

A Review of Plant Antioxidants in the Treatment of Urinary Frequency in Children: A Comprehensive Study in Iranian Traditional Medicine

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Article Info	A B S T R A C T
Article type: Review Article	Objective: Urinary frequency in children is a common issue of the urinary system, which can arise from various factors such as infections, inflammation, or neuro-muscular disorders. In Iranian traditional medicine, medicinal plants rich in antioxidant compounds have been utilized as a natural approach to reduce inflammation and improve urinary system function. This review aims to identify and report on medicinal plants effective in treating urinary frequency in children in Iranian traditional medicine.
Article History: Received: Jan. 19, 2025 Revised: Feb. 18, 2025 Accepted: Feb. 19, 2025 Published Online: July. 27, 2025	Methodology: In this review, keywords including "medicinal plants," "urinary frequency," "children," and "Iranian traditional medicine" were used for literature searches. Credible databases such as Google Scholar, SID, Magiran, PubMed, and Scopus were employed to retrieve the relevant studies.
✉ Correspondence to: Sudip Kumar Mandal	Results: Medicinal plants such as mint, ginger, cinnamon, chamomile, lemon, green tea, marshmallow, walnut, fennel, dill, black cumin, lavender, quince seed, bindweed, valerian, Persian pomegranate, nettle, and fenugreek have been used for the treatment of urinary frequency.
Email: Dr.hashem45@gmail.com	Conclusion: The results of this study show that several medicinal plants with antioxidant properties have been used in Iranian traditional medicine to treat urinary frequency in children. These plants, containing compounds such as flavonoids, tannins, and phenolic compounds, can reduce inflammation, improve bladder function, and strengthen the immune system, thereby helping alleviate the symptoms of this disorder. However, further research is needed to confirm their efficacy and determine appropriate dosages for children.
	Keywords: Urinary frequency, Children, Medicinal plants, Traditional medicine, Iran
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Introduction

Urinary frequency is a common problem in children that can significantly affect their quality of life [1]. This condition arises from various causes, including urinary tract infections, bladder inflammation, diabetes, or neuro-muscular disorders [2], which have high frequency among those with severe renal disease, and several studies have reported the relationship between clinical presentations at onset and prognosis [3]. Affected children often experience increased urination frequency and may suffer from urgent urination or incontinence [3]. These symptoms can result in both physical and psychological issues, requiring thorough investigation and treatment [4]. The pathophysiology of urinary frequency in children may involve several factors, including bladder dysfunction, inflammation, urinary infections, and neurological problems [5]. In some cases, dysfunction in the regulation of bladder nerves and heightened sensitivity to stimuli can lead to abnormal contractions and frequent urination. Additionally, psychological factors such as stress or anxiety may contribute to the exacerbation of this issue [6].

Conventional treatments often include antibiotics, anti-inflammatory drugs, and bladder function regulators [6]. However, these medications may cause side effects, and long-term use may have limitations [7]. Consequently, alternative methods, such as natural treatments based on traditional medicine, have gained attention [8]. Iranian traditional medicine has a long history of using medicinal plants to improve urinary system function [8]. Many of these plants contain compounds with anti-inflammatory, antioxidant, and calming properties [8]. These compounds, such as flavonoids, tannins, and phenolic compounds, can reduce inflammation and regulate bladder function [9]. Recent studies have examined the effects of medicinal plants on urinary disorders [10]. Some studies have shown that medicinal plants can alleviate the symptoms of urinary frequency. However, most of these studies have been conducted on animal models or adults, and sufficient evidence regarding their effects on children is lacking [11].

This review aims to comprehensively explore the sources of Iranian traditional medicine and scientific evidence on medicinal plants effective in treating urinary frequency in children.

Methodology

This review examines articles related to the role of plant antioxidants in treating urinary frequency in children within the framework of Iranian traditional medicine. Reliable databases such as Google Scholar, SID, Magiran, PubMed, and Scopus were utilized to retrieve relevant studies. The search strategy involved combining the keywords "medicinal plants," "urinary frequency," "children," and "Iranian traditional medicine" in the titles, abstracts, and keywords of the articles. Additionally, sources and books on Iranian traditional medicine and herbal medicine were consulted.

