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Effects of *Opuntiaficus-indica* flower extract WS 1261 on mental and psychic function in subsyndromal fatigue – a pilot study

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Abstract

Traditional use, chemical constituents, and results of prior animal studies indicate alleviating effects of *Opuntiaficus-indica* flowers extract on subsyndromalfatigue symptoms in humans 50 healthy subjects of either gender aged 30 to 60 years with subsyndromal fatigue were enrolled in this open-label monocentric single arm proof-of-principle study. 500mg of a hydro-alcoholic extract from *Opuntiaficus-indica* flowers were administered daily over 8 weeks. Mental and psychic function parameters were assessed by numerical analogue scale of Subjective Fatigue Symptoms, Multidimensional Fatigue Inventory 20, Sheehan Disability Scale, Short Form Health Survey 36, Fatigue Impact Scale, and Global Self-Assessment. Also, health-related incidents, laboratory parameters and vital signs were measured during the intervention period. Improvement of fatigue symptoms could be shown in most measurements after week 1and continued further throughout the trial. 70.0% of subjects reported global improvement of their complaints at end of study. A consistent and positive effect of *Opuntiaficus-indica* flowers extract on symptoms of fatigue could be demonstrated.Improvement in all mental and psychic functions could be measured, most of them statistically significant.

Keywords: Fatigue, Flavonoids, Mental and psychic function parameters, *Opuntiaficus-indica*, Proof-of-Principle study, Sokatin

Introduction

A health food that has in the recent past gained increasing importance in the Western world is the *Opuntia* Cactus (Prickly Pear). Prickly Pear cladodes, fruits and flower infusions have, besides their long-established role in traditional Mexican cuisine, also a centuries-old tradition of usage in folk medicine for treatment of inflammations, diabetes, stomach ulcers, renal diseases, and other conditions [1,2]. All parts of the plant are edible, providing health-promoting constituents, such as phenols, dietary fibers, vitamins (C, E, group-B and β-carotene), minerals, and others [3]. High amounts of flavonoids and betalains show in the strong pigmentation of fruit and flowers [4]. Numerous investigations have, among others, shown antioxidant effects of flowers and other parts of the popular sort *Opuntiaficus-indica* (OFI) [4-9], thus encouraging further research on the plant with regard to its beneficial effects in humans. The trial presented here focused on the effect of OFI flowers in subsyndromal fatigue symptoms in humans. Fatigue is commonly defined as a feeling of tiredness, lack of energy, emotional stability and motivation, or difficulty with concentration and memory [10]. The clinical course is often aggravated by a variety of attending symptoms such as headache or muscle pain. Subsyndromal fatigue which can be described as self-reported permanent fatigue lasting between one and six months and not to be explained by any known diseases [11] is to be distinguished from the ICD10-acknowledged Chronic Fatigue Syndrome (CFS) which persists for at least six months and is characterized by severe debilitating exhaustion [12]. An extract from *Opuntiaficus-indica* flowers named Sokatin was used. Sokatin (WS 1261) is a proprietary name of an active ingredient developed by Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany.OFI flowers contain 3-O-glycosides, namely isorhamnetin, kaempferol, and quercetin plus small amounts of other free flavonoides[9,13]. The 3-glycosidic flavonoids isorhamnetin and quercetin mainly found in the cactus flowers were isolated and could be shown by various research groups to be resorbed in humans following single-dose administration [14-16]. Animal studies performed with Sokatin showed good, albeit dose-dependent, bioavailability of isorhamnetin und quercetin after 4 to 8 hours (internal report, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany). Good bioavailability of isorhamnetin following single- or multiple-dose administration of 500 mg Sokatin (equivalent to 50 mg pure

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flavonoid intake or four cups of cactus flower tea infusion) could be demonstrated in humans (internal report, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany). Animal studies could show possible positive effects of Sokatin on motivation, effort, mind, mood, and memory (unpublished results). Park et al were able to demonstrate effectiveness of the OFI compounds quercetin and kaempferol on performance and permanence in mice [17]. These findings encouraged the initiation of a trial on the effects of Sokatin in humans with symptoms of subsyndromal fatigue.

