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Three-week daily supplementation of a 200 or 400 mg Lecithin-based delivery form of Melissa counterbalances emotional distress symptoms

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Abstract

Emotional distress (stress, anxiety, insomnia) is the most prevalent mental health condition worldwide. The aim of the study was to evaluate the potential calming effect of two different daily doses of a standardised phospholipid carrier-based *Melissa officinalis* extract (Relissa, 200 and 400 mg/day) supplemented for 3 weeks to healthy volunteers complaining of a moderate degree of emotional distress and poor sleep conditions. The modulation of emotional distress was assessed using the DASS-21 questionnaires, Pittsburgh Sleep Quality Index (PSQI), Positive and Negative Affect Scales (PANAS), Mental Well-Being Scale (WEMWBS), Quality of Life (WHO-QoL BREF). *Post-hoc* analysis indicated significant reduction in DASS-21 depression, anxiety, stress score, WHO-QoL score and significant increase in WEMWBS score after 3-week with 400 mg/day Relissa. *Post-hoc* analysis indicated significant reduction in PSQI global score, and Negative PANAS score after 3-week with both 200 and 400 mg/day. When two supplementations were compared at the end of the 3-week period, DASS-21 depression, anxiety, stress score, WEMWBS score, WHO-QoL score were significantly lower in 400 than 200 mg/day Relissa-supplemented subjects. No safety concerns were reported during the study observation. In conclusions, Relissa can be safely supplemented at different dosages and resulting in a valid support for emotional distress and poor sleep.

Keywords: Emotional distress; Sleep; *Melissa officinalis* L.; Lemon balm; Relissa; Phytosome; Phospholipids

Introduction

Herbal products have been used since ancient times in folk medicine: even in many primordial texts of Sumeric or Ancient Egyptian populations, there are references to the use of herbs in the relief of unhealthy conditions.

Lemon balm (*Melissa officinalis*, MO) is a perennial herbaceous plant, originally discovered in Mediterranean area, but also found in North Africa and Asia, as well as in the United States [1]. Rosmarinic acid, a hydroxycinnamic acid derivative, represents the major active compound contained in MO extract; many scientifically-reviewed properties [2,3] could be ascribed to rosmarinic acid, such as antioxidant and antinflammatory [4], antinociceptive [5], neuroprotective and calming/anxyolitic [6,7].

Those properties can be due to several mechanisms, included interactions with different receptors, such as GABA [8, 9] and cholinergic [10] receptors.

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Many efforts to improve the accessibility and bioavailability of natural extracts have been carried out over the last few years, and Phytosome™ technology of a food-grade lecithin delivery system, has enabled better-absorbed and more stable natural extracts such as boswellic acids [11], curcuminoids [12], berberine [13].

The Phytosome technique applied to MO led to the recent development of Relissa. Its mechanism of action was recently reported and revealed that Relissa may exert its health benefits thanks to its neuromodulating and neuroprotective properties, its calming and mood-improving activities, and its antioxidant and anti-inflammatory effects [14]. Based on the encouraging calming effects obtained in healthy adults with emotional distress after a 3-week supplementation [15], the presently-described pilot Study was conducted.

The aim of the present study was to evaluate the potential calming effects of two different daily doses of Relissa (200 and 400 mg/day) supplemented for 3 weeks to healthy volunteers complaining of a moderate degree of emotional distress and poor sleep conditions.

Materials and Methods

Standard Protocol Approvals, Registrations

The clinical study was approved by the Ethics Committee of the University of Pavia (protocol number: 1267/21092023), and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, with all ICH and ISO international standards (i.e., ICH Harmonized Guideline for GCP E6 (R2); UNI EN ISO 14155:2012), as well as all the in-force regulations of Regione Lombardia and all national standards of Italy. A written informed consent was obtained from every subject entering the pretreatment phase.

Study design

A 3-week pilot, prospective, open, parallel-group study was conducted in 20 subjects with scores of ≥ 5 by Pittsburgh Sleep Quality Index (PSQI), indicating poor sleep quality. The subjects were recruited from the Dietetic and Metabolic Unit of the "Santa Margherita" Institute, University of Pavia, Italy.

