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CHEMICAL CONSTITUENTS AND PHARMACOLOGICAL EFFECTS OF *HYPERICUM TRIQUETRIFOLIUM*

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Abstract:

Hypericum triquetrifolium contained many biologically active chemicals included acylphloroglucinols triquetrireboudin, triquetriborin, essential and volatile oils and many phenolic compounds. Hypericum triquetrifolium contained hyperforin 0.013 ± 0.000 and hypericin 0.020 ± 0.001 w/w%. Many phenolics were isolated from Hypericum triquetrifolium included chlorogenic acid, caffeoylquinic acid, p-coumaroylquinic acid, epicatechin, rutin, hyperoside, I3,II8-biapigenin, isoquercetine, quercitrine, quercetine, quercetin galactoside, quercetin rutinoside, quercetin-3-O-galactoside, kaempferol-3-O-glycoside, apigenin-7-O-glucoside, kaempferol and amentoflavone. The pharmacological studies showed that Hypericum triquetrifolium possessed antinflammatory, analgesic, antioxidant, cytotoxic, antimicrobial and vasorelaxant effects. This review will highlight the chemical constituents and pharmacological effects of Hypericum triquetrifolium.

Keywords: *Chemical constituents, pharmacology, Hypericum triquetrifolium*

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INTRODUCTION:

Herbal medicine is the oldest form of healthcare known to mankind. Herbs had been used by all cultures throughout history. The World Health Organization [WHO] estimates that 80 percent of the world populations presently use herbal medicine for some aspect of primary health care. However, plants are still providing some of our most valuable medicines [1-35]. Acylphloroglucinols triquetrireboudin, triquetriborin, essential and volatile oils and many phenolic compounds were isolated from *H. triquetrifolium*. *Hypericum triquetrifolium* contained hyperforin 0.013 ± 0.000 and hypericin 0.020 ± 0.001 w/w%. Many phenolics were isolated from *Hypericum triquetrifolium* included chlorogenic acid, caffeoylquinic acid, p-coumaroylquinic acid, epicatechin, rutin, hyperoside, I3,II8-biapigenin, isoquercetine, quercitrine, quercetine, quercetin galactoside, quercetin rutinoside, quercetin-3-O-galactoside, kaempferol-3-O-glycoside, apigenin-7-O-glucoside, kaempferol and amentoflavone. The pharmacological studies showed that Hypericum *triquetrifolium* possessed antinflammatory, analgesic, antioxidant, cytotoxic, antimicrobial and vasorelaxant effects. This review was designed to highlight the chemical constituents and pharmacological effects of *Hypericum triquetrifolium*.

Plant profile:

Synonyms: *Hypericum crispum* [43].

Taxonomic classification:

Kingdom: Plantae, **Subkingdom**: Viridiplantae, **Infrakingdom**: Streptophyta, **Superdivision:** Embryophyta, **Division**: Tracheophyta, **Subdivision**: Spermatophytina, **Class**: Magnoliopsida, **Superorder:** Rosanae, Order: Malpighiales, **Family:** Hypericaceae, **Genus:** Hypericum, **Species**: *Hypericum triquetrifolium* [44-45].

Common names:

Arabic: Roja, Bu krad, Dathi or Nabtat Yohanna; **English**: tangled hypericum [46-47].

Distribution:

It was distributed in Africa [Algeria, Libya, Tunisia]; Asia [Iran, Iraq, Palestine, Jordan, Lebanon, Syria, Turkey]; Europe [Albania, Former Yugoslavia, Greece, Italy, Malta , France, Gibraltar, Spain][46].

Description:

It is a perennial herb to 50 cm high with a dense tangle of thin branches, glabrous but spotted with small black glands. Sap is resinous. It has deep vertical roots and a shallow rhizome system from which new shoots are produced. Leaves are opposite, sessile, simple, 5–15 mm long, the base clasping the stem. Margins of the leaf are wavy, undulate, also with small black or translucent glands. Flowers are 10–15 mm across, shortly stalked in clusters of two to five at the ends of branches, with 5 free yellow petals. Stamens are many in three groups. Sepals are 2 mm long, ovate, without glands. The capsule is three-celled, 3–5 mm long with numerous seeds 1–2 mm long, slightly curved, with a pitted surface [48].