Methods

Study objective and Design

The investigational product was a nutrient supplement containing a hydro-alcoholic extract from *Opuntiaficus-indica* flowers (DEV 5-12 : 1), extraction solvent: ethanol 60% (w/w), named WS 1261, Sokatin. As OFI products are generally accepted as food, this trial was designed as a nutritional trial. The study was conducted as an open single-center single-arm trial. The protocol was reviewed and approved of by an independent ethics committee (Freiburger Ethik Kommission International, Freiburg, Germany). The objective of this exploratory nutritional study was to describe the physiological effects of Sokatin in healthy subjects with subsyndromal fatigue using validated scales of mental and psychic functions. As the study was designed as a proof-of-principle trial with little previous information being available, no statistical hypotheses were formulated. Instead, an explorative data analysis was performed in order to generate hypotheses regarding the central objective of the trial.

Assessment criteria

The following validated parameters of mental and psychic function were rated by the study participants at the scheduled visits: The numerical analogue scale (NAS) of Subjective Fatigue and Health Symptoms comprised five essential fatigue symptoms, namely 'reduced motivation', 'reduced concentration/memory', 'depletion/exhaustion', 'somatic symptoms' and 'reduced capacity'. Study participants rated the symptoms on analogue scales from 0 to 10, with symptoms not present at 0 and worst at 10. The Multidimensional Fatigue Inventory 20 (MFI-20)[18] comprises 20 items measuring fatigue symptoms and consequences for which the subject specifies the extent to which the particular statements relate to him/her on a five-point scale, ranging from "Yes, that is true" to "No, that is not true". The questionnaire covers the dimensions ´general fatigue´, ´physical fatigue´, ´mental fatigue´, ´reduced activity´ and ´reduced motivation´. The Sheehan Disability Scale (SDS)[19,20] assesses the degree to which symptoms of panic, anxiety, depression or phobia disrupt the work, social life and family life of a person. Numerical ratings of the three items can range from 0-10 and are summed into a single dimensional measure of global functional impairment that can range from 0 (unimpaired) to 30 (extremely impaired) with a score >15 considered to be critical. Two additional items capture the degree to which symptoms affect productivity in terms of lost or underproductive days in the past week. The 36-Item Short Form Health Survey (SF-36) [21] measures the health status of subjects in an 8-scale profile of functional health and well-being scores as well as psychometrics-based physical and mental health summary measures. All but one of the 36 items (self-reported health transition) are used to score the eight SF-36 health concepts: limitations in physical activities because of health problems (physical functioning), limitations in usual role activities because of physical health problems (role-physical), bodily pain, and general health perceptions, which constitute the total physical health score; vitality (energy and fatigue), limitations in social activities because of physical or emotional problems (social functioning), limitations in usual role activities because of emotional problems (role emotional), and general mental health (psychological distress and well-being) constituting the total mental health score. Transformed scales result in scores from 0 to 100 with higher scores indicating a better health status. The Fatigue Impact Scale (FIS) [22,23] was developed to improve the understanding of the effects of fatigue on the quality of life. Forty questions are asked to obtain information about the impact of fatigue on cognitive, physical and social abilities. Individual items are scored from 0 for 'no problem' to 4 for 'extreme problem'. The score for each the cognitive and physical dimension can range from 0 to 40 and for the social dimension from 0 to 80 with higher scores indicating higher fatigue impact. Additionally, the total score is calculated as the sum of the scores of the three dimensions, ranging from 0 to 160. A global self-assessment of the participants basing on the Clinical Global Impressions tool for measuring the patients´ self-perception of progress during a trial consisted of two items: Item 1 measuring the symptom severity and Item 2 the global improvement [24]. Both items are rated on a 7-point scale with the severity of symptoms scale using a range of responses from 1 (normal) through to 7 (most extremely). The global improvement scores range from 1 (very much improved) to 7 (very much worse).

