RESEARCH ARTICLE

Efficacy of a nutraceutical based on *Withania somnifera*, *Crataegus monogyna*, magnesium and vitamin B6 in the treatment of patients with stress, anxiety, and sleep disorders: A multicentre study

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ABSTRACT

Stress is the body's physiological response to mental or physical threats. It is often accompanied by anxiety, defined as an unpleasant emotion triggered by anticipation of future events and memories of past events. Exposure to stress and anxiety can cause psychological distress and impaired sleep quality. Stress and anxiety are characterised by a condition of sympathetic hypertonia that can alter blood pressure. The combination of these factors impairs quality of life and performance in daily life. This prospective cohort, noncomparative, multicenter clinical study is part of the search for a nutraceutical that can help meet the need to reduce the perception of stress and anxiety, improve psychological well-being and sleep quality, and help regulate blood pressure to mitigate the effect of these prevalent health risks and reduce the use of drugs, the chronic use of which can expose people to additional health risks. 48 physicians distributed throughout Italy included 503 patients (151 men, 352 women) with a mean age of 50.4 years ± 14.3 years in the study. Patients presented to the physician's observation with anxiety, stress, and anxiety-related

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sleep disturbances and scored a mean score on the Perceived Stress Scale (PSS) questionnaire of 24.3 ± 5.1 and a mean score on the World Health Organisation 5-question Well-Being Questionnaire (WHO-5) of 8.0 ± 3.2. The enrolled patients were evaluated at the time of enrolment (T_0) and 45 days after enrolment (T_1). From the day of enrolment and for 45 days after that, they took one tablet of a nutraceutical containing *Withania somnifera*, *Crataegus monogyna*, magnesium and vitamin B6 in the morning and one in the evening, half an hour before bedtime. At enrolment (T_0), patients completed WHO-5, PSS and a Sleep Quality rating Scale (SQS), while the investigating physicians, together with the patients, completed the Hamilton Anxiety Rating Scale and blood pressure measurements. At T_1, the questionnaires and SQS were repeated, blood pressure was measured, and the patients rated their satisfaction with the therapy. The scores on all questionnaires and the SQS improved significantly at T_1 compared to T_0, and there was also a significant adjustment in blood pressure with higher values being lowered and lower values being raised.

The results of the study show that the tested nutraceutical, taken in the amount of one tablet twice a day, reduces the perception of stress and anxiety, improves sleep quality and psychological well-being and helps regulate blood pressure in stressed and anxious subjects. Finally, the product has been confirmed as safe and appreciated: only one patient discontinued treatment because of the nausea sensation he attributed to taking the product.

Key Words: *Stress; Anxiety; Sleep quality; Blood pressure; Nutraceutical, Withania somnifera; Crataegus monogyna; Magnesium; Vitamin B6*

INTRODUCTION

Any intrinsic or extrinsic stimuli that is interpreted by the body as a physical or mental threat is termed stress and evoke a peculiar compensatory biological response that is known as the stress response. Depending on the type, timing, and severity of the stressful stimulus, stress responses can be a beneficial physiological mechanism for coping with everyday threats or exert various actions on the body ranging from altering homeostasis to compromising survival. Chronic or recurrent stress can cause a decline in general health and complication of existing diseases and is often accompanied by anxiety [1]. The latter is defined as an unpleasant emotion that is triggered by anticipation of future events and memories of past events and manifests itself in different forms, such as panic disorder, phobic anxiety, generalised anxiety, anxiety reactions, and chronic anxiety [2,3]. In Italy, the lifetime prevalence of anxiety varies between 9.3 and 13% [4]. Frequent exposure to stress and anxiety can cause pathophysiological changes in the central nervous system that can lead to mood, behavioural and cognitive disorders [1]. Anxiety and stress often cause sleep disorders that include difficulty falling asleep or staying asleep and nonrestorative sleep. This worsens performance in daily life and negatively affects mood [5]. In developed countries, insomnia rates are estimated at between 13% and 33% [6-8]. To facilitate sleep and improve sleep quality, people occasionally use drugs, herbal products, or food supplements [9-11]. If chronic insomnia sets in, the situation worsens, and maladaptive behaviour may develop, requiring a more radical therapeutic approach [9]. Anxiety, stress, mood, and sleep disorders can adversely affect cardiovascular function. A growing body of evidence suggests that anxiety is an independent predictor of cardiovascular events [12]. Chronic psychosocial stress leads to increased blood pressure and an increased risk of developing hypertension [13,14]. Psychological corollaries of stress, including anxiety, depression, and anger, are considered predictors of hypertension [15].

