Research Paper

The role of *Pueraria lobata*, *Crocus sativus*, *Griffonia simplicifolia*, L-tryptophan, and Magnesium supplementation in the treatment of anxiety and mood disorders

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ABSTRACT: *Anxiety, mood, and sleep disturbances are frequent disturbances that have been treated with natural derivatives since ancient times. The purpose of this work is the evaluation of the impact of a food supplement containing: Pueraria lobata, Crocus sativus, Griffonia simplicifolia, L-tryptophan, Magnesium, and Relaxmel, on the emotional state of patients with anxiety and mood disorders. The study recruited 49 patients aged between 19 and 76 years and 30 controls aged between 19 and 67 years. Affective status was assessed by State-Trait Anxiety Inventory (STAI X1/X2) and Beck Depression Inventory (BDI). STAI X1 showed an average pre/post-treatment value of 68.93 +2.97 and 51.27 +8.07 (p <0.001), STAI X2 an average pre/post-treatment value of 70.07 +3.09 and 51.04 +6.93 (p <0.001) and BDI an average value of 20.12 +4.33 and 10.75 +3.15 (p <0.001). The comparison with control subjects obtained a significant interaction between group and time factors (p<0.0001 for the STAI X1, STAI X2, and BDI), showing that the values of treated subjects decreased significantly for the control group. Treatment tolerability was high with an average value of 9.67 +0.56. Dietary supplementation has proven effective in the treatment of anxiety and mood disorders in a relatively short period (60 days) with excellent tolerability.*
KEYWORDS*: Crocus sativus, Griffonia simplicifolia, Pueraria lobata, anxiety, mood disorders, sleep disturbances.*

I. INTRODUCTION

Pharmacological therapy is the commonly employed treatment for anxiety and mood disorders due to the tolerability, availability of active drugs. There are several therapeutic strategies for the treatment of mood disorders: tricyclic antidepressants, serotonin reuptake inhibitors (SSRI), and serotonin-norepinephrine reuptake inhibitors (SNRI) are employed in the treatment of depression, while benzodiazepines represent the gold standard for anxiety disorders [1]. However, these drugs have important side effects, including drowsiness, weight gain, mental confusion, and constipation: considering the prolonged duration of treatments and the need

to be continuous over time, these side effects could reduce patient compliance and lead to therapeutic failure. Natural products, e.g. *Rhodiola rosea* L. [2], *Crocus sativus* L. [3,4] , *Piper methysticum* L. [5], *Curcuma longa* L. [6], *Hypericum perforatum* L. [7], and *Passiflora incarnata* L. [8] have been used since ancient times for the treatment of mental disorders as a single agent or as a complement to traditional therapeutics. Although the mechanism of action of several medicinal plants has not yet been fully elucidated, the use of natural active agents represents a valid and effective alternative in the treatment of depressive and anxious disorders, since this therapeutic approach could have minor side effects compared to traditional drug therapies [9,10]. Quilli[®] swallowable solution is a nutritional supplement containing: a) *Pueraria Lobata* L. (roots) that have a high content of isoflavones (including puerarin and genistein) with activity on neurotransmitters such as serotonin, glutamate, and GABA. Due to these properties, it can be useful in cases of depression and anxiety, minimizing the severity of mood swings and the frequency of panic attacks [11,12]; b) *Crocus sativus* L. (stigmas) has antidepressant activity, due to the content of crocin analogs (crocin 1 and 2) and crocetine which contribute to maintaining the normal mood. It exerts several potential antidepressant mechanisms of action which include antioxidant, anti-inflammatory, serotonergic, modulating hypothalamic-pituitary-adrenal axis, and neuroprotective effects [13,14]; c) *Griffonia simplicifolia* (DC.) Baill. (seeds) rich in 5-hydroxy-L-tryptophan, a direct precursor in the synthesis of serotonin which promotes relaxation and mental well-being and helps to maintain the normal mood tone, proving effective in the treatment of nervous and psychological problems [15]; d) L-Tryptophan the precursor of serotonin, which however it is not synthesized by the human body for which it must be integrated: supplementation of tryptophan increases the concentration of serotonin in SNC, making it effective in the treatment of the depressive disorder. Conversely, tryptophan depletion significantly alters cognition, anxiety, and mood [16,17]; e) Magnesium (Mg) is an essential mineral to maintain homeostasis, involved as a cofactor in several biochemical reactions. Anxiety disorders are often accompanied by an Mg deficiency, exposure to stressful conditions increases urinary Mg excretion, with a consequent partial reduction of Mg levels. Hence, the hypothesis that its integration can help treat mood disorders through the moderation of the response to stress [18,19]; f) Relaxmel, a special honey produced by feeding bees with selected medicinal herbs including *Passiflora incarnata* L., *Lavandula angustifolia* Mill., *Avena sativa* L., *Vitex agnus castus* L., *Inula helenium* L., and *Humulus lupulus* L. It is known that different floral sources can impart well-defined pharmacological properties to honey [20,21]. The use of plant sources known for their anxiolytic and relaxing activities makes this product useful in the treatment of the pathologies under study. The purpose of this study is to evaluate the effectiveness of Quilli[®] supplementation on the emotional state of patients with anxiety and mood disorders.

