Integration with Spilanthes Achmella in fibromyalgia syndrome: open-label study six months after the treatment

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Abstract

Fibromyalgia, also known as fibromyalgia syndrome (FM), is a rheumatic syndrome which is currently considered idiopathic and multifactorial. It causes an increase in muscle tension associated with stiffness, asthenia (loss of strength with fatigue), cognitive impairment, insomnia or sleep disorders and impaired sensitivity to stimuli.

We performed a prospective evaluation of 149 patients suffering from fibromyalgia syndrome according to the 2010 ACR Criteria. Patients were clinically assessed at baseline and after 1-3-6 months, using the *patient-reported outcomes thermometer - 5-item scale* (5TPROs). In addition to their therapy, all patients received a supplementation with Spilanthes Achmella. This food supplement is characterized by synergy of bioactive compounds, such as *Acmella oleracea* extract, and has neurotrophic, anti-inflammatory and pain-relieving effects. All patients were randomized at baseline to receive Spilanthes Achmella, 2 tablets per day for one month and subsequent tapering to 1 tablet per day for 5 months.

At six months, a statistically significant difference in the following parameters was shown: pain P<0.001, fatigue P<0.001, physical function P<0.001, depression: P<0.001, general health P<0.001. Conversely, the post-hoc analysis data did not report any significant difference for the parameters between the third and sixth month. A drug-sparing effect was observed (P<0.001). The post-hoc analysis revealed a significant difference between T0 and T3 P=0.00066 and between T0 and T6 P=0.00008.

Our data indicate that supplementation with Spilanthes Achmella may lead to a significant improvement in pain, fatigue, physical function, depression and general health in fibromyalgia syndrome.

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Introduction

Fibromyalgia, also known as fibromyalgia syndrome (FM) or Atlas syndrome, is a rheumatic syndrome, currently considered idiopathic and multifactorial, which causes an increase in muscle tension. It is also characterized by diffuse, fluctuating and migrating muscle pain, chronic tissue fibrosis (tendons and ligaments) associated with stiffness, asthenia (loss of strength with fatigue), cognitive impairment, insomnia or sleep disorders and impaired sensitivity to stimuli.[1] These patients may experience a drop in serotonin levels potentially with anxiety and depressive disorders.

Its diagnosis and clinical features have been controversial for a long time and its etiopathogenesis is still unknown. It cannot be considered a mental disorder, although psychophysical stress and anxiety can affect these patients, and specialists still view it as a variable set of symptoms often treated as psychological, in part similar to the conversion effects of depressive disorder.[2]

This syndrome is generally regarded as being due to the job of these debilitated patients, genetic familiarity, allergic reactions or an involvement of the immune system, which has caused a tilt of the major neurological receptors.[3] Another hypothesis is that it is an unidentified muscle and systemic metabolic-mitochondrial disease or channelopathy. Its actual etiology is still unknown; therefore it is now considered a non-typical rheumatic syndrome.[4]

Neither evident signs of blood, neurological and radiographic changes, nor distinctive histopathological aspects (tissue damage

evidenced by microscopic examinations) are present. Inflammatory markers are normal. Fibromyalgia is diagnosed by excluding other conditions (differential diagnosis) and subsequent palpation of tender points, although the overall symptoms of the patient guide the diagnosis.

The pain primarily affects the entire spine, shoulders, pelvic girdle, arms, wrists, and thighs. Generally chronic pain is characterized by periods with acute pain exacerbations , is associated with various symptoms, especially cognitive disorders, collectively named '*fibro fog*', mood and sleep disorders, as well as asthenia, or chronic fatigue. The non-response to common painkillers as well as the '*migrating*' character of the pain are peculiar to fibromyalgia.[5]

Materials and Methods

We performed a prospective evaluation of 149 patients with fibromyalgia syndrome according to the 2010 Wolfe F. New American College of Rheumatology criteria for fibromyalgia[6] (Table 1).

Patients were clinically assessed at baseline and after 1-3-6 months, according to the *patient-reported outcomes thermometer - 5-item scale* (5TPROs)[7] (Table 2). The request for analgesic drugs, opioids, pregabalin, antidepressants was also evaluated.

