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Deep insights into urinary tract infections and effective natural remedies

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Abstract

Background: Urinary tract infection (UTI) is a common occurrence in females, during pregnancy, and in peri- and postmenopausal women. UTIs are associated with significant morbidity and mortality, and they affect the quality of life of the affected patients. Antibiotic therapy is an effective approach and reduces the duration of symptoms. Development of resistance, adverse effects of antibiotics, and other associated problems lead to establishing the research framework to find out the alternative approaches in controlling UTIs. Natural approaches have been extensively used for the management of various diseases to improve symptoms and also improve general health.

Main body: Different databases were employed to identify studies reporting on natural options including herbal medicines, vitamins, trace elementals, sugars, and probiotics without time limitations.

Conclusion: Herbal medicines can be effective at the first sign of the infection and also for short-term prophylaxis. Using vitamins, trace elementals, and/or sugars is an effective approach in preventing UTIs, and a combination of them with other antibacterial agents shows positive results. Probiotics have great potential for the threat of antibiotic over-usage and the prevalence of antibiotic-resistant microorganisms. This study may be of use in developing the efficient formulation of treatment of UTI.

Keywords: Urinary tract infection, Herbal medicine, Vitamin, Probiotics, Supplements, Antibacterial resistance

1 Background

Urinary tract infection (UTI) is one of the most prevalent bacterial infections in women and elderly individuals. This type of infection although can cause less severe life-threatening infections but the patient experienced significant distress [1]. Additionally, this infection is associated with substantial healthcare and societal costs which is only in the USA; UTIs are responsible for 7 million clinic visits annually [2]. Except among infants and the elderly, the infection occurs more commonly in women than in men and it was estimated that about 40–50% of women experience one episode in their lives and 20–30% of them have other episodes [3]. For women between 1 year and up to 50 years, UTI and recurrent UTI (rUTI) are predominantly diseases [3]. rUTI is mainly associated with abnormalities of the urinary tract detected after kidney transplantation or also secondary to end-stage renal disease. Moreover, a significant proportion of patients who develop rUTI have no identifiable causes [4].

UTI is mostly caused by bacteria, through other microorganisms such as fungi and viruses that are rare etiologic agents [5]. This type of infection can be classified as complicated or uncomplicated. Uncomplicated UTI is the most common type of infection and mainly occurs in the absence of functional or anatomical abnormalities within the urinary tract. The complicated one occurs in the presence of an abnormal urinary tract that increases susceptibility to infection [1].

Among the uropathogen, *Escherichia coli* is the most common bacteria (75–90% of isolates) in both the community and hospital infections, whereas other pathogenic bacteria such as *Proteus mirabilis*, *Staphylococcus saprophyticus* (with particularly frequent isolation from

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younger female), *Enterococcus faecalis*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* each are less important [1–3]. The uropathogenic bacteria express fimbrial adhesions that they attach to the glycolipids and glycoproteins on the epithelial surface. In this way, bacteria can overcome the flow of urine and maintain in the urinary tract. The bacteria also produce other substances such as toxins, hemolysin, and colony-necrotizing factors. These agents disrupt epithelial integrity, permit bacterial invasion, and, therefore, enhance the risk of infection [6]. Uropathogens also can internalize into host epithelial cells and divide inside there, so that it provides a reservoir for recurrent infection [1].

In most cases, these uropathogens begin to colonize the surface of the perineum and periurethral and precede the development of infection. Colonization of bacteria could be inhibited by the normal microbiota, such as *Staphylococcus epidermidis*, Lactobacillus spp, and Corynebacteria [7]. Additionally, bacterial colonization and initial infection were eliminated by host defense mechanisms in the bladder. The foreign bodies such as urinary catheters or stone in the urinary tract provide an inert surface for bacterial colonization [3].

Female anatomy, age, sexual activity, certain types of birth control, and menopause are the most risk factors for UTI. Other risk factors are urinary tract abnormalities, blockages in the urinary tract, suppressed immune system, catheter use, and a recent urinary procedure [8].

Several types of antibiotics have been used to treat UTIs. Antibiotic therapy is an effective approach and reduces the duration of symptoms. Empirical treatment is usually with 3 days of antibiotics which achieves a cure in 85–90% of women. This type of regimen is equivalent to longer regimens and also is more effective than a single-dose administration [1, 9]. Various regimens have been used to treat UTI; for men, quick antibiotic therapy for at least seven days is recommended. In the patients treated in the first line, the administration of trimethoprim and nitrofurantoin is currently used. Second-line antibiotics such as quinolones should be considered for patients with prostatitis [10]. NHS Clinical Knowledge Summaries recommend various antibiotic therapy regimens: (1) seven days of ciprofloxacin, co-amoxiclav, or cephalexin or (2) 14 days of trimethoprim for men and non-pregnant women, and (3) 7–10 days of cefalexin for pregnant women. Severe infections require hospital care and treatment with broad-spectrum parenteral antibiotics and admission for intravenous fluids.