II.   MATERIALS AND METHODS

Quilli[®] (Gam Farma, Milan, Italy) was evaluated in an open study, conducted at the Casimiro Mondino National Neurological Institute of Pavia. 49 patients have been treated with Quilli[®] one ampoule/day for 60 days. The evaluation of the anxious state and the depressive state will be determined using self-compiling statistic tools (Psycho diagnostic tests). Based on clinical data collected in a specific data collection form. The tools employed for the diagnosis are the State-Trait Anxiety Inventory (STAI-X1, STAI-X2) and Beck Depression Inventory (BDI-II) [22,23]. The first administration of the tests at the time of the nosographic classification, after the neurological examination (T0); second administration after 60 days (T1). The decreasing measurements are compared with a control group of 30 subjects. Inclusion criteria: patients with anxiety-depressive symptoms. Exclusion criteria: patient with personality disorders/psychosis. Patients' clinical characteristics are summarized in table 1.

Statistical analysis

R 3.6.2 was used for statistical analysis. Statistical significance was set as a *p*-value $<.05$ (two-tailed). Normality testing of data using the Shapiro-Wilks test was performed on all the outcomes. Since all the outcomes for at least one group violate the normality hypothesis, non-parametric tests were used. The differences between pre and post-treatment measurements were analyzed using Wilcoxon test for paired data. The analysis of the influence of interaction between the group factor (Quilli[®] *vs* control) and the time (t0 and t1) on the measurements is performed through a non-parametric repeated measures ANOVA.

Group	Control	Quilli[®]
	N (%)	N (%)
Total	*30*	*49*
Sex		

Male	5 (17%)	7 (14.3%)	
Female	25 (83%)	42 (85.7%)	
Age (mean-range)	42 (19-67)	47 (19-76)	
Diagnosis			
Anxiety disorders	23.5%	16.3%	
Mood disorders	9.8%	8.2%	
Anxiety and mood disorders	66.7%	75.5%	
Insomnia	70%	67.4%	

Table 1: characteristics of the study patients.

III.   RESULTS

49 subjects, 42 females (85.7%) and 7 males (14.3%), with an age between 19 and 76 years (mean 47+14.9) were enrolled in our institute. In detail: 16.3% anxiety disorders, 8.2% mood disorders, 75.5% anxiety and mood disorders, and 67.4% insomnia. The control group is composed of 25 females (83%) and 5 males (17%) with a distribution that is not significantly different from the Quilli® group, with an age between 19 and 67 years (mean 42+11.1). The age of the control group is significantly lower than the Quilli® group (p=0.04). In the control group 23.5% anxiety disorders, 9.8% mood disorders, 66.7% anxiety and mood disorders, and 70% insomnia are reported. Trait anxiety, evaluated by STAI X1, decreased on average by 17.7 points, reporting a p value<0.001. State anxiety, evaluated by STAI X2, a decrease of 19.0 points on average, reporting a p value<0.001. Also, depression, evaluated by BECK, decreased significantly (p<0.001) by 9.4 points on average. Evaluating the tolerability levels on a scale from 0 to 10, the mean value reported is 9.67 (0.56). 69% of subjects report tolerability of 10, 24% tolerability of 9, and only 4% tolerability of 8. No one patient declares a tolerability level less than 8. Statistical tests confirm that the decrease of each scale is significantly different in Quilli® group from the control group (p<0.0001) in terms of anxiety and depression (Table 2).

	Group	T0	T1	Pre-post *p* value	Interaction *p* value
STAI X1	Quilli®	69 (66-71)	51 (44-58)	<0.0001	<0.0001
	Control	68 (65.3-71)	67 (61.3-70)		
STAI X2	Quilli®	70 (68-72)	50 (48-58)	<0.0001	<0.0001
	Control	69 (60-70)	64 (58-66)		
BECK	Quilli®	19 (16-23.3)	10 (9-12.3)	<0.0001	<0.0001
	Control	25 (20.3-32)	22 (20-29.8)		

Table 2: results of Quilli® supplementation in the comparison pre-post and measurements *vs* control group.

