



## **Effects of Medicinal Plants on Nocturia: A Systematic Review**

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### **Authors' contributions**

*This work was carried out in collaboration between all authors. Author MY designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MY and SHS managed the analyses of the study. Authors SHS and RKA managed the literature Searches. All authors read and approved the final manuscript.*

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### **ABSTRACT**

Nocturia is one of the common disorders that are associated with certain complications such as fracture and declined quality of life in addition to disrupting sleep. We, therefore, sought to review the evidence on the effects and action mechanisms of medicinal plants on nocturia.

**Methods:** The search terms of interest were used to retrieve relevant articles published between 2000 and 2018 and indexed in the databases *Institute for Scientific Information*, *PubMed*, and *Scopus* using *EndNote* software.

*Peganum harmala* and *Cannabis sativa* are two of the plants that have been reported to be effective on nocturia. In addition, certain plant-based derivatives such as SagaPro and certain combinations such as Gosha-jinki-gan, paladin kashaya, and PRO 160/120 from *Viola odorata* L. (Violaceae), C.A.Mey. From *Echium amoenum* Fisch. (Boraginaceae), and *Physalis alkekengi* L. (Solanaceae) help improve nocturia through different mechanisms.

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As with other types of treatments, plants and plant-based compounds cannot be used as monotherapy in treating nocturia, and therefore should be used as a complementary therapy alongside available treatments for this disorder to induce the best therapeutic effects.

**Keywords:** Medicinal plant; nocturia; lower urinary tract; symptoms.

## 1. INTRODUCTION

Nocturia is one of the most common disorders of lower urinary tract symptoms (LUTS) [1] and refers to waking up to urinate more than once each night [2]. This disorder is associated with certain complications such as benign prostatic obstruction and overactive bladder as well as serious adverse effects on quality of life in the affected people [1,3]. The people with nocturia are faced with disruption in night's sleep [4,5] that affects different aspects of health adversely. Inadequate night's sleep leads ultimately to increased mortality rate [6]. In addition, these people are likely to fall down and to develop fracture especially femur fracture [7]. Because this disease is multifactorial, single drug therapies are not sufficiently efficacious [8]. Therefore, nocturia is treated by multiple treatments including improvement of lifestyle, chemical drugs, alpha-blockers, antimuscarinic agents, antidiuretic therapy, and surgery [9]. The treatments for night time urination mainly include urotherapy and different drugs such as desmopressin, imipramine, and anticholinergic drugs as well as behavioral therapies [10,11]. However, these treatments should be promoted [10]. Medicinal plants can represent effective treatments for different diseases including urinary tract disorders. The popularity of these plants has increased considerably because of comparatively lower cost and fewer side effects [12-19]. Regarding the complications of nocturia, the present review was conducted to investigate the effects and action mechanisms of the medicinal plants on this night time disorder.

## 2. MATERIALS AND METHODS

To conduct this systematic review, the search terms *Nocturia* or *Nocturnal voids* in combination with *Herb*, *Medicinal plant*, and *Phyto* were used to retrieve relevant articles published between 2000 and 2018 and indexed in the databases *Institute for Scientific Information*, *PubMed*, and *Scopus* using *EndNote* software. Then, the plants and products that were reported to be effective on and therefore control nocturia were identified and, according to the research team's comments, included in the study. Studies that

directly examined their effect on nocturia and showed positive effects were investigated. The studies that Fig. 1 illustrates how the articles were examined for inclusion in the analysis and explains the inclusion criteria.

## 3. RESULTS

The medicinal plants such as *Serenoa repens*, *Pygeum africanum*, *Urtica dioica*, and *Cucurbita pepo* were reported to be the most important medicinal plants effective on nocturia and certain compounds such as isoflavones, lycopene, selenium, and beta-sitosterol are being addressed for treating the symptoms associated with benign prostate hyperplasia (BPH) such as nocturia [20]. Because BPH causes certain symptoms such as nocturia, decreased voided urine volume, the sensory urgency to urinate, the frequency of urination during the day or night, inability to start and stop a urine stream [21], most studies have reported nocturia to be one of the symptoms to measure the severity of BPH. Table 1 summarizes the evidence on the plants and the phytochemical compounds that are effective on nocturia.