Traditional uses:

Hypericum triquetrifolium was used in traditional Arab herbal medicine to treat various inflammatory diseases and as sedative, astringent, anti-spasmodic, for intestine and bile disorders and poisoning [47, 49-50]. It was used in Turkish folk medicine in the treatment of bile and intestinal ailments [51-52].

Chemical constituents:

Hyperforin, hypericin and pseudohypericin are the active markers of *Hypericum* extract. *Hypericum triquetrifolium* contained hyperforin 0.013 ± 0.000 w/w% and hypericin 0.020 ± 0.001 w/w% [52, 53-54].

Hypericin was determined in different parts [leaf, flower and stem] of *Hypericum triquetrifolium* the percents of hypericin in leaves, flowers and stems were 310, 210 and 150 mg/100g, respectively [55].

The variation in the content of hyperforin, hypericin and pseudohypericin was studied in *Hypericum triquetrifolium* growing wild in four locations of Turkey. Hyperforin content ranged from 0.05 to 0.56 mg/g, hypericin from 0.74–1.98 mg/g, and pseudohypericin from 0.72–2.26 mg/g, dry weight. Among the different plant parts, the flowers were found to be the principle organ for hyperforin accumulation, while hypericin and pseudohypericin were accumulated mainly in leaves [51].

Two new acylphloroglucinols triquetrireboudin and triquetriborin were isolated from the petroleum ether extract of the aerial parts of *H. triquetrifolium* [56].

Many phenolics were isolated from *Hypericum triquetrifolium* included chlorogenic acid, caffeoylquinic acid, p-coumaroylquinic acid, epicatechin, rutin, hyperoside, I3,II8-biapigenin, isoquercetine, quercitrine, quercetine, quercetin galactoside, quercetin rutinoside, quercetin-3-O-galactoside, kaempferol-3-O-glycoside, apigenin-7-O-glucoside, kaempferol and amentoflavone [49, 57-61].

Chlorogenic acid, rutin, hyperoside, quercitrin, quercetin, and isoquercetin contents [mg/g dry weight] in vegetative stage of wild-growing

Hypericum triquetrifolium whole plant were 4.45 , 2.47 , 3.22 , 4.52, 0.36 , 17.49; in floral budding stage were 6.86, 5.93, 9.32, 7.64, 0.92, 24.65; in full flowering stage were 7.84, 3.61, 15.67, 7.98, 0.64, 7.33;in fresh fruiting stage were 3.48, 1.22, 5.93, 5.68, 0.62, 9.10; in mature fruiting stage were 0.33, 0.14, 0.37, 0.29, 0.39, 1.38, respectively. While, chlorogenic acid, rutin, hyperoside, quercitrin, quercetin, and isoquercetin contents [mg/g dry weight] in vegetative stage of of green house grown *Hypericum triquetrifolium* whole plant were 2.20 , 0.36, 1.31, 0.61, 0.66, 3.27; in floral budding stage were 9.07, 1.03, 3.31, 1.05, 0.36, 15.01; in full flowering stage were 6.06, 1.52, 3.96, 1.49, 0.99, 15.46; in fresh fruiting stage were 4.58, 1.19, 2.89, 0.51, 0.35, 11.03; in mature fruiting stage were 0.44, 0.04, 0.19, 0.27, 0.27, 0.23, respectively [62].

On the other hand, the plant parts were significantly varied in phenolic content. Among different plant parts, the flowers were found to be the principle organ for chlorogenic acid, hyperoside, apigenin-7-O-glucoside, kaempferol, quercetin and amentoflavone accumulations, while rutin and quercitrin were accumulated mainly in the leaves [61].

Fungal extracts of *Aspergillus niger*, *Fusarium oxysporum* and commercial yeast were added to a liquid MS medium at 0.1, 0.25, 0.5 or 0.75 mg/l. Data showed that the yield of p-OH-benzoic acid and chlorgenic acid in cultures derived from leaf of *Hypericum triquetrifolium* [LCs] treated with 0.5 mg/l yeast extract increased significantly compared with the control. Caffeic acid and tannic acid decreased in LCs significantly after elicitation with all biotic elicitors, but catechin accumulation in LCs increased significantly, when *A. niger* extract was added at all concentrations. Rutin, hypersoid and quercitin production in cultures derived from stem of *Hypericum triquetrifolium* [SCs] increased significantly when treated with the fungal elicitors*; A. niger*, *F. oxysporum* and yeast extracts. Chlorgenic decreased significantly in SCs, after the addition of all biotic elicitors at different concentrations [63].