Studies and systematic reviews have shown that clinically significant anxiety, depression, and stress symptoms are often associated with hypertension, and anxiety-depressive disorders are the most common psychiatric conditions in people with hypertension [16-19]. In a population study conducted in Germany to assess the relationship between chronic anxiety, cardiovascular risk, and mortality, the authors suggest that subclinical levels of anxiety should also be considered as a cardiovascular risk factor [20]. Other studies show that sleep restriction is associated with higher blood pressure and attaches increasing importance to identifying and treating sleep disorders for the prevention and management of hypertension [21]. A recent clinical study shows promising results with the use of a nutraceutical based on *Withania somnifera*, *Crataegus monogyna*, magnesium, and vitamin B6 in reducing perceived anxiety and stress, improving mood and sleep quality [22]. Evidence suggests that therapeutic approaches to reduce stress, anxiety, and related disorders may contribute to blood pressure control. Based on these premises, the present clinical study, thanks to the enrolment of a large sample of patients throughout Italy, is aimed at further verifying the efficacy of the nutraceutical based on *W. somnifera*, *C. monogyna*, magnesium and vitamin B6 in the management of anxiety, in the modulation of the stress response, in the increase the psychological well-being and the quality of sleep, and it is also finalised to carry out a first verification of the effectiveness of the same nutraceutical in the modulation of the alterations of the blood pressure linked to anxiety and stress. The aim is to mitigate the effect of these prevailing health risks and to reduce the use of drugs, the chronic use of which can expose people to limitations in their daily lives and further health risks.

PURPOSE OF THE STUDY

The study aims to test the efficacy of a nutraceutical based on *W. somnifera*, *C. monogyna*, magnesium and vitamin B6, taken for 45 consecutive days by patients suffering from anxiety and stress to reduce anxiety and perceived stress, improve sleep quality and psycho-

-ological well-being and regulate blood pressure. Further study objectives are to evaluate the patient acceptance of the therapy and confirm the nutraceutical's safety.

MATERIALS AND METHODS

Nutraceutical tested

Dianazen® (Dnz-Pharma Line S.r.l. Milan, on the market from March 2021) is a nutraceutical in tablet form based on an extract of *W. somnifera*, extract of *C. monogyna*, magnesium, and vitamin B6. The composition of the product is shown in Table 1.

TABLE 1
Qualitative and quantitative composition of Dnz

Component	Content in 2 tablets	%VNR
Withania somnifera e.s.	400 mg	
of which withanolide glycosides	40 mg	
Crataegus monogyna e.s.	350 mg	
of which vitexin-2-O-rhamonside	10.5 mg	
Magnesium oxide	95 mg	
of which magnesium	57 mg	15
Vitamin B6	8.4 mg	600

Patients

Enrolled patients had to be male or female and aged between 18 years and 75 years. The upper age limit was imposed to prevent the age-related decline in cognitive function from affecting the assessment of therapy outcomes. To be enrolled, subjects had to present themselves to the doctor's observation with signs and symptoms characteristic of anxious patients, score less than 15 on the World Health Organisation-5 (WHO-5) questionnaire, and score at least 14 on the Perceived Stress Scale (PSS) questionnaire [23,24]. Excluded were subjects with clinically significant endocrine, metabolic, renal, hepatic, cardiovascular, gastrointestinal, respiratory, haematological, neurological, or psychiatric disorders that could interfere with the study, restless leg syndrome or sleep apnoea, those receiving continuous psychotropic medication in the last 4 weeks before inclusion in the study or those with alcohol or drug abuse. Pregnant or lactating women were also excluded.

Study design

This is a prospective cohort, noncomparative, multicenter trial. The doctors collected clinical data as part of their daily clinical practice. From the day of the enrolment and for 45 consecutive days the, enrolled subjects took one Dnz tablet in the morning and one in the evening, half an hour before going to bed.

