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ISSN: 2692-4706 DOI: https://dx.doi.org/10.17352/aur

Review Article

Western herbal remedies for Urinary Tract infections

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Received: 26 June, 2020
Accepted: 18 July, 2020
Published: 20 July, 2020

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Keywords: UTIs; Western herbal medicine; Alternative therapy; Herbal anti-adhesives; Herbal anti-microbial

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Abstract

Fourteen medicinal plants native to North America and Europe traditionally used for treatment urinary tract infections (UTIs) were reviewed for their traditional uses, pharmacological activities, Active compounds responsible for its therapeutic potential, mechanism of action of its active compounds and In Vitro and In Vivo studies of its activity in treatment of UTIs. Those medicinal plants were Junipers (*Juniperus spp.*), Uva ursi (*Arctostaphylos uva-ursi*), Rosemary (*Rosmarinus officinalis*), Goldenrod (*Solidago canadensis*, *S. virgaurea* and *S. gigantea*), Common nettle (*Urtica dioica*), Dandelion (*Taraxacum officinale*), Cranberry (*Vaccinium macrocarpon*), Corn silk (*Stigma maydis*), Couch grass (*Agropyrum repens*). Marshmallow root (*Althaea officinalis*), Hosretail (*Equisetum arvense)*, Goldenseal (*Hydrastis canadensis*). Buchu (*Agathosma betulina* and *A. crenulata*) and Oregon grape (*Mahonia aquifolium)*. All of those medicinal plants found to have various pharmaceutical activities making it potent herbal remedies for UTIs in addition to various human diseases.

Introduction

Urinary Tract Infections (UTIs) are one of the most common bacterial infections, with a frequency of 50%-60% in mature females [1] Urinary tract infections could be uncomplicated or complicated. Uncomplicated UTIs affects individuals with no neurological or structural deformities in urinary tract . Uncomplicated UTIs could be separated into infection of lower UTIs (cystitis) and upper UTIs (Pyelonephritis) [2]. Underlying factor for cystitis are gender, former UTI infection, genetic susceptibility, vaginal infection, sexual activeness, overweight and diabetes [3], whereas uncomplicated UTIs arises from presence of factors debilitates host immune defenses including renal transplantation, renal failure, urine retention due to neurological disorders, immunosuppression, presence of foreign bodies with urinary tract like indwelling catheters [4]. In the United states, the indwelling catheters results in 70-80% of complicated UTIs [5] with a total of one million cases per year [6]. Etiology of UTIs includes Gram- negative , gram- positive and fungi. Uropathogenic *Escherichia Coli* (UPEC) is the most common bacterial of all types of UTIs. In the cases of Uncomplicated UTIs, UPEC is followed in frequency by *K. pneumoniae*, *S. saprophyticus*, *Enterococcus faecalis*, Group B *Streptococcus* (GBS), *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida* spp. [7], whereas in complicated UTIs, UPEC is followed in frequency by *Enterococcus spp.*, *K. pneumoniae*, *Candida spp.*, *S. aureus*, *P. mirabilis*, *P. aeruginosa* and GBS [8].

The emergence and exacerbation of the bacterial drug resistance problem, beside other problems of antibiotic therapy as the adverse effects of hepatoxicity, nephrotoxicity, ototoxicity, mutagenicity and carcinogenicity; immunosuppression; eradication of beneficial gut and mucosal surfaces flora and allergic reactions [9], made most of antibiotics worthless in treatment of many cases of UTIs and directed global attention towards finding new therapeutic alternatives.

Herbal medicine is the most important alternative therapy for classical antibiotics. Scientific research on herbal medicine confirmed the therapeutic activity of vast majority of medicinal plants known in traditional medicine of different areas worldwide for their activity in treatment microbial infections and different human diseases [10,11].

Citation: Gatea Kaabi SA, Abdulrazaq RA, Rasool KH, Khassaf SA (2020) Western herbal remedies for Urinary Tract infections. Arch Urol Res 4(1): 049-060. DOI: https://dx.doi.org/10.17352/aur.000019

Medicinal plants in Western herbal medicine

Medicinal plants in Western herbal medicine are those plants native to North America and Europe and know traditionally to have therapeutic potential towards cased of UTIs. Fourteen medicinal plants were selected to reviewed according to its traditional use, Pharmacological activities, Active compounds responsible for its therapeutic potential, mechanism of action of its active compounds and In Vitro and In Vivo studies of its activity in treatment of UTIs.

Junipers. Junipers are coniferous trees and shrubs of the *Juniperus* of the family Cupressaceae. This genus contains about 50 and 67 species of junipers that are distributed throughout the northern hemisphere [12]. The antibacterial activity of different species of genus *Juniperus* was studied for *J. communis* [12], *J. procera* [13], *J. excelsa* [14], *J. phoenicea* [15] and *J. thurifera* [16].

Extracts of berries, aerial parts, fruit and bark of different species of this plant showed anti-bacterial activity towards G+ and G- bacteria and anti-fungal activity beside other beneficial biological activities as hepatoprotective activity [17], (Manvi and Garg, 2010), anti-Inflammatory Activity [18], anti-oxidant Activity [19], anti-diabetic and anti-hyperlipidemic Activity [20], analgesic activity [21], Anti-malarial activity [22], anti-cataleptic activity [23], neuroprotective activity [24] and anti-hypercholesterolemic activity [25].

