CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Review Article

PHARMACOLOGICAL IMPORTANCE OF *HERNIARIA GLABRA* AND *HERNIARIA HIRSUTA* - A REVIEW

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Abstract:
Phytochemical analysis and pharmacological studies revealed that Herniaria glabra contained triterpene saponins: herniaria saponins I-VII [aglycones medicagen, gypsogen, 16-hydroxy-medicagen], flavonoids and hydroxycoumarins: umbelliferone, herniarin, phenolic acids, tannins and essential oil, while, Herniaria hirsuta contained phenolics, flavonoids, flavonols and saponins. The total flavonoid content of Herniaria hirsuta was 4.51% and the total saponin content was 12.74%. Herniaria glabra possessed hypotensive, diuretic, antiurolithiasis, antimicrobial, insecticidal and antioxidant effects, while, Herniaria hirsuta possessed antiurolithiasis, antioxidant, cytotoxic and antibacterial effects. The current review highlighted the chemical constituents and pharmacological effects of Herniaria glabra and Herniaria hirsuta.

Keywords: *Herniaria glabra, Herniaria hirsuta, chemical constituents, pharmacology*

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Please cite this article in press Ali Esmail Al-Snafi., ***Pharmacological Importance of Herniaria Glabra and Herniaria Hirsuta - A Review,*** *Indo Am. J. P. Sci, 2018; 05(04).*

INTRODUCTION:

Medicinal plants are the Nature's gift to human beings to help them pursue a disease-free healthy life. Plants have been used as drugs by humans since thousands of years ago. Recent studies showed that plants are a valuable source of a wide range of secondary metabolites, which are used as possessed a wide range of pharmacological effects [1-16]. Phytochemical analysis and pharmacological studies revealed that *Herniaria glabra* contained triterpene saponins: herniaria saponins I-VII [aglycones medicagen, gypsogen, 16-hydroxy-medicagen], flavonoids and hydroxycoumarins: umbelliferone, herniarin, phenolic acids, tannins and essential oil, while, *Herniaria hirsuta* contained phenolics, flavonoids, flavonols and saponins. The total flavonoid content of *Herniaria hirsuta* was 4.51% and the total saponin content was 12.74%. *Herniaria glabra* possessed hypotensive, diuretic, antiurolithiasis, antimicrobial, insecticidal and antioxidant effects, while, *Herniaria hirsuta* possessed antiurolithiasis, antioxidant, anticancer and antibacterial effects. The current review highlighted the chemical constituents and pharmacological effects of *Herniaria glabra* and *Herniaria hirsuta*.

Plant profile:

Synonyms:

***Herniaria glabra*:**

Herniaria arenaria Kuntze, *Herniaria ceretanica* [Sennen] Sennen, *Herniaria glabra* subsp. *rotundifolia* [Vis.] Trpin, *Herniaria microcarpa* C Presl, *Herniaria rotundifolia* Vis, *Herniaria vulgaris* Spreng. and *Paronychia herniaria* EHL Krause[17].

Herniaria hirsuta:

Herniaria hirsuta var. hirsuta and *Herniaria hirsuta* subsp. hirsuta[18]

Taxonomic classification:

Kingdom: Plantae, **Subkingdom**: Viridiplantae, **Superdivision**: Embryophyta, **Division**: Tracheophyta, **Subdivision**: Spermatophytina, **Class**: Magnoliopsida, **Superorder**: Caryophyllanae, **Order**: Caryophyllales, **Family**: Caryophyllaceae, **Genus**: *Herniaria*, **Species**: *Herniaria glabra* and *Herniaria hirsuta*[19-20].

Common names:

***Herniaria glabra*:**

The genus name Herniaria comes from the Latin word hernia because it was believe that the herb could cure hernia. This belief was also reflected in the English common name of the plant [rupturewort**].** The common names of the plant were: **Arabic**: Showail, **English**: Glabrous rupturewort, Herniary breastwort, Rupturewort, Smooth rupturewort; **French**: Herniaire, **German**: Kahles Bruchkraut, **Italian**: Erniaria glabra, **Spanish:** Herniaria, **Swedish**: Knytling[21-22].

Herniaria hirsuta:

Arabic: Hashishat Al Fatik, Marda, Noman amrad, Dizama; **English**: Hairy rupturewort, **French**: Herniaire velue; **German**: Behaartes Bruchkraut, Behaartes Bruchkraut; **Swedish:** Luddknytling[21].