N-nonane [15%], germacrene-D [13%], caryophyllene oxide [12%], b-caryophyllene [11%], a-pinene [10%], myrcene [5%], b-pinene [4%] and sabinene [3%] were the main components of the oil of *H. triquetrifolium* from Italy [64].

1-Hexanal [18.8%], 3-methylnonane [12.5%], α-pinene [12.3%], caryophyllene oxide [4.7%], 2-methyldecane [4.5%] and α-amorphene [4.2%] were the main components of the essential oil of the aerial parts of *H. triquetrifolium* from Turkey [65].

α-humulene, *cis*-calamenene, δ-cadinene, bi-cyclogermacrene, eremophilene, β-caryo-phyllene, [E]-γ-bisabolene and α-pinene were the main components of the Tunisian *H. triquetrifolium* oil [66].

However, the essential oil of the aerial parts of Tunisian *Hypericum triquetrifolium* obtained by ultrasound extraction, hydrodistillation and Soxhlet/dynamic headspace were analyzed by GC-FID and GC-MS showed the predominance of *n*-octane, α-pinene, β-caryophyllene, 2-methyloctane, *n*-nonane, germacrene- D, α-selinene and β-cubebene [67].

Germacrene-D [21.7%], β-caryophyllene [18.3%], δ-cadinene [6.4%], *trans*-β-farnesene [4.3%], α-humulene [3.8%], β-selinene [3.7%], γ-cadinene [3.3%] and *trans*-phytol [3.2%] were found to be the major constituents of the oil of *Hypericum triquetrifolium* from Iran. The oil of *H. triquetrifolium* consisted of five monoterpene hydrocarbons [3.4%], two oxygenated monoterpenes [0.4%], twenty-two sesquiterpene hydrocarbons [77.1%], eight oxygenated sesquiterpenes [7.9%] and one oxygenated diterpene [3.2%]. Twelve nonterpenic compounds were also consisted 5.1% of the oil [68].

Hexenal, [E] [12.63%], Octane, 2, 3, 3-trimethyl [11.36%], Pentadecane, 7-methyl- [9.7%], Undecane [6.15%] and alpha. -Pinene [5.75%] were the main components of the essential oil of *H. triquetrifolium* from Iraq [69].

The crude methanolic extract of the aerial parts of *H. triquetrifolium* was examined for its potential activity in counteracting and preventing cognition impairment caused by acute and chronic restrain stress in rats. *H. triquetrifolium* methanolic extracts were administrated intraperitoneally [50 mg/Kg]. Rats were tested for spatial memory in radial arm water maze test. Results revealed that chronic psychosocial stress impairs short term memory. Acute stress also impairs both short term memory and long term memory. Chronic *H. triquetrifolium* extract administration prevented stress induced memory impairment in both chronic and acute stressed rats which is confirmed by the correction of stress-induced reduction in BDNF protein levels especially in the hippocampal area of brain[59].

Pharmacological effects:

Antinflammatory and analgesic effects:

The antiinflammatory effect of *Hypericum triquetrifolium* was evaluated in rat model of

carrageenan induced inflammation. Male Wistar rats were treated intraperitoneally with 0.4% dimethylsulphoxide [DMSO] [as control group] and *H. triquetrifolium* extract [25, 50, 60 mg/kg], 30 min before 0.1 ml 1% carrageenan injection. Paw volume was measured before and 1, 2, 3, 4, 5 and 6 h after the injection of carrageenan. Intraperitoneal administration of *H. triquetrifolium* extract [25, 50, 60 mg/kg] inhibited paw swelling dose-dependently at 2, 3, 4, 5 and 6 h after carrageenan injection [[P<0.05]. We can conclude that *H. triquetrifolium* extract may exert an antiinflammatory effect in rats. # 2002 Elsevier Science Ireland Ltd. All rights reserved [70].

