Phytochemical Properties and Medicinal Applications of Galium aparine: A Review

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Abstract:
The phytochemical screening of extracts of Galium aparine revealed that the plant contained phenols, tannins, alkaloids, anthraquinones, coumarins, iridoids asperuloside, alkanes, flavonoids and saponins. Previous pharmacological studies showed that Galium aparine extracts possessed antimicrobial, anticancer and hepatoprotective effects. This review will highlight the chemical constituents and pharmacological effects of Galium aparine.

Keywords: *chemical constituents, pharmacology, Galium aparine*

INTRODUCTION:

Herbal medicine is the oldest form of healthcare known to mankind. Two thirds of the new chemicals identified yearly were extracted from higher plants. 75% of the world's population used plants for therapy and prevention. Plant showed wide range of pharmacological activities including antimicrobial, antioxidant, anticancer, hypolipidemic, cardiovascular, central nervous, respiratory, immunological, anti-inflammatory, analgesic antipyretic and many other pharmacological effects[1-13]. The phytochemical screening of extracts of *Galium aparine* revealed that the plant contained phenols, tannins, alkaloids, anthraquinones, coumarins, iridoids asperuloside, alkanes, flavonoids and saponins**.** Previous pharmacological studies showed that *Galium aparine* extracts possessed antimicrobial, anticancer and hepatoprotective effects. This review was designed to highlight the chemical constituents and pharmacological effects of *Galium aparine*.

Plant profile:

Synonyms:

Aparine hispida Moench, Aparine vulgaris Hill, Asperula aparine [L.] Besser, Asterophyllum aparine [L.] Schimp. & Spenn., Crucianella purpurea Wulff ex Steud., Galion aparinum [L.] St.-Lag., Galium aculeatissimum Kit. ex Kanitz, Galium aparine var. agreste P.D.Sell, Galium aparine subsp. agreste P.D.Sell, Galium aparine var. aparine, Galium aparine var. fructibushispidis Franch. , Galium aparine var. intermedium [Mérat] Bonnet, Galium aparine var. marinum Fr., Galium aparine var. microphyllum Clos, Galium aparine var. minor Hook., Galium aparine var. subglabrum Peterm., Galium aparine var. pseudoaparine [Griseb.] Speg., Galium asperum Honck., Galium australe Reiche, Galium borbonicum var. makianum Cordem. Galium charoides Rusby, Galium chilense Hook.f., Galium chonosense Clos, Galium hispidum Willd., Galium horridum Eckl. & Zeyh., Galium intermedium Mérat, Galium lappaceum Salisb., Galium larecajense Wernham, Galium parviflorum Maxim., Galium pseudoaparine Griseb., Galium scaberrimum Vahl ex Hornem., Galium segetum K.Koch, Galium tenerrimum Schur, Galium uliginosum Thunb. Galium uncinatum Gray and Rubia aparine [L.] Baill[14].

Taxonomic classification:

Kingdom: Plantae, **Subkingdom:** Viridiplantae, **Infrakingdom**: Streptophyta, **Superdivision**: Embryophyta, **Division**: Tracheophyta, **Subdivision**: Spermatophytina, **Class**: Magnoliopsida, **Superorder**: Asteranae, **Order**: Gentianales, **Family**: Rubiaceae, **Genus**: Galium, **Species**: *Galium aparine*[15]

Common names:

Arabic: Hashishat Alafa, Balsak, Galium Abiadh; **English**: catchweed bedstraw, cleavers, cleaverwort, goose-grass, small goose-grass, stickywilly, white hedge; **French:** gaillet gratteron; **Portuguese:** amor-de-hortelã, erva-pegavosa, pega-pega; **Swedish**: snärjmåra [16].

Distribution:

Galium aparine was widely distributed throughout Europe, North America and some parts of Asia, and occured as far north as Alaska and Greenland. It was introduced to Australia, New Zealand, and the sub-Antarctic Islands [17].

Description:

Galium aparine is a climbing plant that attaches to surrounding hosts by its leaves, which are covered by hooked trichomes. Stem: The hairs along the stem point downwards. The stem is very unique in the fact that a cross-section of a stem will roughly be a square

in shape. The nodes are never swollen on this plant, and it tends to grow in tufts and compact clusters. The stem is not very strong. The leaves: are arranged in whorls of six, and are considered simple leaves. The edges of the leaf blade are entire, and the whole leaf is covered with hairs [trichomes] for attaching to other plants. Flowers: The carpels of the flower are all fused to one another. The ovary is considered inferior, and does not always consist of a hypanthium. The flowers form a spiral around the inflorescence axis, consisting of four petals and sepals. The petals are also fused into a corolla tube. Fruit: When the fruit is ripe, it does not split open, but usually turns brown in colour. The fruit can range from 3-5mm in length, and has tiny hairs covering the fruit for a mode of transportation [18].