In the last decades, the extensive use of antibiotics has resulted in the emergence of antibiotic-resistant bacterial pathogens and leads to the spread of antibiotic resistance. Additionally, because of the chronic nature of UTIs and the potential for antibiotic resistance, a promising approach to prevention and treatment is favorable. These days various approaches have been developed to overcome the problems associated with antibiotic resistance [11–13]. Complementary and alternative medicine (CAM) has been recognized as an effective approach for the treatment of infection by antibiotic-resistant bacteria [11, 14–16]. CAM consists of a wide range of products such as natural compounds, dietary supplements as vitamins and minerals, and also probiotics [17]. This type of medicine has been attracted great attention in modern countries. For example, according to statics, 1.8% of children in the USA are treated with CAM. However, the real frequency of CAM is estimated higher than this amount. Clinically research suggests the best natural options for long-term prevention include probiotics, medical herbs, vitamins, and elements that have also been shown to prevent UTIs [18–20]. So, we could hope that using CAM in the treatment of UTI could provide desirable results, especially when combined with a routine antibiotic regimen. In the present review, the most important classes of the compound which have been used in CAM are mentioned. By using these natural remedies along with conventional antibiotic therapies, better results were obtained.

2 Main text

This review was based on data extracted from published papers with the search terms of urinary tract infection, herbal medicine, vitamin, probiotics, supplements, and antibacterial resistance which are available in all relevant databases, especially PubMed, Web of Science, Scopus, MEDLINE, and EMBASE, without limitation up to August 1, 2020.

2.1 Herbal medicine

In recent years, the use of medicinal herbs in the prevention and treatment of various diseases has been increased [13, 21]. Complimentary therapy with medicinal herbs is a research area that may be deserving of special attention. The complementary therapy of antibiotics with medicinal herbs showed mainly synergistic effects [11]. In many studies, herbal medicines could reduce bacterial resistance to antibiotics, remarkably [15, 16]. So, in many cases, patients may benefit from this type of therapy. It was shown that herbal medicines could play an important role in the treatment of a type of UTI [22]. Since several plant antimicrobial compounds contain various functional groups in their structure, the antimicrobial activities are attributed to multiple mechanisms [13]. The chemical compounds presented in herbal medicines evolved to protect the plant from pathogenic microorganisms and therefore could prevent or treat infections in animals. Many of these compounds are renally excreted

so that they are specifically useful as urinary antiseptic agents. Two major mechanisms are involved in the antimicrobial properties of these compounds. Some of them directly kill microbes and some of them interfere with microbial adhesion to epithelial cells [23]. These herbs play an important role in assisting to resolve UTI. Here, we briefly review the role of medicinal herbs and their variant in the treatment of infections. Some of these herbal medicines with more details are illustrated in Fig. 1.

2.1.1 Arctostaphylos uva-ursi

Arctostaphylos uva-ursi (bearberry) is a plant species of the genus Arctostaphylos. The leaves of this plant have been traditionally used because of their diuretic properties [23]. The plant has been used for the treatment of infectious diseases, especially for UTIs. The herb is approved in Germany for the treatment of bladder infections and effective against *E. coli* in the bladder [24].

The leaves of the plant are responsible for the therapeutic actions which contain the glycoside arbutoside. This compound is hydrolyzed in the bowel to glucose and the aglycone hydroquinone which is absorbed and glucuronidated in the liver. Hydroquinone glucuronide is then carried to the kidneys and excreted in the urine. In the alkaline condition of urine, the hydroquinone glucuronide will decompose automatically and hydroquinone