Distribution:

***Herniaria glabra*:**

The plant is distributed in **Africa** [Algeria, Egypt, Libya, Morocco, Tunisia], **Asia [**Armenia, Azerbaijan, Georgia, China, Japan, Kazakhstan, Kyrgyzstan, Tajikistan, Uzbekistan, Mongolia, Russian Federation, Afghanistan, Iran, Iraq, Palestine, Lebanon, Turkey], **Europe** [Belarus; Estonia; Latvia; Lithuania; Russian Federation, Ukraine, Austria, Belgium, Czech Republic, Germany, Hungary, Netherlands, Poland, Slovakia, Switzerland, Denmark, Sweden, United Kingdom, Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Greece, Italy, Macedonia, Montenegro, Romania, Serbia, Slovenia, France, Portugal, Spain] and **Northern America** [Canada and USA][21].

Herniaria hirsuta:

It was distributed in **Africa** [Ethiopia, Algeria, Egypt, Morocco]; **Asia** [Kuwait, Armenia; Azerbaijan; Russian Federation, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan , Iran, Iraq, Palestine, Jordan, Lebanon, Syria, Turkey] and **Europe** [Austria, Belgium, Germany, Hungary, Slovakia, Switzerland, Albania, Bulgaria, Croatia, Greece, Italy, Macedonia, Romania, Slovenia, France, Portugal, Spain][23].

Description:

***Herniaria glabra*:**

It is annual or perennial, yellowish green. Stems spreading, 5–18[–35] cm, glabrous or thinly pilose. Leaf blade elliptic-obovate, 3–7 × 1–3 mm, glabrous, base cuneate, apex obtuse. Glomerules leaf-opposed, 6–10-flowered. Flowers 5-merous, 1.2–1.5[–1.7] mm. Sepals ovate-oblong, ca. 1.5 × 0.5 mm, glabrous, apex obtuse. Stamens 5, short. Style 0.2–0.3 mm; stigma lobes nearly sessile. Achene ovoid, longer than sepals. Seed flat-orbicular, ca. 0.5 mm in diameter[24].

Herniaria hirsuta:

It is annual, gray-green, densely pubescent. Stems prostrate to ascending, 4-20 cm. Leaves opposite proximally, alternate distally; stipules 0.5-1.3 mm; blade elliptic to oblanceolate, 3-12 mm, hirsuta or ciliate, ad-axial surface sometimes glabrescent. Inflorescences axillary, leaf-opposed or on short branches, mostly 3-8-flowered. Flowers 0.9-1.8 mm, densely pubescent; calyx burlike; sepals equal or somewhat unequal, 0.8-1.5 mm, hirsuta, hairs of perigynous zone hooked or tightly coiled, each sepal with 1-2 spinelike hairs at apex; stamens 2-3 or 5; staminodes petaloid, 0.4-0.6 mm; styles distinct or connate in proximal 1/3. Utricles 0.7-0.9 mm, ca. equaling sepals[25].

Traditional uses:

Herniaria glabra, the whole plant, was used as astringent, diuretic and expectorant. It appeared to have an antispasmodic effect upon the bladder and was used in the treatment of dropsy, catarrh of the bladder, cystitis and kidney stones. Externally, it was used as a poultice to speed the healing of ulcers[26-28].

Kozachok *et al*., mentioned that *Herniaria glabra* was officially present in the Pharmacopeias of Poland, Czech Republic, Austria, Hungary and Balkans, it was used traditionally for the treatment of kidney and bladder stones, gouts, urinary bladder infections, renal disease, diabetes, hernias, hypertension, cardiac decompensation, as well as rheumatism, and was externally applied as an antiseptic and skin emollient[29].

The infusion of *Herniaria hirsuta* was used as a remedy for urinary and kidney problems[30].

Both *Herniaria glabra* and *Herniaria hirsut*a were used traditionally as blood purification, circulatory disorders, vascular disorders, to decrease blood pressure, diuretic, bone and Joint conditions, respiratory conditions and breathing disorders, neuritis, neural catarrh and for urinary tract conditions[31].

Infusions of *Herniaria hirsuta*, *Herniaria glabra* and *Herniaria fontanesii* were well known in Moroccon folk medicine for the treatment of biliary dyskinesia, urolithiasis and as a diuretic. Herniariae herba which can contain *Herniaria glabra* and *Herniaria hirsuta* was known in Europe as an urological drug[32].