Several compounds and formulations exist that are used in traditional medicine to treat nocturia. Goshajinki-gan (GJG) is a combination made up of 10 plants that are used in Japanese traditional medicine. This formula includes *Rehmannia Radix*, *Achyranthis Radix*, *Copri Fructus*, *Dioscoreae Rhizoma*, *Plantaginis Semen*, *Alismatis Rhizoma*, *Hoclen*, *Moutan Cortex*, *Cinnamomi Cortex* and *Aconiti Tuber*.

The six-week treatment with this combination (2.5 g GJG mixture x 3/day) can help improve disorders of urination such as nocturia [25]. Another study showed that this combination, without interaction with alpha1-blockers or antimuscarinic agents, contributed to treating nocturia [26]. However, Yoshimura et al. reported that furosemide was more efficient in decreasing nocturia than GJG [27]. Pataladi kashaya that compose of Patola – *Trichosanthes dioica*, *Triphala*, *Amla* – *Emblica officinalis*, *Haritaki* – *Terminalia chebula*, *Vibhitaki* – *Terminalia bellirica*, *Arishta* – *Nimba* – *Neem* – *Azadirachta*

indica, Guduchi – *Tinospora cordifolia*, Dhavani – *Solanum indicum*, Vrisha – Vasa – *Adhatoda vasica*, Karanja – *Pongamia pinnata*, is a drug used in Ayurvedic medicine that is useful to improve BPH symptoms including nocturia in addition to decreasing such symptoms [28].

Oelke et al. studied a plant-based combination called PRO 160/120 (extracts from saw palmetto fruits and stinging nettle roots), and reported that

nocturia score, according to the *International Prostate Symptom Score* (IPSS), decreased [29]. A study on the effects of hydroalcoholic extracts of *Viola odorata* L. (Violaceae), C.A.Mey. (Boraginaceae), *Echium amoenum* Fisch., and *Physalis alkekengi* L. (Solanaceae) showed that this combination caused IPSS including nocturia to decline [30]. It has been even reported that herbal capsules work better in treating nocturia than allopathic medicine [31].