Inclusion criteria were subjects aged 18 years or older, of both genders, with a body mass index (BMI) between 25 and 30 kg/m^2 who provided signed written informed consent.

Exclusion criteria were: subjects with clinically-significant cardiopathies, nephropathies, liver diseases, bronchopneumopathies, haemopathies, dermopathies, or chronic degenerative diseases of the central nervous system; subjects with active peptic ulcers, ulcerative colitis, Crohn's disease, celiac disease, or inflammatory bowel disease; subjects with symptomatic cholelithiasis (at least one episode of biliary colic in the last 6 months) or autoimmune diseases (except autoimmune thyroiditis); subjects with previous or current neoplasms: subjects with epilepsy (current or previous); endocrinopathies (except subclinical hypothyroidism with normal TSH values); subjects with significant motor disability or mental retardation; subjects with confirmed or suspected diagnosis of major depressive disorder, bulimia, panic disorder, obsessive–compulsive disorder, post-traumatic stress disorder, bipolar disorder (I or II), or schizophrenia; a previous history or current diagnosis of drug abuse or alcoholism; subjects with changes in smoking habits or that have quit smoking in the last 6 months; subjects that currently use psychoactive drugs, or that have used psychoactive drugs in the last 3 months.

Dietary supplement

The participants were supplemented for 3 weeks with 200 mg/tablet containing Melissa phospholipids/SF (Melissa Phytosome™, as Relissa™, Indena S.p.A, Italy), 1 or 2 tablets daily after dinner.

Group 1, 10 subjects received 1 tablet/day, i.e. 200 mg/day for 3 weeks, while Group 2, 10 subjects, received 2 tablets/day, i.e. 400 mg/day for 3 weeks.

Primary and secondary endpoints were measured at basal, T0 (just before supplementation), and 3 weeks after supplementation (T1).

Primary endpoint

The primary endpoint was the modulation of emotional distress assessed using the DASS-21 questionnaires, exploring the degree of mood, anxiety, and stress in the form of a total score for each of these conditions, with a higher score denoting a more severe emotional state. Briefly DASS-21 global score was assessed using the 21-item depression, anxiety, and stress scale, validated in Italian, which shows the same factorial structure as the original version: 21 elements making up 3 scales (depression, anxiety, and stress) with 7 elements each. Each element evaluates the degree to which the subjects experienced each symptom during the past week on a 4-point severity or frequency scale: 0 = did not apply to me at all, 1 = applied to me to some degree, or some of the time, 2 = applied to me to a considerable degree or a good part of time, and 3 = applied to me very much or most of the time. The highest scores on each scale correspond to more negative affective states [16].

Secondary endpoints

Anthropometric Measurements: Body weight (to the nearest 0.1 kg) and height (to the nearest 0.5 cm) were measured according to standard procedures, and body mass index (BMI) was derived accordingly [17].

Pittsburgh Sleep Quality Index (PSQI): Sleep relief was assessed through the self-administered 19-item PSQI

Rondanelli M, et al., J Food Sci Nutr Res 2024
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questionnaire. Scores were obtained on each of seven domains of sleep quality: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep perturbations, use of sleeping medication, and daytime dysfunction. Each component is scored from 0 to 3 (0 = no sleep problems and 3 = severe sleep problems). The global PSQI score ranges from 0 to 21 points, with scores of ≥ 5 indicating poorer sleep quality [18]. PSQI global score (defined as the sum of the score of each item) was subjected to statistical analysis.

Positive and Negative Affect Schedule Trait (PANAS) scale: The subjects' emotional states were measured with the standard Positive and Negative Affect Schedule Trait scale, validated in Italian, comprising both positive and negative feelings and emotions. The PANAS scale is a self-reported psychological scale with ten positive markers and ten negative markers. The Positive Attribute (PA) subscale reflects the extent to which a person feels interested, excited, strong, enthusiastic, proud, alert, inspired, determined, attentive, and active. The Negative Attribute (NA) subscale includes stressed, upset, guilty, scared, hostile, irritable, ashamed, nervous, jittery, and afraid. All the items are rated on a scale ranging from 1 ('very slightly or not at all') to 5 ('extremely') [19].

