Biointerface Research in Applied Chemistry
Platinum Open Access Journal (ISSN: 2069-5837)

Review
Volume 11, Issue 3, 2021, 9928 - 9938
https://doi.org/10.33263/BRIAC113.99289938

Hypericum scruglii Bacch., Brullo & Salmeri, a Potential Natural Remedy for Fibromyalgia: A Narrative Review

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Received: 2.09.2020; Revised: 20.09.2020; Accepted: 21.09.2020; Published: 23.09.2020

Abstract: Fibromyalgia (FM) is a disorder of central pain processing marked by widespread chronic pain together with fatigue, sleep disturbances, cognitive dysfunction, and depressive episodes. Tested treatments have expressed limited efficacy. Oxidative stress plays a role in the pathology of FM, while multiple neurotransmitters are involved in this syndrome. Antidepressants are used as conventional treatment, especially those with double action on serotonin and norepinephrine that leads to an increased risk of a manic switch. It should be noted that fibromyalgia is high-frequency comorbidity in bipolar disorder. This narrative review, given the limited literature, consisted of animal and *in vitro* studies, which aims to highlight the positive aspects of *Hypericum scruglii* as a potential remedy against FM. Many *in vitro* and clinical studies confirm the *Hypericum* genus as a natural antidepressant resource. The use of *Hypericum* derivatives in various acute and chronic diseases has been known for a long time. It is reported that the phloroglucinol derivatives from *Hypericum longistylum* improve and accelerate the differentiation of neural progenitor cells. The advantage of *Hypericum scruglii* is that it owns greater antioxidant potential than other species of the Hypericum genus. Suggestions for improving the oral bioavailability of very poor water-soluble molecules of hypericum extracts are also described in this paper.

Keywords: fibromyalgia; *Hypericum scruglii*; *Hypericaceae*; antidepressive; manic switch.

1. Introduction

Fibromyalgia (FM) is a syndrome characterized by diffuse pain as a crucial symptom with various other symptoms such as anxiety, fatigue, mood disorder, sleep disturbances, cognitive decline, and episodes of depression [1]. The prevalence of this syndrome is 3% in the societies of western countries, with a predisposition for more frequent occurrence in women [2]. Fibromyalgia is often associated with irritable bowel syndrome (IBS), chronic fatigue syndrome, temporomandibular disorder (TMD), irritable bladder syndrome, or interstitial cystitis, multiple sclerosis (MS) [3]. Patients with fibromyalgia and associated conditions

experience hyperalgesia (intense pain responses to normally painful stimuli) and/or allodynia (responses accompanied by pain normally nonpainful stimuli) [4, 5]. All of this points to the fact that these patients have problems with sensory processing of pain. Better approaches in understanding fibromyalgia and associated conditions took place after researchers realized that these conditions don't seem to be caused by inflammation or peripheral damage and instead of that begun to analyze the central neural mechanisms, as prototypical central pain syndrome [4].

The severity of this disease, which drastically changes the quality of life of patients, puts it in a group of important public health issues. A limitation in treatments for FM has been shown so far [2]. However, oxidative stress plays a key role in the pathophysiology of FM. In addition, the total antioxidant capacity and plasma levels of antioxidant enzymes are reduced in patients with FM [6]. Contrary, the amount of hydrogen peroxide (H_2O_2) as one of the free oxidative radicals is increased in neutrophils in these patients [7]. Otherwise, increasing evidence suggests that there are a number of modifications in the neurotransmitter systems in fibromyalgia.

As is already known, the key symptom and the main diagnostic criteria for this disease is extensive pain. The central neurotransmitters serotonin and noradrenaline are involved in endogenous pain-inhibitory transmission pathways [8,63]. They are related to circadian rhythms [9]. Serotonin via the 5hydroxytryptamine (5HT3) receptor plays a key role in descending pain facilitation [10]. This neurotransmitter is of great importance because it mediates deep sleep [11]. In general, sleeping is negatively linked to pain in FM patients. These patients experience poor quality of sleep (daytime sleepiness, sleep disturbances, daytime disturbances) along with pain [56]. Moreover, deficiency of serotonin is associated with major depression [12]. As well, studies with proton magnetic resonance spectroscopy have shown that glutamate as a neurotransmitter is increased in the amygdala, insula, cingulate cortex during pain processing [13]. Supporting the fact that the hyperactive glutamate system leads to increased pain sensitivity and may be the cause of other fibromyalgia symptoms, increased glutamate levels in the insular cortex are associated with low-pressure pain thresholds [14].