Subjects

Fifty subjects of either gender between 30 and 60 years of age were included in the study. The main inclusion criterion was subsyndromal fatigue as classified by the NASs of Subjective Fatigue Symptoms. At baseline subjects had to score >5 in three out of five scales ('reduced motivation', 'reduced concentration/memory', 'depletion/exhaustion', 'somatic symptoms' and 'reduced capacity'). Among the exclusion criteria were diseases that can cause fatigue: Chronic infectious diseases (e.g. HIV and hepatitis), autoimmune diseases (e.g. rheumatoid arthritis), neuromuscular disorders (e.g. amyasthenia), metabolic disorders (e.g. hypocalcemia and hypercalcemia) and psychic impairments (e.g. major depression and anxiety disorder). Further

exclusion criteria were consumption of antidepressants or *Opuntia* preparations, severe cardiovascular, gastrointestinal, or other chronic diseases, and substance dependency.

Intervention

Trial eligibility was pre-determined by telephone interview. Subjects were screened and enrolled upon meeting all criteria and giving informed consenton day 0. After baseline visit (day 0) subjects took1x500 mg Sokatinover the course of an eight-week investigation period. Subjects were asked to swallow the tablet 30 to 60 minutes before first food-intake of the day.
Following subject-rated mental and psychic function parameters were assessed at baseline, week 1, week 4 and week 8: NAS of Subjective Fatigue Symptoms , MFI-20, SDS, SF-36, except for Week1, FIS (except for Week1), and Global Self-Assessment. Demographic data, medical history as well as the nutritional habits during the previous 12 months were surveyed at baseline.
Although no health risks were to be expected from a nutritional study, health-related incidents (and serious health-related incidents) were monitored independently of a causal relationship with the *Opuntia* extract. Vital signs were measured during the intervention and a full blood count was performed in order to assess function of kidneys, liver and thyroid gland, and to assess C-reactive protein (CRP) levels at study start and termination.

Statistical analysis

Due to the exploratory design of the study, no statistical hypotheses were formulated and no differentiation in primary and secondary outcome variables was defined. Data were evaluated in an exploratory way to analyze the effect of Sokatin on mental and psychic functions of subjects with subsyndromal symptoms of fatigue and exhaustion. Accordingly, all two-sided *p*-values resulting from any statistical test or model are to be interpreted descriptively. Owing to the trial´s pilot character, the study was performed without a placebo control. No formal estimation of sample size was performed, the significance level was set to 0.05 for all statistical tests without adjustment for multiplicity, and a sample size of 50 subjects was deemed sufficient to serve the purpose of gathering information on the impact of Sokatin on mental and physical performance in the target group and of forming a basis for future investigations. The absolute and relative intra-individual changes between baseline and one week, four weeks and the end of the intake period at eight weeks were evaluated for the above-mentioned outcome parameters. If adequate, time courses of the outcome parameters were analyzed as well. Descriptive statistics were computed to describe the empirical distributions; 95%-confidence intervals for the expected values and medians were calculated.

Categorical data were displayed in frequency tables showing sample size, absolute and relative frequency. Analysis was primarily based on the full analysis set including all subjects having received the *Opuntia* extract at least once and having at least one measurement of one of the mental and psychic test parameters during the active intake period. Missing values of some items or total scores during the treatment period were replaced by the last observation carried forward method (LOCF). In addition, a per protocol (PP) analysis was performed including those subjects of the full analysis set without major protocol violations.
The trial war performed according to the current version of the declaration of Helsinki and to the GCP guidelines.

Results and Discussion

The trial presented was the first to determine the effect of the *Opuntiaficus-indica* flower extract Sokatin on parameters of mental and psychic function in human subjects with subsyndromal fatigue. The results presented in the following sections are based on the FAS which consisted of 50 subjects who received Sokatin at least once and had at least one post-baseline visit. Analyses of the PPS (N=40 subjects without major protocol violations) and subgroups of the FAS confirmed the results obtained for the FAS.

