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Review

Phytochemistry, pharmacology and medicinal properties of *Hypericum perforatum* L.

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***Hypericum perforatum* is known as St. John's Wort. *H. perforatum* extracts and essential oil are important in drug development with numerous pharmacological activities around the world, including Iran. For a long time, *H. perforatum* has been used in traditional medicines for healing skin wounds, eczema, burns, diseases of the alimentary tract, and psychological disorders especially depression. *H. perforatum* has recently been shown to have antioxidant, anticonvulsant, analgesic, anti-inflammatory, cytotoxic and antidiabetic activities. Hypericin, pseudohypericin, hyperoside, rutin, quercetin and hyperforin are the main compounds which are reported in this plant. α-Pinene, caryophyllene, caryophyllene oxide, germacrene D and 2-methyloctane were identified as the major constituents for *H. perforatum* essential oil collected from different parts of the world. Due to the easy collection of the plant, its widespread and also remarkable biological activities, this plant has become a medicine worldwide. This review presents comprehensive analyzed information on the botanical, chemical and pharmacological aspects of *H. perforatum* at preclinical and clinical levels.**

Key words: *Hypericum perforatum*, hypericaceae, hypericin, antidepressant.

INTRODUCTION

Hypericum perforatum, commonly known as St. John's Wort is a flowering plant and is a native from Europe and Asia, especially Iran. It belongs to the Hypericaceae family in the order of Malpighiales that contains about 55 genera and more than 1000 species. *Hypericum* genus has more than 450 species with worldwide distribution in warm, temperate, subtropical and mountainous tropical regions (Hosni et al., 2008) and its species are widely distributed in Europe, Asia, North Africa and North America. In India, it is found in the western Himalayas at altitudes between 3000 and 10500 feet above sea level (Sastri, 1959). *H. perforatum* has been known as “Alaf-e-Chai” or “Gol-e-Raee” in Iran. *H. perforatum* grows in sunny areas and well drained sandy soil, commonly seen growing by the road side and along railroad beds (Alan and Miller, 1998).

H. perforatum is a perennial herb that grows about 40 to 80 cm high (Figure 1) with numerous opposite branch pairs alternating at 90° angles (decussate), sharply ridged at the base of each leaf. Leaves are opposite, stalk less, 2 to 4 cm long on main stalk, 1 to 2 cm long on branches, linear-oblong, non-toothed, covered with translucent glands (Figure 2). Flowers are borne in many-flowered, highly branched, compact, round- to flat-topped inflorescences. The sepals are 4 to 6 mm long, narrow lance-shaped with a pointed tip, and sometimes have a few black glands. Five petals are yellow with black specks concentrated along the margins, 8 to 12 mm long and oblong. The 50 to 80 stamens are clustered in three or five fascicles, the three styles are separated, and the stigmas are in dense head-like clusters (Figure 3). The fruit is a three-chambered capsule containing many rough, 1 to 1.3 mm long seeds (Figure 4).

For a long time, *H. perforatum* has been used as a folklore medicine for the treatment of illnesses such as rheumatism, hemorrhoids, neuralgia, snake bite, sprains, pain and mood disorders (Upton, 1997). It is used also for spasmolytic, stimulant, hypotensive and antibacterial activities (Chopra and Nair, 1956). *H. perforatum* has recently got much popularity as an antidepressant, and is extensively used in many countries for the treatment of depression. It has also been used as an analgesic and

Figure 1. *Hypericum perforatum* (St. John's Wort).

Figure 2. *H. perforatum* leaves.

Figure 3. *H. perforatum* flowers.

Figure 4. *H. perforatum* fruits.

anti-inflammatory agent in traditional practices (Bukahri et al., 2004). *H. perforatum* is also used as a flavouring substance for foods and alcoholic beverages (Meral and Karabay, 2002). Additionally, infusions, alcoholic tinctures and fluid extracts of the plant are used in the flavouring industry to prepare liqueurs, especially digestive and tonic bitters (Maskovic et al., 2011).