The essential oil of berries of *J. communis* showed strong to moderate antimicrobial (Antibacterial and anti-fungal) activity [26,27], whereas Leaves Essential Oil (LEO) showed no or weak antimicrobial activity [28,29]. Solvent and aqueous extracts of *J. thurifera* leaves showed anti-bacterial activity towards only gram-positive bacteria as *S. aureus*, whereas all extracts exhibited anti-oxidant activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical [16].

Uva ursi. The scientific name of this plant is *Arctostaphylos uva-ursi* . The common name for this species is Kinnikinnick in Canada and United states, and it is one of several related species referred to as bearberry. The meaning of species name in Latin (*ūva ursī*) is " grape of the bear" which is similar to meaning of genus *Arctostaphylos* that means " bear grapes". This herb is found in Europe and northern America. Leaves of this plant has long been used as urinary anti-septic and diuretic for treatment of UTIs. The leaf extract of *A. uva-ursi* has been approved for treatment of UTIs in Germany by German Federal Institute for Drugs and Medical Devices. It is an Over-The-Counter (OTC) drug in the United kingdom, United states [30]. It is reported that leaf extract of *A. uva-ursi* has anti-septic, astringent and anti-inflammatory properties [31].

Little, et al. (2010) reported on their screening on 309 women suffering from UTIs that those used Uvacin (an over-the-counter product including uva-ursi) showed faster recovery duration comparing with non-users of this product. Only 14% of women was taken Uvacin under an advice, whereas only 1% without an advice [32]. Also, results for clinical trial on 57 women suffering from recurrent UTI that UVA-E product, which composed of water and alcohol extracts of leaves of *A. uva-ursi* and root extract of dandelion (*Taraxacum officinale*) showed that this product was effective in prevention of recurrent UTIs [33].

Leaf extract of this plant includes set of compounds as hydroquinone glycosides (mainly arbutin), flavonoids, tanins and terpenoids, and iridoids, but the antibacterial activity towards variety of pathogens including *E. coli*, the most causative agent of UTIs, was attributed to Arbutin Figure 1 [31].

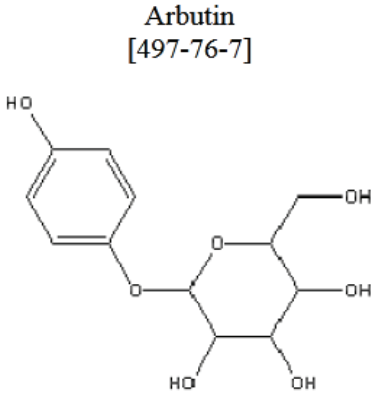

Figure 1: Arbutin , extracted from leaf of ***Arctostaphylos uva-ursi*** [30].

Arbutin, is transformed to Hydroquinone (HQ) that exhibited anti-microbial, disinfectant and anti-oxidant activities. It is also an blocker for melanin production, and thus used in drug formulae for treatment of skin cancer and in cosmetic products for skin-lightening [34,35] (Fujiwara and Suzuki, 1995 pat. appl.; Patrice, 1998 pat.). In a study of an experimental UV-induced pigmentation of forearm of 15 Korean men volunteers (aged 23-27 years old), the hyperpigmentation was suppressed in 43.5% of cases by using arbutin in a concentration of 100 mg/g [36].

Rosemary. *Rosmarinus officinalis* belongs to family Lamiacea. It is popular as a spice and medicinal plant in many countries. Extracts of found to have antibacterial, antifungal, antioxidant, anticancer, antidiabetic, anti-inflammatory and analgesic effects [37-41].

The antimicrobial activity of *R. officinalis* is attributed to diverse compound as phenolic compounds, rosmarinic acid, caffeic acid, carnosol, flavonoids including diosmin, zincquanine, luteolin and monoprenes such as camphor, cineole and borneol [42].

Rosemary is one of the most plant species that has high level of anti-oxidant activity making it most powerful plant in fighting bacteria and cancer. Level of anti-oxidant activity varies in plant samples owing to variation in individual genetic variation, growth conditions, geographical properties, climatic conditions, method of extraction, quality of plant and harvest date [43]. Rosemary is found to have an immuno-boosting properties, in addition to its remarkable antibacterial activity, making it so effective in treatment bacterial infections [44].

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Extracts of rosemary has been found more active towards gram-negative bacteria as than gram-positive bacteria. These extracts are active against many important pathogens as *E. coli*, *P. mirabilis*, *P. vulgaris*, *K. pneumoniae*, *P. aeruginosa* , *S. aureus*, *S. epidermidis* and *B. subtilis* [45-47].

Goldenrod. The scientific name of Canadian goldenrod is *Solidago canadensis.* It is an perennial herbaceous plant belongs to family Asteraceae. This herb is native to northeastern and north-central regions of North America, but it is invasive in other parts of North America, Europe and Asia. It is mostly grown as ornamental in flower gardens *[48]*.

Goldenrod is generally used for treatment of UTIs, Urolithiasis and prostate diseases. Alos, it is used for treatment of many other diseases as rheumatism, arthritis and skin diseases as eczema [49-51].