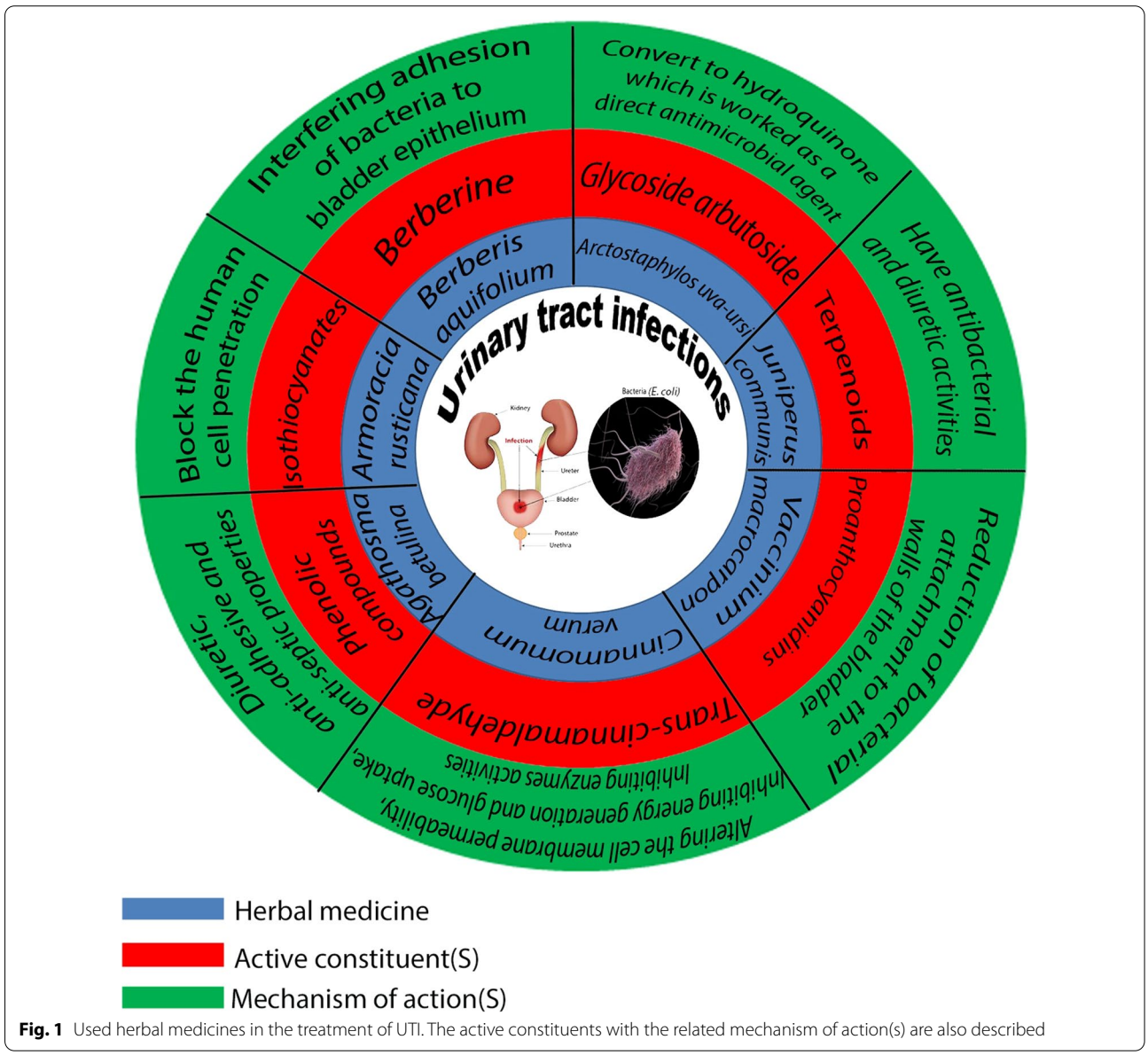

Fig. 1 Used herbal medicines in the treatment of UTI. The active constituents with the related mechanism of action(s) are also described

which is worked as a direct antimicrobial agent will be released [23].

It should be noted that based on information from laboratory researches exposure to synthetic hydroquinone for the long-term may be carcinogenic, so that it is recommended the consecutive consumption of this herbal medicine should not be extended more than two weeks.

Tannins presented in this plant could potentiate the in vitro antibacterial activities of β-lactam antibiotics against methicillin-resistant *S. aureus* (MRSA). Consequently, due to that whole plant extracts contain other constituents that increase antibacterial activities, it is recommended to use whole plant extracts instead of isolated arbutoside.

2.1.2 Juniperus communis

Juniperus communis (juniper), which belongs to the *Cupressaceae* family, and other closely related species including *Juniperus monosperma* (Engelm) Sarg and *Juniperus osteosperma* (Utah juniper) show remarkable antimicrobial activities [25]. It was reported that terpenoids in the leaf of the herbs are responsible for the antibacterial and diuretic activities of the herbs [23]. Schilcer reported that Juniper oil was effective against urinary tract infections [26]. Leaf and berries of the plant show antimicrobial activities against urinary tract infections. The main antibacterial constituent of this plant is terpinen-4-ol, a volatile oil, which plays an important role in the treatment of UTIs [27]. This plant also contains other active agents such as oxygenated sesquiterpene, β-pinene, sabinene, monoterpene hydrocarbons, limonene, and myrcene [22]. It should be noted that the volatile oil of juniper contains nephrotoxic compounds, especially hydrocarbon terpenoids. However, these adverse effects might only be seen after receiving high doses which far exceeded the therapeutic dose [23].

It was indeed previously demonstrated that the extracts presented diuretic activity [27]. The juniper leaf infusions show more diuretic activity than the volatile oil, which suggests that other constituents contribute to the diuretic activity of the herb.

2.1.3 Vaccinium macrocarpon (cranberry)

Many researchers have suggested that cranberry is active against UTIs. The plant belongs to *Ericaceae* family and can be potentially active against *E. coli*, the leading causes of bacteria-mediated UTIs, by reduction of bacterial attaching to the walls of the bladder, and then, the bacteria are more likely to be washed out during urination. Cranberry juice intake leads to measurable protection against both sensitive and resistant strains of *E. coli* [28]. It could also inhibit the binding of bacteria to gastrointestinal mucosa [29]. It was shown that cranberry juice consumption reduced the biofilm formation of both Gram-negative and Gram-positive uropathogens [30, 31].

Cranberry contains proanthocyanidins, which are stable phenolic compounds and contribute to the anti-adhesion activity against *E. coli*. Also, the in vitro antibacterial activities of cranberry extracts and juice against other pathogens such as *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, and *P. mirabilis* have been previously demonstrated [32]. Cranberry proanthocyanidins mainly contain A-type and B-type linkages, while in comparison with B-type linkage, A-type linkage is more effective in preventing adhesion of P-fimbriated uropathogenic *E. coli* to uroepithelial cells of the bladder and responsible for anti-adhesion activities of the extract, therefore inhibiting the ability of *E. coli* to infect the urinary mucosa [33, 34].