The subjects were examined and completed questionnaires at the time of enrolment (T_0) and after 45 days of therapy (T_1). The study duration of 45 days was chosen because Dnz was shown to have measurable, statistically significant effects against anxiety, stress, and sleep disorders after 35 days of therapy in a previous clinical study.

Assessment

At the time of enrolment, the subjects underwent a thorough medical history and objective examination, investigation of work activity, lifestyle, family history of psychiatric disorders, and current treatment. The data collected were recorded on an appropriate form, in which each patient was identified by employing an alphanumeric code. At T_0 and T_1, the enrolled patients completed the WHO-5 questionnaire, the PSS questionnaire, and the Sleep Quality Rating Scale (SQS). In addition, the physician completed the patient data collection form, and the HAM-A questionnaire and measured the patient's blood pressure [25]. The pressure evaluation was carried out by repeating two measurements a few minutes apart and averaging the values collected. At T_1, the enrolled patients also completed a questionnaire to express their satisfaction with the therapy.

Description of questionnaires and rating scales

WHO-5

It provides a measure of psychological well-being and consists of 5 items referring to positive mood (good mood, relaxation), vitality (feeling active, awake, and rested), and general interests (being interested in new things) over the last two weeks. A rating must be given for each item by choosing from six options, along a scale ranging from 0 (never) to 5 (always). The total score is calculated by adding up the numbers of the five answers and ranges from 0 to 25: 0 represents the worst possible quality of life concerning the psychological state, and 25 represents the best possible quality of life. If the total score is less than 15, the subject perceives a state of low psychological well-being. If the score is less than 13 or if the patient has answered 0 or 1 to one of the five questions, an in-depth depression test is indicated.

PSS

It is commonly used to assess subjective perceptions of everyday situations and reactions in response to events perceived as destabilising and risky. It consists of 10 questions concerning feelings and thoughts during the last month. A rating must be given for each item from a choice of five options, along a scale of 0 to 4 depending on the severity. The total score is calculated by adding up the numbers of the ten answers and ranges from 0 to 40: the higher score indicates a higher level of perceived stress. A score between 0 and 13 indicates a low level of stress; between 14 and 26 indicates moderate stress; between 27 and 40 indicates a high level of stress.

HAM-A

It is an instrument developed to measure the severity of anxiety symptoms and consists of 14 items, each of which is defined by a set of symptoms of psychic anxiety (mental agitation and psychological stress) and somatic anxiety (anxiety-related physical complaints).

A rating should be given for each item on a scale of 0 (not present) to 4 (very serious). The total score is calculated by adding up the values attributed to the 14 items and ranges from 0 to 56: a score of 17 or less indicates mild anxiety, 18 to 24 indicates mild to moderate anxiety, 25 to 30 indicates moderate to severe anxiety, and more than 30 indicates severe anxiety.

SQS

A seven-point scale was used in a previous clinical study to assess sleep quality [26]. Subjects rated the overall quality of sleep in the last two weeks using a score as follows: 0 (very bad), 1 (very poor), 2 (poor), 3 (sufficient), 4 (good), 5 (very good), 6 (excellent).

Assessment of patient satisfaction with therapy

Satisfaction with the therapy was assessed by having each patient fill in a specially designed Likert scale at the end of the 45-day treatment period, with a given score for each rating: 0=very dissatisfied, 1=fairly dissatisfied, 2=neither satisfied nor dissatisfied, 3=fairly satisfied, 4= very satisfied.

Statistical analysis

Descriptive statistics were used to summarise the characteristics of the cohorts in terms of median, $25^{th,}$ and 75^{th} percentiles, mean and standard deviation or frequencies when appropriate. The effect of Dnz treatment was estimated in terms of change in outcomes. The significance of differences was determined by applying the non-parametric Mann-Whitney test for paired data when comparing T_1 and T_0 data from the same group of patients or for unpaired data when comparing different groups. The results are considered statistically significant in all analyses at $p<0.05$. The Tukey representation was adopted for the graphs. Data analysis was conducted using the Graph Pad Prism 8.0.2 programme (GraphPad Software, Inc.).

