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RESEARCH ARTICLE

Hypericum scruglii Bacchetta, Brullo& Salmeri, is it a possible natural resource against Fibromyalgia?

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Abstract

Fibromyalgia (FM) is today a serious public health issue. Tested treatments have shown limited efficacy. Oxidative stress probably interacting with the glutamatergic / **gamma - Aminobutyric acid** balance may play a role. Antidepressants improve sleep and mood especially those with double action on serotonin and norepinephrine, but these are also those with a greater risk of manic switch considering the high frequency of comorbidity with bipolar disorders. This narrative review tries to evaluate, on the basis of *in vitro* and animal studies, the potential utility in fibromyalgia of *Hypericum Scruglii*, an endemic species peculiar to the island of Sardinia. The studies that have verified the antidepressant efficacy of Hypericum Perforatum and the first attempts of its use in fibromyalgia are reported as well as the studies that found the phloroglucinol derivatives from *Hypericum longistylum* (well-known in traditonal Chinese medicine) that facilitate the differentiation of neural progenitor cells, and increase the efficiency of differentiation into serotonergic neurons. The advantage of *Hypericum Scruglii* may be represented by the anti-oxidant potential revealed to be greater than in other species of the same genus. The paper also describes new approaches to improving the oral bioavailability of very poor water-soluble molecules of hypericum extracts.

Keywords: Fibromyalgia; Hypericum; Hypericum scruglii; anti-oxidant effect; antidepressant; serotonine

Introduction

Fibromyalgia (FM) is a central sensitization syndrome with around 3% of prevalence in western societies, especially frequent in women [1]. The best-known symptom is chronic widespread pain; other syndromes such as fatigue, anxiety, mood disorders, and dysregulation of biological rhythms with sleep disturbances frequently accompanied by pain [2]. FM worsens the quality of life of people affected, and in cases with comorbid mood disorders the worsening is so high as to be similar to a chronic severe impairing disease such as Multiple Sclerosis [1]. The high frequency of the disorder and its high disabling power also make it a serious public health issue. Tested treatments have shown limited efficacy [1].

Oxidative stress might play a role in the pathophysiology of FM by enhancing excitatory and decreasing inhibitory neurotransmission [3]. In fact, studies using multiple functional magnetic resonance imaging (fMRI) have shown enhanced glutamatergic neurotransmission in the brain insula to be associate with high pain symptoms in people with FM [4]. Glutamatergic neurotransmission appears in fact to be a key point of central sensitization [4]. Conversely, a diminished inhibitory neurotransmission resulting from lower concentrations of GABA within the right anterior insula was found in women with FM [5].

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It has been demonstrated that some dietary elements protect people with FM against oxidative stress and also improve functional capacity and psychological status, probably interacting with the glutamatergic/GABA balance [6].

Antidepressants have been found efficacious in treating some of the syndrome components of fibromyalgia (particularly pain, mood and sleep disturbances). Fibromyalgia has a close association with bipolar disorder and the use of powerful antidepressants can seriously increase the risk of manic switch [7]. This is probably the reason why antidepressants do not change long-term outcome indicators of remission [8].

The mechanism of action of antidepressants in fibromyalgia is still unknown, mood stabilization and improved sleep have been hypothesized as playing a role. However the most powerful antidepressants in the treatment of fibromyalgia are those that have a double action in strengthening serotonin and norepinephrine, but these are also those with greater risk of manic switch [2].

Material and Methods

This narrative review tries to evaluate, on the basis of *in vitro* and animal studies, the potential utility in fibromyalgia of *Hypericum Scruglii,* an endemic species peculiar to the island of Sardinia.

Results and Discussion

Hypericum in depressive disorders

Hypercum L is a genus inside the family Hypericaceae of flowering plants whose most known element in the medical field is *Hypericum perforatum*. A consistent body of studies, based on randomized controlled trials and meta-analyzes, supports the efficacy and safety of *Hypericum perforatum* L. (also known as St. John's wort) and its active ingredients, hypericin and hyperforin, in depressive disorders similar to those of tricyclic antidepressants and selective serotonin reuptake inhibitors, but with fewer and milder side effects [9] and with significantly lower discontinuation/dropout [10].

Moreover, *Hypericum perforatum* extract is rich in active antioxidant flavonoids such as quercetin and rutin and, like these, is expected to reduce oxidative stress and increase gene expression of antioxidant enzymes [11, 12].

Hypericum is also known to interact at the pharmacokinetics levelwith many drugs, thus caution is recommended for patients on medication in the use of high dosages of active principles of the plant. However, its use in depression has proved useful even at low doses as a food supplement, therefore with little potential for interaction with other drugs [9].

Recently, a Chinese study has found that one of the phloroglucinol derivatives from *Hypericum longistylum* Oliv., well known in traditional Chinese medicine, facilitated the differentiation of neural progenitor cells and increased the efficiency of differentiation into serotonergic neurons. In possible relationship with these effects on neurogenesis, this compound was shown to improve the behavior of mice placed in a stressful environment and reduce signs of depression [13].