Cranberry also contains other biologically active constituents such as anthocyanidin, catechin, flavanols, myricetin, quercetin, and phenolics which are supposed to be responsible for its activities [35].

The other possible mechanism of action of cranberry might be related to acidification of the urine; however, it only causes temporary effects, and the changes last about 15 min in most people. Therefore, this mechanism could not be of relevance.

Due to these health benefits of cranberry extract, different commercial formulations of the extract exist in the market. In acute situations, the usual dose of the juice is 250–500 ml two to three times daily and for prevention consumption of 250–500 ml per day is enough. The solid dosage forms such as capsules that contain concentrated cranberry extract are also available. In acute situations, taking 2–3 capsules two to four times per day and taking 1 two to three times daily for prevention are recommended [36].

In summary, the existing data indicate the beneficial effects of cranberry preparations against UTIs; however, these effects are mainly related to prophylactic activities by preventing the development of infections or in combination with conventional antibiotics and solely intake of the herb is not recommended for UTI treatment.

2.1.4 Vaccinium myrtillus (Blueberry)

Blueberry has extensively been used traditionally to treat and prevent UTI. Blueberry extracts contain similar constituents as cranberry extracts, and the extracts possess similar anti-adhesive activities against uropathogenic bacteria and the bacteria are significantly less able to adhere to the walls of the bladder [24, 37]. Tannins are the most active constituents of blueberry extracts against UTI.

2.1.5 Cinnamomum verum (Cinnamon)

Cinnamon belongs to the Lauraceae family and shows antioxidant and antibacterial activities. It contains bioactive phytochemical compounds such as trans-cinnamaldehyde, eugenol, trans-cinnamyl acetate, and proanthocyanidins which have been used in the treatment of UTI.

Amalaradjou et al. showed that trans-cinnamaldehyde as an essential oil was able to inhibit biofilm formation of *E. coli* on urinary catheters by downregulating major virulence genes in the bacteria.

Various mechanisms are involved in antibacterial activities of essential oils: (I) due to their hydrophobicity, these molecules could target the lipid-containing bacterial cell membrane and mitochondria and alter the permeability which finally leads to leakage of ions and other cell contents, (II) inhibiting energy generation and glucose uptake, and (III) inhibiting activities of important enzymes such as amino acid decarboxylases [38].

2.1.6 Agathosma betulina (buchu)

A. betulina is one of the oldest known herbs for the treatment of uncomplicated UTI [39]. The leaves of the herb contain various phenolic compounds and have been used as an herbal remedy for urinary tracts, because of the diuretic and antiseptic properties. In a study, it was demonstrated that the ethanolic leaf extract of *A. betulina* showed antibacterial activities against *E. coli*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, *S. aureus*, *Staphylococcus saprophyticus,* and *E. faecalis* [40]. For a preparation containing the leaves extract of *A. betulina*, the anti-adhesive properties were investigated, and the results showed the anti-adhesive effects of the preparation by interacting with T24 cells [41].

2.1.7 Hybanthus enneaspermus

H. enneaspermus was studied to evaluate the in vitro antibacterial activity of various types of extracts against the major UTI including *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *P. mirabilis*, *E. faecalis,* and *S. aureus*. Among the extracts, ethanol extract showed the most antibacterial activities against the pathogens. The extract has various bioactive compounds such as flavonoids, terpenes, phenolic, and alkaloids that the therapeutic values are attributed to the presence of them.

2.1.8 Armoracia rusticana (horseradish)

A. rusticana (synonyms: *Cochlearia armoracia*, *Radicula armoracia*), which belongs to the family *Brassicaceae*, traditionally has been used to treat UTI. It shows favorable results for the prevention of recurrent UTI in pediatric patients [42]. It was demonstrated that the isothiocyanates of horseradish are responsible for their antibacterial activities of the herb. It was shown that these bioactive compounds could block the pathogenic process of human cell penetration by uropathogenic *E. coli* [43].

2.1.9 Hydrastis canadensis (Goldenseal)

H. canadensis (Goldenseal) has been used traditionally to treat various diseases such as digestive disorders, UTI, and skin diseases and also to check internal hemorrhage [44]. The rhizome, rootlets, and root hairs of the herb produce bioactive alkaloids and isoquinoline alkaloids [45]. These bioactive compounds may act similarly to proanthocyanidins, which are found in cranberry, in inhibiting bacteria from sticking to the bladder walls [24].

Berberine is a bioactive herbal alkaloid which presents in various medicinal plants such as *H. Canadensis*, *Berberis aquifolium*, *B. vulgaris*, and *B. aristata* [13]. This compound has been used in the treatment of UTI [46]. Notably, berberine exerts its antibacterial activities against UTI with interfering adhesion of *E. coli* to bladder epithelium.