Part used medicinally:

The herbs, the stems and the aerial parts were used medicinally[21, 30, 33].

Chemical constituents:

Herniaria glabra*:*

Herniaria glabra contained triterpene saponins: herniaria saponins I-VII [aglycones medicagen, gypsogen, 16-hydroxy-medicagen], flavonoids and hydroxycoumarins: umbelliferone, herniarin, phenolic acids, tannins and essential oil[20, 34].

Quantitative analysis of monosacchirides of *Herniaria glabra* showed that they were consisted of [mg/g]: D-rhamnose: 5.36, D-arabinose: 11.51, D-fucose: 1.79, D-xylose: 1.48, D-manose: 0.99, D-glucose: 33.40, D-galactose: 13.88, -[+] pinitol: 16.80, myoinositol: 1.28, D-mannitol: 1.60 and D-dulcitol [galactiol]: 2.84. The free carbohydrates [mg/g] of *Herniaria glabra* were: D-glucose: 0.26, D-galactose: 0.15, -[+] pinitol: 16.76, myoinositol: 0.63, D-mannitol: 0.19, D-fructose: 0.12-0.15 and D-saccharose 15.53[29].

Herniaria glabra contained saponins, the content of the sum of triterpenic saponins in terms of escin in *Herniaria glabra* herb was 16.52±0.60%[35].

Three flavonoids [isoquercitrin, luteolin and rutin], two phenolic acids [caffeic and chlorogenic acid] and nine amino acids [alanine, asparaginic acid, glutaminic acid, glycine, histidine, isoleucine, leucine, phenylalanine and threonine] were identified. The quantitative analysis of flavonoids and phenolic acids showed that *Herniariae glabra* contained 0.29 % flavonoids and 0.34 % phenolic acids[36].

On the other hand flavonols content of *Herniaria glabra* was 6.9 mg QG/g, phenolic acids 10.2, iridoids 11.8 mg LA/g and the sum of main phenolics was 28.8 mg/g[37].

Flavonoids and their derivatives isolated from *Herniaria glabra* were included [rutin, isorhamnetin rhamnose-hexose, hexoside-rhamnoside kaempferol and hydroxyferulic acid derivative]. Iridoids included [Iridoide], phenolics and others included [3-FQA feruloylquinic acid and quinic acid, 3-*p*-coumaroylquinic acid, 4′-Caffeoylquinic, caffeoylquinic acid, 5′-caffeoylquinic acid, 5′-caffeoylquinic acid, feruloylquinic acid *trans*, 4 FQA tri-feruloylquinic acid *trans*, 4 FQA tri-feruloylquinic acid *cis* *and* 5 FQA tri-feruloylquinic acid]. Quantitative analyzes amounted to 0.69% for flavonoids [expressed as isoquercitrin], 1.02% for phenolic acids [expressed as chlorogenic acid] and 1.18% for iridoids [expressed as loganic acid][37].

Eight saponins were identified in *Herniaria glabra* by 2–dimensional thin layer chromatography. The hydrolysis products showed 7 aglycons and 4 sugars [glucose, rhamnose, glucuronic acid and fucose][38].

Three saponins were isolated from *Herniaria glabra*. The structures were established as O-α-L-rhamnopyranosyl-[1→4]-O-β-D-glucopyranosyl-[1→6]-O-(β-D-gluco-pyranosyl- [1→2)]-β-D-glucopyranosyl medicagen-28-ate; O-β-D-glucopyranosyl-[1→3]- O-α-L-rhamnopyranosyl-[1→2] -O-[β-(3R)-D-apiofuranosyl-[1→3]] -β-D-4-O-acetylfucopyranosyl 3-O-[β-D-glucurono pyranosyl]-16α-hydroxy medicagen-28-ate; and O-α-L-rhamnopyranosyl-[1→4]-O-β-D-glucopyranosyl-[1→6] -O- [β-D-6-O-acetylglucopyra nosyl-[1→2]]-β-D- glucopyranosyl medicagen-28-ate[39].

An acetylated triterpene saponin was isolated from *Herniaria glabra*. its structure was elucidated as 28-O-[beta-D-glucopyranosyl-[1→3]-alpha-L-rhamnopyranosyl-[1→2]- [beta- D-glucopyranosyl-[1→3]]-4-acetyl-beta-D-fucopyranosyl[1→]]-medicagenic acid-3-O-beta-D-glucuronide[40].