The extracts of *S. canadensis*, *S. virgaurea* and *S. gigantea* exhibits 6 major pharmacological activities as anti-bacterial, anti-inflammatory, immunomodulatory, anti-spasmodic, angalgesic and diuretic effects making these extracts an optimal herbal option for treatment of urinary tract infection [52,53].

A Non-randomized clinical trial study for the efficacy of extracts of S. *virgaurea* on treatment human cases of cystitis and irritable bladder by complex therapy with chemical drugs and extracts of S. virgaurea showed 90-100% increasing in the effectiveness of therapy, acceleration of recovery and reduction of likelihood of relapses with only 0.3% side effects in study population [54].

The antibacterial activity of *S. virguarea* was attributed to clerodane diterpenes, solidagoic acids C-I, cleroda-3,13(14)-dien-16,15:18,19-diolide and cleroda-3,13(14)-dien-15,16:18,19-diolide extracted and characterized after extraction by ethanol–ethyl acetate in a ration of (1:1) with extract of *S. virguarea* Figure 2 [55].

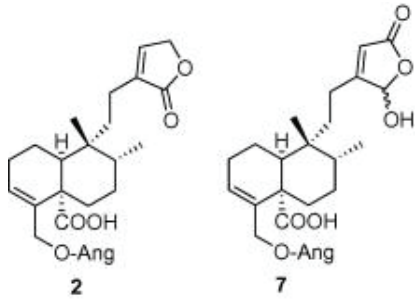

Figure 2: Cloredano diterpens isolated, purified and characterized by extraction of ***S. virguaurea*** with ethanol–ethyl acetate (1:1) [54].

Extraction of aboveground parts of 3 species of *Solidago* (*S. canadensis* , *S. gigantean* and *S. virgaurea*) by ethanol and hexane showed potent activity of such extracts towards Gram-positive bacterial pathogens of *S. aureus*, *S. faecalis*, *B. subtilis*, and Gram-negative pathogens of *E. coli*, *K. pneumoniae* and *P. aeruginosa*. The ethanolic extracts of *S. canadensis* showed strongest activity towards Gram-positive bacteria with minimal inhibitory concentration of 5-10 mg/ml, whereas ethanol extracts of *S. canadensis* and *S. gigantea* showed strongest activity towards Gram-positive bacteria too with minimal inhibitory concentration of 5-10 mg/ml [50].

Solvent and aqueous extracts of *S. canadensis* of rhizome and areal parts showed potent anti-oxidative activity by using three methods of assay of, Phosphomolybdenum assay, DPPH radical scavenging activity and lipid peroxidation assay. Extracts of areal parts with ethyl acetate and diethyl ether were most potent in equal measure , but reaction was slower in the case of diethyl ether assay. For rhizome extracts, The most potent anti-oxidative activity resulted from extract of ethyl acetate followed by extracts of butanol, diethyl ether, water and n-hexane, respectively [56].

The Essential Oils (EOs) of *S. canadensis* were tested for its antimicrobial activity towards plant fungal and bacterial pathogens and showed high activity towards most of plant fungal and bacterial pathogens [57].

Common nettle. Stinging nettle and nettle leaf are common names of *Urtica dioica* [Urticaceae]. This plant is worldwide distributed but it is native to Europe, much of temperate Asia and western North Africa. This species divided into 6 subspecies, 5 of them harbored stinging hollow hair on leaves and stems called trichomes, which act as hypodermic needles to inject " histamine " in human skin causing a stinging sensation up on contact that called " contact urticarial", a form of contact dermatitis [58].

Common nettle has many pharmacological activities, which are anti-oxidant activity, Anti-diabetic activity, Hepatoprotective activity, Anti-hyperlipidemic Activity, Diuretic Activity, Antiviral Activity, Antimicrobial Activity, Cardiovascular Effect, Anti-inflammatory, Analgesic and Anti-arthritic Activity, Immunomodulatory Activity, Anthelmintic Activity, Effect on Benign Prostatic Hyperplasia, Anticancer Activity, Hypotensive Effect [59].

Many of pharmacological activities of common nettle made it an ideal herbal remedy for UTIs and many other human diseases. Extracts of this plant showed antibacterial activity towards G+ and G- pathogens as *S. pyogenes, S. aureus*, *S. epidermidis*, *E. coli*, *P. aeruginosa* and *K. pneumoniae,*, but it is highly active against G+ bacteria [60-63]. The flavonoids patuletin isolated from extracts of this plant showed high antimicrobial activity towards bacterial and fungal pathogens with MIC of 0.001 , 0.002 and 0.02 g/ml for *C. albican*, *S. faecalis* and *S. aureus*, respectively Figure 3 [64].

The aqueous extract of whole plant found to have diuretic and natriuretic activity in rabbits [65]. Aqueous extracts of areal parts of this plant given orally at small dose (4 mg/kg/h) and big dose (24 mg/kg/h) resulted in an elevation of diuresis of 11 and 84% , respectively, and natriuresis of 28 and 143%, respectively, which indicated for potential diuretic activity [66]. The ethanolic extracts of this plant at dose 1 1 g/kg (p.o) had no diuretic activity , but in dose of 500 mg/kg (i.p), it resulted

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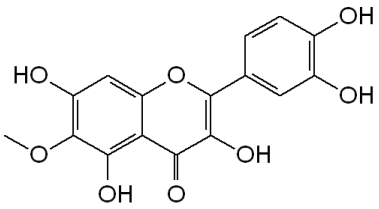

Figure 3: Patuletin extracted from Urtica dioica that has antibacterial and antifungal activity [58].

in increased urine output [67]. In rat model , an increase of 20% in urine production was reported after administration of oral dose of 1g/kg of 10% decoction of leaves powder [67]. The diuretic activity of nettle leaf is approximately equal to 25% of that achieved by hydrochlorothiazine (25 mg/kg) [68].