A number of chemical constituents such as volatile substances, anthraquinone derivatives (naphtodiantrones), prenylated phloroglucinols, tannins, volatile substances and flavonoids have been isolated from the plant (Maskovic et al., 2011). Hypericin exhibited antibacterial, antiviral and anti-inflammatory activities (Singh, 2005), while hyperforin is the major antidepressive compound (Couceiro et al., 2006). From current pharmaceutical studies, additional pharmaceutical applications of *H. perforatum* have revealed antidepressant, antioxidant, anticonvulsant, analgesic, anti-inflammatory, cytotoxic and antidiabetic effects among others (Maskovic et al., 2011; Lozano–Hernandez et al., 2010; Bukahri et al., 2004; Zou et al., 2004; Roscetti et al., 2004; Hosseinzadeh et al., 2005; Arokiyaraj et al., 2011).

Since review and systemic analysis of chemistry, pharmacology and clinical properties of *H. perforatum* have not been reported, we were prompted to provide the currently available information on traditional and local knowledge, ethno biological and ethno medicinal issues, identification of pharmacologically important molecules and pharmacological studies on this useful plant. The aim of the present review is to introduce *H. perforatum* as a potent medicinal plant by highlighting its traditional applications as well as the recent findings for novel pharmacological and clinical applications.

CHEMICAL COMPOUNDS OF *H. PERFORATUM*

The commonly known phytochemical compounds from *H. perforatum* are anthraquinone derivatives (naphtodiantrones), prenylated phloroglucinols, tannins, flavonoids and volatile substances (Bukahri et al., 2004; Saddiqe et al., 2010). There have been numerous investigations of *H. perforatum* essential oils and they have showed a wide variability in composition (Sharopov et al., 2010). α-Pinene (61.7%), δ-3-carene (7.5%), (*E*)-caryophyllene (5.5%), myrcene (3.6%) and cadalene (3.2%) were identified as the major constituents of the *H. perforatum* grown in Turkey (Sharopov et al., 2010) while caryophyllene oxide (7.7 to 34.0%), spathulenol (4.5 to 11.0%) and viridiflorol (0.5 to 11.1%) were identified for the Lithuanian sample (Sharopov et al., 2010). The main volatile components from Iranian *H. perforatum* was characterized as α-pinene (29.3%) (Sharopov et al., 2010). Greek *H. perforatum* oil was rich in germacrene D (16.9 to 22.8%), 2-methyloctane (10.8 to 17.8%), (*E*) -caryophyllene (6.6 to 10.3%), α-pinene (5.2 to 10.1%), and bicyclogermacrene (4.1 to 4.8%) while *H. perforatum* growing in Uzbekistan showed (*E*)-caryophyllene (11.7%), caryophyllene oxide (6.3%), spathulenol (6.0%), α-pinene (5.0%) as the most abundant components (Sharopov et al., 2010).

Compounds including hypericin, pseudohypericin, hyperforin, rutin, hyperoside, quercetin, isoquercitrin, avicularin, quercitrin, and chlorogenic acid accompanied with proanthocyanins, biflavonoids, xanthones, phenylpropanes flavonols and flavones such as amentoflavone are determined in the flowering aerial parts of *H. perforatum* (Crockett, 2010; Silva et al., 2005; Zou et al., 2004; Birt et al., 2009). Chemists have developed novel synthetic pathways for key flavones, acyl phloroglucinols, hyperolactones and a tetralin that have been found in *H. perforatum* and these compounds are used as standards and for bioactivity studies (Birt et al., 2009). The highest amounts of phenols (17.6 mg EPC/g dry extract) and flavonoids (16.85 mg EPC/g dry extract) were found in the acetone extract of *H. perforatum* (Maskovic et al., 2011).

Antidepressant properties

Nowadays, phytotherapy based on *H. perforatum* extracts is commonly and widely employed for the treatment of mild to moderate forms of depression around the world. Despite controversial data with regard to the antidepressant effects of *H. perforatum*, clinical (Kasper et al., 2008) and preclinical (De Vry et al., 1999; Müller et al., 2001) studies have reported that some extracts from the aerial parts of this plant possess a pharmacological profile similar to clinically effective antidepressants, such as tricyclics and selective serotonin reuptake inhibitors, but some side effects have been detected at preclinical and clinical levels (Rodríguez-Landa and Contreras, 2003). In this way, two commercially available products of *H. perforatum* produces effective antidepressant-like effects at experimental level, in a similar fashion than fluoxetine (Lozano-Hernández et al., 2010), a selective serotonin reuptake inhibitors clinically effective in management of depression. The antidepressant effect is posited to be mainly exerted by two of the major chemical compounds contained in *H. perforatum* extracts, hypericin and hyperforin (Butterweck et al., 1997) (Figure 5), with the possible participation of other less abundant chemical compounds, such as flavonoids, biflavonoids, phloroglucinols, naphthodiantrones, xanthones, proanthocyanidins, acid phenols, essential oils and other phenolic compounds (Barnes et al., 2001; Hostettmann and Wolfender, 2005).