Two triterpene glycosides, glabrosides B and C were isolated from *Herniaria glabra*. Analysis showed that the first compound was the β-D-glucopyranosyl-[1→6] -β-D-glucopyranoside, and the second was the O−β−D−glucopyranosyl−[1→4] O - β - D - fucopyranosyl - [1→2] α−L - rhamnopyranoside - [1→17] of medicagenic acid[41].

Herniaria hirsuta:

Herniaria hirsuta contained phenolics, flavonoids, flavonols and saponins. The total flavonoid content of Herniaria hirsuta was 4.51% and the total saponin content was 12.74%[32].

The lyophilized infusion of *Herniaria hirsuta* contained phenols 90±1[mg GAE/g lyophilized infusion], flavonoids 46±3 [mg CE/g lyophilized infusion], esters 38±1[mg CAE/g lyophilized infusion] and flavonols 26±1[mg QE/g lyophilized infusion][42].

However, the ethanolic and aqueous extract of *Herniaria hirsuta* contained phenols 28.2 and 22.4 mg of GA/g of extract, flavonoids 4.6 and 3.7 mg of CE/g of extract, tannins 12.1 and 8.2 mg of GA/g of extract, anthocyanins 3.4 and 3.8 mg of C3GE/g of extract, and saponins 16.2 and 8.4 mg of QSE/g of extract respectively [43].

Two triterpene saponins, 28-*O*-{[*β*-D-xylopyranosyl-[1 → 4]-*α*-L-rhamnopyranosyl-[1 → 2]]-[*β*-D-glucopyranosyl-[1-6]]-*β*-D-glucopyranosyl}-medicagenic acid and 3-*O*-[*α*-L-rhamnopyranosyl-[1 → 3]-*β*-D-glucuronopyranosyl]-28-*O*-{[*β*-D-glucopyranosyl -[1 → 3]-*β*-D-xylopyranosyl-[1 → 4]-[*β*-D-apiofuranosyl-[1 → 3]-*α*-L-rhamnopyranosyl-[1 → 2]-*β*-D-fucopyranosyl}-medicagenic acid and three flavonoids, quercetin-3-*O*-[2″-*O*-*α*-L-rhamnopyranosyl]-*β*-D-glucuronopyranoside, rutin, and narcissin [isorhamnetin-3-*O*-rutinoside] were isolated from the plant[44].

Two monodesmosidic saponins, herniaria saponins E and F, were isolated from the aerial parts of *Herniaria hirsut*a, their structures were established to be 2-O-acetyl medicagenic acid 28-O-beta-D-xylopyranosyl- [1→4]-alpha-L-rhamnopyranosyl [1→2]-[beta-D-glucopyranosyl[1→6]]-be ta- D-glucopyranoside [herniaria saponin E] and medicagenic acid 28-O-beta-D-xylopyranosyl[1→4]-alpha-L- rhamno-pyranosyl [1→2]-[alpha-L-rhamnopyranosyl-[1→4]-beta-D- glucopyranosyl-[1→6]]-beta-D-glucopyranoside [herniaria saponin F][45].

Pharmacological effects of *Herniaria glabra*:

Hypotensive and diuretic effects:

The antihypertension action of *Herniaria glabra* saponins was studied in rats in comparison with that of furosemide. Hypertensive rats were treated with *Herniaria glabra* saponins at a dosage of 200mg/Kg bw. Treatment led to progressive decline in both systolic and diastolic blood pressures. After one month of therapy, pressure declined to 141.60 / 90.40 mmHg versus 187.60/ 119.10 mmHg [P<0.001]. *Herniaria glabra* saponins didn't change heart rate, however it decreased blood pressure by many mechanisms[46].