The anti-inflammatory mechanism of *Hypericum triquetrifolium* was studied by measuring the expression and release of pro-inflammatory cytokines, tumor necrosis factor-*α* [TNF-*α*] and interleukine-6 [IL-6], and inducible nitric oxide synthase [iNOS] in human monocytic cells, THP-1. The effects were assessed by measuring the levels of secretory proteins and mRNA of TNF-*α* and IL-6, the levels of nitric oxide [NO] secretion and the expression of iNOS in THP-1 cells. Cells were treated with 5 *μ*g lipopolysaccharide/ml [LPS] in the presence and absence of increasing concentrations of extracts from the aerial parts of *H. triquetrifolium*. During the entire experimental period, extract was used in concentrations [up to 250 *μ*g/ml] that had no cytotoxic effects, measured with MTT and LDH assays. *Hypericum triquetrifolium* extracts remarkably suppressed the LPS-induced NO release, significantly attenuated the LPS-induced transcription of iNOS and inhibited in a dose-dependent manner the expression and release of TNF-*α*. No significant effects were observed on the release of IL-6 [50].

The anti-inflammatory activity of *Hypericum triquetrifolium* extracts [HT-extract] was evaluated on lipopolyssacharide -stimulated human monocytic [THP-1] cells and human peripheral blood mononuclear cells [PBMNCs]. The expression and production of pro-inflammatory cytokines tumor necrosis factor-α [TNF-α] and interleukin 6 [IL-6], as well as the anti-inflammatory cytokine interleukin 10 [IL-10] were evaluated by assessing the levels of proteins and mRNA's of TNF-α, IL-6 and IL-10 in both cell types. Cells were exposed to 5 μg lipopolyssacharide [LPS] /ml in the absence and presence of increasing concentrations of 50% ethanol extracts from the aerial parts of Hypericum triquetrifolium. The anti-inflammatory efficacy experiments were performed with HT-extract concentrations up to 250 μg/ml that had no cytotoxic effects as assessed with MTT and LDH assays. HT-extract remarkably inhibited the expression and secretion of TNF-α and IL-6 at a concentration of 250 μg/ml. HT-extract remarkably elevated IL-10 secretion and mRNA levels at 125 μg/ml. Furthermore, HT-extract exhibited relatively high antioxidant activity [IC50 of 5 μg/ml] as measured with DPPH assay [71].

The antinociceptive activity of *Hypericum triquetrifolium* lyophilized extract was investigated in mice. Formalin paw test and tail flick tests were used for the evaluation of the antinociceptive activity. The extracts caused a significant dose-related inhibition of the first phase [50, 60 mg/kg, ip] and second phase [10, 25, 50 and 60 mg/kg, ip] of formalin induced hindpaw licking. Additionally, the extract administration [50, 60 mg/kg, ip] increased the tail flick latencies. No significant change was observed in any of the treatment groups in the sensorimotor performance test [72].

Antioxidant effect:

The total phenolic content of the aqueous extract of *Hypericum triquetrifolium* was 44.6 mgGE/g dry weight, and methanolic extract was 40.6 mgGE/g dry**.** The antioxidant activity of the aqueous extract was 457.4 mmol TE/g dry weights, and methanolic extract was 535.5 mmol TE/g dry weights [73].

The phenolic compounds extracted from the aerial parts of *Hypericum triquetrifolium* showed strong antioxidant activity as tested using an in vitro method based on sodium arachidonoate, bleomycin and thiobarbituric acid with alpha-tocopherol as the reference solution. The antioxidant investigation of the methanol extract of *Hypericum triquetrifolium* aerial part, revealed that IC50 between 0.062 and 1 mg/ml [49, 57].

The antioxidant effect of 80% methanolic extract of *H. Triquetrifolium* [whole plant] was investigated using *in vitro* antioxidant assays were used: total antioxidant capacity, DPPH free radical scavenging, ferric reducing, ferrous chelating, total phenols and flavonoids. Among 12 tested plant extracts, *H. triquetrifolium* extracts possessed the highest total antioxidant capacity, the highest DPPH free radical scavenging activity and the highest reducing power [74].