In fact, flavonoids have been reported to be necessary for *H. perforatum* extracts to produce their antidepressant-like effects in behavioral models of depression. To date, H. *perforatum* appears to have multiple mechanisms of action involving nonselective serotonin, norepinephrine and dopamine re-uptake inhibition and

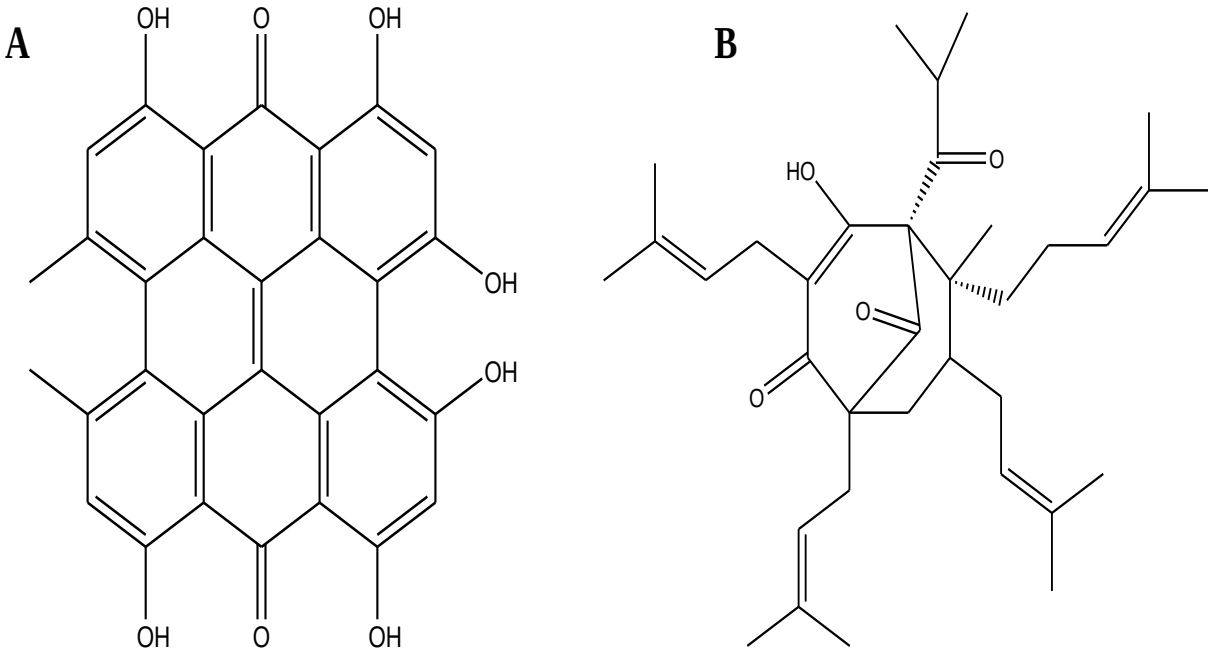

Figure 5. Structures of Hypericin (A) and Hyperforin (B) from *H. perforatum.*

inactivation of monoamine oxidase enzyme activity. This multiple actions on brain neurochemistry function have been thought to participate in the multiple side effects reported of *H. perforatum* extracts (Rodríguez-Landa and Contreras, 2003). Moreover, facilitation of γ-aminobutyric acid (GABA) action on the $GABA_A$ receptor and activation of sigma-1 receptors have also been shown to be involved (Lozano–Hernández et al., 2010).