Hypericum scruglii as a potential tool in the treatment of fibromyalgia

The antidepressant properties of the Hypericum genus, together with the possible action on the serotonergic system involved in pain circuits have indicated a potential use of this plant genus in the treatment of fibromyalgia [9]. This was also suggested owing to the low profile of side effects and, more specifically, since [no virgola] at the dosages used in antidepressant therapy there are few descriptions of inductions of manic states. A recent review of world literature found a total of 12 reports of cases of people taking *Hypericum perforatum* for depression who had a manic switch [14]. This is a very low figure considering that the survey has been conducted on nearly 4,000 patients who took derivatives or plant extracts. In addition, one case was a patient who was treated with testosterone and a conventional selective serotonin reuptake inhibitor antidepressant, but continued to take St John's wort against medical advice [15]; another was a case of mania induced by higher-than-usual assumed doses of *Hypericum perforatum* [16] and in general, a review of all the cases described show that the average dosages used were higher than usual. This aspect is relevant considering the close association of fibromyalgia with bipolar disorder. The risk of manic switch in fibromyalgia should always be properly assessed, monitored and not underestimated.

In addition, in vivo studies have found the efficacy of low doses of the extract of H. perforatum (0.3% hypericins; 3-5% hyperforins) in inducing analgesia in both acute and chronic hyperalgesic conditons and improving opioid action [17]. Clinical studies (carried out both in traditional and conventional medical frameworks) highlighted dental pain conditions as a usual application [17, 18]. Analgesia appears at low doses, thus minimizing the risk of herbal-drug interactions produced by hyperforin, a potent inducer of Cytochromes P450 enzymes (CYPs) [18] but also minimizing the manic switch in people with co-morbid bipolar disorders.

Hypericum scruglii is an endemic species distributed in central-east and southeast Sardinia, in particular in the Sarcidano, Barbagia of Seulo, Ogliastra and Quirra subregions. It is generally linked to calcareous substrates such as limestone,

conglomerate, travertine, sandstone and marl, where it grows exclusively on damp soil near freshwater springs or streams. Occasionally, it is found in pools. It is especially linked to subalkaline and alkaline soils, not much developed from the pedogenetic point of view [19]. This plant has characteristics that could make it a privileged target in fibromyalgia studies: in vitro and in vivo this species has been seen to have a greater anti-ossidant potential than other Hypericum species, including *Hypericum perforatum* [20].

In addition to the recognized properties of all member of the Hypericaceae family, this aspect is particularly relevant; *Hypericum scruglii* shows in fact a specific feature that could act with different steps on the pathogenesis of fibromyalgia and on several phases of the short circuits that cause relapses [2].

These can be summarized as follows:

1) The specific antioxidant effect can act on the glutamate / Gaba balance

2) The anti-pain / analgesic effect can interact with the symptom described as the most disabling

3) The serotoninergic effect may regulate sleep

4) The antidepressant effect can act, by improving basic mood, on the "catastrophic" cognitive cascade described by cognitive behavioral psychologists as a consequence of hypersensitivity to pain that paradoxically increases the likelihood of chronicity [2].

Availability of new approaches to improving the oral bioavailability of very poor water-soluble molecules of hypericum extracts.

An innovative approach to modulating pharmacokinetic and pharmacodynamic activity of extracts by I improving their bioavailability is the use of nanocarriers. Nanomedicine is widely acclaimed as circumventing the obstacles of poor pharmacokinetics, especially in oral administration. However, the use of these systems has traditionally been confined to optimization of synthetic drug formulations and only in the last decade have their possible challenges been explored to improve pharmacokinetics of natural active molecules or extracts [21] . Among the different nanocarriers, modified liposomes have shown a good ability to improve the local and systemic efficacy of natural molecules or extracts [22, 23]. These formulations can improve the oral bioavailability of very poor water-soluble molecules such as hyperforin, hypericin, quercetin and rutin, which are present in the hypericum extracts. In a previous study, cyclodextrin and liposomal preparations were investigated for improving delivery of hypericin through the intestinal epithelium by passive transcellular diffusion.

The efficient extraction of bioactive phytocomplex from *H. scruglii* and its suitable nanoformulation in ad hoc modified liposomes should improve the efficacy of the extract in counteracting FM symptoms and the compliance of patients in reducing the dose and the number of required administrations.

Conclusions

In vivo and *in vitro* studies in animals appear to indicate that *H. scruglii* may enhance the therapeutic effects on fibromyalgia that other members of the Hypericaceae family have shown in preliminary clinical studies on fibromyalgia.

Phase 1 and 2 studies would be needed to prepare randomized controlled trials on the efficacy of *H. scruglii* extracts in fibromyalgia. The serious public health issues posed by this disorder, for which no therapy is known, reinforces the need for this kind of study.

Authors' contributions

The work was born from an idea of MGC which was followed by discussions with contributions from botany (GLB), pharmacology and drug preparation (MMi), molecular biology (GO) and clinic and pathophysiology of fibromyalgia and pain (MCC, MMu, GF). MGC has prepared the first draft, all the authors have contributed to the improvement of the same. All authors approved the final content of the paper.

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