RESULTS

Patient characteristics

The period of patient enrolment and treatment was extended from June 2021 to January 2022. Patients were enrolled with personal identification data and signed regular informed consent to both the proposed therapy and the processing of personal data. 574 patients were enrolled but, after excluding 71 patients due to non-compliance with the inclusion and exclusion criteria or incomplete data, 503 patients were included in the study. Table 2 contains the demographic and anamnestic data of the patients included in the study. In contrast, Table 3 shows the most recurrent categories of drugs taken chronically by the patients included in the clinical study at the time of enrolment. The time interval between the first visit (T_0 and the second visit (T_1 averaged 47.5 days ± 5.7 days. One patient did not complete the course of taking the product because of a feeling of nausea that he related to taking the product. Analyses were then conducted using data from the remaining 502 patients.

TABLE 2
Demographic and anamnestic data of the patients involved in the study. Data are expressed as mean ± SD unless otherwise stated

Age in years	50.4±14.3
Sex, % F (n)	69.9%(352)
Height (cm)	167±8.51
Weight (kg)	69.5±13.9
BMI	24.9±4.35
Smoking (n=471), % yes (n)	21.2%(100)
Ex-smokers (n=471), % yes (n)	16.3%(77)
Lifestyle (0 = very sedentary to 4 = very active)	1.76±1.01
Family history of psychiatric disorders, % yes (n)	6.1%(31)
Diagnosis of hypertension, % yes (n)	21.1%(106)
Chronic or recurrent intake of medication, % yes (n)	38.5%(194)
Taking medication that affects blood pressure, % yes (n)	22.6%(114)

TABLE 3
The most common drugs taken chronically by patients only included in the clinical trial

Drug category	Number of patients
ACE inhibitor	35
Statin	34
Proton pump inhibitor	28
Sartan	25
Levothyroxine	25
Beta-blocker	20 17
Metformin	15
Vitamin D	13
Diuretic	13
Calcium antagonist	1
Other antihypertensive	1
Low-dose acetylsalicylic acid	10

Clinical results

The results of the assessments of perceived stress, anxiety, psychological well-being, and sleep quality are summarised in (Table 4). The PSS questionnaire score improved statistically significantly at T_1 compared to T_0 (Table 4, Figure 1A). At T_0, the questionnaire score of 100% of the subjects is equal to or greater than 14, indicating that the study population is under moderate to high-stress conditions. To confirm this, at T_0, the median is 24.0, and the mean is 24.3 ± 5.1. At T_1, the median falls to 15.0, and the mean falls to 14.3 ± 6.2. At T_1, 42.7% of the treated patients showed a low or no stress level detectable by the PSS test.

The HAM-A questionnaire score improved significantly at T_1 compared to T_0 (Table 4, Figure 1B). The median score at T_0 is 26.0, while the mean is 25.8 ± 8.3. This corresponds to 83.6% of patients suffering from moderate to severe anxiety. At T_1, the median falls to 14.0 and the mean to 14.3 ± 7.9. At T_1, the questionnaire score of 65.5% of the patients was less than or equal to 17, indicating that this percentage of the study population, at the end of 45 days of treatment, was either suffering from mild anxiety or no longer suffering from anxiety detectable by the HAM-A test.

TABLE 4

Medians, 25th and 75th percentiles and average ± SD of the HAM-A, PSS, WHO-5 and SQS questionnaire scores before the start of intake (T_0) and after 45 days of Dnz intake (T_1) and statistical significance of comparisons

Questionnaire or parameter	Number of patients	T_0 Median (25°; 75°) Average ± SD	T_1 Median (25°; 75°) Average ± SD	$T_1 - T_0$ Median (25°; 75°) Average ± SD	P-value
PSS	489	24.0 (21.0; 28.0) 24.3 ± 5.1	15.0 (10.0; 19.0) 14.3 ± 6.2	-9.0 (-14.0; 0) -10. ± 6.1	< 0.0001
HAM-A	501	26.0 (19.0; 31.0) 25.8 ± 8.3	14.0 (8.0; 20.0) 14.3 ± 7.9	-11.0 (-15.0; -7.0) -11.5 ± 6.9 5.0 (3.0;	< 0.0001
WHO-5	472	8.0 (6.0; 10.0) 8.0 ± 3.2	14.0 (12.0; 17.0) 14.0 ± 3.9	8.0) 6.0 ± 4.1	< 0.0001
SQS	496	2.0 (2.0; 3.0) 2.1 0. ± 9	4.0 (3.0; 4.0) 3.7 1. ± 0	2.0 (1.0; 2.0) 1.6 1. ± 0	< 0.0001