Anti-inflammatory and analgesic properties

Although a number of steroidal or non-steroidal anti-inflammatory drugs have been developed, researchers are changing their focus to natural products to develop new anti-inflammatory agents due to the side-effects of chemical drugs (Hyun and Kim, 2009; Shokrzadeh and Saeedi Sarvari, 2009). As a result, the search for other alternatives seems necessary and beneficial. *H. perforatum* flowering aerial parts are an open door for new and effective compounds. Many cells and mediators are involved in proceeding inflammation. For example, macrophages are representative inflammatory cells involved in acute or chronic inflammatory responses by over-production of pro-inflammatory cytokines [for example, tumor necrosis factor (TNF)-α, interleukin (IL)-1 β and granulocyte/ macrophage colony stimulating factor (GMCSF)] and inflammatory mediators (Rhee et al., 2009; Lundberg, 2003; Walsh, 2003). *H. perforatum* has been functionally used as a traditional crude drug for the relief of rheumatism, hemorrhoids, neuralgia, snake bite sprains and analgesia. It has also been used as analgesic and anti-inflammatory agent in traditional practices (Bukahri et al., 2004).

H. perforatum extract exhibited inhibitory effect on acid induced abdominal contraction and licking responses in both phases (neurogenic and inflammatory) of formalin induced pain at the dose of 100 mg/kg. Apparently, analgesic effect of *H. perforatum* is probably mediated via inhibition of the prostaglandin synthesis whereas central inhibitory mechanisms cannot be ruled out (Bukahri et al., 2004).

H. perforatum has also shown marked antinociceptive properties when examined in the hot plate assay and tail electric stimulation test. The anti-inflammatory activity of *H. perforatum* was also examined by inhibition of carrageenan induced paw edema in rat. The effect was dose dependent, with a maximal reduction in edema of 75.3%. This could suggest interference with the actions of histamine, serotonin, or kinins, the inflammatory mediators implicated in the early phase of the carrageenan-induced inflammatory response (Abdel–Salam, 2005). Standardized 50% aqueous ethanolic extract of the Indian variety of *H. perforatum* was also examined for the putative anti-inflammatory and analgesic activity at the doses of 100 and 200 mg/kg, p. o. The experimental paradigms used were carrageenan induced pedal edema and cotton pellet induced granuloma for anti-inflammatory activity, whereas the tail deoxyribose degradation in a concentration-dependent manner in site-specific assay but poor effect in non-site-specific assay, which suggested that chelation of metal

ion was the main antioxidant action. According to the flick, hot plate and acetic acid induced writhing methods were used to assess analgesic activity. The extract showed significant anti-inflammatory and analgesic activity at both dose levels, in all the paradigms used. Additionally, the plant extract potentiated the anti-inflammatory activity of indomethacin and analgesic activities of pentazocine and aspirin (Kumar et al., 2001). Pseudohypericin which is contained in the plant extract accounted for a significant part of the extract's inhibitory activity on PGE2, NO, factor-α (TNF-α), and interleukin-1β (IL-1β) in RAW 264.7 as well as peritoneal macrophages. Pseudohypericin was the most important contributor of the anti-inflammatory potential (Huang et al., 2011). These results validate the traditional use of the plant as analgesic and other conditions associated with pain such as trauma, burns, rheumatism and neuralgia.

Antioxidant activity

An antioxidant is defined as 'any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate' (Rhee et al., 2009; Halliwell and Gutteridge, 1990; Wiseman et al., 1997; Mates et al., 1999). Antioxidants are of interest to biologists and clinicians because they help to protect the human body against damages induced by reactive free radicals generated in atherosclerosis, ischemic heart disease, cancer, Alzheimer's disease, Parkinson's disease and even in aging process (Aruoma, 2003; Hemati et al., 2010). There are many evidences that natural products and their derivatives have efficient anti-oxidative characteristics, consequently linked to anti-cancer, hypolipidemic, anti aging and anti-inflammatory activities (Rhee et al., 2009; Hallwell et al., 1995; Wiseman et al., 1997; Hogg, 1998; Mates et al., 1999; Aruoma, 2003; Cho et al., 2006). Anti-oxidative capacities of *H. perforatum* were evaluated by determining its effect on 2,2-diphenyl-1-picrylhydrazyl free radical (DPPH) and superoxide radical scavenging, and lipid peroxidation inhibition (Zou et al., 2004).