Part used medicinally:
The whole plant and aerial parts [19-23].

Traditional uses:
It was eaten as a vegetable. Their seed was roasted to prepare a sort of coffee substitute. It was also used in traditional medicine as an infusion to treat kidney problems, skin disorders and high blood pressure [17].

Modern herbalists and homoeopaths used the plant for the treatment of scurvy, scrofula, psoriasis, eruptions and many other skin diseases. The infusion was used in cases of insomnia and calming effects. A wash made from the plant was used in sunburn and freckles, a decoction or infusion of the fresh herb also applied to the face by means of a soft cloth or sponge for the same purpose. The crushed herb was applied in France as a poultice to sores and blisters [19].

Galium aparine aerial parts were also traditionally used for the treatment of skin disorders, especially psoriasis; enlarged lymph nodes and cystitis. It was also used for growths or deposits of a nodular character in the skin or mucous membranes. Its main actions were lymphatic and diuretic, although Cleavers was highly regarded in Europe as a depurative with efficacy against conditions such as eczema and psoriasis and other chronic inflammatory conditions. It was also used for the treatment of stranguria with turbid urine, hematuria, traumatic injury, acute appendicitis, furuncle and otitis media [20-23].

Physico-chemical characteristics:
Galium aparine herb yield 3.02% lipophilic complex. It was oleiferous mass of dark-green colour with specific herbaceous smell. The complex was soluble in chloroform, hexane and acetone, insoluble in water and water-alcohol mixtures [24].

Chemical constituents:
The preliminary phytochemical screening of ethyl acetate and methanol extracts of *Galium aparine arial* parts revealed that the plant contained phenols, tannins, alkaloids, anthraquinones, coumarins, iridoids asperuloside, alkanes, flavonoids and saponins [25-27].

Quantitative analysis revealed that *Galium aparine* seeds contained: 2.76±0.03% alkaloids, 0.99±0.03 % saponins, 6.36±0.03 % flavinoids and 16.96±0.01% tannins[25].

Anthraquinone aldehyde nordamnacanthal [1,3-dihydroxy-anthraquinone-2-al] was identified in *Galium aparine* [28].

The total phenolic contents in the plant extracts were 50.00± 0,036 mg GAE/g in ethyl acetate extract, and 41.00 ± 0.280 mg GAE/g in methanol extract. 598.2 ppm rutin was detected in 1 ml ethyl acetate extract, and 597.7 ppm in 1ml methanol extract[13].

The total phenolic contents in methanol extract of *Galium aparine* from Pakistan appeared higher [124.8 µg of Gallic acid equivalent][29].

The total polyphenolic compounds of 70% ethanolic extracts of *Galium aparine* from Transylvania [NW of Romania] was 2.40 ± 0.24 g, gallic acid equivalents /100 g dry mass and the total flavonoids was 1.60 ± 0.53 g, rutin equivalents /100 g dry mass, while the total Caffeic acid derivatives was 0.348 ± 0.09 g, caffeic acid equivalents /100 g dry mass. The polyphenolic compounds isolated from 70% ethanolic extracts of *Galium aparine* were: caftaric acid: <0.2, gentisic acid: <0.2, gentisic acid : <0.2, caffeic acid: <0.2, chlorogenic acid: <0.2, p-coumaric acid : 1.404 ± 0.28, ferulic acid: 3.793 ± 0.31, hyperoside: 0.300 ± 0.03, isoquercitrin : 0.967 ± 0.13, rutin: 7.983 ± 0.30, quercetin: 5.679 ± 0.26, luteolin: 0.467 ± 0.07 mg /100 g dried vegetal material[30].

Six phenolic compounds were isolated from the ethyl acetate-soluble part of the 95% ethanol extract of the plant, and their chemical structures were identified as 1-[4-hydroxyphenyl]-ethanone; vanillic acid; 3,4-dihydroxybenzoic acid, p-hydroxycinnamic acid; gallic acid and 4-hydroxytruxillic acid[31].