A methanolic extract of aerial parts of this plant was assayed for its anti-urolithiatic activity in a rat model of renal stone induced by ethylene glycol and ammonium chloride. In control group, results showed an increase in urinary calcium oxalate and creatinine levels in addition to increased level of renal deposition of calcium, oxalate and creatinine, whereas in treatment group with ethanolic extracts of this plant, a significant decrease in urinary level of calcium and oxalate and significant decrease in the level renal deposition of calcium and oxalate [69].

Dandelion. The *Taraxacum spp*. is commonly named dandelion. It perennial herbaceous plant of family Asteraceae (Compositae). Dandelion is corruption of the French *" dent de leon"*, meaning “lion’s tooth due to shape of toothed margins of leaves. The genus is native to Eurasia and North America [70].

Extracts of different parts of Dandelion of roots, leaves and flowers had various biological activities or pathological state in which activity has been documented as anti-oxidant activity, anti-inflammatory, anti-hyperlipidemia activity, anti-hyperglycaemic activity, anti-cancer activity, thromposis and ischaemia, liver disorder, gastroenterology, antibacterial and antiviral activity, analgesic activity, immunomodulatory acitivity and urinary disorders [71].

Hexane extract of *T. officinale* leaves showed high antibacterial activity against *S. aureus* with MIC of 200□g/ml, moderate activity towards *E. coli* and *K. pneumoniae* with MIC of 400 μg/ml and low activity towards against P. mirabilis with MIC of 800 μg/ml [72].

Similar results were reported with methanol hydrophobic crude extract of *T. officinale* . Methanol extract of *T. officinale* showed strongest activity against *S. aureus* and *B. subtilis* [73].

Dandelion leaf extract has potent diuretic activity as those of furosemide [74]. Dandelion exhibits high diuretic activity much more than those of other herbs as equisetum and juniper berry [75,76].

A clinical trial study on human for confirmation of diuretic activity of dandelion leaves showed that ethanol extracts of dandelion exerted diuretic action on sample size of 17 volunteers [77].

Cranberry. *Vaccinium macrocarpon* known as large Cranberry or American cranberry belongs to the family Ericaceae. it is an evergreen groundcover shrubs that grow up to four meters. Cranberry is native to North America. Its flower is pink colored and berries are reddish black in color. This plant is widespread throughout cool temperature northern hemisphere [78].

Cranberry used by native American indians for treatment of UTIs [79]. Chemical composition of cranberry fruit is water (Up to 88%), Catechins, anthocynidins, Flovonoids, Triterpinoids, in addition to high concentration of Vitamin C of about 200 mg / kg of fresh fruit [79]. The anthocyanidins and proanthocyanidins (PAC) are responsible for plant defense against microbes [79,80]. Numerous studies reported a connection between administration of Cranberry and prevention of UTIs [80-84]. The underlying mechanism of ability of cranberry in prevention and treatment of UTIs is based on prevention of bacterial adherence to uroepithelial cell, hence, stop colonization and invasion of bacterial pathogens. This property is attributed to two components of cranberry, Fructose and proanthocyanidins (PACs). The Fructose blocks type 1 fimbriae (Mannose sensitive) and PACS blocks P fimbriae (mannose resistant). PACs are subdivided into Type A and B. Only Type A, that present in Cranberry, can block P fimbriae. Figures 4,5 [85].

Cranberry products are available commercially now at different pharmaceutical forms as capsules, pills, Juice, syrup and lozenges. Hundreds of cranberry products are available now as cranberry alone or with other components as a herbal remedies for treatment of UTIs.

corn silk (*Stigma maydis*). *Zea mays* L. [Faimily Gramineae]. Native to central parts of America and distributed along parts of North America, and distributed to all over the world [87]. Corn silk (CS) or stigmas is the yellowish threads extends from female flower of *Z. mays* [88]. Historically, the native Indian

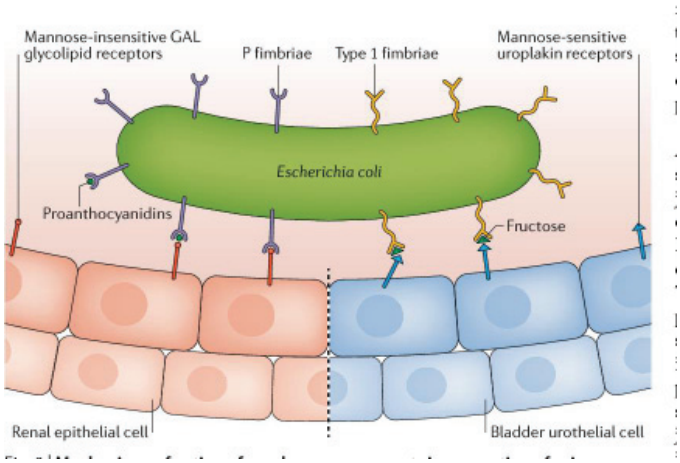

Figure 4: Mechanisms of action of anti-adhesive activity of Cranberry. On Renal epithelial cells (Pink cells), Proanthocyanidins binds P fimbriae and prevent it from binding to Mannose-insensitive GAL glycolipid receptors. On bladder epithelial cells, Fructose binds to Type 1 fimbriae preventing it from binding to Mannose-sensitive uroplakin recptors [85].

