

# Efficacy on Subthreshold Anxiety Disorders of a New Drug Containing *Passiflora Incarnata* L. Herba in 76 Patients with Anxious Symptoms

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## Abstract

With the aim of verifying the anxiolytic and hypnotic effect of *Passiflora incarnata* L. Herba we conducted a prospective open label study in 76 outpatients who had sought psychiatric consult in private clinical practice for anxiety/sleep in subthreshold/full blown DSM-IV anxiety spectrum disorders. According to patients' needs a clinician proposed and prescribed a formulation containing dry extract of *Passiflora incarnata* L., Herba at a dosage of 1 or 2 tablets daily (200-400 mg/day for six weeks). The comparison of Hamilton-anxiety and insomnia index scales mean scores reported at T0 versus T1 showed a statistically significant decrease ( $p < 0.001$ ). In clinical global impression scale, the 84% of the sample was found to be improved, (60% minimally improved and 24% much improved) while 16% showed no change. The 54% of the sample reported an anxiolytic effect and the 58% reported a pro-hypnotic effect. No side-effects were reported during the treatment with no drop-out. Furthermore, from this study it emerged a double effect, anxiolytic and pro-hypnotic, attributed to *Passiflora* that misses to antidepressants and benzodiazepines tend to lose overtime. A pharmacological treatment with a new drug containing as active principle *Passiflora Incarnata* L. Herba could be a valid option in the treatment of anxiety spectrum disorders in monotherapy or in add-on to serotonergic antidepressants.

**Keywords:** Drug; *Passiflora incarnata* L. Herba; Mild anxiety; Sleep disturbances

## Introduction

Anxiety is a universal human experience a natural response to perceived threats and an adaptive mechanism that has evolved over millennia to ensure our survival. However, for millions of individuals worldwide, anxiety transcends its evolutionary purpose and becomes an overwhelming often debilitating force that disrupts daily life. The landscape of anxiety disorders is far more intricate than commonly perceived encompassing a spectrum of conditions that vary in severity, symptomatology and underlying etiology. These conditions collectively constitute

a significant public health concern with profound implications for individual well-being and societal functioning. While established pharmacological and psychotherapeutic treatments have demonstrated efficacy in managing anxiety disorders a growing body of research suggests that alternative complementary approaches may hold promise in alleviating the burden of anxiety and its subthreshold manifestations [1-4]. Among these approaches dietary supplements, comprising natural compounds, probiotics and prebiotics have garnered attention for their potential to offer a more holistic and accessible means managing anxiety-related symptoms [5,6]. Herbal medicines containing *Passiflora* species have been widely used to treat anxiety, insomnia, diarrhea, painful menstruation, convulsions since ancient times. *Passiflora incarnata* L. Herba is a medicinal plant with edible fruits rich in vitamins A, C, B1 and B2, as well as calcium, phosphorus and iron. This species is native to South America, Australia and Southeast Asia and is predominantly cultivated today to obtain raw materials for pharmaceutical use [7]. The primary phytochemical compounds found in *Passiflora* are flavonoids (apigenin, luteolin, quercetin and kaempferol) and flavonoid glycosides (vitexin, isovitexin orientin and isoorientin) [8].

In 2014, *Passiflora incarnata* was officially recognize as non-benzodiazepine drug by European Medicines Agency today is often used as an anxiolytic and sedative due to its putative GABAergic properties: Flavonoids works by partially agonizing GABA-A receptors, similar to benzodiazepines and inhibiting the reuptake of GABA within synapse [9,10]. Tractana® (dry extract of *Passiflora incarnate* L. Herba) is a drug approved in Italy by AIFA (Agenzia Italiana del Farmaco) as a medical product since November 2020 available in 200 mg tablets. A study in rats demonstrated that long-term use of passionflower was associated with reduced stress levels, leading to increased motivation and improved motor activity [11]. Beneficial effects of *Passiflora* on human memory function have also been confirmed [12]. Just as in individuals with chronic insomnia, it may have a therapeutic effect in managing sleep disorders, memory loss and degenerative brain diseases. Through its sedative action, *Passiflora incarnata* L. Herba can be helpful in treating insomnia as well as in episodes of anxiety, restlessness and depressive states [13,14].

