loganin, a component of BWDHW, improves substance-P-induced bladder hyperactivity in rats via attenuation of neurokinin-1 receptor signalling, NF-κB/iCAM-1 expression and leukocyte infiltration [46].

Difficulties in testing traditional medicines

It is important to note that herbal formulations are complex mixtures containing numerous bioactive compounds. The chemical makeup can vary depending on various factors, such as the species of plant used, the method of extraction and the storage conditions. This poses challenges in ensuring consistency in research studies to identify their mechanisms of action. Even if the same formulation is used in different studies, there can be variation in the quality and potency of the herbal ingredients, as well as in the manufacturing and preparation processes. These factors can have a significant impact on the observed effects of the herbal formulation, which in turn can make it difficult to draw reliable conclusions about mechanisms of actions from laboratory-based studies.

Despite some promising findings, more rigorous studies are needed to establish the safety and efficacy of Chinese herbal formulations in managing OAB. In addition, the lack of standardisation in herbal products and the potential for herb-drug interactions should be considered when prescribing these formulations [47]. Chinese herbal formulations have shown potential as an alternative or complementary therapy for the management of OAB, but further research is needed to establish their safety and efficacy, and healthcare professionals should exercise caution when recommending these formulations. Nonetheless, the growing interest in TCM and natural therapies for OAB highlights the need for more comprehensive and personalised approaches to managing this condition.

[D] Mimicking the bladder's natural barrier

In this section the focus turns to emerging natural therapies, currently experimental, that may be alternative surface-active intravesical treatments for conditions such as interstitial cystitis/bladder pain syndrome (IC/BPS), recurrent UTIs and radiation cystitis.

The urothelium is an effective barrier to urine and its contents, whilst also playing a very active signalling role in concert with the underlying afferent sensory nerves, myofibroblasts and muscle in the bladder wall, to help us sense bladder filling and pain ([48], Fig. 1). The barrier is achieved via tight junctions between the urothelial cells, the uroplakin proteins on the apical umbrella cells and other adherence proteins. The glycosaminoglycan (GAG) layer on the surface also has an important role to play in this barrier function [48]. Composed of linear

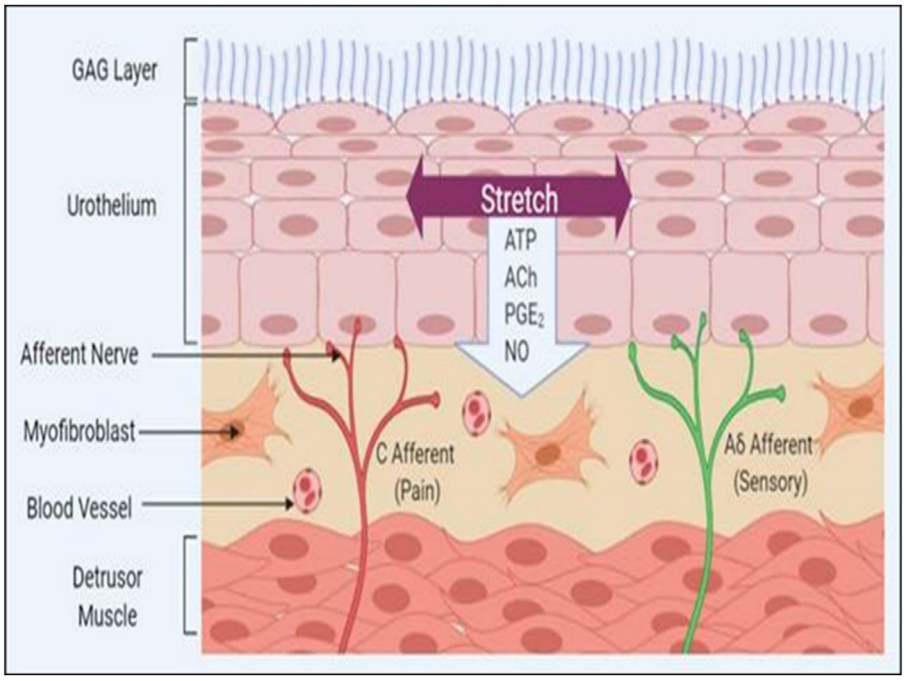

Fig. 1. Restoring the function of the urothelium. The apical surface has an outer layer of glycosaminoglycans (GAG) to exert a barrier function, but the urothelium exerts significant effects on the underlying tissue via the release of mediators such as ATP, acetylcholine (ACh), prostaglandins (PG) and nitric oxide (NO). These can be altered during inflammation. Lubricin may restore the barrier function and its anti-inflammatory actions possibly normalise urothelial function and mediator release.

sugar chains bound to protein backbones on the urothelial surface, this layer forms a trapped water microenvironment, with the predominant glycosaminoglycan chondroitin sulphate, along with hyaluronic acid, having a central role in maintaining barrier integrity, signalling and anti-inflammatory actions [49]. In IC/BPS, loss of the GAG layer is thought to be a pathological deficit, resulting in urothelium disruption, loss of barrier function, and increased bladder permeability to ions, solutes, irritants, and pathogenic bacteria, and consequently inflammation, hypersensitivity in neural pathways, pain and urinary symptoms such as frequency [50].