Inclusion and Exclusion Criteria

Inclusion Criteria

Articles discussing the traditional effects of medicinal plants on urinary frequency in children.

Studies conducted in the field of Iranian traditional medicine and medicinal plants' therapeutic applications.

Published research articles, clinical trials, and review studies from reputable academic journals.

Exclusion Criteria

Articles focusing on non-herbal treatments or chemical medications.

Studies involving adults or non-child populations.

Articles published in languages other than Persian or English.

Studies lacking scientific data, appropriate methodology, or precise results were excluded.

Results

An examination of Iranian traditional medicine sources reveals a wide range of medicinal plants used to treat urinary frequency in children. These plants include mint, ginger, cinnamon, chamomile, lemon, green tea, marshmallow, walnut, fennel, dill, black cumin, lavender, quince seed, bindweed, valerian, Persian pomegranate, nettle, and fenugreek. Table 1 provides the botanical characteristics and therapeutic effects of these plants in traditional medicine.

Table 1: Botanical Characteristics, Therapeutic Effects, and Mechanisms of Action of Medicinal Plants Effective Against Urinary Frequency in Children in Traditional Iranian Medicine [12-28]

Persian Name	English Name	Scientific Name	Herbal Family	Mechanism
Pouneh	Pennyroyal	<i>Mentha pulegium</i>	Lamiaceae	Reduces bladder irritation and alleviates muscle spasms
Zanjabil	Ginger	<i>Zingiber officinale</i>	Zingiberaceae	Reduces inflammation and improves bladder function
Darchin	Cinnamon	<i>Cinnamomum verum</i>	Lauraceae	Reduces inflammation and enhances kidney function
Babouneh	Chamomile	<i>Matricaria chamomilla</i>	Asteraceae	Reduces bladder nerve irritation
Limou	Lemon	<i>Citrus limon</i>	Rutaceae	Increases urination and cleanses the kidneys from waste
Chayesabz	Green tea	<i>Camellia sinensis</i>	Theaceae	Regulates bladder muscle contractions and reduces inflammation
Golekhatmi	Marshmallow	<i>Althaea officinalis</i>	Malvaceae	Protects bladder mucosa and reduces irritation
Gerdou	Walnut	<i>Juglans regia</i>	Juglandaceae	Reduces inflammation and improves kidney function
Razianeh	Fennel	<i>Foeniculum vulgare</i>	Apiaceae	Reduces inflammation and regulates hormones affecting kidney function
Shevid	Dill	<i>Anethum graveolens</i>	Apiaceae	Increases urine volume and improves kidney function
Zirehsabz	Black cumin	<i>Bunium persicum</i>	Apiaceae	Reduces bladder irritation and regulates its activity

Ostokhodous	Lavender	<i>Lavandula angustifolia</i>	Lamiaceae	Reduces stress and soothes bladder muscles
Behdaneh	Quince seed	<i>Cydonia oblonga</i>	Rosaceae	Reduces dryness and inflammation of the bladder
Alafehatband	Knotgrass	<i>Polygonum aviculare</i>	Polygonaceae	Increases urine volume and reduces kidney inflammation
Sonboloteib	Valerian	<i>Valeriana officinalis</i>	Caprifoliaceae	Reduces stress and controls abnormal bladder contractions
Golnar farsi	Persian pomegranate flower	<i>Punica granatum</i>	Lythraceae	Reduces inflammation and enhances kidney function
Gazanehsefid	White dead-nettle	<i>Lamium album</i>	Lamiaceae	Increases urine volume and reduces kidney inflammation
Shanbalileh	Fenugreek	<i>Trigonella foenum-graecum</i>	Fabaceae	Regulates urine secretion and reduces bladder inflammation