Demographic and nutritional data

The average age of the subjects was 47.7 ± 9.0 years (mean ± SD), 64% were women. Average body mass index (BMI) of all subjects was 26.2 ± 4.9 kg/m . A validated self-administered food frequency questionnaire (FFQ) [25]was applied at baseline in order to assess the intake of selected German foods during the previous 12 months and thus exclude nutrient deficiencies as a possible cause of fatigue. FFQ assessment showed that the average nutrient intake was comparable to that of the general population in Germany [26]

Health-related incidents

Twelve subjects (24.0%) experienced 12 health-related incidents during the intake period, resulting in an overall incidence rate of 0.004 events per observation day. Seven health related incidents were of moderate intensity (58.3%) and five of mild intensity (41.7%). The majority of health related incidents were allocated to the System Organ Class ‘Infections and Infestations’, reflecting the higher occurrence of viral infections in winter. No serious health-related event was observed during the eight-week intake, and no subject discontinued the investigation due to a health-related incident. Moreover, no relevant changes in laboratory parameters or vital signs were observed in the course of the study.

Physiological effects

Study participants rated the five Subjective Fatigue and Health Symptoms on NAS from 0 to 10 (Table 1, Figure.1). As detailed in *Methods*, the values at baseline served as the main inclusion criteria for this trial. A highly significant improvement in all items was found after eight weeks of intake (two-sided Wilcoxon signed-rank test: $p<0.001$). Values of NAS decreased in all five categories (reduced motivation, reduced concentration/memory, depletion/exhaustion, somatic symptoms and reduced capacity) by at least 2.48 ± 2.73 points between baseline and week 8. Even after seven days (W1) of Sokatin intake, study participants' subjective impairment in all categories had decreased significantly, at least by 1.14 ± 2.28 points (in item ´reduced concentration/memory´). Greatest reduction of symptoms was by 1.80 ± 2.84 points for ´somatic symptoms´. Further improvement in all items was seen at Week 4 (W4) and Week 8 (W8).

Table 1: Numerical analogue scale (NAS) (mean ± SD, median, two-sided Wilcoxon signed-rank test *p*-value; FAS)

Items	Baseline	W1	W4	W8	Diff (W8-Baseline)	*p*-value (Baseline-W8)
Reduced motivation	6.82±2.03 7.00	5.04±2.81 5.00	4.50±2.72 5.00	4.22±3.03 3.00	-2.60±3.06 -3.00	<0.001
Reduced concentration/ memory	7.36±1.31 7.00	6.22±2.28 6.00	5.30±2.48 5.50	4.88±2.70 5.00	-2.48±2.73 -3.00	<0.001
Depletion/ Exhaustion	8.12±1.02 8.00	6.64±2.12 7.00	5.90±2.48 6.00	5.24±2.75 5.00	-2.88±2.81 -3.50	<0.001
Somatic symptoms	6.38±2.48 7.00	4.58±2.94 5.00	4.50±2.79 5.00	3.48±3.02 3.00	-2.90±3.58 -3.50	<0.001
Reduced capacity	7.94±1.22 8.00	6.32±2.12 7.00	5.70±2.38 6.00	5.16±2.89 5.00	-2.78±2.77 -3.00	<0.001
Mean status of health score	7.32±1.01 7.30	5.76±2.00 6.30	5.18±2.24 5.10	4.60±2.59 3.70	-2.73±2.55 -3.40	<0.001