2.1.10 Equisetum arvense (Horsetail)

E. arvense (Horsetail) is one of the oldest and most famous herbal medicine. The plant has a vast variety of therapeutic properties such as antibacterial activities [47, 48]. It was shown that the ethanol extract of the herb showed antibacterial activities against urinary tract pathogens including *E. coli*, *K. pneumonia*, *P. mirabilis*, *P. aeruginosa*, *S. aureus*, *S. saprophyticus,* and *E. faecalis*. The commonly known phytochemical compounds from Horsetail are alkaloids, phytosterols, tannin, triterpenoids, and phenolics [49]. Among them, phenolic compounds, especially flavonoids, present in the plant extracts are responsible for the antibacterial activities [50]. The essential oil of the herb was shown to possess broad-spectrum antimicrobial activities against tested strains.

2.1.11 Urtica dioica (nettle)

U. dioica (nettle) is a perennial plant of the *Urticaceae* family and has been traditionally used for the treatment of various diseases such as arthritis, rheumatism, UTI, kidney stones, and gingivitis [51].

It was shown that the plant extracts exhibit antimicrobial activities against various Gram-positive and Gram-negative bacteria such as *Bacillus subtilis*, *Lactobacillus plantarum*, *P. aeruginosa*, *E. coli*, *K. pneumoniae*, *S. aureus,* and *S. epidermidis* [52]. The leaf of the herb is a valuable source of biologically active compounds that show antimicrobial activities and could be used to treat infectious diseases [53].

It should be noted that the role of nettle in the treatment of UTI might be due to the diuretic activities of the herb [54].

2.1.12 Plantago major L.

P. major L. belongs to the Plantagináceae family and is used traditionally for the treatment of several diseases such as infectious diseases, pain relief, and reducing fever. The major chemical compositions of the herb include mucilage, organic acids, polysaccharides, and flavonoids. The herb traditionally has been used in Iran for pulmonary infections, stomach ulcers, and infections [55].

2.1.13 Other herbs

The essential oil of *Salvia officinalis* showed inhibitory activities against clinically isolated uropathogens [56]. *Barosma betulina* has been used traditionally for the treatment of various diseases such as UTI, catarrhal cystitis, and urethritis. The in vitro studies showed its antimicrobial effects against uropathogens. Other herbs that have been used for the treatment of UTIs but are not yet adequately studied include *Mentha piperita*, *Allium sativum*, *Terminalia chebula*, *Taraxacum officinalis,* and *Zingiber officinale* [22].

2.2 Nutrition therapy

Using nutrients is an integral part of the management, prevention, and treatment of UTIs. In most cases, micronutrients have been used to this end and they are included vitamins and minerals in general. The role of each agent in the prevention or treatment of UTIs is illustrated in Fig. 2.

2.2.1 Vitamins

Vitamin C possesses antimicrobial activities and is frequently used as an important supplement to antibiotic therapy for UTI [57]. Vitamin C is considered as a nonenzymatic antioxidant that slows down the production of free radicals and oxidation, which leads to strengthening the immune system and the deficiencies of vitamin C could place the persons at risk for infections due to the negative impacts on immune function [58]. Various studies have been conducted to show the efficacy of vitamin C in the management of UTIs. Yousefichaijan et al. studied the efficacy of vitamin C supplementation on UTI in children for 14 days. The results showed that vitamin C supplementation was able to control the symptoms of UTI, including dysuria, fever, urinary urgency, and also dribbling urine [59]. Ochoa et al. investigated the role of a daily intake of vitamin C for its effect on UTIs during pregnancy. They showed that daily usage of vitamin C has significant effects on the reduction of UTIs and also improving the health level of the women [60]. The formation of struvite stones is associated with UTIs by urease-producing bacteria. It was shown that the vitamin can modulate the struvite crystal formation in the presence of uropathogenic bacteria [61]. In another study, the combination of cranberries, a probiotic (*Lactobacillus rhamnosus*), and vitamin C has been used to evaluate the clinical benefits due to their additive or synergistic effects. The results showed that the approach might represent a safe and effective option in UTI management [62]. It was shown that nitrite may be generated by bacteria in urine during UTI. Acidification of nitrite leads to the formation of nitric oxide (NO) and other reactive nitrogen oxides that are toxic for a wide range of microorganisms. In a study, NO formation and bacterial growth in mildly acidified urine containing nitrite and vitamin C as a reducing agent were investigated. The growth of bacteria was markedly reduced by the addition of nitrite to acidified urine. Additionally, the inhibition was enhanced by vitamin C. These results help to explain the bacteriostatic effects of acidified nitrite because of the release of NO and other toxic reactive nitrogen intermediates and also the role of vitamin C in the treatment and prevention of UTI [63].

The positive role of vitamin A supplementation in the prevention and treatment of UTI has been mentioned previously [64]. Vitamin A has been used in the management of UTIs in children. The results of the study indicated that in the group of the children who received 200,000 IU of the vitamin in combination with antibiotics, the incidence of UTIs was lower than the control group [65]. In another study, vitamin A supplementation in addition to antimicrobial therapy was used to improve UTI symptoms and preventing renal scarring in girls who suffer from acute pyelonephritis. The results showed that vitamin A supplementation is an effective approach for improving the clinical symptoms of UTI and also reducing the renal injury and scarring following acute pyelonephritis [66]. Sobouti et al. studied the effects of vitamin A or E supplementation in addition to antimicrobial therapy for the prevention of renal scarring in acute pyelonephritis. According to the results, vitamins A or E supplements were effective in reducing renal scarring secondary to acute pyelonephritis [67]. The other study was conducted to determine the effect of vitamin A supplementation on the rate of permanent renal damage in children with acute pyelonephritis. It was demonstrated that the administration of vitamin A leads to a significant reduction in permanent renal damage [68].