Discussion

Pennyroyal (*Mentha pulegium*) contains pulegone, which acts as a bladder relaxant, helping reduce contractions and regulate urinary function. In traditional medicine, this plant is used to soothe bladder irritability and alleviate frequent urination in children [29]. Ginger (*Zingiber officinale*), rich in gingerol, possesses anti-inflammatory properties and enhances bladder function. It is utilized to reduce inflammation and facilitate urine flow [30]. *Cinnamomum verum* containing cinnamaldehyde and eugenol, increases urinary flow and improves bladder function [30]. *Matricaria chamomilla*, with its active compound apigenin, provides anti-inflammatory and antispasmodic effects, aiding in reducing bladder inflammation and contractions [32]. *Citrus limon* has diuretic properties due to its citric acid and flavonoids, helping regulate bladder function and prevent irritation [33]. *Camellia sinensis* contains catechins, which offer antioxidant effects that protect bladder tissues from damage [34]. *Althaea officinalis* contains mucilage, which helps soothe inflammation and alleviate bladder irritation [35]. *Juglans regi* is rich in polyphenols and fatty acids, which strengthen kidney function and reduce urinary tract inflammation [36]. *Foeniculum vulgare* contains anethole, which enhances urine flow and alleviates urinary issues in children [37]. *Anethum graveolens* helps regulate kidney function and reduces bladder irritation due to its carvacrol content [38]. *Bunium persicum* with camphene contributes to bladder relaxation and alleviates abnormal contractions [39]. *Lavandula angustifolia* reduces bladder inflammation and soothes it with its active compound linalool [40]. *Cydonia oblonga* contains mucilage and anti-inflammatory properties, effectively soothing bladder inflammation [41]. *Polygonum aviculare* contains silica and flavonoids, which enhance kidney function and promote increased urine flow [42]. *Lamium album* helps regulate urination and strengthen kidney function due to its phenols and saponins [43]. *Trigonella foenum-graecum* contains saponins, providing anti-inflammatory effects and strengthening bladder function, thus reducing urinary frequency [44,45]. Kidney and urinary tract diseases are of particular importance, especially in children, as they can cause significant pain and discomfort [46,47]. In this regard, the use of natural and herbal medicines can offer an effective and safe approach to managing these conditions [48]. In many diseases and disorders [49-54], turning to nature and embracing traditional or natural therapeutic approaches can serve as a beneficial and complementary strategy helping to alleviate symptoms, support overall well-being, and enhance patients' quality of life [49]. In many diseases and disorders [49-54], turning to nature and embracing traditional or natural therapeutic approaches can serve as a beneficial and

complementary strategy helping to alleviate symptoms, support overall well-being, and enhance patients' quality of life [55].

Conclusion

This review highlights numerous medicinal plants with antioxidant and anti-inflammatory properties used in traditional Iranian medicine to treat frequent urination in children. These plants, with their various compounds such as flavonoids, mucilage, and polyphenols, help improve bladder function and reduce inflammation. Further research is necessary to confirm the efficacy and establish appropriate dosages for these plants in treating urinary frequency in children.

Statements and Declarations

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Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Author contributions

HM: Conceptualization, the original draft writing, investigation, writing including reviewing and editing and investigation and formal analysis; MV: Conceptualization, supervision, and project administration; MV and HM Conceptualization, the original draft writing, investigation, writing including reviewing and editing