Mental Well-Being Scale (WEMWBS): Feelings and functioning aspects of the Mental Well-Being Scale focus on positive attributes of mental health, such as optimism, energy, and confidence. Validated in Italian, it contains 14 items with response scales ranging from 1 (none of the time) to 5 (all of the time). A score of 40 or below suggests low mental wellbeing. The validated Italian version was used for the study [20].

Quality of Life (WHO-QoL BREF): Quality of life assessed by WHO-QoL (quality of life)-BREF questionnaires for each participants by evaluating the impact on overall quality of life, by addressing four health domains: physical health, mental health, social relationships and environmental health.

Safety and Compliance: Safety and compliance were monitored and any adverse event registered.

Statistical evaluation

Data from each variable were statistically evaluated by two-way (treatment, time) ANOVA with repeated treatment on the factor 'time', followed by Sidak's test for *Post-hoc* analysis.

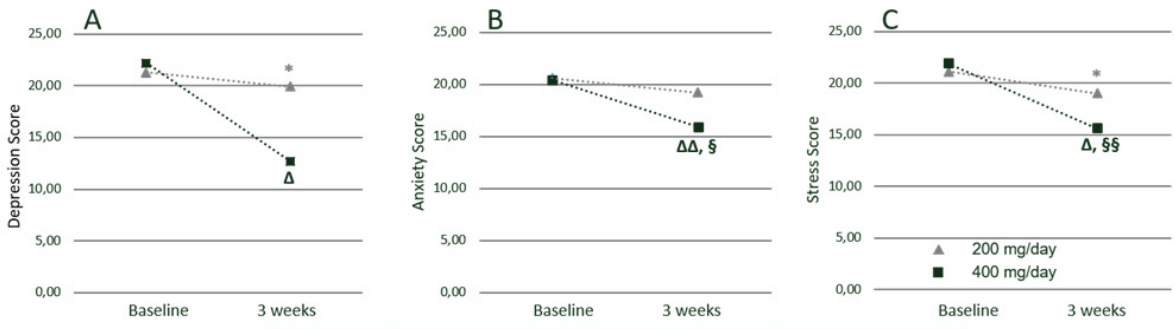
Results

25 volunteers were screened, 4 declined to participate, 1 did not match the inclusion criteria, and 20 subjects were enrolled in the study. All participants (10 men and 10 female) completed the study, and no serious adverse events were reported after randomization. At enrolment, the mean age of the participants was 51 ± 7 years, the mean BMI was 25.6 ± 1.5 kg/m^2, and the PSQI score was 8.7 ± 2.3, globally > 5, as for inclusion criteria.

Primary endpoint

DASS-21 depression score

Post hoc analysis indicated a significant reduction in DASS-21 depression score after 3 weeks with 400 mg/day Relissa supplementation (Figure 1A); the magnitude of this reduction averaged approximately 45%. When the two supplementations were compared at the end of the 3-week period, DASS-21 depression score was significantly lower in 400 than 200 mg/day Relissa supplemented subjects (Figure 1A).



DASS Score	Depression Score	Anxiety Score	Stress Score
T0 200 vs T1 200	**P<0.005***	P>0.05	**P<0.005***
T0 400 vs T1 400	**P<0.0001$^{\Delta}$**	**P<0.0005$^{\Delta\Delta}$**	**P<0.0001$^{\Delta}$**
T0 200 vs T0 400	P>0.05	P>0.05	P>0.05
T1 200 vs T1 400	P>0.05	**P<0.05§**	**P<0.005§§**

Figure 1: DASS-21 scores A. depression, B. anxiety, C. stress; evaluated at baseline and after 3-week supplementation with Relissa △ 200 mg/day or ■ 400 mg/day. A 2-way (treatment, time) ANOVA with repeated treatment on the factor "time", followed by *Post hoc* analysis (Sidak's test), was performed.