Different mechanisms have been mentioned for the implication of vitamin D on the management of UTI. It was shown that tight junction proteins play important roles in preventing the bacterial invasion of the epithelial

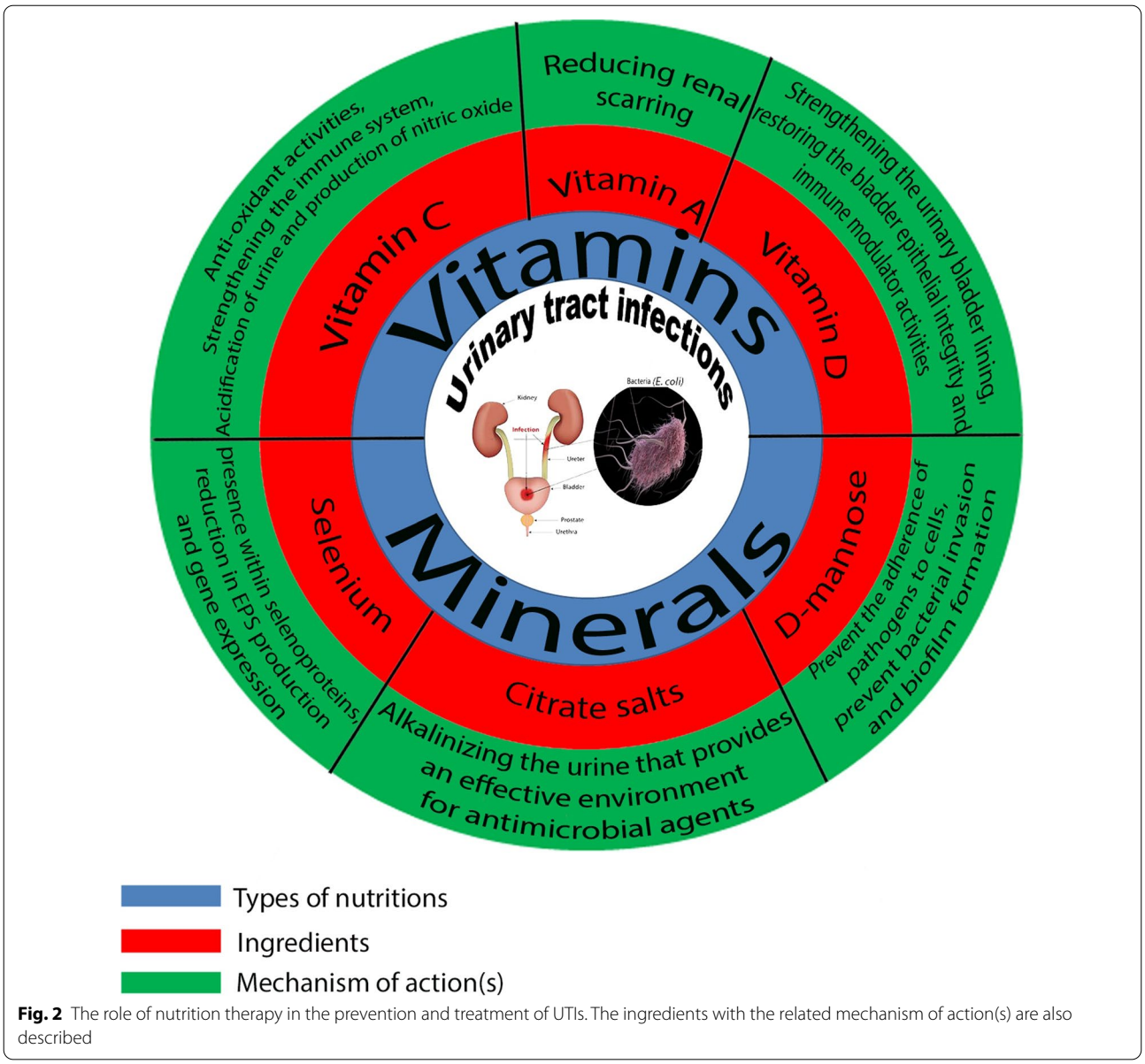

Fig. 2 The role of nutrition therapy in the prevention and treatment of UTIs. The ingredients with the related mechanism of action(s) are also described

barrier and supplementation with vitamin D could strengthen the urinary bladder lining and restore the bladder epithelial integrity [69]. Additionally, on the one hand, vitamin D could act as a local immune response mediator in UTI and on the other hand, enhancing vitamin D levels leads to modulate the innate immune system and provides a protective response to infection [70, 71]. The relation between the status serum level of vitamin D and the risk of UTI has been studied extensively, and the results showed a significant association between increased risk of UTI and vitamin D insufficiency, as an independent risk factor, especially in children [72–74]. Women with vitamin D deficiencies show a higher risk level of UTI during pregnancy [75]. Vitamin D deficiency is common and the proven risk factor for UTIs especially in girls and supplementation with vitamin D could prevent first-time UTI [76]. In a randomized clinical trial, the subjects who received vitamin D3 (20,000 IU per week) for five years showed better prevention against UTI [77]. Together, these results demonstrate that vitamin D supplementation provides a potent weapon in the prevention of UTI.