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References

1. Mahmoudzadeh H, Valizadeh M, Hajilou Z. Evaluation of Dimercaptosuccinic Acid Scan (DMSA) findings and its correlation with clinical and paraclinical parameters in children with pyelonephritis. *J Biomed Univ Med Sci*. 2025;32(1):27–36.
2. Mahmoudzadeh H, Valizadeh M. Evaluation of the frequency of urinary tract infection in children with febrile seizures hospitalized in Shahid Motahari Hospital, Urmia, from 2020 to 2021. *Studies Med Sci*. 2024;35(12):976–984. doi:10.61186/umj.35.12.976
3. Nikibakhsh AA, Mahmoodzadeh H, Karamyyar M, Hejazi S, Noroozi M, Macooie AA. Treatment of severe henoch-schonlein purpura nephritis with mycophenolate mofetil. *Saudi J Kidney Dis Transpl*. 2014 Jul 1;25(4):858–63.
4. Gondim R, Azevedo R, Braga AANM, Veiga ML, Barroso Jr U. Risk factors for urinary tract infection in children with urinary urgency. *Int Braz J Urol*. 2018;44(2):378–83.
5. houman n, esfahani st, mohkam m, derakhshan ali, gheysari e, vazirian sh, mortazavi fas, ghaneshherbaf f, falak alafaki b, otukesh h, madani a, sharifian dorcheh m, mahdavi ali, esmaeili mohammad, naseri mitra, azhir a, merikhi ar, mohseni p, ataei na, falahzadeh mh, basiratnia m, hosseini alhashemi gh. the outcome of iranian children on continuous ambulatory peritoneal dialysis: the first report of iranian national registry. *archives of iranian medicine* [internet]. 2009;12(1):24–28. available from: <https://sid.ir/paper/280390/en>
6. Nieuwhof-Leppink AJ, Schroeder RP, van de Putte EM, de Jong TP, Schappin R. Daytime urinary incontinence in children and adolescents. *Lancet Child Adolesc Health*. 2019;3(7):492–501. doi: 10.1016/S2352-4642(19)30113-0
7. Abbasi E, Ghazavi A, Valizadeh M, Farshi M, Radvar M. Complications of Antiepileptic Drugs in Hospitalized Patients in Shahid Motahari Hospital of Urmia from 2010 till the end of 2016. *Stud Med Sci*. 2020 Aug 10;31(6):499–506.
8. Adams J, Andrews G, Barnes J. Traditional, complementary and integrative medicine: an international reader. Bloomsbury Publishing; 2017 Sep 16.
9. Jones EA. Urinary incontinence in children. In: *Urologic diseases in America*. 2007. p. 423–36.
10. Dos Santos J, Lopes RI, Koyle MA. Bladder and bowel dysfunction in children: an update on the diagnosis and treatment of a common, but underdiagnosed pediatric problem. *Can Urol Assoc J*. 2017;11(1-2 Suppl 1): 64. doi: 10.5489/cuaj.4411
11. Bag A, Bhattacharyya S, Chattopadhyay R. Medicinal plants and urinary tract infections: An update. *Pharmacogn Rev*. 2008;2(4):277.
12. Ahmadipour SH, Vakili M, Ahmadipour S. Phytotherapy for children's nocturnal enuresis. *J Med Biomed Sci*. 2017;6(3):23–9.
13. Shaheen G, Akram M, Jabeen F, Ali Shah SM, Munir N, Daniyal M, et al. Therapeutic potential of medicinal plants for the management of urinary tract infection: A systematic review. *Clin Exp Pharmacol Physiol*. 2019;46(7):613–24. doi: 10.1111/1440-1681.13092.
14. Khan A, Bashir S, Khan SR. Antiuro lithic effects of medicinal plants: results of in vivo studies in rat models of calcium oxalate nephrolithiasis—a systematic review. *Urolithiasis*. 2021;49(2):95–122.
15. Zargari A. Medicinal Plants of Iran. Tehran: University of Tehran Press; 1989.
16. Mozaffarian V. Medicinal Plants of Iran (Volume 1). Tehran: Tehran University Press; 2008.
17. Khazdair MR. Iranian Medicinal Plants in Traditional Medicine. 1st ed. Tehran: Science and Technology Publications; 2016.
18. Nazari M, Vatanpour H. Traditional Persian Medicine: An Overview of Medicinal Plants Used in Iran. Tehran: Mehr Press; 2015.
19. Sadeghi N. Phytotherapy in Iran: Herbal Remedies and Practices in Persian Traditional Medicine. 2nd ed. Tehran: Amirkabir Press; 2017.
20. Aghili Khorasani M. Makhzan al-Advieh (The Treasure of Remedies). 1st ed. Tehran: Islamic Publishing House; 2006.
21. Asgarpanah J. Herbal Medicine in Iran: A Comprehensive Overview of Iranian Herbal Therapy. 1st ed. Tehran: University Press; 2013.
22. Karami M, Khazdair MR. Pharmacological Properties of Iranian Medicinal Plants. 1st ed. Isfahan: Isfahan University of Medical Sciences Press; 2014.
23. Vahdati M, Asgarpanah J. Medicinal Plants in Iranian Traditional Medicine. 1st ed. Tehran: Tehran University Press; 2018.
24. Ghaffari M, Davoodi S. Ethnobotany and Medicinal Plants of Iran. 1st ed. Tehran: Research Institute of Forests and Rangelands; 2011.
25. Roudbari H. Healing with Plants in Iranian Traditional Medicine. 2nd ed. Shiraz: Shiraz University Press; 2012.
26. Fadaei R. Medicinal Plants and Their Role in Iranian Healthcare Systems. 1st ed. Tehran: Qom University Press; 2015.
27. Jafari M. The Role of Herbs in Persian Traditional Medicine: An Overview of Plant-Based Remedies in Iran. 1st ed. Tehran: Payam-e-Noor Press; 2014.
28. Sadeghi N, Valiollahi Z. Herbal Drugs and Their Medicinal Uses in Iranian Folk Medicine. 1st ed. Tehran: Behzad Publications; 2016.