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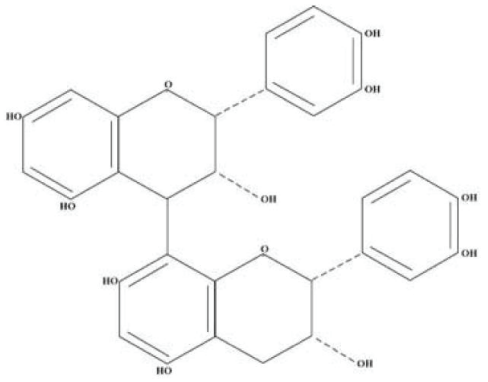

Figure 5: Proanthocyanidin.

American used CS for treatment of UTIs beside treatment of malaria and heart problem (?). It is used traditionally worldwide for treatment of different diseases related with genitourinary system as cystitis , prostate disorders, renal stones, urinary infections and bedwetting [89-92].

CS has many pharmacological activities as antioxidant activity [93,94], Kaliuresis and Diuresis Effect [91], Hyperglycemia Reduction [95], Anti-depressant Activity [96], Anti-hyperlipidemic Effects [97], Anti-diabetic Effects [96], Anti-inflammatory Activity [98], Neuroprotective Effects [99].

Alam (2011) reported that CS had no anti-bacterial action towards G+ and G- bacteria [100], but many other studies confirmed high antibacterial activity towards Gram-positive pathogens [101-103].

Many compounds present in CS extracts with different solvents active against different bacterial and yeast pathogens. Flavonoid glycosides are amongst the most potent antibacterial compounds in CS. Two compounds of flavonoid glycosides were isolated and tested towards bacterial pathogens and *Candida albicans*. Figure 6. Those compounds were found to active towards G- bacterial pathogens like *P. aeruginosa*, *P. mirabilis*, *P. vulgaris*, *Shigella sonnei*, *Sh. flexneri*, *Salmonella paratyphi*, *S. typhi*, and G+ pathogens like *S. aureus*, *B. subtilis*, *B. cereus* and *Enterobacter aerogenes*, but not against *E. coli* and *Candida albicans* [102].

A Clinical trial study on 42 volunteer patients for treatment

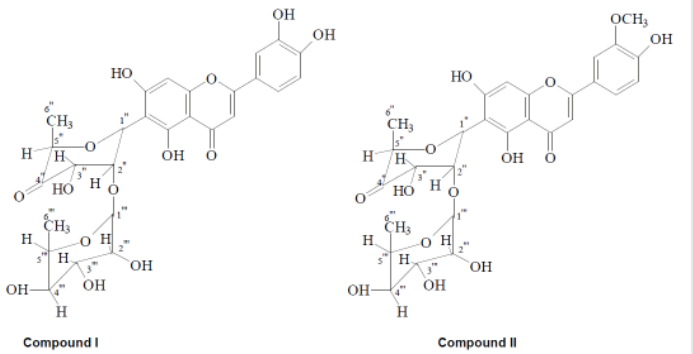

Figure 6: Chemical structure of two flavonoid glycosides isolated from solvent extraction of corn silk by methanol and fractionation with n-butanol . Compound I: is Maysin, Compound II: is maysin-3'-methyl ether [101].

of UTIs by oral administration of aqueous extracts of CS showed significant decrease in symptoms of UTIs accompanied with decrease in urine content of Pus cells , Red blood cells and Crystals with no side effects reported during study period. Those results were indicated for the efficacy and safety of CS extract in treatment of UTIs [104].

Couch grass [*Agropyrum repens*]. A perren. Or Common couch is, a perennial herb native to Most parts of Europe, Arctic region, Asia and northwest parts of Africa [105]. Extracts of rhizomes of this grass used traditionally in Europe as a remedy for uncomplicated urinary tract infection [106]. The European Medicines Agency published on 2011 that couch grass has diuretic activity and it is beneficial in the cases of minor urinary complaints to increase the flow of urine to alleviate pain related with such complaints [107].

Animal Rat model confirmed the diuretic activity of couch after oral and intra-peritoneal administration of aqueous extracts of this plant [108]. Two uncontrolled clinical studies showed positive effects of hydrochloric extracts of couch on cases of cystitis, irritable bladder, urethritis and prostatitis [109] in addition to cystitis and prostatic adenoma [110].

Various pharmacological properties of couch were reported including hypoglycemic activity [111], anti-hyperlipidemic activity [112], Anti-inflammatory activity [113] that is comparable to activity of glucocorticoid activity [114] and diuretic activity [115] and Anti-adhesive activity [116].