The effect of saponins from *Herniaria glabra* was studied on blood pressure and renal function in spontaneously hypertensive rats. The oral administration of 200 mg/kg/day of saponins from *Herniaria glabra* for 30 days, resulted in a significant decrease in blood pressure in hypertensive rats. The systolic and diastolic blood pressure decreased significantly and respectively from 187.60 ± 20.63/119.00±7.09 mmHg at day 0 [D0] to 141.60 ± 7.51/90.40 ± 7.68 mmHg at day 30 [D30] [P<0.001], [vs. 186.30 ± 11.27/114.10 ± 12.00 mm Hg at D0 to 154.50 ± 6.38/132.3 ± 7.68 mmHg at D30 in furosemide-treated group, p < 0.001]. The effect of saponins of *Herniaria glabra* on renal function revealed that glomerular filtration rate was

constant in the control rats and increased significantly in the hypertensive rats after saponins treatment [5.55 ± 0.32 vs. 6.03 ±0.43 ml/min/kg in the control [C] and saponins [S] groups, respectively, P<0.05]. Saponins administration provoked an increase in urinary flow [59.38 ± 5.85 ml/kg/24 h vs. 36.92 ± 5.17 ml/kg/24 h, P<0.001]. Saponins also increased potassium excretion [6.89 ± 0.81 mmol/kg/24 h vs. 5.40 ±0.51 mmol/kg/24 h, P<0.001] and sodium excretion [10.74 ± 1.21 mmol/kg/24 h vs. 7.25 ±0.54 mmol/kg/24 h, P<0.001] as well as chloride excretion [13.59 ± 1.04 mmol/kg/24 h vs. 9.67 ± 0.77 mmol/kg/24 h, P<0.001][47].

Antiurolithiasis:
The effect of a botanical formulation of *Herniaria glabra*, *Agropyron repens*, *Equisetum arvense*, and *Sambucus nigra* was studied as a preventive agent in an experimentally induced urolithiasis model in rats [0.75% ethylene glycol [EG] and 1% ammonium chloride for three days]. Rats were treated with 30-500 mg/Kg of the plant extract formulation [PEF]. Animals treated with 125 mg/Kg of the PEF had statistically significantly lower calcium oxalate crystals deposits content compared to the control group. All PEF doses were significantly decreased the number of microcalcifications compared to the control group. Furthermore, the number of kidneys showed subcapsular fibrosis was significantly higher in control group than in groups treated with the PEF. The diuresis of the 125 mg/Kg and 500 mg/Kg PEF-treated groups was statistically significantly higher than that of the control group[48].

Antimicrobial effect:
Phytoligands were investigated on multiple drug resistance [MDR], *Salmonella typhi*, *Staphylococcus aureus*, and *Vibrio cholera*. The inhibitory properties of these ligands against drug targets were studied by molecular docking. Herniarin from *Herniaria glabra* was identified as the best leads against dfrA1 of *Vibrio cholera* [49].

The effects of many medicinal plants extracts included *Herniaria glabra* extract were studied against bacterial survival and virulence factors involved in tissue colonization and biofilm formation of the uropathogenic *Escherichia coli*. The results indicated significant differences between investigated extracts in their antimicrobial activities. The extracts of *Herniaria glabra* showed the highest growth-inhibitory effects [P<0.05]. Surface hydrophobicity of autoaggregating *Escherichia coli* strain changed after exposure to all plant extracts and all extracts exhibited the anti-biofilm activity[37].

Insecticidal effect:
Sisalana oil and herniarin [a constituent of *Herniaria glabra*] exhibited heavy knockdown effect coupled with high insecticidal activity against the larvae of semilooper[50-51].

Antioxidant effect:
DPPH [1,1-diphenyl-2-picryl hydrazyl] radical was used for evaluation of free radical scavenging of methanol extracts from 54 plant species of 30 families. The IC50 of radical scavenging activity of total methanol extract of whole *Herniaria glabra* was >200 µg/ml[52].

Pharmacological effects of *Herniaria hirsuta*:
Effect on biliary cholesterol and lipid profile:
An *in vivo* experiment to evaluate the cholesterol lowering effect of a infusion of *Herniaria hirsuta* [HG] in the gall bladder of dogs was carried out. Dogs were divided into 3 groups i.e. control dogs [CG], dogs treated with ursodeoxycholic acid [UDCA] [2×7.35mg/kg bw/day] and dogs treated with the standardized infusion of *Herniaria hirsuta* [2×48.5mg/kg bw/day]. Dogs were fed a fatty diet during 120 days after which a diet without additional fat was introduced till day 180. Treatment started 30 days after introduction of the fatty diet and lasted till the end of the experiment. A bile and blood sample of each dog was collected every 30 days, after which the concentration of cholesterol was determined. The experiments showed a minor difference for bile cholesterol between CG and HG after 30 days of treatment with the infusion, and the difference was more pronounced after 90 days of treatment. Even 30 days after discontinuation of the cholesterol-rich diet a significant difference remained between CG and HG. There was no statistically significant difference in blood cholesterol. Accordingly, the prolonged use of this standardized *Herniaria hirsuta* extract resulted in a cholesterol-lowering effect in the bile of dogs. Since this pharmacological effect prevented the formation of gallstones and can contribute to solving existing gallstones[32].

