

Review Article:

Nocturnal Enuresis in Children and Its Herbal Remedies in Medieval Persia: A Narrative Review



Monireh Sadat Motaharifard¹, Mohammad Effatpanah², Fatemeh Nejatbakhsh^{1*}

1. Department of Persian Medicine, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran.

2. School of Medicine, Ziaiean Hospital, International Campus, Tehran University of Medical Sciences, Tehran, Iran.



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ABSTRACT

Context: Nocturnal Enuresis (NE) refers to intermittent involuntary voiding during sleep in a child aged five years or more without any other urinary tract symptoms. Although pharmacological interventions are useful, the NE of most children relapses after the medication is discontinued. Persian Medicine (PM), as a complementary and alternative medicine, offers some useful herbal remedies to manage this disorder. This study aimed to introduce the most common medicinal plants used in Iranian Traditional Medicine (ITM) for the treatment of NE in children.

Evidence Acquisition: In this study, we collected and classified the information about nocturnal enuresis in the old reliable Persian medical texts. Then the achieved information was compared with contemporary medical findings in credible published articles.

Results: NE is a well-known disorder mentioned in PM. Lifestyle modification, in addition to herbal, animal, and mineral medicines, have been used to treat NE; however, most remedies have focused on medicinal herbs. In our investigation, 29 plants were used in ITM as the most frequently used herbs for the treatment of NE in children. These therapeutic herbs were used alone or in combination with other compounds in various forms. Most of them control NE with their anticholinergic and antispasmodic effects. Through literature review, it was found that few studies have investigated the utilization of these plants in children with enuresis.

Conclusion: Despite the vast use of these herbs in PM, evidence of their effectiveness in children with enuresis is not strong, so clinical trials and pharmacological tests are required to evaluate safety and efficacy of these herbal remedies.

1. Context

Nocturnal Enuresis (NE) is defined as episodes of urinary incontinence during sleep in a child aged five years or more (1). The bed-wetting must occur at least twice per week

for at least 3 months or must have a negative impact on other important areas of functioning (2). Enuresis can be primary or secondary. Primary enuresis is diagnosed in a child who has never achieved nighttime dryness, while secondary enuresis is when the child has no enuresis for at least 6 months and starts up again. About

* Corresponding Author:

Fatemeh Nejatbakhsh, MD.

Address: Department of Persian Medicine, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran.

Tel: +98 (912) 6511384

E-mail: nejatbakhsh@tums.ac.ir

(90%) of patients have primary enuresis (3). Prevalence of enuresis is approximately (5-10%) among 5 years old children, (1. 5-5%) among 9-10 years old children, and about (1%) among people 15 years and older (2).

These figures may vary according to cultural, racial, and health variables among countries, and there is a slightly higher prevalence in boys (4). This disorder has a multifactorial etiology. Genetics, environmental factors (physical, neurologic, psychological factors) and other medical conditions have been implicated, so far (5). Children with NE may show signs of delayed maturation of the nervous system (6). Studies have suggested that detrusor muscle overactivity has an essential role in children with enuresis (7).

Although bedwetting is pathologically benign and has a high rate of spontaneous remission, it may affect the quality of life and self-esteem, which can be cured with successful treatment. Medical treatments include using anticholinergic drugs (with antispasmodic effects), smooth muscle relaxants, tricyclic antidepressants, and antidiuretics. Behavioral interventions involve using alarms, overlearning, scheduled waking, star charts, reward systems, retention control training, and multidimensional behavioral treatments (8). Because of insufficient efficacy and significant side effects of the current interventions, many families are interested in complementary and integrative approaches (9).

Dating back to 1550 BC, a broad spectrum of alternative therapies have been used for the treatment of bedwetting (6). Today, different types of complementary and alternative medicines are being practiced in most parts of the world based on their availability and affordability. Hypnosis, acupuncture, chiropractic, diet (restricted foods), medicinal herbs, homeopathy, and traditional medicines, including Traditional Persian Medicine (TPM) are used to cure bedwetting (5). There is a lot of information in Iranian classic medical books about medicinal herbs used by pioneering practitioners for the treatment of enuresis in children. The present study aimed to introduce the most commonly used medicinal plants used in TPM for the treatment of nocturnal enuresis in children.