Several studies have suggested the efficacy of *Passiflora* in anxiety disorders in a double blind randomized controlled trial, *Passiflora Incarnata* L. Herba dry extract showed similar efficacy as compared to oxazepam but significantly less adverse effect [15,16]. In the open label by ansseau and colleagues the same active principle (a dry extract of *Passiflora Incarnata* L. Herba) also demonstrated, in a large sample of patients (around 3000) an improvement in the Hamilton anxiety score from 25, 7 to 15, 4 after 2 weeks of treatment [17].

Anxiety spectrum disorders are highly prevalent psychopathological phenomena in today's society and one of the most frequent reasons for seeking therapeutic support it is useful to delve into the effectiveness of new compounds in the landscape of therapeutic options for treating these disorders. Therefore, with the aim of a more targeted placement of effectiveness in individual anxiety spectrum disorders, we propose a prospective naturalistic study on a sample of patients attending psychiatric and psychological request, selecting those suffering from anxiety spectrum disorders and adding *Passiflora Incarnata* L. Herba treatment to observe the evolution on anxiety symptoms [18].

## Materials and Methods

We enrolled 76 outpatients who had sought psychiatric consult in private clinical practice for anxiety symptoms. All patients were screened using the Structured Clinical Interview (SCID-I) to assess the psychiatric diagnosis at recruitment time, considering spectrum condition as a clinical picture which does not necessarily meet all the criteria requested for the diagnosis according to the DSM-IV-TR (APA, 2000) [19,20]. However, in terms of psychometric assessment, inclusion criteria required a minimum score of 8 at the Hamilton anxiety scale and/or of 7 at the insomnia severity index [21,22]. According to patients' needs, a clinician proposed and prescribed a formulation containing dry extract of *Passiflora Incarnata* L. Herba at a dosage of 200-400 mg/die, corresponding to 1 or 2 tablet daily. Inclusion criteria also required the subscription of written consent to participate into the study that was approved by the ethics committee of the university of Pisa. At recruitment time (T0) and after 6 weeks (T1) of treatment with the test drug, we administered to all patients the following rating scales: (1) The Hamilton Anxiety Scale (HAM-A), quantifying the severity of anxiety symptoms through the investigation of 14 specific items of the anxiety spectrum; (2) The Insomnia Severity Index (ISI), a rating scale for sleep disorders divided into seven multiple-choice questions on sleep quality and its influences in daily life; (3) The Clinical Global Impression scale (CGI) indicating the overall clinical evaluation by a clinician in terms of severity and improvement, respectively of the clinical picture as a whole. Finally, (4) The therapeutic evaluation was assessed using the Dosage Record and Treatment Emergent Symptom Scale (DOTES) [23,24], recording concomitant treatments and the presence of side effects due to the ongoing treatment. Statistical analysis was performed using SPSS version 21 (USA). Qualitative and quantitative analysis of response were conducted. Considering a clinical response to treatment of anxious symptoms a decrease by half of the HAM-A and/or ISI score at T1

and patients who reported marked improvement to CGI. Response rate was compared according to the diagnosis and in patients who took *Passiflora Incarnata* L. Herba dry extract as monotherapy versus add on treatment. Parametric variables were described as mean and Standard Deviation (SD) and were compared by paired t-test or independent t-test. Categorical variables were compared by  $\chi^2$  test. Statistical significance was assigned for  $p < 0.05$ .

