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Review

Hypericum perforatum (St John's wort) beyond depression: A therapeutic perspective for pain conditions

Nicoletta Galeotti*

Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), Section of Pharmacology, University of Florence, Viale G. Pieraccini 6, 50139 Florence, Italy

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Amentoflavone
Hyperforin
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ABSTRACT

Ethnopharmacological relevance: *Hypericum perforatum* L. (Hypericaceae), popularly called St. John's wort (SJW), has a rich historical background being one of the oldest used and most extensively investigated medicinal herbs. Many bioactivities and applications of SJW are listed in popular and in scientific literature, including antibacterial, antiviral, anti-inflammatory. In the last three decades many studies focused on the antidepressant activity of SJW extracts. However, several studies in recent years also described the antinociceptive and analgesic properties of SJW that validate the traditional uses of the plant in pain conditions.
Aim of the review: This review provides up-to-date information on the traditional uses, pre-clinical and clinical evidence on the pain relieving activity of SJW and its active ingredients, and focuses on the possible exploitation of this plant for the management of pain.
Materials and methods: Historical ethnobotanical publications from 1597 were reviewed for finding local and traditional uses. The relevant data on the preclinical and clinical effects of SJW were searched using various databases such as PubMed, Science Direct, Scopus, and Google Scholar. Plant taxonomy was validated by the database Plantlist.org.
Results: Preclinical animal studies demonstrated the ability of low doses of SJW dry extracts (0.3% hypericins; 3–5% hyperforins) to induce antinociception, to relieve from acute and chronic hyperalgesic states and to augment opioid analgesia. Clinical studies (homeopathic remedies, dry extracts) highlighted dental pain conditions as a promising SJW application. In vivo and in vitro studies showed that the main components responsible for the pain relieving activity are hyperforin and hypericin. SJW analgesia appears at low doses (5–100 mg/kg), minimizing the risk of herbal-drug interactions produced by hyperforin, a potent inducer of CYP enzymes.
Conclusion: Preclinical studies indicate a potential use of SJW in medical pain management. However, clinical research in this field is still scarce and the few studies available on chronic pain produced negative results. Prospective randomized controlled clinical trials performed at low doses are needed to validate its potential efficacy in humans.

1. Introduction

Hypericum perforatum L. (Hypericaceae), commonly called St. John's wort (SJW), has been one of the most prominent and best investigated medical plants during the last two decades, the focus of interest clearly being on its potential as an herbal antidepressant. The flowering herb of SJW is the starting material for well-established medicinal products for the treatment of mild to moderate depression. This use has been accepted by a monograph of the Herbal Medicinal Product Committee (HMPC) of the European Medicines Agency, thus validating the positive results of a multitude of clinical trials, as evaluated in the corresponding assessment report (EMEA 2008; 2009b). In recent years, the consumption of SJW-derived products has increased dramatically, and it is presently one of the most consumed medicinal plants in the world (Ekor, 2014).

SJW has been used since antiquity to treat ailments ranging from snake bites to nervous disturbances. The traditional use was mainly characterized by external applications in the form of oils and tinctures,

Abbreviations: CREB, cyclic AMP response element binding protein; CYP, cytochrome P450; EMA, European Medicines Agency; HMPC, Herbal Medicinal Product Committee; iNOS, inducible nitric-oxide synthase; NO, nitric oxide; NF-kB, nuclear factor-kB; P-gp, P-glycoprotein; PKC, protein kinase C; SJW, St. John's wort; STAT-1, Signal Transducer and Activator of Transcription-1; STZ, streptozotocin

* Correspondence address: Department of NEUROFARBA, Section of Pharmacology, University of Florence, Viale G. Pieraccini 6, I-50139 Florence, Italy.
E-mail address: nicoletta.galeotti@unifi.it.

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and for internal use (Butterweck, 2003), but SJW has also retained a position in the contemporary list of medicinal plants of pharmaceutical importance. Over the past 30 years, the plant has been extensively investigated in clinical and laboratory studies. Pharmacological studies clearly described numerous bioactivities of SJW other than the antidepressant activity, including wound-healing (Fedorchuk, 1964; Rao et al., 1991; Wölfle et al., 2014), antifungal (Rancic et al., 2005; Milosevic et al., 2007), anti-inflammatory (Mascolo et al., 1987; Kumar et al., 2001a, 2001b; Saddiqe et al., 2010; Hammer and Birt, 2014), antimycobacterial (Frisbey et al., 1953; Fitzpatrick, 1954) and antiviral activities (Richer and Davies, 1995; Birt et al., 2009).

In recent years, in addition to the widely described anti-inflammatory action (Abdel-Salam, 2005; Tedeschi et al., 2003; Uchida et al., 2008), several scientific reports also described the capability of SJW to modulate pain perception. The present review encompasses the literature on the pain relieving activity of extracts of SJW and compounds isolated from these extracts.

2. Ethnobotany

2.1. Traditional uses

From the rich diversity of medicinal plants in herbal and homeopathic remedies SJW is one of the oldest with a history of more than 2000 years. Appropriately dubbed by many as a magical plant, SJW carries a rich history, full of cultural nuances and mystical legends. Historical information dating back to 400 b.C. tells the story of SJW and its medicinal and spiritual evolution: the ancient Greeks and Romans noted the medical use of SJW whereas other noted uses of the herb extended into the spiritual or mystical realm as they believed the SJW scent of incense, alone, would surely drive off evil spirits, offering protection against the devil's temptations. Paracelsus wrote of the plant in the early 1500s that it could be used as an amulet against enchantments and apparitions (Alleyne, 1733). SJW was used in early pre-Christian religious practices in England with many legends written about it (Pratt, 1898).