2.2.2 Minerals

The role of zinc in the management of the infectious disease has been described extensively [17, 78]. It was shown

that the element increases the response to treatment in many infections and active against different pathogens such as *E. coli*, *Mycobacterium tuberculosis*, *Salmonella* typhi, and *Streptococcus pyogenes* [79–81]. The incidence of zinc deficiency in infectious disease clinics has been reported extensively [82, 83]. The results of the Mohsenpour et al. study showed that serum zinc levels in people with recurrent UTI were lower than those in the control group. So, the zinc level could be assumed as a risk factor for recurrent UTI [84]. In another study, the relation between serum zinc levels in children inflicted with UTI and the control group was assessed. According to the data, lower zinc levels were associated with susceptibility to UTI, and therefore, zinc administration has been suggested [85].

Microbial infections are often associated with selenium deficiencies. The main physiological properties of this micronutrient are directly attributed to its presence within selenoproteins [11]. Selenium at a certain concentration was effective in preventing uropathogenic *E. coli* biofilm formation on urinary catheters. Further, the inhibitory effects were associated with a reduction in EPS production and gene expression of the bacteria. Additionally, at higher concentrations, selenium was effective in inactivating preformed bacterial biofilms on catheters within 3 days of incubation. These observations suggested that selenium could be potentially used in the control of bacterial biofilms on the catheters [86]. Also, it was shown that selenium-containing analogs of L-proline and L-cystine are effective in the treatment of UTI [87]. A study was conducted to compare the blood level of retinol and selenium in a person who suffered from minor lower urinary lesions. The results showed that there was a significant difference in the mean blood level of selenium between cases and control groups [88].

Copper, Cu, is an essential micronutrient for optimal innate immune function, and the nutritional deficiency of this element leads to increased susceptibility to bacterial infections [11]. During clinical UTI, uropathogenic *E. coli* upregulated the expression of copper efflux genes in patients. And, this element as a host effector could be involved in protection against pathogen colonization of the urinary tract [89]. Moreover, Cu export transport in bacteria has been addressed as an important virulence and fitness determinants during UTI [90]. Copper supplementation in drinking water has been suggested as an effective approach to reducing *E. coli* colonization in the urinary bladder of the animal model [91].

2.2.3 Other agents

Citrate salts could be used in the management of UTI due to their ability to alkalinize the urine, and alkaline urine is helpful for UTI symptoms such as dysuria. It was shown that by the administration of sodium citrate in women with UTI problems for 48 h, the symptoms were significantly improved in 80 percent of the subjects [92]. Additionally, alkalinity in the urine provides an effective environment for some of the antimicrobial agents such as uva-ursi and berberine to perform their function [37]. The role of these salts in the treatment of urinary candidiasis has been mentioned in an earlier study [93].

Simple sugars such as D-mannose could prevent the adherence of pathogens to uroepithelial cells. Various evidences show that the implementation of mannose exerts beneficial results in the treatment of UTI. It was shown that a mannose-specific lectin exists on the surface of adherent strains of *E. coli* and the sugar acts as the primary bladder cell receptor site for UPEC to bind [94]. Likewise, it was reported that in the adhesion of UPEC to the uroepithelial cells, the first step is the binding of FimH adhesin to the bladder epithelium through the interaction of mannose moieties with the host cell surface [95]. So, the use of the sugar or its analogs can help to block the adhesion of *E. coli* to the bladder epithelium. The efficacy of these sugars in controlling UTI has been studied previously [96–98].

An in vivo study indicated that demonstrated D-mannose in mice not only blocked adhesion of *E. coli* to the epithelium of the urinary tract but also prevent bacterial invasion and biofilm formation [99]. Also, in the presence of D-mannose, the adherence of clinical isolates of *E. coli* was inhibited remarkably [100]. Oral supplementation of D-mannose decreases the perception of lower urinary tract symptoms in postmenopausal women [101]. The results of another study indicated that D-mannose efficiently blocked the adhesive properties of all type 1 fimbriae-positive isolates of *E. coli* in low concentration, but did not show any bacteriostatic effects [102]. The results of another study demonstrated that antibiotic therapy in combination with long-term enrichment of the diet with D-mannose leads to prolongation of the inter-relapse period of uncomplicated UTI [97].

The effects of different derivatives of the sugar in the control of UTIs were studied. Klein et al. synthesized and evaluated the efficacy of these sugars in blocking bacterial-host interaction. Among them, para-substituted biphenyl derivative was the most effective agent in controlling UTIs. Following oral administration of this compound, bacterial numbers were reduced by twofold and fourfold in the urine and bladder, respectively [103].