Phenolic extract of *H. perforatum* was an effective scavenger in quenching DPPH and superoxide radical with IC50 of 10.63 and 54.3 µg/ml, respectively. A linear correlation between concentration of the extract and reducing power was observed. 150 µg of the extract obviously decreased the peroxidation of linoleic acid but the amount of the extract over 150 µg did not show statistically significant inhibitory effect of peroxidation of linoliec acid. The plant extract exhibited inhibitory effect of peroxidation of liposome induced both by hydroxyl radical generated with iron-ascorbic acid system and peroxyl radical and showed prominent inhibitory effect of results, the antioxidant mechanism of the phenolic extract of *H. perforatum* might be attributed to its free radical scavenging activity, metal-chelation activity, and reactive oxygen quenching activity (Zou et al., 2004).

Since oxidative stress is implicated in the pathophysiology of dementia, scopolamine-induced amnesia in rats is a valid animal model to screen for drugs with potential therapeutic benefit in dementia. *H. perforatum* extract has shown activity on brain oxidative status of rats treated with amnestic dose of scopolamine. Administration of 1.4 mg/kg of scopolamine impaired retrieval memory of rats and such amnesia was associated with elevated malondialdehyde (MDA) and reduced glutathione (GSH) brain levels. Pretreatment of the animals with *H. perforatum* extract (12 mg/kg) resulted in an antioxidant effect through altering brain MDA, glutathione peroxidase (GSHPx), and GSH level. Exposure of animals to conditioned fear may be suggested to impair the balance between the rate of lipid peroxidation and the activation of GSHPx as a compensatory antioxidant protective mechanism. Low doses of *H. perforatum* extract, demonstrating antioxidant activity, may be of value for demented patients exhibiting elevated brain oxidative status. Since depression commonly coexists with dementia, *H. perforatum* extract as a drug with documented antidepressant action may also be a better alternative than several other antidepressant medications that have not been evaluated to test their effect on brain oxidative status during amnesia (El-Sherbiny et al., 2003).

Anticonvulsant activity

H. perforatum is used in traditional medicine for its anticonvulsant property. Anticonvulsant activity of the aqueous and ethanolic extracts of *H. perforatum* aerial parts in mice has been shown. The pentylenetetrazole (PTZ) and the maximal electroshock seizure (MES) tests were used for assessing the anticonvulsive effects of this plant. In the PTZ test, the extracts (0.1 to 1 g/kg, i.p.) delayed the onset of tonic convulsions and protected mice against mortality. In the MES test, both extracts did not show an antiseizure activity. L-NAME (1-10 mg/kg, i.p.), a nitric oxide (NO) synthase inhibitor, reduced the anticonvulsant activity of the extracts. The results indicated that the extracts of *H. perforatum* could contribute to the control of petit mal seizure and this effect may be partially mediated by nitric oxide pathway (Hosseinzadeh et al., 2005).

Antibacterial and antifungal activities

H. perforatum has been valued for its important biological and chemical perspectives and its use in the treatment of infectious diseases has been documented in ethno-botanical reports. Recently, interest in *H. perforatum* has focused on its antimicrobial activity evaluated against a

number of bacterial and fungal strains. The antibacterial activity of crude extracts can be related to the use of the herb as a wound healer in ancient times. The sole antibacterial principle isolated is a phloroglucin derivative, hyperforin. Hyperforin exhibited an excellent effect against methicillin-resistant strains of *Staphylococcus aureus* with a minimum inhibitory concentration (MIC) value of 1.0 µg/ml. It has shown a higher antibacterial activity against Gram-positive than Gram-negative bacteria (Saddiqe et al., 2010; Reichling et al., 2001). Petrolether extract of the areal parts of *H. perforatum* was also reported to be active against Gram-positive bacteria. Butanol fraction of this plant revealed anti-*Helicobacter pylori* activity with MIC values ranging between 15.6 and 31.2 µg/ml. Recently, aqueous extract of *H. perforatum* were found to be anti-microbially effective against Gram-positive bacteria with special activity towards methicillin-restistant strains of *S. aureus* (MIC values: 1.3 to 2.5 mg herb/ml) (Reichling et al., 2001).