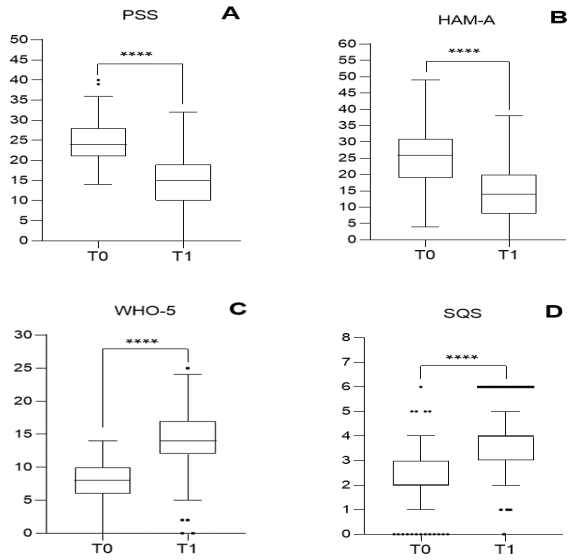

Figure 1 *Dnz administration significantly improves patient's quality of life. (A)Treatment with Dnz for 45 days (T_1) results in a significant reduction in PSS (B) HAM-A scores (C) a significant increase in WHO-5 (C) SQS (D) scores (****p<0.0001.(Tukey's representation was adopted for the graphs)*

The WHO-5 questionnaire score improved statistically significantly at T_1 compared to T_0 (Table 4, Figure 1C). At T_0, the questionnaire score of 100% of the patients is less than 15, confirming that the study population does not enjoy a state of psychological well-being. In fact, at T_0, the median is 8.0, and the mean is 8.0 ± 3.2. At T_1, the median increased to 14 and the mean to 14.0 ± 3.9, attesting to improved patients' psychological well-being. In particular, at T_1, 48.9% of the patients scored 15 or higher, the threshold value above which the patient is considered to be psychologically well.

The SQS score significantly increased after 45 days of treatment (Table 4, Figure 1D) At T_0, the median is 2.0, and the mean is 2.1 ± 0.9, confirming that the enrolled patients had, on average, poor quality of sleep. At T_1, the median increased to 4.0 and the mean to 3.7 ± 1.0, indicating a clear improvement in sleep quality. In particular, at T_1, 91.5% of the patients scored 3 or higher, i.e. they achieved sleep quality between sufficient and excellent.

Considering the whole sample of patients, both systolic and diastolic blood pressure decreased from T_0 to T_1 statistically (Tables 5 and 6). At T_0, the median systolic pressure is 125.0 mmHg while the mean is 124.4 mmHg ± 12.8 mmHg (Table 5). At T_1, the median falls to 120.0 mmHg, while the mean falls to 121.0 ± 10.9 mmHg. At T_0, the median diastolic pressure is 80.0 mmHg, while the mean is 77.9 ± 7.9 mmHg (Table 6). At T_1, the median falls to 77.5 mmHg, while the mean falls to 76.4 mmHg ± 6.8 mmHg.

It is extremely interesting what emerges from the analysis of the subgroups (Tables 5 and 6). Blood pressure is significantly reduced in patients diagnosed with hypertension and in patients who have not been diagnosed with hypertension. Still, in the former, the extent of the reduction is greater. Patients with systolic blood pressure value greater than or equal to 120 mmHg and diastolic blood pressure values greater than or equal to 80 mmHg at T_0 show a significant reduction in blood pressure after 45 days of Dnz. Patients with

systolic blood pressure values below 120 mmHg at T0 and diastolic blood pressure values between 70 mmHg and 79 mmHg were unchanged after 45 days of Dnz. Patients with diastolic blood pressure values of less than 70 mmHg at T0 experience a significant increase in blood pressure values after 45 days of Dnz.