The medical use of SJW top flowering parts was originally documented by ancient Greek medical herbalists Hippocrates (ca. 460-370 b.C.; “Corpus Hippocraticum”), Theophrastus (371-286 b.C.; “De Historia Plantarum”), Dioscorides (first century; “De materia medica”), and Galen (ca. 130–220) who recommended it as treatment for a variety of medicinal indications, such as snake or reptile bites, menstrual cramping, gastrointestinal distress, ulcers, depression or melancholy, superficial wounds, burns, but also for sciatica (Gunther, 1968; Bombardelli and Morazzoni, 1995; Hobbs, 1990; Leung and Foster, 1996; Upton, 1997). In particular, Dioscorides recommended SJW in his “De materia medica” for the healing of burns or sciatic pain syndrome (Gunther, 1968).

One of the earliest known mentions of SJW as a medical plant is found in the Naturalis Historiae by Pliny the Elder (23–79 b.C.) as a treatment for burns, but also as an astringent which arrests diarrhea, and as a diuretic (Mayhoff, 1906). Several herbalists after the 16th century wrote very favourably of the wound healing virtues of SJW with beneficial properties also against stings and bites of poisonous animals (Gerard, 1597, 1633; Culpeper, 1652). The use of SJW oil (made by macerating the flowering tops of the plant in oil and then placing them in the sun for two or three weeks) as a therapy for wounds and bruises was so effective that not only was used by surgeons to clean wounds but was also included in the first London pharmacopoeia as Hyperici Oleum (Urdang, 1944).

In addition to SJW oil, there are aqueous and ethanolic SJW extracts which differ considerably in the nature of the constituents from oil (i.e. SJW oil does not contain hypericin). Traditional use is reported also for SJW extracts, and infusions prepared with water were widely used in the traditional medicine in Central and Southern Europe. Uses described in European folk medicine, after oral administration or topical application, were as an antiphlogistic agent in the treatment of inflammation of the bronchi and urogenital tract (Hill, 1808), in treatment of biliary disorders, bladder irritation, the common cold (Greene, 1824), burns, skin diseases, diabetes mellitus, dyspepsia, neuralgia, neurasthenia (Fernie, 1897; Barone, 1963; List and Hörhammer, 1976; Bombardelli and Marazzoni, 1995; Anon, 1998; Blaschek et al., 2008; WHO, 2002; Camangi et al., 2003; Camangi and Tomei, 2003). In addition to these uses, benefits on several pain conditions, such as migraine, headache, myalgia, sciatica, rheumatism, lumbago, injuries to the spinal cord, lacerated or injured nerves and tooth extraction, were described (Madaus, 1938; Flamm et al., 1940; Bombardelli and Marazzoni, 1995; Barnes et al., 2002; WHO monographs, 2002).

A number of *Hypericum* species were used by American Indian tribes. Records of the use of SJW are known from the Cherokee, Iroquois and the Montagnais (Moerman, 1998; Vogel, 1970). All these tribes seemed to have used the plant as a febrifuge/cough medicine, but the Cherokee made broader use of the plant. Today, modern American herbalists still use SJW for many of the same conditions for which it has been recommended throughout the ages (Lust, 1974; Moore, 1979).

Since the time of the Swiss physician Paracelsus (ca. 1493–1541), it has been used in traditional European medicine for centuries to treat psychiatric disorders, including neuralgia, anxiety, neurosis, and depression (Reuter, 1998; Rasmussen, 1998). To date, the use of SJW as antidepressant is the only one supported by clinical data and accepted as well-established medicinal use by the European Medicines Agency (EMEA, 2009b).

Among all the described uses in popular medicine, the official 2009 HMPC monograph of the European Medicines Agency – traditional use – (EMEA, 2009a) accepts the use of oral SJW preparations for the relief of temporary mental exhaustion and mild gastrointestinal discomfort, and of topical SJW preparations for the symptomatic treatment of minor inflammations of the skin and minor wounds. In the absence of preclinical or clinical data, there is no traditional indication for other uses described in folk medicine.

2.2. Source

SJW is a spontaneous perennial herbaceous plant, belonging to the *Hypericaceae* family and is largely diffused in Europe, Asia, Northern Africa and in North America.

SJW grows in sunny locations with well-drained, limey soil mostly at roadsides, slopes, wood borders and stone quarries and reaches a height of 50–100 cm. The bright yellow, star-shaped flowers, often clustered in a trio, have five petals and the leafs contain tiny transparent oil glands resembling perforations. When the black dots are rubbed between the fingers, the fingers become red (Hobbs, 1990; Bombardelli and Morazzoni, 1995).

Herbal products containing SJW have been among the top-selling herbal preparations in developed countries in recent years (Ekor, 2014). The dry herb (consisting mainly of the flowering tops, including leaves, unopened buds and flowers) is the part used pharmaceutically and is reported in the European Pharmacopoeia as ‘Hyperici Herba’. The harvesting period in Europe is shortly before or during the bloom. After collection, the plant must be dry immediately, in warm weather in a drying room, to avoid degradation of its active principles, especially hyperforins (Wichtl, 1989; Melzer et al., 1998).

3. Biologically active components

The most common SJW preparations used are hydroalcoholic extracts of the aerial portion of the plant. These contain at least ten different kinds of biochemical compounds: flavonoids (including rutin, hyperoside, quercetin, quercitrin), naphtodianthrones (including hypericin and pseudohypericin), acylphloroglucinols (including hyperfor-