A role may also be played by the gamma-aminobutyric acid (GABA) neurotransmitter, which is the principal inhibitory neurotransmitter in the central nervous system. Certain pharmacological studies have shown some efficacy of GABAergic agents for pain, fatigue, and sleep, suggesting that this neurotransmitter may be involved in the pathophysiology of fibromyalgia [15]. Several studies have shown that dietary elements improve the functional and psychological status of FM and, at the same time, protect the body from oxidative stress due to establishing a balance between glutamate and GABA [16]. It is well known that fibromyalgia is associated with depressive, bipolar and anxiety disorders. Data on the increased incidence of panic and generalized anxiety disorders in patients with FM are an indirect indicator of the risk of bipolar disorder (BD). Furthermore, patients with bipolar disorder are known to have an increased risk of anxiety disorders [17, 64]. Due to the association of FM with bipolar disorder, the use of antidepressants with a double-action in strengthening serotonin and norepinephrine can significantly increase the risk of a manic switch. Obviously, this is why antidepressants do not change long-term outcome remission indicators [18, 57].

What's more, fibromyalgia is intimately linked with PTSD, and, together, they cause a catastrophic impairment of the quality of life [58-61]. The point is that antidepressants are effective because they not only act on depressive episodes but also on the pain circuits. But on the other hand, the risk of the manic switch is high (due to the association with bipolar

disorder). This probably explains the lack of long-term efficacy [65-69]. The aim of this review is the necessity to explore the possibility of other remedies for FM.

2. Materials and Methods

This narrative review, based on *in vitro* and *in vivo* animal studies, aims to evaluate the efficacy of *Hypericum scruglii* Bacch., Brullo & Salmeri, an endemic plant found in Sardinia, Italy, on fibromyalgia.

3. Results and Discussion

3.1. Hypericum in depressive disorders.

Hypericum L. is a genus of flowering plants that belong in the family Hypericaceae. *Hypericum perforatum* L. (better known as St John's wort) is an herbaceous perennial plant frequently found in Asia and Europe. It's a preferred herbal remedy recommended by traditional Chinese medical (TCM) practitioners for the treatment of depression [19]. This is evidenced by the fact that it is prescribed to patients and licensed in a number of European countries [20]. The active ingredients of *Hypericum perforatum* are hypericin and hyperforin. Hyperforin is considered to be a major component of this plant in the fight against depressive disorders, as it inhibits the reuptake of the neurotransmitters serotonin, noradrenaline, and dopamine. In the way, it is observed that it is similar to the effect of tricyclic antidepressants and selective serotonin reuptake inhibitors, but with milder and to lesser extent side effects and with significantly lower discontinuation/dropout due to side effects [21, 22]. The main effects of Hyperforin observed *in vitro* (at concentrations of 0.1–1 μM) are non-selective inhibition of uptake of GABA, glutamate, and choline. It is important to note that this active ingredient inhibits serotonin reuptake in experimental conditions in a dose-dependent procedure [23]. In addition, the findings of a meta-analysis only confirmed the fact that St John's wort extract is more effective and safer than standard SSRIs. One of the disadvantages of this extract is the occurrence of pharmacokinetic interactions during concomitant use of drugs [21]. This is due to the fact that the hypericin component is an activator of the hepatic metabolic enzyme CYP1A2, while the hyperforin component is an activator of CYP3A4. This is significant because these two enzymes are involved in the metabolism of numerous drugs. It should be noted the danger of developing life-threatening serotonin syndrome as a result of an excess of the central serotonin while taking other drugs, e.g., SSRIs [24]. However, if this extract is used in low doses as a dietary supplement, then there is a small risk of drug interactions [21]. Moreover, ethanol extracts of *H. perforatum* contain phenolic components such as flavonoids and phenolic acids that have a strong antioxidant function [25]. Recently, a Chinese *in vitro* study published results about key phloroglucinol derivatives of *Hypericum longistylum* Oliv., which had a positive effect on neuronal differentiation and serotonergic neuron production. Association of the impact of components of *H. longistylum* and neurogenesis is thought to be the reason for improved behavior in mice under stressful conditions, and a reduction in depressive symptoms simultaneously [26].