Two iridoid glycosides were isolated from the aerial parts of *Galium aparine*, asperulosidic acid and 10-

deacetylasperulosidic acid. Furthermore, chlorogenic acid was also isolated from *Galium aparine* [32].
The petroleum ether phase of *Galium aparine* 60% ethanol extraction contained β-sitosterol, daucosterol, dibutyl phthalate and other substances[20].

Phytochemical profile of lipophilic complexes from *Galium aparine* revealed the presence of 4.79% total volatile substances, 0.29% dicarboxylic acids, 0.04% aromatic acids, 0.95% saturated fatty acids, 1.68% unsaturated fatty acids, 2.64% total fatty acids content, 0.68% terpenoids and 0.04% steroids[33].

The essential oils from aerial parts of *Galium aparine*, collected from Ankara and Kastamonu were analyzed by GC/MS. Seventy-two compounds representing 64.7% of the essential oil *Galium aparine*, were identified. The major component of the essential oil obtained by acid hydrolysis from *Galium aparine* was hexadecanoic acid [22.3%][34].

Galium aparine herb yield 3.02% lipophilic complex. By means of chromatography-mass-spectrometry 36 compounds have been identified and quantified [mg/kg] included: benzaldehyde: 23.4; propiophenone: 69.9; cinnamaldehyde: 22.4; methylacetophenone: 71.8; caprylic acid: 52.5; 1,2,3,4-tetrahydro-1,1,6- trimethylnaphthalene: 25.9; phenylacetic acid: 67.5; 2-methoxy-4-vinylphenol: 68.7; 1,2-Dihydro-1,1,6-trimethylnaphthalene: 31.4; 1,2-dihydro-1,6,8-trimethyl naphthalene: 18.2; Vanillin: 16.8; capric acid: 95.5; dihydroactinidiolide: 218.3; loliolide: 761.2; myristic acid: 504.0; trans-neophitadiene: 3485.5; cis-, trans-neophitadiene: 747.6; cis-neophitadiene: 1237.5; palmitoleic acid: 436.4; palmitic acid: 13742.2; heptadecanoic acid: 220.2; linolenic acid: 692.9; linoleic acid: 18937.3; tricosane :229.1; 4,8,12,16-tetramethylheptadecane-4-olide: 120.6; tetracosane: 65.1; pentacosane :221.2; octacosane: 788.5; heptacosane: 300.4; squalene: 264.0; nonacosane :3315.9; triacontane: 248.5; stigmasta- 3,5-diene: 127.0; vitamin E: 154.0; untriacontane: 297.9 and γ-sitosterol 265.4[24].

Pharmacological effects:
Antimicrobial effects:
The ethanolic extracts of *Gallium* species were tested for the antimicrobial activity against two Gram-positive bacterial strains [*Staphylococcus aureus* [ATCC 49444], *Listeria monocytogenes* [ATCC 13076]], two Gram-negative bacterial strains [*Escherichia coli* [ATCC 25922], *Salmonella typhimurium* [ATCC 14028]] and one fungal strain: [*Candida albicans* [ATCC10231]]. Ethanolic extracts of *Gallium aparine* showed no antibacterial activity against the tested microorganisms [30].

The antibacterial and antifungal activities of *Galium aparine* herb lipophilic complex were investigated against *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Proteus vulgaris* ATCC 4636, *Bacillus subtilis* ATCC 6633 and *Candida albicans* 885-663. The results revealed that *S. aureus* [Zone of growth inhibition: 35.4±0.1mm, Minimum inhibitory concentration 31.25 µg/ml and Minimum bactericidal concentration 62.50 µg/ml], *P. aeruginosa* [Zone of growth inhibition: 26.0±0.4mm, Minimum inhibitory concentration 62.50 µg/ml and Minimum bactericidal concentration 125.00 µg/ml] and *C. albicans* [Zone of growth inhibition: 33.1±0.2 mm, Minimum inhibitory concentration 31.25 µg/ml and Minimum bactericidal concentration 62.50 µg/ml] were highly sensitive; *B. subtilis* [Zone of growth inhibition: 23.1±0.3mm, Minimum inhibitory concentration 125.00 µg/ml and Minimum bactericidal concentration 250.00 µg/ml] showed moderate sensitivity; while, *E. coli* [Zone of growth inhibition: 10.0±0.1mm, Minimum inhibitory concentration 250.00 µg/ml and Minimum bactericidal concentration 500.00 µg/ml] and *P. vulgaris* [Zone of growth inhibition: 14.2±0.1mm, Minimum inhibitory concentration 250.00 µg/ml and Minimum bactericidal concentration 500.00 µg/ml] were nonsensitive to *Galium aparine* herb lipophilic complex[24, 33].