All patients have introduced in therapy an integration with Spilanthes Acmella in addition to the standard therapy. The dosing regimen was 2 tablets per day for one month followed by subsequent tapering to 1 tablet daily for the next 5 months.

Alpha-lipoic acid and L-acetylcarnitine have well documented beneficial effects in the treatment of painful peripheral neuropathies.[8,9] A fixed combination of *Zingiber officinale* and *Acmella oleracea* extracts, formulated using the phytosome technology. This manufacturing technique allows better oral solubility and consequent optimal gastrointestinal absorption by using a *food-grade* lecithin formulation.[10]

Gingerols and Shogaols, the main active compounds of *Z. officinale*, inhibit crucial enzymes related to inflammation processes, including cyclo-oxygenase COX-2, prostaglandin synthetase, nitric oxide synthase iNOS and 5-lipoxygenase.

The new *A. oleracea* extract is characterized by alkylamides (mainly represented by spilanthol), which are anti-inflammatory and painkiller phytocannabinoid compounds (chemically related to anandamide).[10]

Statistical analysis

Friedman's analysis of variance (ANOVA) was employed for multiple repeated measures across different time points. Wilcoxon tests were used for the post-hoc analysis. A Bonferroni correction was applied setting the level of significance at 0.0167. Categorical variables were evaluated with Cochrane's Q test and analyzed post-hoc with McNemar's test.

Results

The statistical variations of the parameters evaluated are listed in Table 2: pain, fatigue, physical function, depression, general state of health. The evaluation after six months showed a statistically significant difference for: pain P<0.001, fatigue P<0.001, physical function P<0.001, depression: P<0.001, general health P<0.001. Conversely, the post-hoc analysis data did not show any significant differences for the parameters between the third and sixth month. A drug-sparing effect was also observed with P<0.001. The post-hoc analysis revealed a significant difference between T0 and T3 P=0.00066 and between T0 and T6 P=0.00008.

Discussion

Some attention has been recently paid to the role of nutraceutical supplementation and diet in the treatment of FM.[11] A study of co-enzyme Q10 supplementation in FM patients treated with pregabalin found that it provided an additional benefit in terms of pain relief possibly by improving mitochondrial function, reducing inflammation, and decreasing brain activity.[12] An interesting study on the effects of dietary supplementation with (mainly) a salmon (semen) milk

Table 1. Demographic and clinical characteristics of the patients at baseline.

Characteristic	Total
Age (y)	63 (median); 27-79 (range)
Gender	
Female	106 (71%)
Male	43 (29%)
Concomitant treatments	36/149 (n)
Duloxetin	14
Pregabalin	14
Pregabalin and/or venlafaxine	8
Body mass index	Range: 20-25
Fibromyalgia disease duration	6 months (median)
Comorbidities	- Hypertension controlled with medication (7.9%) - Non-insulin dependent diabetes (2.3%)
Exclusion criteria	- Active cancer - Autoimmune diseases and/or active immunosuppressive treatment - Pregnancy and breast-feeding

Table 2. Parameters evaluated.

Variable	Median	Interquartile range
Pain T0	7.00	1
Pain T3	6.00	3
Pain T6	5.00	3
Fatigue T0	7.00	1
Fatigue T3	6.00	4
Fatigue T6	6.00	3
Physical function T0	7.00	0
Physical function T3	5.00	2
Physical function T6	5.00	3
Depression T0	7.00	2
Depression T3	5.00	2
Depression T6	5.00	2
General health T0	7.00	3
General health T3	5.00	4
General health T6	5.00	3

extract on symptoms and proinflammatory blood molecules in FM patients found that it led to a reduction in TNF and substance P levels. and a significant improvement in functioning, fatigue and pain, as well as the general perception of disease.[13] The supplementation we used with Spilanthes Achmella provided beneficial effects on pain, fatigue, physical function, depression and general health, as well as savings in taking medications such as pregabalin and duloxetine. The components of our supplement have a scientific rationale as an adjunct in the treatment of FM syndrome.

Alpha-lipoic acid (ALA) is an organosulfur antioxidant compound that enters Krebs cycle as a cofactor for some enzymatic complexes, increasing the energy available from glucose.