2. Evidence Acquisition

We reviewed eight original important textbooks of TPM; Qanun fi al-Tibb by Avicenna, Al Havi by Rhazes, Qarabadin-e-azam by Nazim Jahan, Exir-e-Azam by Nazim Jahan, Kholase al-Hekmah by Aghili Khorasani, Mufarrih al-Qulub by Arzani, Kamel al-sanaya al-tebbia by Ahwazi and

Makhzan-ul-Adviah by Aghili Khorasani (10-17). In these books, the chapters containing information on NE were evaluated, and relevant data were collected, categorized, and analyzed. Then, the scientific names of the proposed plants were obtained using botanical textbooks of Popular Medicinal Plants of Iran and the annex of Makhzan-ul-Adviah (17-19).

Next, their active ingredients were evoked from the Physicians' Desk Reference (PDR) for Herbal Medicines (20). We considered the scientific names of the plants in combination with "enuresis" OR "incontinency" and "children" OR "pediatric" as key words. Based on these key words, we established literature search in scientific databases of PubMed, Web of Science, Google Scholar, and some Iranian databases like SID and IranMedex. We tried to find out recent scientific documents in modern medicine to obtain any in vitro, animal, and clinical evidence related to NE in children to establish the relationship between traditional knowledge and current findings. The search was conducted on publications from all years until late 2018 and outputs were restricted to those completed studies published in English or Persian. The first author read and selected the related articles. The collected data from TPM books and modern sources were submitted to other authors; thus, all authors were involved in the process of analysis.

3. Results

NE is a well-known disorder mentioned in TPM. In 1472, Paulus Bagellardus of Padua published a book on diseases of children including one chapter entitled "on incontinence of urine and bedwetting". He followed the Galenic doctrine of humours closely and mentioned the treatment of enuresis by contemporary Iranian physicians, including Rhazes and Avicenna (21). Avicenna (980-1037 AD), the famous Iranian scientist, in his book "The Canon of Medicine" wrote that the most important cause of enuresis was "sterkha" meaning loosening of external sphincter's muscular tone due to moisture in the muscle fibers. Loose muscle cannot contract strongly on the bladder's neck, so it fails to prevent the involuntary outflow of urine (10).

Another cause of enuresis is bladder weakness due to coldness that decreases the intrinsic natural power of bladder to hold urine during sleep (22). From the perspective of TPM, children and elderly are two at-risk groups for urine incontinence (23). Children for two reasons are prone to enuresis: high humidity and wetness dominancy in their temperament and deeper sleep that prevents