The antioxidative potential of the ethanol extracts of *Hypericum triquetrifolium* was investigated using 1,1-diphenyl-2-picrylhydrazyl [DPPH], metal chelating, reducing power, hydroxyl radical, total antioxidant activity, and lipid peroxidation inhibition assays. The extract was found to be highly active in

the DPPH radical scavenging assay with IC50 of 39.0 µ g/ml. The ethanol extracts exhibited a high reducing power, suggesting that the extract had strong electron-donating capacity. The degradation of deoxyribose by hydroxyl radicals was shown to be inhibited by the extract, mainly by scavenging hydroxyl radicals rather than as chelators of iron ions. The total antioxidant activity of ethanol was comparable with vitamin E[75].

The ability of *Hypericum triquetrifolium* to prevent oxidative damage to bovine serum albumin [BSA] induced by Fe3+/H2O2 and ascorbic acid was investigated. The ethanol extracts of *Hypericum triquetrifolium* at different concentrations [50-1,000 µg/ml] efficiently prevented protein oxidation induced by hydroxy radical as assayed by protein oxidation markers including protein carbonyl formation and polyacrylamide gel electrophoresis. The effect of ethanol extract of *Hypericum triquetrifolium* on DNA cleavage induced by UV-photholysis of H2O2 using pBluescript M13+ plasmid DNA was also investigated. The extract significantly inhibited DNA damage induced by reactive oxygen species [ROS][76].

Cytotoxic and genotoxic effects:

The Sulforodamine B [SRB] assay was used to test cytotoxicity of antioxidant constituents isolated from *Hypericum triquetrifolium* against four human cancer cell lines and one normal cell line, large cell lung carcinoma cell line COR-L23, the hepatocellular carcinoma cell line HepG-2, renal cell adenocarcinoma ACHN, the amelanotic melanoma cell line C32 and normal human foetal lung MRC5. The results showed that I3-II8-biapigenin exhibited strong cytotoxic activity [IC50 = 5.73 micro g mL[-1]] showing a certain degree of selectivity against the different cell types [77].

Two cancer cell lines: Colon and Lung [HCT-116, A549] and one normal [control] cell line [skeletal muscle, L6] were selected to test the efficacy of *Hypericum triquetrifolium* different extracts in apoptosis induction. The cells were treated with an increasing concentration of [distilled water, 50%water- 50% ethanol, and hexane] plant extract [0, 8, 16, 32, 62, 125, 250, 500, 1000 and 2000µg/ml] for 24h. Then MTT assay was used to test cytotoxicity of the extracts. The results showed that *Hypericum triquetrifolium* extracts induced apoptosis in colon cancer cell line [HCT116], muscle cell line [L6], and lung cancer cell line [A549] at the concentration of 500µg/ml through mitochondrial dependent pathway by releasing cytochrome c [78]. The cytotoxic effect was investigated using Vero cell lines. They showed low cytotoxic effect [CC50 ranged between 0.58 mg/ml and 12.00 mg/ml][79].

Hypericum triquetrifolium aqueous extract were studied for its toxic and the possible clastogenic effects in vivo on the bone marrow and spermatozoa cells of Swiss albino mice. The lethal dose of the aqueous extract was considered to be 10.33 g/kg of the body weight, injected subcutaneously. *H. triquetrifolium* extract induce statistically significant increases in the average numbers of micronucleus[MN] at the dose 2 g/kg and chromosome aberrations at the doses 2 and 1 g/kg ,the majority of aberrations observed were chromatid breaks, centromeric breaks, acentric fragments. The extract was found to inhibit mitotic index [MI] in a dose-dependent manner. Moreover the plant extract showed a significant induction of sperm abnormalities in all concentrations used [2, 1, and 0.25 g/kg] comparing with the untreated animals. The most frequent types of sperm abnormalities of the treated groups were; amorphous, pseudo-droplet defect, bent mid piece defect and corkscrew mid piece defect. However, the lowest dose 0.25 g/kg body weight was the most effective one which markedly increased the corkscrew midpiece defect. The results indicated that the mixture of the compounds found in the aqueous extract caused cytotoxicity and induced different cytogenetic effects in both somatic and germ cell [47]

Antimicrobial effects:

Methanolic extract was active against *Bacillus subtilis, Salmonella typhimurium, Staphylococcus aureus* and *Escherichia coli;* acetone extract was active against *Bacillus subtilis, Salmonella typhimurium* and *Staphylococcus aureus*; CHCL3 extract was active against *Bacillus subtilis, Salmonella typhimurium, Staphylococcus aureus, Micrococcus luteus, Candida albicans* and *Candida utilis* [80-82] .