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Rondanelli M, et al., J Food Sci Nutr Res 2024
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DASS-21 anxiety score

Post hoc analysis indicated a significant reduction in DASS-21 anxiety score after 3 weeks with 400 mg/day Relissa supplementation (Figure 1B); the magnitude of this reduction averaged approx. 20%. When the two supplementations were compared at the end of the 3-week period, DASS-21 anxiety score was significantly lower in 400 than 200 mg/day Relissa supplemented subjects (Figure 1B).

DASS-21 stress score

Post hoc analysis indicated a significant reduction in DASS-21 stress score after 3 weeks with both 200 and 400 mg/day Relissa supplementations (Fig. 1C); the magnitude of this reduction averaged approx. 10% and 30%, respectively. When the two supplementations were compared at the end of the 3-week period, DASS-21 stress score was significantly lower in the 400 than 200 mg/day Relissa supplemented subjects (Figure 1C).

Secondary endpoints

PSQI global score

Post hoc analysis indicated a significant reduction in PSQI global score after 3 weeks with both 200 and 400 mg/day Relissa supplementations (Figure 2); the magnitude of this reduction averaged approx. 15% and 35%, respectively.

PANAS score

A tendency toward an increase in Positive PANAS score was observed after 3 weeks with both 200 and 400 mg/day Relissa supplementations (Figure 3A). Regarding Negative PANAS score, *Post hoc* analysis indicated a significant reduction after 3 weeks with both 200 and 400 mg/day Relissa supplementations (Figure 3B); the magnitude of this reduction averaged approx. 10% and 20%, respectively.

WEMWBS score

Post hoc analysis indicated a significant increase in WEMWBS score after 3 weeks with 400 mg/day Relissa supplementation (Figure 3C); the magnitude of this increase averaged approx. 20%. When the two supplementations were compared at the end of the 3-week period, WEMWBS score was significantly higher in 400 than 200 mg/day Relissa supplemented subjects (Figure 3C).

WHO-QoL score

Post hoc analysis indicated a significant increase in WHO-QoL score after 3 weeks with 400 mg/day Relissa supplementation (Figure 3D); magnitude of this increase averaged approx. 20%.

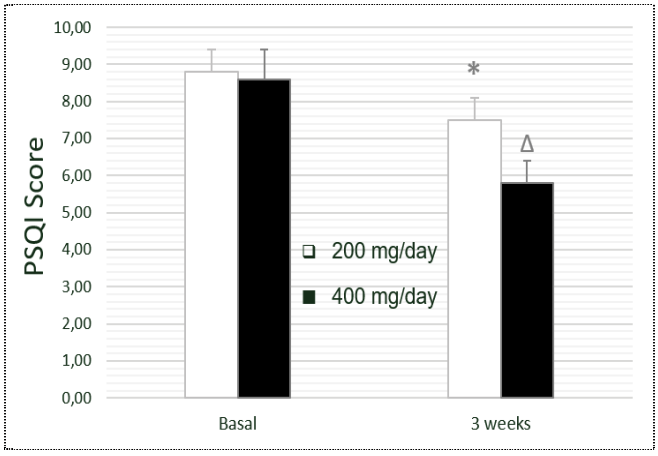

Figure 2: PSQI score at baseline and after 3-week supplementation with Relissa 200 mg/day (light grey) or 400 mg/day (dark grey). A 2-way (treatment, time) ANOVA with repeated treatment on the factor "time", followed by *Post hoc* analysis (Sidak's test), was performed. *P<0.005 and ΔP<0.0001 vs baseline.