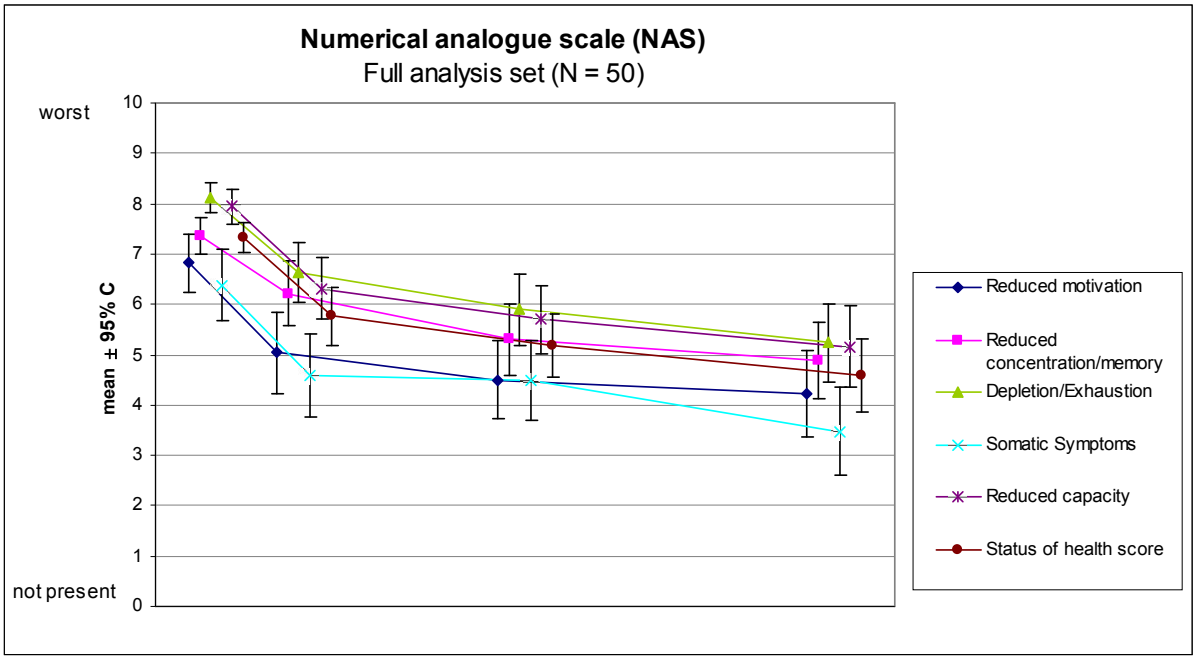

Figure. 1: Numerical analogue scale (NAS) – Items (mean ± 95% CI; FAS, LOCF)

Subjects further assessed their health status on the following validated scales (Table 2). MFI-20: Positive effects of the intake of the extract were found in all subscales of MFI-20 during the entire intervention period. Symptoms of fatigue improved mainly between

baseline and W4, but the scores of the various fatigue symptoms even continued to decrease between W4 and W8. SDS: Highly significant improvements were also seen in the SDS, where the total score comprising the subscales 'work/school', 'social life' and 'family life/home responsibilities' improved by7.78 ± 7.24 points compared to baseline (two-sided Wilcoxon signed-rank test: $p<0.001$).

Table 2: Self-rated scales MFI-20, SDS, SF-36, FIS and CGI (mean ± SD, median, two-sided Wilcoxon signed-rank test *p*-value; FAS)

Scales/Subscales	Baseline	W1	W4	W8	Diff (W8-Baseline)	*p*-value (Baseline-W8)
MFI-20						
General fatigue	17.12±2.45 18.00	15.36±3.64 16.00	14.12±4.13 14.50	12.76±4.49 12.50	-4.36±4.56 -5.00	<0.001
Physical fatigue	15.76±3.09 15.00	14.52±3.76 16.00	13.20±4.11 13.50	12.08±4.51 12.00	-3.68±4.74 -3.00	<0.001
Mental fatigue	16.04±2.84 16.50	14.28±4.01 15.00	12.56±4.24 12.00	12.08±4.39 12.00	-3.96±4.13 -5.00	<0.001
Reduced activity	15.30±3.29 16.00	13.50±3.80 14.00	12.62±3.92 12.00	11.70±4.62 10.00	-3.60±4.69 -4.00	<0.001
Reduced motivation	12.74±3.14 13.00	11.28±3.46 11.00	10.86±3.55 10.50	10.02±4.10 9.00	-2.72±4.22 -2.50	<0.001
SDS						
Work/School	6.54±3.21 8.00	6.16±2.73 7.00	5.00±2.98 5.00	4.44±3.16 4.00	-2.10±3.55 -2.00	<0.001
Social life	6.94±1.85 7.00	5.84±2.26 6.00	5.10±2.41 5.00	4.12±2.65 4.00	-2.82±2.55 -3.00	<0.001
Family life/Home responsibilities	7.00±1.95 7.00	5.84±2.52 6.00	5.24±2.37 5.00	4.14±2.89 3.50	-2.86±2.88 -3.00	<0.001
Days lost	1.58±2.43 0.00	1.50±2.32 0.00	1.50±2.42 0.00	1.38±2.42 0.00	-0.20±1.87 0.00	0.344
Days underproductive	3.96±2.51 4.50	2.72±2.44 2.50	2.20±2.10 2.00	1.40±2.04 0.00	-2.56±2.84 -2.00	<0.001
Total score: Global impairment (1-3)	20.48±4.77 20.00	17.84±5.81 18.00	15.34±6.36 16.00	12.70±7.46 12.00	-7.78±7.24 -9.50	<0.001
SF-36						
Physical functioning	63.50±21.12 65.00	n. a.	72.10±21.00 77.50	77.20±21.24 80.00	13.70±18.87 10.00	<.001
Role-Physical	30.00±34.99 25.00	n. a.	50.00±37.80 50.00	61.50±40.16 75.00	31.50±54.35 25.00	<0.001
Bodily pain	46.42±25.33 41.00	n. a.	56.12±27.76 57.00	65.74±26.19 67.00	19.32±23.84 16.00	<0.001
General health	43.08±19.51 40.00	n. a.	48.62±21.29 45.00	55.40±23.06 62.00	12.32±16.62 10.00	<0.001
Vitality	22.90±15.26 25.00	n. a.	40.90±22.12 40.00	44.90±24.25 47.50	22.00±23.36 20.00	<0.001
Social functioning	42.75±22.74 50.00	n. a.	55.50±22.75 56.25	67.00±25.60 68.75	24.25±29.50 25.00	<0.001