The diuretic activity of couch is attributed to sugar " Mannitol " present in high percentage of chemical constituents in this herb, and it is called as an 'osmotic diuretic' as it is absorbed totally from large intestine and excreted largely from kidney tubules , hence, kidney tubules excreted large amounts of water to maintain osmotic pressure. Besides, Vanillin and saponins present in Couch extract results in diuretic effects. Both of anti-adhesive and diuretic activities of couch results in flushing out bacterial pathogens in cases of UTIs [115]. The commercial product for the fluid extract of rhizomes of couch grass (Acorus® drops) directed for treatment of UTI or irritable bladder were monitored for its efficacy on clinical cases. Results of treatment of 313 patients for duration of 12 days with 50-60 Acorus® drops showed that 69-91% of patients were relieved during therapy course and between 32-53% of patients were recovered completely from all symptoms of their disease. Acorus® drops was well tolerated from patients with no side effects seen in any patients towards that drops making it an effective and safe therapy for UTI and irritable bladder [109]. In an open clinical trial of ethanolic extract of couch (60 drops ×3 times daily) for 28-31 days on 99 volunteer patients with micturition disorders. Results showed that symptoms of dysuria, nycturia, urge incontinence owing to presence of prostatitis or adenoma of prostate or cystitis were mostly reduced in 44.4 to 100% of patients. Urinalysis showed all parameters of blood cells, pus cells, protein and epithelial cells were normalized and 96% of patients confirmed that this therapy is good or very good while no adverse effects reported in any case [109].

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The an acetone extract (AAE) of couch showed significant anti-adhesive activity towards T24 bladder cells at concentration of 250 µg/ml. Bioassay fractionation of AAE revealed that the compound hexadecyl-coumaric acid ester ((E)-hexadecyl-3-(4-hydroxyphenyl)-acrylate) was responsible for the anti-adhesive activities of AAE of couch by specific invasion assay [106].

Marshmallow root. *Althaea officinalis* L. (Malvaceae) *known as marshmallow and althaea, is a perennial* herb about 60-120 cm high. Marshmallow is native to USA, Asia and Europe [116]. Traditionally it is used for treatment of different infectious and inflammatory diseases of skin, gastrointestinal and urinary tracts [117].

Various pharmacological activities were reported for *A. officinalis* as Anti-complement activity [118], Anti-Inflammatory and immunostimulant activity [118,119], Antitussive activity [120], Antiviral activity [121], Antioxidant activity [122], Antimicrobial activity [123], Antibiofilm activity [124], Antifungal activity [123], Cytotoxic activity [121], Antitubercular activity [125], Hypoglycemic effect [126].

Extracts of *A. officinalis* found to be active towards Gram-positive bacteria as *S. aureus* but not towards Gram-negative bacteria [127]. Water extracts of aerial parts of *A. officinalis* and *A. cannabina* exerted anti-bacterial action towards food-borne bacteria of Gram-positive bacteria and Gram-negative bacteria of *Bacillus* spp., *Enterobacter hormachei*, *Kocuria rosea* and *Acidovorax facilis* [128]. Extracts of aerial parts of *A. officinalis* showed varying degrees of antibacterial effects *S. aureus* and *St. agalactiae*, *E. coli* and *K. pneumoniae* , but most powerful effects were towards *E. coli* and *K. pneumoniae* [129].

Hosretail (*Equisetum arvense)*. Commonly known as common horsetail or field horsetail is a perennial fern of family Equisetaceae. Native to the arctic and temperate parts of northern hemisphere, particularly Europe [130]. Traditionally it is indicated in the cases of suppressed urination accompanied by blood and severe pain during urination (dysuria) [131].

Horsetail has many pharmacological properties as antioxidant and anti-inflammatory activity [132], diuretic activity ([132], anti-bacterial acitivity [130,133], Anticancer activities [134,135].

Ethanol and water extracts of *E. arvense* showed anti-bacterial activity towards bacterial pathogens of UTIs as *E. coli*, *K. pnuemoniae* , *P. mirabilis*, *P. aeruginosa*, *S. aureus*, *S. saprophyticus*, *Enterococcus faecalis*. Ethanolic extracts had higher antibacterial activity than aqueous [133].

Rat animal model for treatment of experimental UTI with a food containing 0.2% ethanolic root extract of *E. arvense* in one group, and only regular food in another as a negative control was studied. Results for cystometry with acetic acid study of two groups showed that administration of root extract resulted in decrease in bladder muscle contraction in treatment group comparing with control group. Levels of adrenaline and noradrenaline hormones in rat plasma were much more lower in treatment group than those of control group. Furthermore, levels of urinary adenosine triphosphate in treatment group were smaller than those of control group. These results approved efficacy of ethanolic extracts of horsetail in affecting activity of bladder by decreasing urinary adenosine trip-phosphate making it effective therapeutic option for diseases of urinary tract [136].

Goldenseal (Hydrastis canadensis). Belongs to family Ranunculaceae. It is native to north America and found naturally from Ontario to Arkansas, up to Southern regions of United states to Georgia and north to Quebec [137].

Numerous studies confirmed that extracts of *H. canadensis* have antibacterial activity towards bacterial pathogens *In Vitro* and *In Vivo* [138-142]. The antibacterial activity of *H. canadensis* is attributed to the alkaloid compounds, berberine [142,143], that has antibacterial activity against Gram-positive pathogens, including MRSA [144]. Root extract are rich in alkaloids as berberine, hydrastine and canadine. Figure 7. [145]. Root/leaf extract of goldenseal showed anti-bacterial activity towards *S. aureus* and *Campylobacter jejuni*, whereas showed minimum impact towards beneficial bacterium *Lactobacillus acidophilus* [146].