3.2. Hypericum genus as a possible tool in the treatment of fibromyalgia.

Its antidepressant properties, along with its potential effect on the serotonergic system, which is a major driver of pain cycles, make *Hypericum* genus the type of possible treatment

for fibromyalgia. The effectiveness and safety of *H. perforatum* in the treatment of depressive disorders have been extensively studied in clinical trials with various designs (open trials or randomized, controlled trials); diverse populations (adolescents, adults, or the elderly); and different control groups (antidepressant or placebo). Moreover, contrary to all other antidepressants, St. John's wort also has a clear inhibitory impact on the synaptosomal uptake of the neurotransmitters L-glutamate and (GABA). Understandable is the fact that despite St. John's wort share some mechanisms of action with conventional antidepressant drugs, it is possible to perform via novel mechanisms of action, which needs further investigation [21].

On behalf of its possible effects on the serotonergic system, which in turn plays a role in pain circuits, as well as its properties as an antidepressant and supremely low profile of side effects, the Hypericum genus is gaining importance as a potential plant genus for the treatment of fibromyalgia [21]. However, have been reported cases of induction of manic state, especially when plants of this genus have been used as an antidepressant. There is interesting evidence from a review in which mania appears as the main consequence of using various herbal plants, including *H. perforatum*.

This plant shows a forceful association with manic switch. It is described that patients, due to depression and relief of post-traumatic stress symptoms, decided for therapy with Hypericum perforatum. Significantly, symptoms of mania and hypomania occurred in fourteen patients, out of thirty-five patients. It has to be considered the fact that three patients from this group are with a history of bipolar disorder [28]. The explanation for this phenomenon lies in the knowledge that these patients have a greater predisposition to bipolar disorder, fluctuation of the already confirmed affective disorder, antidepressant, and plant-induced mania [29]. The mechanism by which this plant works for mania inclination is not yet sufficiently clarified. The enigma is growing as it becomes difficult to distinguish between spontaneous manic episodes and those caused by antidepressants [30]. Other interesting related cases have been described in the literature.

There is a patient who underwent a bilateral orchidectomy for cryptorchidism. The same patient develops depression. Firstly, he was treated with testosterone and a conventional selective serotonin reuptake inhibitor antidepressant. Then, he resumed therapy with St. John's wort, against medical advice. The name of the used preparation and its dosage was imprecise. As a result, he afterward developed a manic episode [31]. The discussion of the etiological factors that led to the occurrence of manic episodes in this patient can be conducted in different directions. On the one hand, it is known that SSRI antidepressants in small doses in unipolar disorder can be a trigger for mania and hypomania [32]. On the other hand, studies have shown that Hypericum has been recognized as an inhibitor of the monoamine oxidase A (MAO-A) and MAO-B in mitochondrial extracts of rat brain [33]. Another interesting report is the described case of mania in a patient with unilateral cryptorchidism. More importantly, in this patient are found elevated LH (luteinizing hormone) level, while testosterone level was within the normal range. The mechanism for elevated LH was probably as a result of reduced feedback on the hypothalamic-pituitary axis [34]. Furthermore, a case of hypericum-induced mania in a patient with depression without concomitant use of other drugs and without a history of mania or hypomania has also been reported.

St. John's wort may be one of the principal precipitation factors of mania, hypomania, or increased cycling of mood conditions, especially in patients with occult bipolar disorder [35]. In general, the fact that the dose of the plant taken is unknown or greater than the recommended dose for the occurrence and course of the reported manic episode is vital. Due

to the link between fibromyalgia and bipolar disorder, these findings should be the basis for understanding the pathophysiological processes for manic switching in patients with FM. The risk of a manic episode in FM should be properly assessed, estimated, and monitored.