2.3 Probiotics

Probiotics are living microorganisms which when administered in certain numbers exert a health benefit on the host [104]. The clinical efficacy of probiotics for adjunct treatment in the treatment of different

gastrointestinal and urinary tract infections has been addressed previously [105]. They have demonstrated positive effects in the treatment and prevention of rotavirus diarrhea and alleviation of the antibiotic-associated intestinal adverse effects by recognizing the commensal microbiota and also restoration of the microbial ecosystem after an imbalance or infection [106]. Probiotics are clinically proven to be effective in the management of UTI including accelerating recovery after UTI and also decreasing recurrent UTI in children [107]. It must be emphasized that, for better effectiveness of probiotics, they must be able to colonize in the intestinal and/or urogenital region [108]. These positive effects of probiotics might be attributed to the intrinsic properties of microorganisms. For example, lactobacilli are able to grow in an environment with $pH \leq 4.5$, where they could multiply and produce additional antibacterial molecules, such as bacteriocin and hydrogen peroxide [109, 110]. Besides these advantages, probiotics could produce biosurfactants that inhibit the growth of uropathogens by reducing the adhesion of the pathogens to the uroepithelium. Moreover, lactobacilli could co-aggregate with uropathogens and block their adhesion to the urinary tract and also displace previously adherent uropathogens from uroepithelium. This process can create a microenvironment in which the inhibitory products of lactobacilli can concentrate on the pathogens and therefore inhibit the pathogens [111]. It is worth noting that the most effective lactobacilli for controlling UTI are *L. rhamnosus* GR-1 and *L. reuteri* B-54 and RC-14 which have been proven [108].

The common vaginal Lactobacillus species were used to investigate the inhibition of *E. coli* growth. The results showed that when *L. crispatus* was incubated with clinical *E. coli* strains, the growth of *E. coli* was inhibited in the acidic environment [112]. Wolff et al. studied the changes in the ratio between uropathogens and Lactobacillus (U/L) within the lower UTI in response to oral probiotic supplementation. Based on the results, there were no changes between groups in terms of microbiota diversity and the use of oral probiotic did not alter the U/L ratio [113]. The physicochemical cell surface, adhesion properties, and the antagonistic activity of recombinant *Lactococcus lactis* containing the Ama r 2 gene against the *E. coli* causing UTI in humans were studied. The results indicated that this recombinant probiotic showed desirable properties and the Ama r 2 gene expression did not affect the positive probiotic properties [114].

The ability of a clinically isolated probiotic, *L. fermentum* strain 4–17, to adhere to human intestinal was studied. *L. fermentum* strain 4–17 showed appropriate anti-adhesive properties against human pathogenic bacteria [115].

Osset et al. [116] studied the antimicrobial activities of 15 Lactobacillus species against pathogens. Among them, *L. crispatus* could block pathogen adhesion efficiently.

The results of another study revealed that a pyelonephritic *E. coli* was sensitive to *L. rhamnosus*, *Bifidobacterium lactis,* and *Bifidobacterium longus* and these probiotics were able to suppress the growth of enteric and urinary pathogens [117].

Oral administration of multispecies probiotic formulations showed antimicrobial activities against the pathogens that are responsible for vaginal dysbiosis and infections [118].

The effects of vaginal suppositories of probiotics for the prevention and treatment of UTI have been studied previously. The concept for instilling probiotic into the vagina might be related to the belief that by the presence of probiotic as the dominant bacterium the ascension of uropathogens into the bladder was restricted by various mechanisms, such as interfering with pathogen adhesion, biofilm formation reduction, reducing the expression of virulence factors, and also modulation of the host's defense systems to better combat infection [108]. The *Lactobacillus* strains inhibited the growth of *E. coli* via the production of organic acids. Additionally, the adhesion and internalization of *E. coli* into HeLa cells were reduced by probiotics [119]. Reid et al. investigated the effect of probiotic lactobacilli in controlling acute UTI in women. Based on the results, recurrence reduced remarkably in the Lactobacillus group compared to the placebo group [120].

Taken together, the results of these aforementioned studies demonstrated the potential benefit of probiotics in controlling UTI.

Additionally, site-oriented probiotic therapy has been recognized as one of the most promising therapeutic alternatives for the prevention of UTI in post-antibiotic therapy [112].

While most clinical research showed using these natural substances represents a promising approach, further studies are needed to prove their mechanism of action and clinical effectiveness. It should be noted that formulating these substances in a single dosage form and their side effects and interactions with each other are the main limitations of developing a new formulation.

3 Conclusion

Treatment with non-antibiotic agents is a good approach to reduce the risk of incidence of UTI and also decrease the symptoms of the illness. Among these agents, natural substances, nutrients, and probiotics attract attention. Each of these agents acts by a different mechanism, and therefore, co-formulation of them in a single dosage form maybe provides the natural formulation that is effective

for both preventive and therapeutic approaches in the management of UTI.

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BK collaborated in the original idea, concept, design, and writing and drafting the article. SDF and RA contributed to data interpretation, writing, and drafting of the article. BSFB contributed to all stages of the process and mainly participated in drafting the article, writing, and editing the final version to be published. All the authors read and approved the final version of the manuscript.

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