TABLE 5

Medians, 25th and 75th percentiles and average ± SD of systolic blood pressure values before initiation of intake (T_0) and after 45 days of Dnz intake (T_1) and statistical significance of comparisons

Systolic blood pressure (n patients)	T_0 Median (25°; 75°) Average ± SD	T_1 Median (25°; 75°) Average ± SD	$T_1 - T_0$ Median (25°; 75°) Average ± SD	P-value
All patients (495)	125.0 (116.5; 132.5)	120.0 (115.0; 129.5)	-2.5 (-7.5; 0.0)	<0.0001
	124.4 ± 12.8	121.0 ± 10.9	-3.4 ± 7.3	
Diagnosis of hypertension (106)	132.5 (125.0; 140.0)	129.3 (122.5; 133.1)	-5.0 (-7.9; 0.0)	<0.0001
	133.1 ± 10.8	128.6 ± 8.3	-4.5 ± 7.2	
No diagnosis of hypertension (389)	121.5 (113.5; 130.0)	120.0 (110.0; 125.0)	-2.5 (-7.5; 0.0)	<0.0001
	122.1 ± 12.3	118.9 ± 10.7	-3.2 ± 7.3	
≥ 140 mmHg (58)	142.5 (140.0; 147.9)	135.0 (130.0; 140.0)	-10.0 (-15.3; -5.0)	<0.0001
	145.1 ± 6.5	134.8 ± 7.9	-10.3 ± 7.4	
≥ 140 mmHg - untreated pharmacol. (29)	141.0 (140.0; 146.5)	130.0 (127.5; 137.5)	-12.5 (-16.3; -7.5)	<0.0001
	143.6 ± 4.6	132.3 ± 7.1	-11.3 ± 6.7	
From 130 to 139 mmHg (144)	132.5 (130.0; 135.0)	127.8 (122.6; 130.0)	-5.00 (-9.9; -2.5)	<0.0001
	132.9 ± 2.9	127.4 ± 6.1	-5.5 ± 6.0	
From 120 to 129 mmHg (155)	122.5 (120.0; 125.0)	120.0 (119.0; 122.5)	-2.5 (-5.0; 0.0)	<0.0001
	122.7 ± 2.7	120.2 ± 6.6	-2.5 ± 6.6	
< 120 mmHg (138)	110.0 (105.0; 115.0)	110.0 (105.0; 115.0)	0.0 (-3.0; 2.5)	0.7963
	108.9 ± 7.2	109.3 ± 7.8	0.4 ± 6.3	

HAM-A, PSS, WHO-5, and SQS scores and blood pressure values are not affected by patient gender. HAM-A, WHO-5, and SQS scores and blood pressure values were not affected by the age of the patients, whereas the PSS questionnaire score was affected by the age of the patients. In fact, the PSS questionnaire scores of the 133 patients aged 18 years - 41 years were reduced significantly more than the scores of the 129 patients aged 61 years-75 years (-11.1 ± 6.4 vs -9.1 ± 5.8 respectively; p=0.0111), although in both groups the PSS questionnaire score was reduced in a statistically significant manner.

Patient satisfaction and adverse effects

After 45 days of therapy (T_1), patients treated with Dnz expressed their satisfaction with the therapy using a specially designed Likert scale (0=very dissatisfied to 4=very satisfied). The average rating was 3.11 ± 0.71 (n=498).

TABLE 6

Medians, 25th and 75th percentiles and average ± SD of diastolic blood pressure values before the start of intake (T_0) and after 45 days of Dnz intake (T_1) and statistical significance of comparisons