3.3. Hypericum extracts and providing analgesia.

In vivo studies have shown the ability of low doses of the extract of *H. perforatum* (0.3% hypericin; 3-5% hyperforin) in modulating the pain threshold, thus providing analgesia in acute and chronic pain conditions. Moreover, this improves its activity as an opioid [36]. As for acute pain, the dry extracts of *H. perforatum* given orally have been shown to increase the pain threshold in chemical and thermal pain in mice [37]. The activity of this plant related to pain has also been shown in humans. Dry extracts used in the form of ear drops reduce pain in children with otitis media [38]. On the other hand, managing chronic pain is a common medical issue. Treatment of myalgia, lacerated or injured nerves, with dry extracts of this plant is well-known since ancient times [39]. A number of studies have also shown an effect of improving neuropathic pain. According to some clinical studies (implemented both in traditional and conventional medical frameworks) is also used for pain after tooth extraction, as well as for dental pain [39]. Analgesia occurs at low doses and, at the same time, minimizes the risk of herbal-drug interactions produced by hyperforin, a powerful inducer of Cytochromes P450 enzymes (CYPs) and the manic switch in people with concurrent bipolar disorders [40]. Further on, enzyme assays made on rat brains proved that hypericin and pseudohypericin are selective and potent inhibitors of the enzyme protein kinase C (PKC). PKC belongs to the group of enzymes that play a role in various cellular responses, including modulation of the pain threshold [41]. As well, it should be pointed out that St. John's wort has been used as adjuvant therapy with morphine in the treatment of chronic neuropathic pain [40]. Table 1 summarizes the effects of Hypericum extracts in different acute and chronic pain conditions.

3.4. General features of Hypericum scruglii.

Recently, *H. scruglii* have been identified as shikimic and chlorogenic acids, quercitrin, hyperoside, hypericin, and two phloroglucinol derivatives. Although discovered in small quantities, it is still significant due to its chemotaxonomic role [42]. It should be noted the α-glucosidase and antioxidant inhibitory activity of this species. Usually, it can be found in the pools. Overall, *H. scruglii* is associated with calcareous substrates such as conglomerate, limestone, sandstone, travertine, and marl, where it develops simply on damp soil, near springs or streams with fresh water. On top of that, *H. scruglii* is disseminated in the southeast and central-east parts of the island of Sardinia, especially in the Barbagia of Seulo, Sarcidano, Quirra, and Ogliastra regions [43]. According to one study, *H. scruglii*, was characterized by high quercitrin, 3-geranyl-1-(2'-methylbutanoyl)-phloroglucinol and 3-geranyl-1-(2'-methylpropanoyl)-phloroglucinol content. In addition, *H. scruglii* showed the highest antioxidant and anti-α-glucosidase activity than *H. perforatum*. These traits make *H. scruglii* an advantageous target in fibromyalgia studies [42]. Due to specific possessing characteristics makes this species as a potential carrier in the fight against the pathogenetic mechanisms of fibromyalgia and short turns that lead to relapses [18].

We can conclude the following: 1) The analgesic (anti-pain) effect can be the best solution for most disabling symptoms reported by the patients; 2) The antidepressant effect can improve the basic mood, part of the "catastrophic" cognitive cascade, which occurs as a

consequence of hypersensitivity to pain that paradoxically grows the possibility of chronicity [18]; 3) The specific antioxidant effect can take part in the establishment of a balance between glutamate and GABA neurotransmitters; 4) The serotoninergic effect can modulate sleep.

3.5. Accessibility of new approaches for developing the oral bioavailability of very poor water-soluble molecules of the extracts of Hypericum.

Oral delivery of drugs is considered as the most appropriate route to reach therapeutic and prophylactic outcome against different diseases, especially chronic conditions, such as FM [45]. Bioavailability is investigated to be one of the crucial effects associated with the pharmacokinetics of drugs.