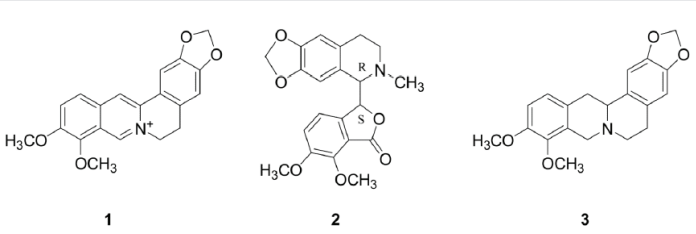

Figure 7: Three alkaloids of root extract of Hydrastic canadensis. 1) Berberine . 2) Hydrastine. 3) Canadine (tetrahydroberberine) [144].

The efflux pump inhibitory activity in *H. candensis* is associated with areal part extracts [145]. Five bands in thin layer chromatogarapy and Bio-autographic studies were related to the efflux pump inhibition activity. The chemical identity of those bands could not be diagnosed with GC/MS due to its volatility, but LC/MS analysis revealed a list of possible compounds in those bands [146].

Inhibition of efflux pumps is very important to overcome the drug-resistance problem of bacterial pathogens. Efflux pumps work to pumps out the antibiotic and increases the minimum inhibitory concentration (MIC) of the antibiotic. Thus, the inhibition of efflux pumps would render bacterial cell sensitive to antibiotic and decrease its MIC to be more effective towards bacterial pathogens [147].

Leaf extracts of showed potent efflux pumps inhibition activity towards different pump superfamilies in both *S. aureus* and *C. jejuni*. These extracts resulted in reduction in MICs of antimicrobials at least 2 fold reduction for antimicrobials against *S. aureus*, and 16 folds reduction in MICs for antimicrobials directed against *C. jejuni* by combining antimicrobials agents. Leaf extracts works to inhibit MDR efflux pumps via repressing genes coding for these pumps [146].

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Buchu (*Agathosma betulina* and *A. crenulata*). Belongs to family Rutaceae. Native people in South Africa first used buchu as a medicinal plant for European immigrants in the Cape , and spread subsequently from them to Europen and America where it was became famous as a herbal medicine [148]. Traditionally, buch used as a herbal medicine for treatment of different disease and to achieve different activities as a diuretic and treatment of urinary disorders, respiratory and gastrointestinal disorder [148]. The primary use of buchu leaves in western herbal medicine is for treatment of genitourinary diseases like infections of kidney , bladder, urethra and prostate in addition of kidney stones and incontinence linked to prostate [149].

The antibacterial activity of buchu leaves have been attributed to essential oil of the oil glands located on underside of leaves. These oils consists of monoterpene, diosphenol. These oil absorbed by the stomach and excreted in kidney to pass through genito-urinary tract and exert its antibacterial effects towards bacterial pathogens [149].

The GC–MS reference analysis for structure of essential oil of buchu showed that EO of *Agathosoma crenulata* had high content of pulegone of 50-66%, whereas those of *A. betulina* has a percentage of 15-35% of diosphenol, 12-30% of pseudo-diosphenol, 4-26% of isomenthone and 5-24% of limonene. Figure 8 [150].

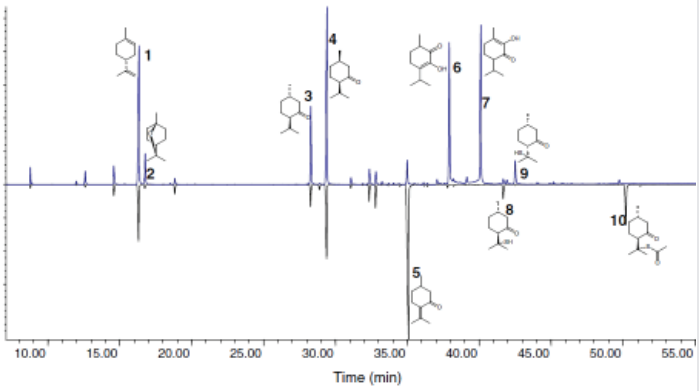

Figure 8: GC chromatograph of essential oil (OS) of ***Agathosoma betulina*** (Upper) and ***A. crenulata*** (lower) illustrating the chemical composition revealed. 1) Limonene , 2) Cineole, 3) Menthone, 4) Isomenthone, 5) Pulegone, 6) Pseudo-diosphenol, 7) Diosphenol, 8) trans-8-Mercapto-menthan-3-one, 9) cis-8-Mercapto-menthan-3-one, 10) trans-3-Oxo-pmenthane- 8-thiol acetate [149].

Moola (2005) reported that essential oil and non-volatile compounds of leaf extract of *A. betulina* had antibacterial activity towards *S. aureus*, *B. subtilis* and *K. pnueumoniae* [148]. Others found that essential oils of *A. betulina* and *A. crenulata* had antibacterial action towards *Enterococcus hirae* and *P. aeruginosa* and very low activity against *E. coli* , *S. aureus* and *Saccharomyces cerevisiae* [151]. O'Brien (2005) confirmed that essential oils of A. betulina had no antimicrobial activity towards urinary tract pathogens, but only anti-oxidant activity [152].