Diastolic blood pressure (n patients)	T_0 Median (25°; 75°) Average ± SD	T_1 Median (25°; 75°) Average ± SD	$T_1 - T_0$ Median (25°; 75°) Average ± SD	P-value
All patients (495)	80.0 (72.5; 82.5)	77.5 (70.0; 80.0)	0.0 (-5.0; 0.0)	<0.0001
	77.9 ± 7.9	76.4 ± 6.8	-1.5 ± 5.5	
Diagnosis of hypertension (106)	81.5 (77.9; 87.5)	80.0 (75.0; 82.8)	-2.5 (-5.3; 0.0)	<0.0001
	82.1 ± 6.3	79.2 ± 6.1	-2.9 ± 5.3	
No diagnosis of hypertension (389)	79.5 (70.0; 80.0)	77.5 (70.0; 80.0)	0.0 (-5.0; 0.0)	<0.0001
	76.8 ± 7.9	75.6 ± 6.8	-1.2 ± 5.5	
≥ 90 mmHg (34)	90.0 (90.0; 93.5)	84.0 (80.7; 90.0)	-7.5 (-10.0; -2.5)	<0.0001
	91.7 ± 2.4	84.1 ± 5.5	-7.6 ± 5.6	
≥ 90 mmHg - untreated pharmacol. (20)	90.0 (90.0; 92.8)	82.5 (80.5; 88.3)	-7.8 (-10.8; -2.5)	<0.0001
	91.4 ± 2.1	83.6 ± 5.3	-7.8 ± 5.8	
From 80 mmHg to 89 mmHg (236)	80.0 (80.0; 85.0)	80.0 (77.5; 80.4)	-2.5 (-5.0; 0.0)	<0.0001
	82.3 ± 2.9	79.0 ± 4.7	-3.3 ± 4.2	
From 70 mmHg to 79 mmHg (176)	72.5 (70.0; 76.5)	72.5 (70.0; 77.5)	0.0 (-2.4; 2.5)	0.2085
	73.5 ± 3.2	74.0 ± 5.3	0.5 ± 4.4	
<70 mmHg (49)	62.5 (60.0; 65.8)	67.5 (60.0; 70.0)	2.5 (0.0; 8.8)	0.0003
	62.7 ± 3.9	66.5 ± 7.1	3.8 ± 7.0	

During the period of Dnz intake, 5 patients reported mild drowsiness in the morning after waking up, and 2 of them reduced their daily dose from 2 tablets to 1 tablet. In addition, 3 patients reported mild abdominal tension, 2 reported moderate asthenia, one reported epigastralgia, and one reported mild headache and nocturnal tachycardia. None of these patients stopped taking Dnz. Only one patient complained of nausea after taking the nutraceutical and discontinued therapy after a few days.

DISCUSSION

The study results show a significant reduction in anxiety and perceived stress, a significant improvement in psychological well-being and sleep quality, and blood pressure modulation in patients treated with Dnz for 45 consecutive days. Dnz contains a dry extract of *W. somnifera* which has been shown in animal studies to be effective in reducing anxiety, improving mood, and promoting relaxation and sleep, and it has been suggested that these effects are due to GABA-mimetic action or modulation of the GABA-ergic system and action on adrenergic and serotonergic neurotransmission pathways [27,28].