ALA plays an essential role as antioxidant. Lipoate, or its reduced form, dihydrolipoate, stabilizes and inhibits reactive oxygen species such as superoxide ions, hydroxyl radicals, peroxyl radicals, and singlet oxygen. It also protects membranes by interacting with vitamin C and glutathione, which may in turn recycle vitamin E.

In various animal models of diabetic neuropathy, ALA is able to improve nerve blood flow and distal nerve conduction (neurotrophic agent). Several clinical studies on peripheral neuropathies confirmed positive results in terms of symptom relief (pain, allodynia, dysesthesia, paresthesia) and patient safety.[8,14]

L-acetylcarnitine is the acetyl ester of L-carnitine, which plays an essential role in the metabolism of fatty acids in mitochondria.

Aside from its role in fatty acid oxidation, L-acetylcarnitine modulates the activity of nerve growth factor (NGF) in the nervous system, increases the activity of choline acetyltransferase, and modulates various neurotransmitter systems including the cholinergic and dopaminergic systems.

The antinociceptive effect of L-acetylcarnitine was shown in a number of pain models in rodents, and several mechanisms were proposed. Indirect activation of muscarinic receptors as well as the activation of the PLC-IP3 pathway was postulated to mediate the antinociceptive effect of L-acetylcarnitine in experimental models of acute pain. Moreover, increased expression of metabotropic glutamate receptor 2 (mGlu2) in regions of the nervous system involved in pain transmission after chronic administration of L-acetylcarnitine was proposed to account for the antinociceptive efficacy of the drug in acute and chronic pain after nerve injury in rats.

Loss of small sensory fibers, demyelination and changes in nerve conduction velocity are common features in various forms of neuropathies. In this regard, L-acetylcarnitine has been shown to be effective in the treatment of painful manifestations due to its dual mechanism, which includes a significant analgesic effect when administered chronically and the ability to promote peripheral nerve regeneration.[9,15]

Vitamin B6 and vitamin E boast health claims authorized by the European Food Safety Authority (EFSA) to support neurotrophic and antioxidant activity. *Z. officinale* and *A. oleracea* was investigated for the first time in order to assess a direct agonism on CB2 endocannabinoid receptors, involved both in pain and inflammatory modulation. The agonism on human CB2 receptor was evaluated on an established cell-based assay for the human CB2 (CHOchAMPion-hCB2) using EMCCD camera FLIPR Tetra (MDC) technology.

Compounds marketed in recent decades, such as palmitoylethanolamide (PEA), together with *Piper nigrum* and myrrh dry natural extracts, which showed analgesic/anti-inflammatory activities in classical *in vivo* tests in rodents (*i.e.*, tail immersion, hot plates, formalin test), were included in the study for comparative purposes.

On the contrary, PEA and myrrh dry extract showed no effects on that assay, up to the maximum concentration tested (50 µg/mL). A positive effect was expected at least for PEA, which is reported to interact with other pathways/mechanisms, like for example peroxisome proliferator-activated receptor PPAR.[16]

The muscle relaxant activity of Acmella phospholipid extract was tested in an *in vitro* model that reproduced muscle contractions. This model was obtained with a co-culture of motor neurons with human muscle cells that form striated muscle fibers, which, once innervated, contract spontaneously.[17] Muscle contractions were counted in the presence and absence of Acmella extract with reduction of contractions after co-culture supplementation.[17-19]

These results in vitro may support and possibly explain the positive data obtained in a recent clinical study performed on 50 subjects with moderate knee osteoarthritis. A 30-day supplementation with *Z. officinale* and *A. oleracea* led to significant improvements both on primary endpoints like Pain Intensity and knee function indexes, and secondary outcomes as C-reactive protein and erythrocyte sedimentation rate biomarkers, related to inflammation, along with a good safety profile.[20]

In conclusion, these data together with the results of our study indicate a strong rationale for the use of *Z. officinale* and *A. oleracea* as a natural adjuvant in pain management to relieve the symptoms caused by fibromyalgia syndrome. The lack of a statistically significant difference between the third and sixth month of treatment sets the stage for further studies for a possible dosage adjustment in this disease.

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