Lis-Balchin reported that extract of A. betulina acts on cyclic adenosine monophosphate and exerts spasmolytic action [151]. Antispasmodic drugs relax the smooth muscles of the urinary bladder. The anti-spasmodic drugs acts on smooth muscles of bladder, thus, increasing the capacity of bladder and effectively decrease or evenly eliminate urge incontinence [153]. The spasmolytic action of essential oil of *A. betulina* may be attributed to healing effects of the plant for UTIs.

Oregon grape (*Mahonia aquifolium). Mahonia is the second largest genus of family Berberidaceae and composed of nearly 70 species that are native to central and north of America and eastern parts of Asia* [154]. *M. aquifolium* is native to Pacific Northwest of the United States of America. Owing to its yellow flower and red fruit, it spread to other parts of the world to be used as an ornamental plant in gardens [155].

M. aquifolia has various pharmacological activities as anti-oxidant activity and anti-inflammatory activity [156-158], Anti-bacterial [155,159,160], Anti-fungal activity [161], Antitumoral and Immunomodulatory activity [162].

The anti-bacterial activity of *M. aquifolium* is attributed to two of major alkaloids, of stem bark, berberine chloride and oxyacanthine sulphate and shown to have bactericidal bactericidal activity towards nice species of oral pathogens. Figure 9. [155]. The antimicrobial activity of berberine extract was evaluated towards 17 bacterial and fungal species. Bacterial species were *E. coli* , *P. aeruginosa*, *S. aureus* and *B. subtilis*, whereas fungal species were Aspergillus niger, *Penicilium chrysogenum*, *Trichoderma viride*, *Aureobasidium pullulans*, *Mycrosporum gypseum* ,*Fusarium nivale*, *Trichoderma viride*, *Saccharomyces cerevisiae* and Candida albicans. All extracts showed antimicrobial activity against all test microbes [163].

Berberine is responsible for the golden yellow appearance of Oregon grape root. Berberine is also found in few other plants as Chinese goldenthread, goldenseal and desert berberry. Berberine acts to prevent attachment of E. coli to uro-epithelial cells through reduction of expression of genes encoding Fimbriae. The anti-infectious activity of Berberine in is attributed to suppressive activity of this compound for genes responsible for synthesis and assembly of fimbrial subuints that is results in prevention of adhesion and colonization of *E. coli* associated UTIs Figure 10 [163].

Conclusions and recommendations

The fourteen medicinal plants illustrated in details above showed various pharmaceutical activities as Anti-microbial, Anti-inflammatory, anti- oxidant, anti-adhesive, diuretic activities associated with treatment of UTIs, and other activities related with treatment of other human diseases. It highly recommended to study the therapeutic activities of all medicinal plants alone and in combination with each other to obtain highest pharmaceutical activities for treatment of UTIs *In Vitro* and *In Vivo*. Further phytochemical studies are required to reveal the chemical composition for all potential compounds responsible for all pharmaceutical activities of the fourteen medicinal plants. Toxicological and genetical studies concerning all potential adverse effects, mutagenic and carcinogenic activities of those medicinal plants are highly recommended to complete the picture of pharmaceutical importance of those medicinal plants.

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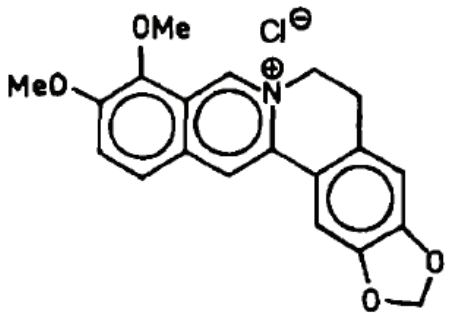

Figure 9: Berberine chloride [162].

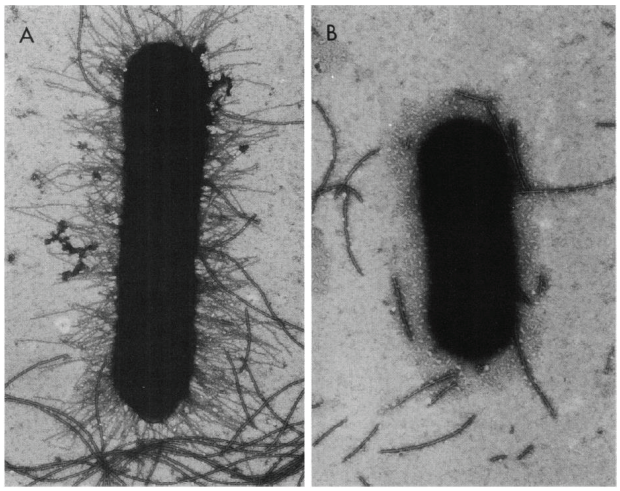

Figure 10: (A) Strain ***E. coli*** C16 seen heavily piliated and flagellated after growing in brain-heart infusion broth for 18 hrs. (B). Losing of piliation and disruption of flagella in ***E. coli*** C16 after incubation in brain-heart infusion broth for 18 hrs in the presence of 200 mcg / ml of media. Magnification is × 33200 [163].

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