IV.   DISCUSSION

In modern society, people suffer from various psychiatric disorders, especially depression, anxiety, and insomnia. These well-known forms of psychiatric disorders have been affecting many people from all around the world. Anxiety disorders are considered the most frequently occurring category of mental disorder in the general population: anxiety is an experience of everyday life. Estimates of the lifetime prevalence of anxiety disorders have ranged between 10% and 25 % [24]. Several studies have demonstrated the high prevalence of sleep complaints related to anxiety. As much as one-third of the adult population reports difficulty sleeping and sleep disturbance is considered the second most common symptom of mental distress [25]. Mood disorders are common mental health problems, afflicting millions of people around the world [26]. Mood disorders exist in many forms, including unipolar depression, bipolar depression, mania, mixed syndromes, and subsyndromes, and these conditions can co-occur with other psychiatric and physical disorders. Pharmacological therapy is currently the most commonly used treatment for anxiety and mood disorders. Although many drugs appear to have an important role in cases of most severe mental illness, many complain that the drugs are not effective for

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all patients and incur diverse adverse events, as well as tolerance (if used for a long time). There are several therapeutic strategies for the treatment of mood disorders: tricyclic antidepressants, serotonin reuptake inhibitors (SSRI), and serotonin-norepinephrine reuptake inhibitors (SNRI) are employed in the treatment of depression, while benzodiazepines represent the gold standard for anxiety disorders: however these drugs have important side effects, including drowsiness, weight gain, mental confusion, and constipation: considering the prolonged duration of treatments and the need to be continuous over time, these side effects could reduce patient compliance and lead to therapeutic failure. Therefore, it is desirable to seek fast-acting, better-tolerated, more effective, and fewer side effects antidepressants. Numerous studies have demonstrated that the use of complementary and alternative medicine (CAM) among psychiatric disorders, especially depression and anxiety is a common phenomenon: increasing attention is being paid worldwide to Ayurveda, yoga, naturopathy, Unani medicine, Siddha, and homeopathy [27]. Meanwhile, herbal medicine is the most commonly used form of complementary and alternative medicine therapies [28]. Nutraceuticals have largely been used to promote mental and physical health, prevent illness, and treat diseases, with substantial benefits [5]. Numerous herbs are known to contain bioactive substances, although the clinical significance of these needs further investigation [29]. Hence, our study proposes to evaluate the effectiveness of Quilli[®] supplementation on the emotional state of patients with anxiety and mood disorders. The evaluation of the anxious and the depressive state was done using two validated scales as State-Trait Anxiety Inventory (STAI-X1, X2) and Beck Depression Inventory (BDI-II). The study included patients with anxiety-depressive symptoms excluding patients with personality disorders or psychosis. Anxiety and depression levels are evaluated before and after the treatment with Quilli[®] one oral ampoule/day for 60 days. Statistical tests confirm that the decrease on each scale is significant. Treatment tolerability was high and body weight showed no statistically significant differences before and after treatment. Finally, based on these data we can affirm that Quilli[®] can be considered a valid treatment for patients with anxiety and mood disorders. Complementary therapies are disciplines of holistic conception that operate on the discomfort and disorders of the person. The main criticism regarding complementary therapies relates to the lack of scientific rigor. The evidence of the facts is fundamental but it needs a solid scientific basis. In the absence of well-conducted research, the placebo effect is often cited by conventional medicine as an explanation for the results of unconventional therapies. Currently, complementary or alternative therapies are used together with conventional treatments, rather than as a substitute, especially for anxiety and mood disorders and painful syndromes (headaches, arthralgia, back pain) which are among the major causes of the use of complementary therapies. The term "complementary" aims to underline the aims that these disciplines pursue, which do not want to be an alternative to allopathic medicine but of support. In this way, complementary holistic medicine aims to treat the subjectivity of the individual through numerous techniques, leaving purely scientific objectification to allopathic medicine which has always pursued the treatment of health through the treatment of the pathological symptom.

V. CONCLUSION

Complementary Therapies are mainly concerned with the well-being and quality of life of the person by taking care of the homeostatic aspect, that is the individual's balance, so that the organism as a whole restores and maintains its natural state of balance. The term "complementary therapies" therefore does not correspond to the real characteristics of these medical arts, which want to support medical science and not replace it. They represent important strategies: in particular for the treatment of anxiety and mood disorders. If the principles of unconventional therapies could be combined with the efficacy of a carefully evaluated and flexible drug regimen, as well as with the use of other conventional techniques, most disorders, in particular, could be successfully treated by complementary therapies. Clinical experiences show how complementary therapies can be a valid non-pharmacological therapeutic alternative in the forms in which anxiety and mood play an important role; it is also to be considered in those patients in whom drug treatment is contraindicated, such as in childhood and pregnancy. There is a clear need for coordinated studies, focused on the use of Complementary Therapies, to establish what therapeutic role we have in anxiety and mood disorders and consequently quantify their effectiveness. Supplementation with Quilli[®] proved statistically significant in the treatment of anxiety and mood disorders in a relatively short period of treatment (60 days), showing excellent tolerability and no weight influence. Larger randomized studies are warranted to confirm the effectiveness of this dietary supplement.

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