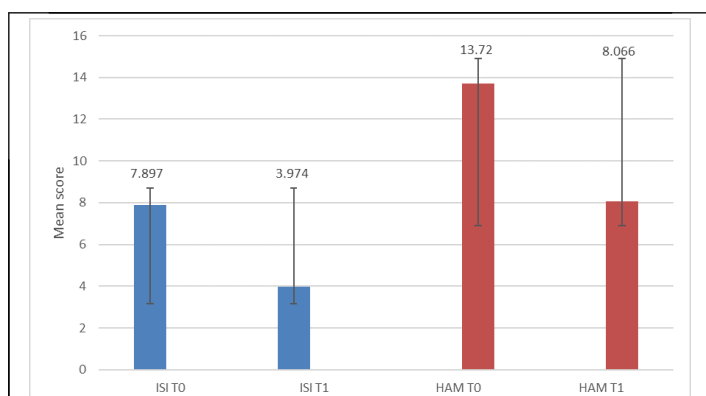
## Results

Of the 76 patients enrolled (53 females, 68,4%) 80% met criteria for anxiety spectrum disorders (patients with anxious symptoms not meeting all the criteria necessary for diagnosis of anxiety disorders according to DSM-IV TR), 11,8% had panic disorder and 9,2% Eating Disorder (Table 1). After 6 weeks of treatment with *Passiflora Incarnata* L. Herba dry extract as monotherapy or in add on to an antidepressant or associated to a cognitive behavioral psychotherapy the second evaluation showed that 60% of patients are minimally improved at the CGI scale, 24% much or very much improved while 16% had no change. The comparison of HAM-A score (T1 versus T0) documented a statistically significant reduction of the mean scores ( $13.72 \pm 4.02$  vs.  $8.07 \pm 4.66$ ,  $p < 0.0001$ ). Moreover, we observed a significant reduction of the mean scores comparing T1 vs. T0 at ISI scale ( $7.99 \pm 4.30$  vs.  $3.97 \pm 3.68$ ,  $p < 0.0001$ ) (Figure 1). Considering a clinical response to treatment of anxious symptoms a decrease by half of the HAM-A and ISI score at T1, we documented a clinical response respectively in the 54% for anxious symptoms and in 58% for sleeping disorder. When comparing the response to the new drug containing *Passiflora Incarnata* L. Herba as active principle in the three subgroups of treatment, just *Passiflora*, antidepressant +*Passiflora* and psychotherapy+*Passiflora* we didn't find any statistical significance difference. However, patients with the association passionflower and antidepressant seemed to have a better score's reduction than other subgroups. Patients who took two TRACTANA® tablets compared to those who took one showed a better response to the insomnia scale (70% versus 46%) without reaching statistical significance. There were no differences in clinical response based on gender, age, occupation and diagnosis. The analysis of the collected reports dots scores revealed that the drug was not associated with any side effects.

**Table 1:** Clinical and demographic features of the study sample.

Variables	Overall sample 76	%
Age group	18-30 yrs	29
	31-45 yrs	46
	46-60 yrs	18,4
	>60 yrs	6,6
Gender	Females	68,4

Occupation	Student	21
	Employed	67
	Unemployed	9
	Retired	3
Diagnosis	Anxious Syndrome	80
	Panic Disorder	11,8
	Eating Disorder	9,2
Treatment	Passiflora	24
	Passiflora +Antidepressant	30
	Passiflora +Psychotherapy	46
Dosages	200 mg by day	66
	400 mg by day	34



**Figure 1:** Rating scale mean scores course at T0 and T1. **Note:** (■): Insomnia scale at T0 and T1; (■): Hamilton scale at T0 and T1, Rating scales comparison with statistically significance  $p < 0.0001$ .

## Discussion

Anxious symptoms and sleep disturbances are very common in general population and their persistence over time is associated with a worsening of symptoms with a tendency to chronicity configuring anxiety disorders above threshold. Consequences are social and professional impairment conditioning quality of life and a higher risk to envelope substance addictions in particular alcohol and benzodiazepines. For the treatment of anxiety spectrum disorder are indicated in general practice: Psychotherapy, antidepressants and benzodiazepine only for short term use. Cognitive behavioral psychotherapy is the most common used to control anxious symptoms including sleep disturbances but have some limitations in terms of costs, duration and difficulties to establish and to maintain a continuative therapeutic alliance with the psychotherapist [25,26].