Antioxidant effects:
The *in vitro* antioxidant activity of ethanol extract of *Gallium aparine* was evaluated using was assessed by the DPPH radical bleaching method. The ethanol extract of *Gallium aparine* showed high radical scavenging activity [IC50 116.43 ± 0.46 µgm/l]. This activity was well correlated with total polyphenols content [30].

The antioxidant activity of *Gallium aparine* arial was determined using DPPH free radical scavenging assay, H2O2 scavenging assay and metal ion chelating ability. Ethyl acetate and methanol extracts showed strong DPPH• radical scavenging activity [52.30±0.001 and 97.70±0.003% at concentration of 300 µg/ml, respectively][26].

Galium aparine extracts were screened for their antioxidant activity using DPPH radical scavenging ability. Methanol extract of the selected plant had the highest antioxidant for reducing DPPH [84.33%] while its water extract exhibited least antioxidant activity for reducing DPPH [8.77%]. The total

phenolic contents were positively correlated with the DPPH radical scavenging results [29].

Methanol extract and its n-hexane, ethyl acetate, butanol and aqueous fraction of *Galium aparine* were evaluated *in vitro* for their antioxidant capacity [DPPH, superoxide radical, phosphomolybdate assay] and reducing power [ABTS, hydroxyl, hydrogen peroxide, to reduce Fe3+ to Fe2+ ions]. The results showed that aqueous fraction strongly scavenge the DPPH, ABTS, hydroxyl, hydrogen peroxide and superoxide radicals. A significantly high correlation coefficient existed between IC50 values of DPPH and superoxide radical with total phenolic content, and phosphomolybdate assay with total flavonoid contents [35].

Anticancer effects:

Anticancer effects were determined against human breast cancer cells [MCF-7] [ATCC HTB-22], human colon cancer cells [Caco-2] [ATCC HTB-37] and human peripheral lymphocytes. Ethyl acetate showed higher cytotoxic and apoptotic effect on human peripheral lymphocytes compared to methanol extract. Ethyl acetate extract exhibited concentration-dependent cytotoxic effect on MCF-7 cell line [34.35%, 43.27% and 49.30%, for 100, 200 and 300 µg/ml respectively]. Methanol extract showed higher cytotoxic effects on MCF-7 cells [34.30±0.063, 55.67±0.131 and 71.14% for 100, 200 and 300 µg/ml respectively]. *Galium aparine* ethyl acetate and methanol extracts exerted concentration - dependent apoptotic effects on MCF-7 and Caco-2 cells lines after 48 h, methanol extract appeared more effective[26].

The *in vitro* anti-proliferative activity of petroleum ether phase of *Galium aparine* 60% ethanol extraction was investigated in leukemia cell K562 using MTT method. Results showed that *Galium aparine* petroleum ether contained β-sitosterol, daucosterol, dibutyl phthalate and other substances. The three compounds inhibited the proliferation of leukemia cell K562 with dose- dependent and time-dependent relationship, of which dibutyl phthalate has strongest activity and β-sitosterol with moderate activity [20].

The potential anti-proliferative and apoptotic effect of *Galium aparine* methanol extract were evaluated against MCF-7 and MDA-MB-231 human breast cancer cells and MCF-10A untransformed breast epithelial cells. The extract showed anticancer effects against both breast cancer cell lines in a concentration and time dependent manner, it caused G1 block after 72h exposure. However, it produced no effect against MCF-10A breast epithelial cells. Flow cytometry analyses revealed that apoptosis was induced in MDA-MB-231 cells, and necrosis was induced in MCF-7 cells [36].

Hepatoprotective effects:

The hepatoprotective effects of mixture of *Berberis lycium*, *Galium aparine* and *Pistacia integerrima* were evaluated in carbon tetrachloride [CCl4]-induced hepatic toxicity in rats. The results indicated that a mixture of *Berberis lycium*, *Galium aparine* and *Pistacia integerrima* possessed hepatoprotective effects through correction of biochemical parameters. These medicinal plants showed more curative than preventive effects[37].

Dose:

Dried herb 2-4g or by infusion three times daily. Liquid extract 2-4ml [1 :1 in 25% alcohol] three times daily. Expressed juice 3-15 ml three times daily[38].

CONCLUSION:

This review discusses the chemical constituent, pharmacological and therapeutic effects of *Galium aparine* as promising herbal drug because of its safety and effectiveness.

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