The essential oils of *Hypericum triquetrifolium* from five different Tunisian localities [Fondouk DJedid, Bou Arada, Bahra, Fernana and Dhrea Ben Jouder] were evaluated for their antimicrobial activities against bacterial and fungal strains[*Bacillus cereus, Escherichia coli, Vibrio alginolyticus, Vibrio cholerae, Pseudomonas aeruginosa, Salmonella typhimurium, Aeromonas hydrophila, Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermidisa, Aspergillus niger, Fusarium solani, Botrytis cinerea, Candida albicans. Candida glabrata* and *Candida krusei*]. The results showed a good antibacterial activity against a wide range of bacterial strains, MIC values ranging between 0.39-

12.50 mg/ml and MBC values between 1.56-25.0 mg/ml. The essential oils showed antifungal activity with MIC values ranging between 0.39 µg/ml and 12.50 µg/ml; MFC values ranged between 3.12 µg/ml and 25.00 µg/ml. The essential oils did not show antiviral activity against coxsakievirus B3[79].

Five extracts and pure compounds from the aerial parts of *Hypericum triquetrifolium* were tested for antibacterial activity against 31 gram-positive and gram-negative strains using the agar dilution method. The ethyl acetate extract exhibited a weak antibacterial activity against Staphylococcus strains, quercetin and I3,II8-biapigenin were the active components of the extract [83].

H. triquetrifolium showed antibacterial and antifungal activities with diameter of growth inhibition of [10-16mm]: *Escherichia coli K12* [12 mm, 60µg/disc], *Escherichia coli PBR322* [10 mm, 40µg/disc], *Escherichia coli PUC9* [10 mm, 40µg/disc], *Bacillus brevis ATCC*[10 mm, 40µg/disc],*Bacillus cereus DM65*[12 mm,40µg/disc], *Streptococcus pyogenes DM41*[12 mm, 40µg/disc], *Pseudomonas aeruginosa DMC66* [12 mm,40µg/disc], *Staphylococcus aureus DMC70* [16 mm,40µg/disc] and *Candida albicans DM31*[12 mm,40µg/disc][84].

The protective effect:

The possible protective effect of *Hypericum triquetrifolium* [HT] was investigated against cyclophosphamide [CP] -induced hepatotoxicity. The results revealed that 25, 50 and 100 mg/kg HT, caused an important decrease in the [CP] toxicity. In the groups given both CP plus HT, there was a rise in serum total anti-oxidant status levels, while the levels of AST, ALT, ALP, LDH, TOS and OSI showed a remarkable decrease. Liver histological gave further evidence for the protective effect of *Hypericum triquetrifolium* [85].

Vasorelaxant effect:

The vasorelaxant effect of the total extract of *Hypericum triquetrifolium* was investigated on rat isolated aortic rings. Contractions with phenylephrine and KC1 were compared after the tissues were incubated with different concentrations of *Hypericum triquetrifolium* extract. In addition, the inhibitory effect of *Hypericum triquetrifolium* extract [105-103 g/ml] on the sustained contractions of aorta with phenylephrine and KG was also investigated. The maximal inhibition obtained by the extract for the phenylephrine contractions was 93.95 ±5.23%, while the maximal inhibition was found as 85.78 ± 4.87 % for KC1 contractions. However, *Hypericum triquetrifolium* extract inhibited both phenylephrine and KC1 induced contractions in a concentration-dependent manner [86].

Toxicity:

The lethal dose of the aqueous extract was considered to be 10.33 g/kg of the body weight, injected subcutaneously in mice [47].

CONCLUSION:

The review highlighted the chemical constituent, pharmacological and therapeutic effects of *Hypericum triquetrifolium* as promising source of drugs because of its safety and effectiveness.

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