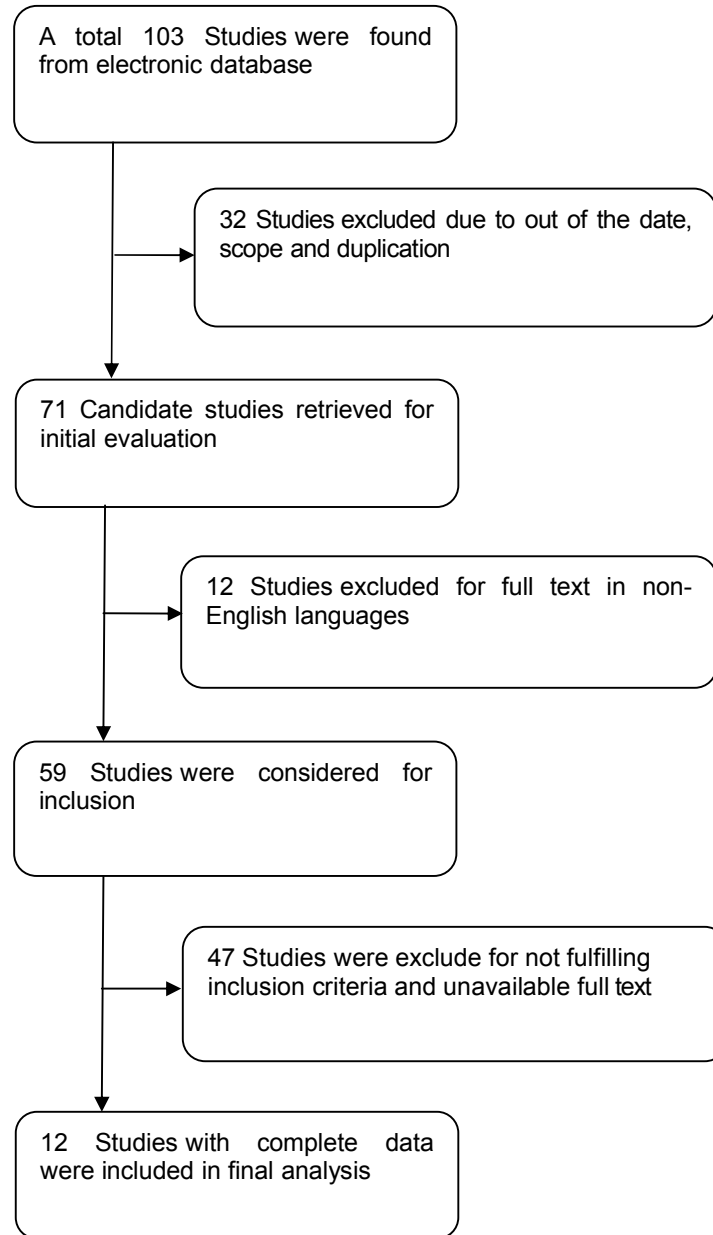


Fig. 1. The flowchart of examining articles according to exclusion and inclusion criteria

**Table 1. Medicinal plants and their phytochemical compounds effective on nocturia**

Plants/ phytochemicals name	Part of plant/ Isolated from	Main effects and mechanisms	References
<i>Cannabis sativa</i>	Extracts containing delta-9-tetrahydrocannabinol and cannabidiol	Effect on cannabinoid receptors in the bladder and nervous system	[22]
<i>Peganum harmala</i>	Extract	Improvement in BPH symptoms including nocturia	[23]
SagaPro	<i>Angelica rchangelica</i>	Reduce the score of nocturnal bladder capacity index (NBC index)	[24]

A number of non-clinical and *in vitro* studies have reported that some plants are effective on nocturia. For example, *Pygeum africanum* [32-34], *rye pollen* [35], and *Serenoa repens* [36-41], and also plant compound such as Cernilton [32,42,43] and beta-sitosterols (B-sitosterol) [44] have been found to decrease one of the complications associated with nocturia.

Antiandrogenic action, the antiproliferative effect exerted through the inhibition of growth factors, anti-inflammatory/anti-oedematous effect and prolactin signal modulation are certain mechanisms that have been proposed for treating BPH and associated complications [40]. However, the action mechanisms of the medicinal plants in treating nocturia remain ambiguous. Certain plants and their derivatives have been reported to control nocturia through decreasing irritable bladder via affecting spinal kappa-opioid receptors [45] distributing water among different organs of the body and decreasing urination [45] and decreasing oxidative stress. Oxidative stress through damage to the urothelium imposes an adverse effect on sensitizing bladder afferent [46]. Besides that, oxidative stress leads to the overactive bladder through mediating capsaicin-sensitive C-fibers [47].

Plants and their compounds exert good antioxidant effects due to phenolic compounds and vitamins E and C; therefore, they can control oxidative stress and help treat nocturia. Although plants and their derivatives can effectively decrease LUTS, some studies have reported that monotherapy is not effective in decreasing the symptoms especially nocturia [48-50]. In addition, it is necessary to use a combination of the plants or their compounds to treat the disease so that more optimal results can be achieved [51].

Accordingly, as with routine treatments for these two disorders, phytotherapies should be used as complementary therapies to achieve better outcomes. In addition, some plants can exert diuretic effects. Prescribing these plants for the people with this disorder should be taken into account to avoid an increase in the associated complications [52].

Regarding nocturnal enuresis in children, there is convincing evidence on the effects of herbal drugs in treating this disorder [53]. Therefore, finely-designed clinical trials on their active compounds and with large sample size should be conducted to supplement available evidence on this subject.

Nocturia is multifactorial disease and more common among women [54,55] but In the elderly nocturia is more frequent among men [54] and it should be noted that in the treatment with medicinal plants, the causes of nocturia and gender differences should be considered. For example, nocturnal polyuria and decreased nocturnal bladder capacity are the major causes of nocturia in women [56]. Testosterone deficiency and prostatic hyperplasia (BPH) are the leading cause of nocturia in men [57,58]. Hence, in the use of medicinal plants, must considering the gender factor and underlying disorders that cause nocturia,

#### 4. CONCLUSION

Plants and plant-based compounds cannot be used alone to treat nocturia and should be used as a complementary therapy with routine treatments to produce best therapeutic effects. Many studies have been conducted on nocturia as a symptom of BPH but very few studies have investigated it independently. Further clinical

trials should be therefore conducted to obtain more reliable evidence.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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