29. Ayatollahi S. Plants and Healing in Iranian Traditions. 1st ed. Tehran: Cultural Research Bureau; 2010.
30. Hadi MY, Hameed IH, Ibraheam IA. Mentha pulegium: medicinal uses, anti-hepatic, antibacterial, antioxidant effect and analysis of bioactive natural compounds: a review. Res J Pharm Technol. 2017;10(10):3580–4. doi:10.5958/0974-360X.2017.00648.5
31. Bager S, Ovesen L. Assessment report on Zingiber officinale Roscoe, rhizoma. Committee on Herbal Medicinal Products (HMPC). 2012;44:43.
32. Webster DE. NAME: Cinnamon (Cinnamomum verum, syn. C. zeylanicum). Winston & Kuhn's Herbal Therapy & Supplements. 2008;128.
33. Sharifi H, Minaie MB, Qasemzadeh MJ, Ataei N, Gharehbeglou M, Heydari M. Topical use of Matricaria recutita L. (Chamomile) oil in the treatment of monosymptomatic enuresis in children: a double-blind randomized controlled trial. J Evid Based Complement Altern Med. 2017;22(1):12–7. doi: 10.1177/2156587215608989.
34. Sharma YK, Gilhotra UK. Effect of Citrus limon (L.), Citrus aurantium and Citrus medica on ethylene glycol-induced urolithiasis in rats. J Pharm Negative Results. 2022;13.
35. Potawale SE, Mantri RA, Luniya KP, Mehta UK, Sadiq MWM, Dhalawat HJ, et al. Camellia sinensis: An ethnopharmacological review. Pharmacol J. 2008;3:1–25.
36. Kianitalaei A, Feyzabadi Z, Hamed S, Qaraaty MJ. Althaea officinalis in traditional medicine and modern phytotherapy. J Adv Pharm Educ Res. 2019;9(S2):155.
37. Paniagua-Zambrana NY, Bussmann RW, Kikvidze Z, Khojimatov OK. Juglans regia L. Juglandaceae. In: Ethnobotany of the Mountain Regions of Eastern Europe: Carpathians. Cham: Springer International Publishing; 2024. p. 1–22. doi:10.1007/978-3-030-57408-6_132
38. Rahimi R, Ardekani MRS. Medicinal properties of Foeniculum vulgare Mill. in traditional Iranian medicine and modern phytotherapy. Chin J Integr Med. 2013;19:73–9. doi: 10.1007/s11655-013-1327-0.
39. McIntyre A. Herbal Treatment of Children: Western and Ayurvedic Perspectives. Elsevier Health Sciences; 2005.
40. Motaharifard MS, Effatpanah M, Nejatbakhsh F. Nocturnal enuresis in children and its herbal remedies in medieval Persia: a narrative review. J Pediatr Rev. 2020;8(1):15–22.
41. Seol GH, Lee YH, Kang P, You JH, Park M, Min SS. Randomized controlled trial for Salvia sclarea or Lavandula angustifolia: differential effects on blood pressure in female patients with urinary incontinence undergoing urodynamic examination. J Altern Complement Med. 2013;19(7):664–70. doi: 10.1089/acm.2012.0148.
42. Ashraf MU, Muhammad G, Hussain MA, Bukhari SN. Cydonia oblonga M., a medicinal plant rich in phytonutrients for pharmaceuticals. Front Pharmacol. 2016;7:163.
43. Kupczyński R, Szumny A, Bednarski M, Piasecki T, Śpitalniak-Bajerska K, Roman A. Application of Potentilla anserina, Polygonum aviculare, and Rumex crispus mixture extracts in a rabbit model with experimentally induced E. coli infection. Animals (Basel). 2019;9(10):774. https://doi.org/10.3390/ani9100774