Role-Emotional	33.33±42.06 0.00	n. a.	54.67±42.46 66.67	71.33±34.35 100.00	38.00±50.40 33.33	<0.001
Mental health	46.64±18.58 44.00	n. a.	61.28±18.10 62.00	63.20±17.50 64.00	16.56±16.00 16.00	<0.001
Total score: Physical health	45.75±18.93 41.63	n. a.	56.71±22.12 58.25	64.96±22.52 69.13	19.21±22.12 20.25	<0.001
Total score: Mental health	36.41±17.74 32.50	n. a.	53.09±19.67 55.04	61.61±18.94 61.69	25.20±23.02 28.29	<0.001
Self-reported health transition	3.48±0.79 3.00	n. a.	2.74±1.14 3.00	2.58±1.18 2.50	-0.90±1.20 -1.00	<0.001
FIS						
Cognitive	27.62±6.39 28.00	n. a.	20.12±10.13 20.50	18.04±10.82 16.00	-9.58±9.45 -9.50	<0.001
Physical	24.68±6.10 27.00	n. a.	19.08±8.87 20.50	15.56±10.64 15.50	-9.12±9.46 -9.50	<0.001
Social	47.00±10.63 46.50	n. a.	34.12±16.74 33.00	28.58±18.66 26.00	-18.42±16.23 -18.50	<0.001
Total score	99.30±18.94 99.00	n. a.	73.32±33.33 73.00	62.18±37.87 56.00	-37.12±33.11 -40.00	<0.001
Global self-assessment						
Item 1 (severity of symptoms)	5.42±0.84 5.50	4.92±1.08 5.00	4.44±1.33 5.00	4.04±1.41 4.00	-1.38±1.47 -1.00	<0.001

The changes in the individual subscales were statistically significant as well. Even the degree to which productivity was affected by symptoms of fatigue in terms of underproductive days decreased from 3.96 ± 2.51 days to 1.40 ± 2.04 days per week after eight weeks of Sokatin intake (two-sided Wilcoxon signed-rank test: $p<0.001$). Only a slight reduction was seen in the number of complete days lost per week due to the low starting point of 1.58±2.43 days. SF-36: Subjects recovered significantly in all categories of physical and mental health during the intervention. Especially the average mental health total score increased by 16.7±19.8 points after four weeks and by 25.2±23.0 points after eight weeks (two-sided Wilcoxon signed-rank test: $p<0.001$), mainly driven by the marked improvements in item´emotional functioning´. The pronounced increases regarding the average physical health total score was mainly based on improvements in item ´role-physical functioning´. FIS: All dimensions of quality of life affected by fatigue improved considerably during the eight-week intake. The total FIS score decreased by 37.12±33.11 points (two-sided Wilcoxon signed-rank test: $p<0.001$). Global self-assessment: Severity of symptoms improved by 1.38 ± 1.47 points to 4.04 ± 1.41 points from baseline to week 8 with statistically significant reductions at week 1, week 4 and week 8 (two-sided Wilcoxon signed-rank test: $p<0.001$).