Intravesical GAG replacement, using natural or semi-synthetic agents, has long been used as second line therapy to relieve the symptoms of IC/BPS. Instillation of high concentrations of the agent are used to coat the bladder surface whilst avoiding possible systemic adverse effects, the aim being to replenish and stimulate repair of the native barrier, decrease the release of inflammatory mediators and reduce immune cell infiltration. These agents include hyaluronic acid, chondroitin sulphate and heparin, or combinations of these agents (eg. iAluril®) instilled together, with local anaesthetics, steroids or analgesics, to provide immediate relief and restore impermeability to the natural urothelial barrier. Currently used agents are linear polymers, whilst the natural GAG layer is more complex, forming a dense hydrophilic layer that is thicker than that formed by the instilled linear polymers [49]. Whilst long clinical experience supports use in some patients, and clinical guidelines include GAG replacement therapy as a second line therapy for IC/BPS, recent systematic reviews and meta-analyses suggest that evidence for efficacy is moderate at best [51] and direct comparisons between the different products have not been performed to date in well designed, long term RCTs. The combination therapies seem to have better success rates, but often there are large placebo effects, non-responders and the effects are mostly short lived. This has lead to a surge in research effort to develop agents that have less clearance/enhanced accumulation in the bladder, and longer lasting physiological actions.

Several novel natural or semisynthetic GAG replenishment strategies are emerging, many through the recent advances in bioengineering approaches to produce modified GAGs with branched chains and specific biological functions [52]. Lubricin, or proteoglycan 4, a natural lubricant in the body, has a unique 'bottle brush' structure, and is highly hydrophilic, with a highly glycosylated protein core, enabling it to trap water and solvents in a deeper layer than the clinically used GAG replacement therapies. It prevents cellular death and decreases cellular inflammation, being an antagonist of TLR2 and TLR4 receptors [53]. Currently in clinical trials for dry mouth in radiotherapy patients in Australia, pre-clinical evidence supports the intravesical use of lubricin for disorders of the bladder, with an ability to restore urothelium barrier integrity [54]. Other potentially therapeutic agents include high molecular weight SuperGAG biopolymers, shown to be effective in restoring urothelial impermeability and reducing pain in mouse models of IC/BPS [55]. Therapeutic semi-synthetic GAG-ethers or SAGEs can restore the mucosa, with intrinsic analgesic and anti-inflammatory effects [56]. In combination with novel drug delivery systems, such as thermo-responsive silk-elastin like protein biopolymers (SELP), which transition from a liquid to an erodible solid gel, there is enhanced accumulation of these GAGs in the bladder in experimental studies [56]. Other bioengineered approaches which decrease inflammation and permeability in models of IC/BPS include a high molecular weight hyaluronic acid phasic dispersion [57], nanoplatelets with a flattened morphology composed of polysaccharide 'hydrogels' [58], sulfhydryl hydrogels [59] and hyaluronic acid derivatives combined with Hydeal-D, a long lasting commercially available product [60].

Several novel agents are under investigation for replacement of the natural barrier, at varying stages of development, and the area has potential to expand rapidly with the recent advances in engineered cell production systems, allowing scalable synthesis of molecules that may be fine-tuned to biological function. These novel GAGs and GAG derivatives are semi-synthetic and so not entirely natural, but are showing great promise. Of real interest is the range of inherent biological and physiological effects these molecules have, not only restoring the GAG layer, but anti-inflammatory, anti-apoptotic and signalling properties. Novel delivery strategies may aid longevity of therapeutic effects, and there are safety advantages, in that these compounds are synthesised from natural compounds. Whilst further experimental and clinical testing is needed, the fact that some of these molecules are already in clinical trials for other indications, may see some of these agents rapidly incorporated into clinical use.

2. Summary and conclusions

Experimental laboratory studies have shown that many natural products have cellular actions that would explain their popularity when considering their use in treating urinary incontinence. However there are few well-controlled clinical trials using these agents to support their use in patients with LUTS. The lack of evidence of effectiveness is not surprising considering the many problems encountered in testing these agents such as the difficulties in standardising plant extracts when dealing with variable plant compositions and different extraction methods. To these must also be added the difficulties in funding studies where there is no obvious patent and potential financial reward to motivate research. These obstacles hinder the discovery of new natural therapies and their development into clinical use.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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