Table 1. Plants used by TPM practitioners to treat nocturnal enuresis

Scientific Name	Traditional Name	Plant Family	Used Part	Effective Ingredients	Related Function in TPM*	Pharmacological Action
Alpinia officinarum Alpinia galangal	Khoolanjan	Lamiaceae	Root	Tannins, flavonoids	Astringent/ heating kidney	Anticholinergic (30)
Boswellia carterii Boswellia serrata	Kondor	Burseraceae	Resin	Volatile oil, tannins	Astringent/ siccative	-
Bunium persicum	Komon	Umbelliferae	Seed	-	Astringent/ siccative	Anticholinergic/ muscle relaxant (31)
Caesalpinia bonduc	Nardin	Fabaceae	Root	Tannins, flavonoids	Heating bladder	Antispasmodic (32)
Cannabis sativa	Shahdanaj	Cannabaceae	Fruit	Flavonoids	-	Spasmolytic/ anticholinergic (33)
Cocos nucifera	Narjil	Arecaceae	Fruit	Tannins, flavonoids	Heating bladder	-
Commiphora myrrha	Morr	Burseraceae	Resin	Volatile oil	Astringent/ siccative	-
Cupressus sempervirens	Sarve	Cupressaceae	Leaf	Essential oil	Astringent/ bladder tonic	-
Cyperus longus Cyperus rotundus	Soed	Cyperaceae	Root	Tannins	Siccative/ heating bladder	-
Inula helenium	Rasen	Asteraceae	Root	Volatile oil	Bladder tonic	-
Iris spp	Soosan	Iridaceae	Flower	Flavonoids, volatile oil	Astringent/ siccative	-
Lens culinaris	Adass	Fabaceae	Bran	Tannins, flavonoids	Astringent	Anticholinergic/ Antispasmodic (34)
Liquidambar orientalis	Mayee	Hamamelidaceae	Resin	Volatile oil	Astringent/ bladder tonic/ siccative	-
Matricaria chamomilla	Babooneh	Asteraceae	Flower	Flavonoids, volatile oil	Heating bladder/ siccative	Spasmolytic/ anticholinergic (35)
Mentha aquatica	Poodineh nahri	Labiatae	Leaf	Flavonoids, volatile oil	-	Antispasmodic (36)
Moringa arborea	Ban	Moringaceae	Seed	-	Heating bladder	-
Myristica fragrans	Jowz bavva	Myristicaceae	Seed	Volatile oil	Astringent	Anticholinergic/ antibacterial (37)
Myrtus communis	Mourd	Myrtaceae	Seed/ leaf	Tannins, volatile oil	Astringent/ bladder tonic	Antispasmodic/ anticholinergic (38)
Nigella sativa	Shooniz	Fumariaceae	Seed	-	Heating bladder/ siccative	Anticholinergic/ muscle relaxant (39)
Phyllanthus emblica	Amolaj	Euphorbiaceae	Fruit	Tannins, flavonoids	Astringent	Spasmolytic/ Anticholinergic (40)
Piper cubeba	Kababeh	Piperaceae	Fruit	Volatile oil	Astringent	
Piper longum	Darfelfel	Piperaceae	Fruit	Tannins, volatile oil	Heating bladder	Spasmolytic (41)
Pistacia lentiscus	Mastaki	Anacardiaceae	Resin	Volatile oil	Astringent	-
Punica granatum	Golnar	Lythraceae	Flower	Tannins	Astringent/ bladder tonic	Antispasmodic (42)
Quercus brantii	Mazu	Fagaceae	Shell	Tannins, tannic acid	Astringent	-
Quercus ilex Q. infectoria Q. brantii	Baloot	Fagaceae	Fruit	Tannins	Astringent/ siccative	Anticholinergic (43)

Scientific Name	Traditional Name	Plant Family	Used Part	Effective Ingredients	Related Function in TPM*	Pharmacological Action
Saussurea costus	Qost	Asteraceae	Root	Volatile oil	Astringent/ bladder tonic	-
Terminalia chebula	Halileh	Combretaceae	Fruit	Tannins	Astringent	Anticholinergic (44)
Terminalia bellerica	Balileh	Combretaceae	Fruit	Tannins	Astringent/ siccative	Anticholinergic / Antispasmodic (45)

*Traditional Persian Medicine

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them from waking to urinate voluntarily. The wetness decreases when children grow up, so enuresis reduces (13).

In Persian Medicine (PM), lifestyle modification in addition to herbal, animal, and mineral medicines have been used to treat NE; however, most remedies have focused on medicinal herbs. Conservative management includes refraining from taking any beverages and diuretics at night, minimizing the amount of food consumed for dinner, avoiding heavy sleep, and waking up children frequently during the night (to ask them to urinate) (24). To resolve enuresis, strengthening the bladder and external sphincter by warming up the bladder and removing moisture from the external sphincter is necessary (14). For this purpose, TPM texts have mentioned many herbal remedies that are used in various forms like oral preparations, topical poultice, medicated oils, sitz baths, and fumigation. Table 1 presents these plants with their scientific name(s), plant family, type of application and related function(s) in alphabetic order.

The specific mechanism of action of these herbs is unknown, but most of them have tannin content that strengthens the muscles. Tannins are astringent and can also be useful in protecting the kidneys. Reportedly, they have antibacterial effects and are used as antidiuretics for internal uses (25, 26). Besides, their flavonoids are well known for their antispasmodic activity that can have a beneficial role in enuresis treatment (27). Also some of these plants have essential or volatile oils which are possible to have anticholinergic activity (28). Certain drugs commonly prescribed for urinary incontinence, produce a direct antispasmodic action by inhibiting the muscarinic action of acetylcholine on smooth muscle and then relaxing the detrusor muscle (29). Table 1 presents medical plants that have also been investigated for this condition.