It consists of two important components, how fast the drug presents the systemic circulation and how much of the formal strength come to circulation [46]. Poor bioavailability indicates the non-success of the drug to reach the minimal productive concentration in the blood to turn-out the wanted therapeutic effects. To overcome these issues, new approaches are created. Not long ago, nanomedicines have achieved attention for growing the bioavailability of drugs in their dosage forms, mostly poorly water-soluble drugs [47].

Table 1. A therapeutic perspective of Hypericum extracts for pain conditions.

Title of publication	Authors, year	Character of the pain	Type of pain	Animal/Patient	Consequence/Effect
Anti-inflammatory and analgesic activity of Indian *Hypericum perforatum* L. [27]	Kumar *et al.*, (2001)	Acute	Thermal	Mouse	Thermal antinociception
Anti-inflammatory and analgesic activity of Indian *Hypericum perforatum* L. [27]	Kumar *et al.* (2001)	Acute	Chemical	Mouse	Chemical antinociception
Efficacy of naturopathic extracts in the management of ear pain associated with acute otitis media [44]	Sarrell *et al.* (2001)	Acute	Acute otitis media	Children	Advancement in ear pain score
John's Wort relieves neuropathic pain through a hypericin-mediated inhibition of the protein kinase C gamma and epsilon activity [51]	Galeotti *et al.* (2010)	Chronic	Chronic constriction injury	Rat	Rebuilding of thermal and mechanical hyperalgesia
The effect of *Hypericum perforatum* on the wound healing and scar of cesarean [52]	Samadi *et al.* (2010)	Acute	Surgical childbirth	Women	Mitigation of the pain
An experience with paediatric burn wounds treated with a plant-derived wound therapeutic [53]	Mainetti S, Carnevali F. (2013)	Acute	Burn wounds	Children	Mitigation of the pain [62]
St. John's Wort potentiates antinociceptive effects of morphine in mice models of	Sanna *et al.* (2016)	Chronic	Antiretroviral-induced neuropathy	Mouse	Rebuilding of thermal and mechanical hyperalgesia

Title of publication	Authors, year	Character of the pain	Type of pain	Animal/Patient	Consequence/Effect
neuropathic pain [54]					
Hypericum perforatum (St. John's Wort) as a possible therapeutic alternative for the management of trigeminal neuralgia (TN)-A case report [55]	Assiri *et al.* (2017)	Chronic	Trigeminal neuralgia	Patients	Reduction of the pain

Nanonization as an approach is very important because it improves the solubility and pharmacokinetics of drugs, and on the other hand, reduces systemic side effects [48]. In the middle of the different nanocarriers, modified liposomes have shown a good capacity simultaneously to increase the local and systemic efficacy of natural molecules or extract [49, 50]. These formulations may boost the oral bioavailability of very poor water-soluble molecules such as hypericin, hyperforin, quercetin, and rutin, which are available in the hypericum extracts. In a previous study, cyclodextrin and liposomal preparations were investigated for improving the transportation of hypericin through the intestinal epithelium by passive transcellular diffusion. The successful removal of bioactive phytocomplex from *H. scruglii* and its satisfactory nanoformulation in ad hoc modified liposomes should upgrade the efficacy of the extract in preventing FM symptoms and the accordance of patients in reducing the dose and the number of compulsory administrations.

4. Conclusions

In vivo and *in vitro*, animal studies show that it is possible to improve the therapeutic properties of *H. scruglii*. All this is due to the fact that this species shows better results in preliminary clinical studies on fibromyalgia compared to other species of the family Hypericaceae. The authors appraise that in phase 1 and phase 2 studies should be prepared randomized controlled trials to evaluate the efficacy of *H. scruglii* extracts in fibromyalgia. The need for this type of study is inevitable due to the fact that fibromyalgia and its consequences are major public health problems, for which to date, there are few effective therapies, and they import a greater risk of the manic switch.

Funding

This research received no external funding.

Acknowledgments

Goce Kalcev (MD) was participating in the writing of this paper, in the framework of the International PhD in Innovation Sciences and Technologies at the University of Cagliari, Italy.

Conflicts of Interest

The authors declare no conflict of interest.

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