Other animal studies have shown the extract to have adaptogenic, neuroprotective, and perceived stress-reducing effects, attributed to its ability to reduce cortisol levels and antioxidant action [29]. Clinical studies confirm the efficacy of dry extract of *W. somnifera* in promoting psychological well-being by reducing anxiety and related disorders, reducing perceived stress and serum cortisol levels, improving mood in chronically stressed subjects, and improving cardiovascular function, in particular by reducing blood pressure and heart rate in anxious chronically stressed subjects [26-32] A clinical study demonstrates the efficacy of the extract in improving mood in subjects with psychiatric disorders [32,33]. In addition, clinical studies have been published demonstrating the superiority of the extract in promoting relaxation and sleep over a placebo [34]. Dnz also contains the dry extract of *C. monogyna* titrated to 3% vitexin-2-O-rhamnoside, which, in the European Medicines Agency monograph, is considered a traditional medicine used to relieve cardiac symptoms caused by temporary nervous disorders, such as palpitations due to anxiety. This extract is also traditionally used in nervous disorders such as anxiety, insomnia, and vertigo [35]. Studies *in vivo* and *in vitro* show that extracts of *Crataegus spp.* exert several actions on the cardiovascular system, including hypotensive, anti-inflammatory, and antioxidant action, positive inotropic action, vasodilator, antiarrhythmic and hypolipidemic action. Systematic reviews and meta-analyses of clinical studies have confirmed that treatment with extracts of *Crataegus spp.* induces both subjective and objective improvements in patients with mild forms of heart failure (NYHA I-III), hypertension, and hyperlipidaemia [36]. *C. monogyna* extract has a positive inotropic and negative chronotropic effect and can help reduce heart rate and blood pressure in anxious and stressed individuals. These actions are thought to be attributable to inhibitory activity on 3',5'-AMP cyclic phosphodiesterase [35,37]. In addition to the two plant extracts, Dnz also contains vitamin B6 and magnesium. Scientific evidence shows that inadequate long-term availability of micronutrients involved in numerous physiological and biochemical processes inevitably leads to metabolic dysregulation with consequent clinical manifestations [38]. In patients suffering from anxiety and stress, the requirements for vitamin B6 and magnesium [39-41] tend to increase, and deficiency conditions may occur. This can lead to an impairment of cellular biochemical functions that depend on these nutrients, a reduction in the efficacy of the therapies undertaken, and the onset of progressive disease states. Animal model and clinical studies demonstrate the role played by vitamin B6 and magnesium in improving the body's response to stress, counteracting anxiety, and improving mood and sleep quality [42-49]. Vitamin B6 may bring about these benefits due to its fundamental role in synthesising neurotransmitters, including dopamine, serotonin, glutamate, GABA, and histamine [50,51]. Magnesium is involved in more than 300 metabolic pathways that also affect the functions of the nervous system and the regulation of the sleep-wake cycle [52]. Therefore, the scientific literature provides a wealth of evidence regarding the usefulness of Dnz ingredients in reducing anxiety and stress, improving psychological well-being, sleep quality, and modulating blood pressure. This study aimed to carry out an organic collection of clinical data and a statistical evaluation to check whether taking Dnz for 45 consecutive days was able to bring about significant benefits in patients suffering from stress, anxiety, psychological malaise, sleep disturbances, and altered blood pressure because of sympathetic hypertonia. The results confirm the action of Dnz and help reinforce the hypothesis that its ingredients may have a synergistic action, as could already be assumed based on the scientific evidence available in the literature. The results of the study provide further evidence of the adaptogenic action that the extract of *W. somnifera,* thanks also to the contribution made by the other ingredients in Dnz, can perform. In the 1990s, a group of scientists, consisting of Hildebert Wagner, George Wikman, and Alexander Panossian, conducted studies on adaptogenic substances and proposed the following definition: adaptogens are natural bioregulators that increase the body's ability to adapt to negative environmental factors and avoid the damage they can cause. The advantage offered by adaptogens is that they minimise the body's response to stress, reducing negative reactions during the alarm phase and eliminating, or at least diminishing, the onset of the exhaustion phase, which is part of the so-called general adaptation syndrome [53]. The parameters measured in this study confirm the ability of the combination of substances in the composition of Dnz to improve the body's response to disturbances caused by stress. In fact, after 45 days of taking Dnz, without intervening in the patient's daily habits, activities, and lifestyle, there was a reduction in perceived stress and anxiety, an increase in psychological well-being, and an improvement in sleep quality and regulation of blood pressure. The lack of a control group can be seen as a limitation of this study, but, firstly, such a comparison was not considered necessary as the scientific literature already contains numerous clinical studies in which the therapeutic effects of the plant extracts, magnesium, and vitamin B6 in Dnz proved to be superior to those induced by placebo in the treatment of stress, anxiety, mood, and sleep disorders. Secondly, some physicians conducted the study as part of their usual clinical practice. Therefore, they did not consider it ethically acceptable to draw several patients to receive a placebo.

CONCLUSION

The study results show that, in stressed and anxious patients, Dnz reduces the perception of stress and anxiety and improves sleep quality and psychological well-being. In addition, it reduces blood pressure in individuals with high blood pressure due to the sympathetic hypertonia that characterises stress and anxiety.

The study confirms the efficacy of the extracts of *W. somnifera* and *C. monogyna* that have already emerged in the scientific literature and makes a further contribution to the hypothesis that the ingredients of Dnz exert a synergistic action. Finally, Dnz proved to be safe and appreciated: only one patient stopped treatment because of the feeling of nausea he attributed to taking the product.

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STATEMENT OF ETHICS: This research was conducted in accordance with the ethical principles originating in the Declaration of Helsinki, and written informed consent was obtained from all subjects. The tested product is a dietary supplement, had already been approved by the Italian Ministry of Health and was already on the market.

CONFLICT OF INTEREST: The investigating physicians, who collected the data presented in the study, declare that they have no business or other relationships that could pose a conflict of interest concerning the article presented. Stefano Agostini, who carried out the statistical processing and wrote the article, is an employee of Pharma Line.

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