4. Discussion

One of the known forms of therapeutic application is anointing the bladder area with hot nature oil. Herbal oils are easily prepared and continued to be used as practical therapeutic interventions in ITM (46). Trans-

dermal delivery is convenient and offers several advantages. They have been recently introduced in the medical literature for the treatment of detrusor muscle overactivity (47).

Nowadays herbalists suggest *Hypericum perforatum*, infusions of horsetail or corn silk (*Zea mays*), to be given through the day to encourage normal nervous control of the bladder but few published studies exist about their use (6, 48). There was no article related to our topic in Persian. There are few trial studies on complementary herbal therapies for NE, especially in children. Most of them have studied the effects of Chinese traditional herbs on children's enuresis. In three trials, different preparations of Chinese medicinal herbs were compared with imipramine, and the herbs seemed to be better than imipramine both during and after the treatment (9). Some clinical trials assessed the efficacy and safety of "Suoquan" (a herbal medicine) used in traditional Korean and traditional Chinese medicine for the treatment of enuresis (49). "Yokukansan" is a Japanese traditional herbal prescription that is a candidate for the second-line therapy of nocturnal enuresis (50).

According to our search in scientific databases, only one clinical trial exists that confirms the effectiveness of medicinal plants listed in Table 1 on children's enuresis. It is a double-blind, randomized clinical trial and concludes that the topical use of chamomile oil can decrease the episodes of enuresis in children compared with using a placebo (35). A few other studies have investigated these plants (listed in Table 1) for urological problems in adults. A study in India in 2014 showed that the combination of *Boswellia serrata* (Kondor) and *Cyperus scariosus* plus pelvic floor muscle training in stress incontinence in women of reproductive age was more effective than that in the control group (51). A double-blind placebo-controlled study showed that *Saussurea costus* (Qost) oil was effective on female urinary incontinence (52).

Enuresis is one of the frequently-seen problems during childhood, so, logically, it needs the most effective treatments. There are currently no specific medications

to target incontinence symptoms without having side effects, so we need to find new medicines for the prevention or treatment of urinary incontinence. Herbal medicines have been broadly used in the treatment of a wide range of pediatric disorders such as NE and are considered safe and effective treatments. The purpose of this study was to investigate the opinions of Iranian practitioners about the herbal remedies for the treatment of NE in children.

A review of Rhazes' opinion (854-925/935 AD), a genius Iranian physician, about NE, shows that medical practice in the past was comparable to our modern medicine yet tries avoiding the side effects in modern therapeutic approach (24). According to PM practices, the first step in NE treatment is to modify the lifestyle. Persian practitioners have introduced some natural remedies for this problem besides principles of lifestyle modification. In the present research, 29 plants have been extracted from ancient Persian documents which are supposed to be the most frequently-used herbs used for the treatment of NE in children. These medicinal herbs can be used alone or formulated with pharmaceutically acceptable compositions with a favorable delivery profile.

Most of these plants are warm and dry, which are recommended for cold and wet temperament diseases such as urinary incontinence. The definite mechanisms for the effect of these plants in treating NE have remained unknown. Based on the principles of TPM, the expected function of these medicinal plants are warming up the bladder by promoting venous circulation to the kidneys and bladder area, being siccative to remove waste from bladder and being astringent to improve bladder tone and strengthen kidneys and bladder.

5. Conclusion

In this review, we tried to connect TPM knowledge and current pharmacological data to identify new efficient drugs. Despite the extensive use of many of these herbs, little evidence supports their use, and proper randomized trials should be done to demonstrate their effectiveness. All traditional drugs and therapeutic approaches for using in our current medical practice should be evaluated and standardized with current standards of pharmaceuticals and medical procedures.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article.

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Authors contribution's

Conceptualization, investigation, writing-original draft: Monireh Sadat Motaharifard; Methodology, writing-review & editing: Mohammad Effatpanah, Fatemeh Nejatbakhsh; Reading and approving the final manuscript: All authors.

Conflicts of interest

The authors declared no conflict of interests.

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