The modifications of gallbladder bile lipid induced by oral intake of an infusion of *Herniaria hirsuta* was studied in the dog. *Herniaria hirsuta* induced modifications of gallbladder bile lipids in treated dogs, it significantly reduced the biliary cholesterol in dogs from 2.37 ± 0.36 mmol/l at day 0 [D0] to 0.72 ± 0,23 mmol/l at day 90 [P<0.01]. These levels remained stable in control dogs [2.19 ±0.33 mmol/l at D0 and 2.15 ± 0.28 mmol/l at D90 [not significant]. Biliary phospholipid concentration decreased slightly but significantly in treated dogs as compared to control dogs [P<0,05][53].

Anti- urolithiatic effect:

Herniaria hirsuta was evaluated in nephrolithiasis in rats as a preventive therapy against the development of kidney stones. The experiment was conducted in normal and calcium oxalate [CaOx] nephrolithiasic rats during 3 weeks. The results showed that water intake and urinary volume increased in nephrolithiasic rats, but their urinary pH decreased especially in the third week of treatment. Urinary oxalate increased significantly during the second week in untreated rats and remained constant in rats treated with Herniaria decoction. However, urinary calcium decreased significantly in week 2 in untreated rats and remained constant in the treated rats. Qualitative analysis of crystalluria showed that untreated rats excreted large CaOx monohydrate and few dihydrate crystals while treated animals excreted mostly small CaOx dihydrate crystals. The examination of kidney sections revealed that CaOx deposition was decreased in the treated compared to untreated rats[30].

The effects of *Herniaria hirsuta* and *Agropyron repens*, as herb infusion, combined with different diets [standard, high glucidic, high protein] on the calcium oxalate urolithiasis were studied in rats. The results revealed that the antilithiasic effects of the *Herniaria hirsuta* infusion clearly depends on the diet. Thus, a clear increase in the citraturia was only detected when such infusion was administered with the high protein diet[54].

The effectiveness of an extract of *Herniaria hirsuta* on calcium oxalate crystallization was studied *in vitro*. Crystallization was induced in whole normal human urine samples in the absence or presence of the extract. Crystals generated in the urine were harvested and analysed by scanning electron microscopy. The nucleation and aggregation of calcium oxalate crystals were measured separately using spectrophotometric methods. The results showed the extract of *Herniaria hirsuta* promoted the nucleation of calcium oxalate crystals, increasing their number but decreasing their size. It also promoted the formation of calcium oxalate dihydrate crystals, despite the presence of calcium oxalate monohydrate particles. The extract may contain substances that inhibit calcium oxalate crystal aggregation[55].

The prophylactic effect of oral administration of *Herniaria hirsuta* decoction was also investigated in experimentally induced calcium oxalate [CaOx] nephrolithiasis in rats. *Herniaria hirsuta* has an impressive prophylactic effect on CaOx stones in nephrolithic rats, the effect which did not mediated by biochemical or diuretic changes[56].

Cystine stones represent 1% of urinary calculi in adults and 10% in children and were especially recurrent and resistant. In Morocco, various plants, *Herniaria hirsuta*, *Opuntia ficus-indica*, *Zea mays* and *Ammi visnaga* were used against nephrolithiasis. The effect of plant extracts on the disolution of cystine stones was studied *in vitro*. The results revealed that the studied herbal extracts were efficient for dissolving cystine stones, probably by formation of complexes between cystine and polyhydroxylated molecules present in the extracts[57].

The interaction of calcium oxalate crystals with renal epithelial cells is a critical event in kidney stone formation. The effect of aqueous extract from *Herniaria hirsuta* on the adhesion of calcium oxalate monohydrate [COM] crystals to cultured renal cells was investigated. Calcium oxalate monohydrate crystal binding to cells was inhibited by the extract in a concentration dependent manner. It was suggested that the extract coated the crystals and inhibited their attachment to cells[58].