Furthermore, 70.0% of the study participants experienced a global improvement after eight weeks of intervention (Item 2; Figure. 2). All outcome parameters showed that the administration of 500mg/d Sokatin had a consistent and clearly positive effect on the fatigue symptoms assessed. The steady and substantial improvement was, with only few exceptions, statistically significant for all variables as early as one week after the intervention, indicating a prompt and sustained effect of Sokatin on mental and psychic functions. These consistent results were confirmed by analyses of the PPS and subgroups as well as by repeated measurement analyses.

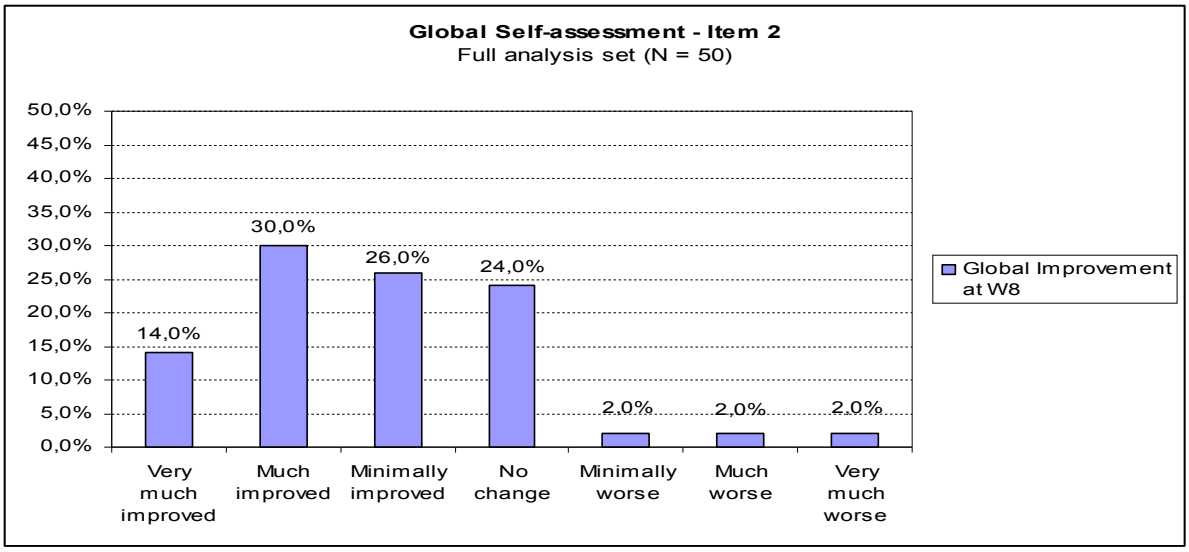

Figure. 2: Global Self-assessment – Global Improvement (mean; FAS, LOCF)

A literature review was conducted with regard to the relevance of the above results and led to two studies: a triple-blind, placebo-controlled clinical trial to evaluate individualized homeopathic treatment (HM) in reducing subjective symptoms of chronic fatigue syndrome (CFS) in patients meeting the corresponding Oxford criteria [27]. The study with a treatment duration of six months and a sample size of 103 adult patients was conducted in the United Kingdom. The outcome parameters were, among others, MFI-20 and FIS [28]. Another multicenter, randomized, double-blind, placebo-controlled clinical trial was conducted in the United States and Puerto Rico to confirm the efficacy of duloxetine, a potent serotonin-norepinephrine reuptake inhibitor, on patient-rated global improvement in fibromyalgia (FM) symptoms. One of the secondary outcome measures was the Multidimensional Fatigue Inventory for 530 randomized outpatients after 12 weeks of intervention [29].

The results of these two studies when compared with those of the present study in terms of MFI-20 (Figure. 3) and FIS indicatethat the significant results obtained in this study are relevant and most likely caused by a specific effect of Sokatin. Due to partially missing information on variability in the publications only the mean score values are presented.