In terms of efficacy, SSRI (Selective Serotonin Reuptake Inhibitors) antidepressant, SNRI (Serotonin and Norepinephrine Reuptake Inhibitors) antidepressant (venlafaxine), TCA (Tricyclic Antidepressants) antidepressant and Benzodiazepines may be effective with little difference between classes. Among the SSRIs paroxetine and fluoxetine seem to have stronger evidence of efficacy than sertraline [27,28]. Even if there is a good tolerability, sexual dysfunction and weight gain are the most common side effects of SSRI and SNRI antidepressants and the most cause of poor adherence treatment. Benzodiazepines are also widely used in patients with anxiety symptoms but should be taken for short periods due to tolerance and addiction [29]. However, their easy availability make these compounds widely consumed but are poorly effective in the long term compromising cognitive ability. Treatment choices should always balance therapeutic effects with side effects and behavioral consequences. Natural compounds are always well tolerated and can be used in addition to traditional treatments in mental disorders for example when tapering benzodiazepines to promote the result [30]. *Passiflora incarnata* L. Herba has an anxiolytic and hypnotic effect that can help all that cases of mild anxiety. In our sample of 76 patients with anxiety spectrum disorder treated with a new drug containing a dry extract of *Passiflora incarnata* L. Herba as stated by EMA (European Medicines Agency's) monography, 200-400 mg daily (1-2 tablets) for 6 weeks, 84% improve their symptoms from "minimally improved" to "very much improved". This is documented by the reduction of mean HAM-A and ISI score from T0 to T1 with statistical significance. Moreover, hypnotic action was providing with success in 58% of patients, especially who took 400 mg daily (two tablets). Advantages using TRACTANA® are: Absence of side effects, providing in special population (adolescents, elderly, pregnancy, oncologic patients) easy to combine with antidepressants and benzodiazepines, limitation of benzodiazepines use, good patient acceptance. Even if *Passiflora Incarnata* L. Herba has a GABAergic activity, it doesn't induce any tolerance and dependence effects because of the different mechanism of action when confronted with BDZs (pre-synaptic GABA reuptake inhibition). Furthermore, from this study it emerged a double effect, anxiolytic and pro-hypnotic, attributed to the active principle of *Passiflora Incarnata* L. Herba that misses to antidepressants and that benzodiazepines tend to lose overtime. The availability of a new drug containing as active principle a dry extract of *Passiflora Incarnata* L. Herba could be a valid option in the treatment of anxiety spectrum disorders in monotherapy or in add-on to serotonergic antidepressants. In the interpretation of the presented results the following methodological limitations need to be taken into account. The study was not conceived as a controlled randomized study and it was specifically focused on the short-term treatment. In addition, the studied population was not homogenous in terms of diagnosis, severity and concomitant treatment, being composed by diagnostic subgroups or category that in some cases were too small in order to detect a statistically significant difference. Nonetheless, we believe that the present uncontrolled report may help in designed future controlled investigation of the anxiolytic and pro-hypnotic effects of *Passiflora incarnata* L. Herba in patients with anxiety disorders [31].

## Conclusion

The present open-label study found a significant short-term anxiolytic and pro-hypnotic effect of a new drug containing as active principle a dry extract of *Passiflora incarnata* L. Herba 200-400 mg daily in patients with anxiety spectrum disorders. According to the last review including nine clinical trials on *Passiflora* and anxiety disorder authors evidence the anxiolytic effect in terms of rating scale score reduction. Also sleep disturbances can benefit from this natural compound especially at dosage of 400 mg (2 tablets) daily. The absence of side effects of *Passiflora* can improve the compliance to treatment enhancing quality of life. Future double-blind, randomized controlled studies are needed to evaluate the efficacy and safety of *Passiflora incarnata* treatment in the long-term.

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## Conflicts of Interest

The authors report no conflicts of interest in relation to the content of the present study.

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