The methanol extract of *Herniaria hirsuta* was fractionated to determine the nature of compound responsible for the beneficial effect of *Herniaria hirsuta* in prevention and cure of urolithiasis. The fractions were then assayed on calcium oxalate crystallization in *in vitro* and *in vivo* models. In the whole human urine, only the fraction eluted with ethanol/water was associated to formation of smaller crystals composed of calcium oxalate dihydrate, similarly to the aqueous extract. When tested at 5 mg/day, it reduced significantly crystal deposition in lithiasic rats. Preliminary identification of the fraction showed the presence of saponins which may be responsible for the beneficial effect of *Herniaria hirsuta* in the treatment of kidney stones[59].

Antioxidant effect:

Antioxidant activity [EC50 values] of the infusions prepared from *Herniaria hirsuta* were: DPPH scavenging activity: 729±50 µg/ml, reducing power: 570±4 µg/ml, β-carotene bleaching inhibition: 1110±96 µg/ml and TBARS formation inhibition: 481±36 µg/ml[42].

Cytotoxic effect:

Cytotoxic properties [GI50 value] of the infusions prepared from *Herniaria hirsuta*, against MCF7 [breast carcinoma], NCI H460 [non-small cell lung carcinoma], HeLa [cervical carcinoma], HepG2

[hepatocellular carcinoma], and PLP2 [porcine liver cells] was >400 µg/ml[42].

Antibacterial effect:

Herniaria hirsuta extracts were examined for antibacterial activity against *E. coli* MAR strain. The minimal inhibitory concentrations [MICs] for ethanol and aqueous extracts of *Herniaria hirsuta* against hospital *E. coli* strain were 250 and 500 µg/ml, and against *E. coli* ATCC 25922 strain were: 100 and 250 µg/ml respectively[43].

Umbelliferone, extracted from *Herniaria hirsuta* 300mg, arbutin 60mg, and Nacetylcysteine 150mg were able to reduce *E. faecalis* colonization and biofilm development on the surface of urinary catheter[60].

Toxicity and side effects:

Health risks or side effects following the proper administration of designated therapeutic dosages were not recorded[34].

However, the safety of the aqueous extract of *Herniaria glabra* was investigated by determining its potential toxicity after acute and sub-chronic administration in rodents. For the acute study, a lyophilized aqueous extract of *Herniaria glabra* was administered to adult mice in single doses of 5-14.5 g/kg given by gavage. General behavior adverse effects and mortality were determined for up to 14 days. In the sub-chronic dose study, the *Herniaria glabra* extract was administered orally at doses of 1, 2 and 4 g/kg daily for 90 days to rats. Selected biochemical and hematological parameters were investigated after 30, 60 days, and at the end of 90 days of daily administration. In the acute study in mice, the crude aqueous extract of *Herniaria glabra* caused dose-dependent general behavior adverse effects and mortality. The no-observed adverse effect levels [NOAEL] of the *Herniaria glabra* extract was 5 g/kg and the lowest-observed adverse effect levels [LOAEL] was 5.5 g/kg. Mortality increased with increasing doses, the calculated LD50 was 8.50 ±0.42 g/kg in mice. In the sub-chronic study in rats, daily oral administration of the crude *Herniaria glabra* extract for up to 90 days resulted in a significant attenuation of the normal increase in the body weight. Highest dose of the *Herniaria glabra* extract caused a significant increase in erythrocytes, leukocytes [WBC], platelets, and eosinophils, but it had no effect on the differential WBC counts [lymphocytes, monocytes, neutrophils and basophils]. Only at the highest dose, the *Herniaria glabra* extract caused a significant increase in serum levels of the liver enzymes, alanine aminotransferase and aspartate aminotransferase, as well as serum creatinine, indicating toxic effect of the high dose of the extract on the liver and kidney. The organ toxicity was confirmed by histopathological examination, which showed centrolobular sinusoidal congestion, disruption of the central vein and hepatocellular necrosis in the liver, and interstitial and intraglomerular congestion, tubular atrophy, and inflammation in the kidney[28].

Dose:

To make a tea for diuretic purposes, one to two grams [one teaspoon] of the herb is added to hot water [not boiling] and allowed to steep for a while. The usual recommended intake is two to three cups a day[6]. Or, water is poured over 1.5 grams [approximately 1 teaspoonful = 1.4g] of chopped rupturewort herb and brought to a boil and after five minutes strained. Herb tea is taken 2-3 times per day[31, 34].

CONCLUSION:

The current review highlighted the chemical constituents and pharmacological effects of *Herniaria glabra* and *Herniaria hirsuta* as a promising sources of future drugs.

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