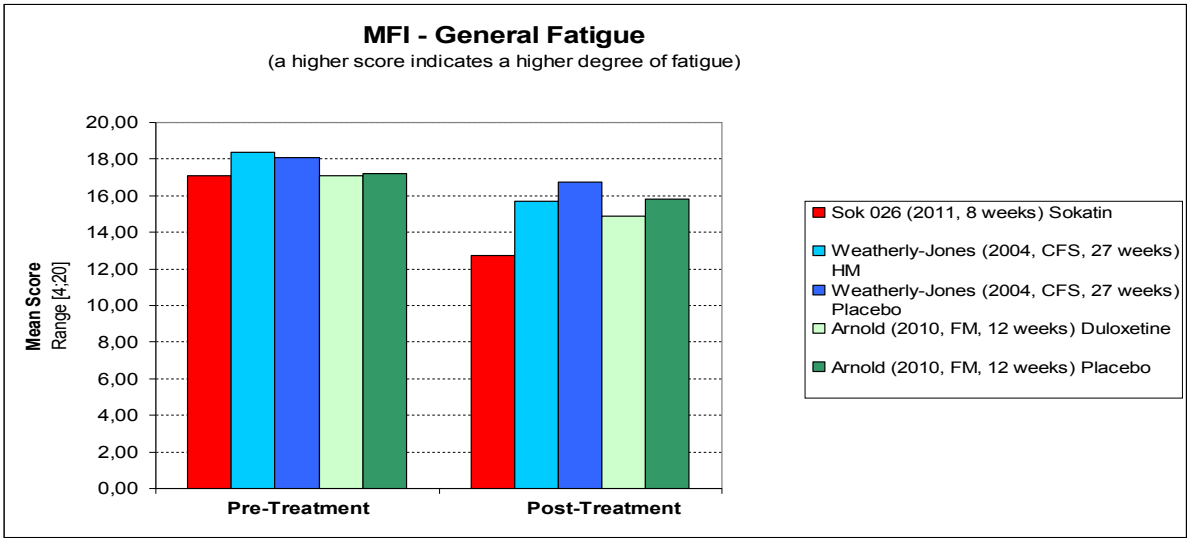

Figure. 3: MFI comparison – Pre-/Post-Treatment due to partially missing information on variability in the publications only the mean score values are presented

Interestingly, the subjective impairment of healthy subjects by their subsyndromal fatigue measured using the MFI-20 scale, may approach the order of magnitude for fibromyalgia patients in this sub-sector, although the core symptoms in fibromyalgia are related to pain. A scale for severity measurement may just not be used to determine a disease as evidenced here again.

Shortcomings

A limitation of the trial was the lack of an active control or placebo, thus limiting the comparative use of the study. Due to the trial´s design as an open proof-of-principle study, however, investigators were able to include a broad panel of subjects, to give evidence of the extract´s efficacy as suggested by animal studies, to prove the nutritional benefit of Sokatin in humans suffering from subsyndromal fatigue, and to confirm an effective dosage [30,31].

Conclusion

The first trial on the effects of *Opuntiaficus-indica* flowers extract in subsyndromal fatigue in humans revealed consistent and clearly positive results. The efficacy of WS1261, Sokatin could be demonstrated on an exploratory significant level. Subjects who were administered500mg/d Sokatin took a favorable course of their symptoms with regard to all mental and psychic functions measured, improving in various fatigue symptoms related to alertness and attention, or to productivity and quality of life in particular. The trial presented here provides a basis for a further evaluation of the efficacy of Sokatin in fatigue. Randomized and placebo-controlled trials are needed to confirm the encouraging results.

Competing interests

AZ, SK, AD are employees of Dr. Willmar Schwabe GmbH & Co. KG, the sponsor of the investigation.

Authors' contributions

All authors were involved in the design of the study and the writing of the protocol, GK, JW, HK and AH conducted the study, AZ undertook statistical analyses. All authors contributed to and have approved the final manuscript.

Trial registration

Current Controlled Trials ISRCTN27842378

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