44. Olas B, Różański W, Urbańska K, Sławińska N, Bryś M. New light on plants and their chemical compounds used in Polish folk medicine to treat urinary diseases. Pharmaceuticals (Basel). 2024;17(4):435. doi: https://doi.org/10.3390/ph17040435
45. Bahmani M, Shirzad H, Mirhosseini M, Mesripour A, Rafeian-Kopaei M. A review on ethnobotanical and therapeutic uses of fenugreek (Trigonella foenum-graecum L.). J Evid Based Complement Altern Med. 2016;21(1):53–62. doi: 10.1177/2156587215583405
46. Mahmoudzadeh H, Nikibakhsh AA, Pashapour S, Ghasemnejad-Berenji M. Relationship between low serum vitamin D status and urinary tract infection in children: a case-control study. Paediatrics and Int Child Health 2020; 2;40(3):181-5.
47. Abbasi A, Valizadeh M, Fahimi D, Moghtaderi M, Bazargani B, Mojtahedi SY, Fazel M, Hosseini-Asl SH, Raoofi E. Health-related quality of life in Iranian children with nephrotic syndrome. Iran J Pediatr 2022 Jan 1;32(2): 118426.
48. Nyagumbo E, Nyirenda T, Mawere C, Mutaramutswa AM, Ngorima G, Kapanga DT, et al. A systematic review and perspective analysis of medicinal plants used in Zimbabwe for the treatment and management of genitourinary infections. Journal of Biochemicals and Phytomedicine. 2024; 3(2): 100-158. doi: 10.34172/jbp.2024.24.
49. Darvishi M, Nava AO, Karimi E, Nouri M, Meigooni SS, Hejripor SZ. Human and animal bites. Caspian J Environ Sci. 2023;21(2):445–456.
50. Mahmud Hussien B, Noori M, Sayad B, Ebadi Fard Azar M, Sadri Nahand J, Bayat M, Babaei F, Karampour R, Bokharaei-Salim F, Mirzaei H, Moghooei M. New potential MicroRNA biomarkers in human immunodeficiency virus elite controllers, human immunodeficiency virus infections, and coinfections with hepatitis B virus or hepatitis C virus. Intervirology. 2023 Dec 20;66(1):122–135.
51. Ghanbari A, Nouri M, Darvishi M. Evaluation of relationship between serum hemoglobin A1C level and severity of diabetic foot ulcers based on Wagner criteria. J Med Chem Sci. 2023;6:2234–2241.
52. Darvishi M, Nouri M, Zahir M, Asli M, Hejripor SZ, Karimi E. Overview of human papillomavirus

- infection. *Infect Disord Drug Targets*. 2024 Mar 1;24(2):65–76.
53. Nouri M, Kamakifar P, Khodabandehlou N, Nahand JS, Tavakoli A, Norooznezhad F, Sorayyayi S, Babaei F, Mostafaei S, Moghoofei M. Association between Parvovirus B19 and anemia in HIV-infected patients. *Med J Islam Repub Iran*. 2019 Dec 16;33:137.
 54. Darvishi M, Noori M, Nazer MR, Soleiman-Meigooni S, Forootan M. The relationship between *Helicobacter pylori* and extra-gastrointestinal infections. *Iran J Med Microbiol*. 2020 Nov 10;14(6):543–565.
 55. Darvishi M, Hashemi Rafsanjani SMR, Nouri M, Abbaszadeh S, Heidari-Soureshjani S, Kasiri K, Rahimian G. Biological mechanisms of polyphenols against *Clostridium difficile*: A systematic review. *Infect Disord Drug Targets*. 2025 May;25(3):18715265313944. doi: 10.2174/0118715265313944240726115600