Ethanol extract of *H. perforatum* at a concentration of 25 mg/disk exhibited the highest inhibitory effect on the growth of *Penicillium canescens, Fusarium oxysporum, Alternaria alternata, Aspergillus glaucus and Phialophora fastigiata*, by the disk diffusion method (Maskovic et al., 2011).

Antidiabetic properties

H. perforatum extract has shown significant effect on nociceptive perception of STZ-diabetic animals based on its potential antidiabetic and antinociceptive activities. One week administrations of *H. perforatum* extract (125 and 250 mg/kg) induced significant decrease in high blood glucose levels of three weeks streptozotocin (STZ) diabetic rats and improved their dysregulated metabolic parameters. In addition, the extract treatment caused restoration in the mechanical hyperalgesia of diabetic animals (Can et al., 2011).

The efficiency of the *H. perforatum* ethyl acetate extract to maintain the blood glucose levels in normal and STZ induced diabetic rats has been indicated. Rats treated by administration of *H*. *perforatum* ethyl acetate extract showed a significant decrease in the level of blood glucose and an increase in the level of serum insulin. The extract may potentiate the insulin effect of plasma by increasing either the pancreatic secretion of insulin from the existing beta cells or by its release from the bound form. Treatment with *H*. *perforatum* ethyl acetate extract significantly increased muscle and liver glycogen content, demonstrating that the defective glycogen storage of the diabetic state was partially corrected by the extract. It also decreased the activity of glucose-6-phosphatase and gluconeogenesis (Arokiyaraj et al., 2011). *H. perforatum* ethyl acetate extract showed significant reduction in serum triglycerides and total cholesterol in STZ-diabetic rats. Thus, it is reasonable to conclude that *H. perforatum* ethyl acetate extract could modulate blood lipid abnormalities at the experimental level (Arokiyaraj et al., 2011).

Antitumor activity

Methanolic extract of *H. perforatum* and purified hypericin has shown cytotoxic activity on the growth of a human erythroleukemic cell line (K562). The effects on cell growth were determined by viable cell count, flow cytometry analysis and fluorescence microscopy. Purified hypericin had only a weak inhibitory effect on cell growth and no effect in inducing apoptotic cell death. In contrast, the *H. perforatum* flower extract showed a significant concentration-dependent and long-lasting inhibition of cell growth, and induced apoptotic cell death. These results indicate the interesting role of *H. perforatum* in cancer therapy and strongly support the hypothesis that agents, other than hypericin, present in the total extract can impair tumor cell growth acting separately or in a combined manner (Roscetti et al., 2004).

H. perforatum has shown anticancer effect, through inhibition of tumor cells development and elevating the white blood cells level. This might be the basis of new pharmaceutical remedies using *H. perforatum* as a wide spread species in many parts of the world (Prodan, 2002). Antitumor effects of peptide extracts from *H. perforatum* and a mixture of *Chelidonium majus L., Inula helenium L., Equisetum arvense L.,* and *Inonotus obliquus* on slowly growing mammary adenocarcinoma in CBRB-Rb have also been studied. The antitumor effect of a single injection of the test peptides was evaluated by the delay of the appearance and growth of palpable breast cancer in mice over 4 weeks and exhibited maximum activity (Tepkeeva et al., 2008).

CONCLUSION

The objective of this article is to show the recent advances in the exploration of *H. perforatum* as phytotherapy and to illustrate its potential as a therapeutic agent. With the current information, it is evident that *H. perforatum* has pharmacological functions including antidepressant, antioxidant, anticonvulsant, analgesic, anti-inflammatory, cytotoxic and antidiabetic activities, among others. As the current information shows, it is also possible that hypericin and hyperforin might be useful in the development of new drugs to treat various diseases. However, the present results suggest a possibility that these compounds can be further developed as a potential disease-curing remedy. It must be kept in mind that clinicians should remain cautious until more definitive studies demonstrate the quality and efficacy of *H. perforatum*. For these reasons, extensive pharmacological and chemical experiments, together with

human metabolism will be a focus for future studies. Last but not the least, this review emphasizes the potential of *H. perforatum* to be employed in new therapeutic drugs and provide the basis for future research on the application of transitional medicinal plants.

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