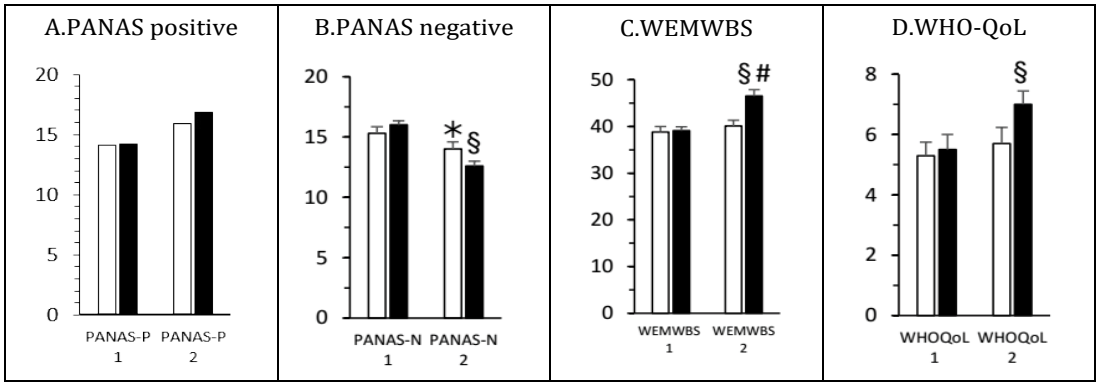

Figure 3: A. PANAS positive score; B. PANAS negative score; C. WEMWBS score; D. WHO-QoL score at basal and after 3-week supplementation with Relissa 200 mg/day (white) or 400 mg/day (black). A 2-way (treatment, time) ANOVA with repeated treatment on the factor "time", followed by *Post hoc* analysis (Sidak's test), was performed, when statistically permitted. *P<0.01 vs 200 mg at baseline; §P<0.0005 vs 400 mg at baseline (1); #P<0.05 vs 200 mg after 3-week supplementation (2).

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Safety and Compliance

No adverse events were reported after Relissa supplementation at both doses and compliance resulted high in all groups.

Discussion

Oral supplementation of 400 mg of Relissa tablets for 3 weeks confirmed to lead to significant improvements in mood, anxiety, stress, negative emotions, overall mental wellbeing, and quality-of-life scores. The comparison between two daily dosages revealed that even at a lower dose of 200 mg, Relissa is able to support sleep quality, overall negative emotional feelings, together ameliorating the general quality of life. Moreover, Relissa confirmed its good tolerability and compliance as no adverse events occurred during the study.

The results of this study are in agreement with a 3-week Relissa supplementation (400 mg/day), placebo-controlled, clinical trial conducted in 100 healthy adults with a moderate degree of depression, anxiety or stress [15]. That study, involving a larger number of subjects than the present study, showed the beneficial effects on mood, sleep and emotional distress produced by the standardised phospholipid carrier-based formulation of Melissa.

The neuromodulating and neuroprotective properties of *Melissa officinalis* extract fo rmulated in phospholipids may be mediated by the GABA-T and MAO-A inhibitory properties demonstrated very recently in in vitro models [14]. Further studies could deeply investigate those mechanisms.

The limited number of subjects and the absence of a placebo group represent the major limits of the present study; however, the supplementation of two different doses, and in particular the lower dose of 200 mg/day already active in some of the examined parameters, represents both the novelty and strength of the present study.

In conclusion, Relissa can be safely supplemented at different dosages for the benefit of general quality of life, resulting in a valid support for emotional distress and poor sleep condition, in respect to the individual needs.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Ethics Committee of University of Pavia (ethical code number: 1267/21092023).

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available inside the article.

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Authors' contribution

Conceptualization, M.R.; methodology, S.P.; software, G.M and C.G.; validation, F.M, C.G. and G.C.B.; investigation, G.M. G.C.B.; resources, M.R.; data curation, G.M. C.G, G.M; writing—original draft preparation, M.R., P.M.; writing—review and editing, M.R, P.M.; visualization, M.R, P.M.; supervision, M.R.

All the Authors contributed to the manuscript in revising and reading and approved the final version of the manuscript.

Conflict of interest

The authors declare no conflicts of interest

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