Evidence for Self-Medication
International Review Journal

Stress symptoms: Evidence supporting a phytopharmaceutical product with new marketing authorisation in Germany

Christiane Kolb, PhD and Heba Aziz-Kalbhenn, PhD

Phytotherapeutics are used in many countries to treat stress symptoms such as mild sleep disorders, anxiety, increased irritability, tension and nervous restlessness. An established combination preparation is now also available in Germany. Two studies prove the benefit, both with real-life data and in a controlled volunteer study.

In 2021, the phytopharmaceutical Calmalaif® received marketing authorisation in Germany with a composition that was not previously represented on the German market. The preparation contains a combination of the dry extracts of various medicinal drugs: valerian root, passion flower herb, hawthorn leaves with flowers, and black nettle herb[1]. This combination is recommended to improve well-being during nervous stress and to promote sleep. The current marketing authorisation is a good reason to summarise the state of knowledge here.

Real-life data: Mild sleep disturbances and mild anxiety are common

In an open, multicentre, prospective observational study, the effects of the four-drug combination, which has been available in France for more than 30 years, were evaluated.

More than 210 general practitioners from different regions of France were initially asked about their experience treating patients with mild sleep disorders and/or mild anxiety in their daily practice [1]. The investigators reported that 19.1 (± 14.6) patients per week visited their practices for mild anxiety and/or mild sleep disorders, with 73.3% of them estimating that this number was tending to increase. 82.9% of the physicians commented that phytotherapy could be a first-line treatment before switching to psychotropic drugs if necessary. The reasons given for this were the very good tolerability (89.3%) and the fact that it did not become addictive (89.3%).

Significant benefit under real-life conditions

The above-mentioned prospective study included 888 patients (mean age 42 ± 15 years), mostly female (69.9%), who had been suffering from psychological problems for a long time (14 months on average), including anxiety (58.9%), nervousness (53%) or irritability (40%). In addition, there were several accompanying somatic symptoms such as palpitations, the feeling of a lump in the throat, tightness in the chest or abdominal cramps, which can be attributed to these psychological problems.

The study participants took the above-mentioned combination of four plant-based drugs for 15 days. The dosage was according to the manufacturer's instructions and ranged from one to two tablets in the evening to one to two tablets three times a day, depending on the symptoms [2, 3].

At the end of the 15-day treatment, a significant decrease in the frequency of both psychological and somatic symptoms that had led to medical consultation was observed (**Figs. 1** and **2**).

The PSM-9 (Psychological Stress Measure) was used to assess the stress level, in which the investigators each rated nine

[1]Medically active ingredients: Dry extracts of valerian root (29 mg, 3–6 : 1, extraction agent 60% ethanol), passion flower herb (13 mg, 4–7 : 1, extraction agent 60% ethanol), hawthorn leaves with flowers (5.4 mg, 4-7 : 1, extraction agent water), black nettle herb (4.5 mg, 4–6 : 1, extraction agent water).

The study product was the product Euphytose®, which is licensed in France: dry extracts of valerian root (50 mg, extractant 60% ethanol), passion flower herb (40 mg, extractant 60% ethanol), hawthorn leaves with flowers (10 mg, extractant water), black nettle herb (10 mg, extractant water) [2].

Differences in the quantities stated between the two products are due to declaration requirements: In the previous authorisation of Euphytose® in France, the extract preparation including primary excipients was stated, whereas the quantities in Calmalaif® include the proportion of native extract alone [3]

Evid Self Med 2022;2:220039 | https://doi.org/10.52778/efsm.22.0039
Affiliation/Correspondence: Christiane Kolb, PhD, Steigerwald Arzneimittelwerk GmbH, R&D Phytomedicines Development Center, Bayer Consumer Health, Darmstadt; Heba Aziz-Kalbhenn, PhD, Steigerwald Arzneimittelwerk GmbH, R&D Phytomedicines Development Center, Bayer Consumer Health, Havelstr. 5, 64295 Darmstadt (heba.aziz-kalbhenn@bayer.com)

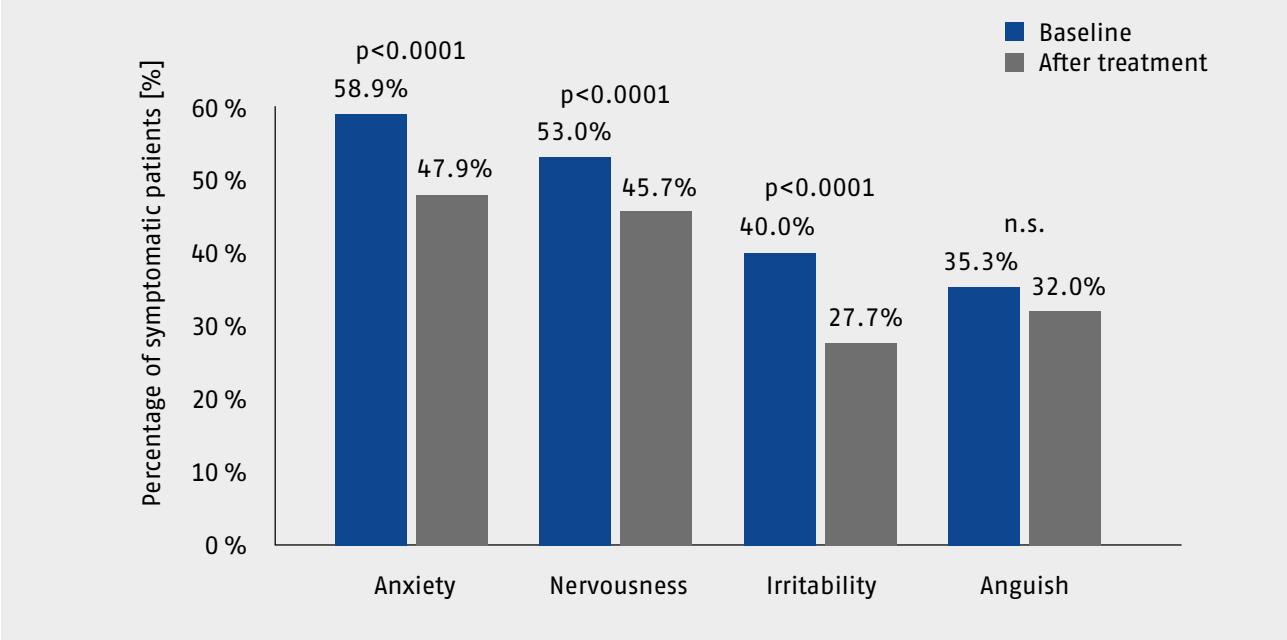

Fig. 1. Changes in psychological symptoms

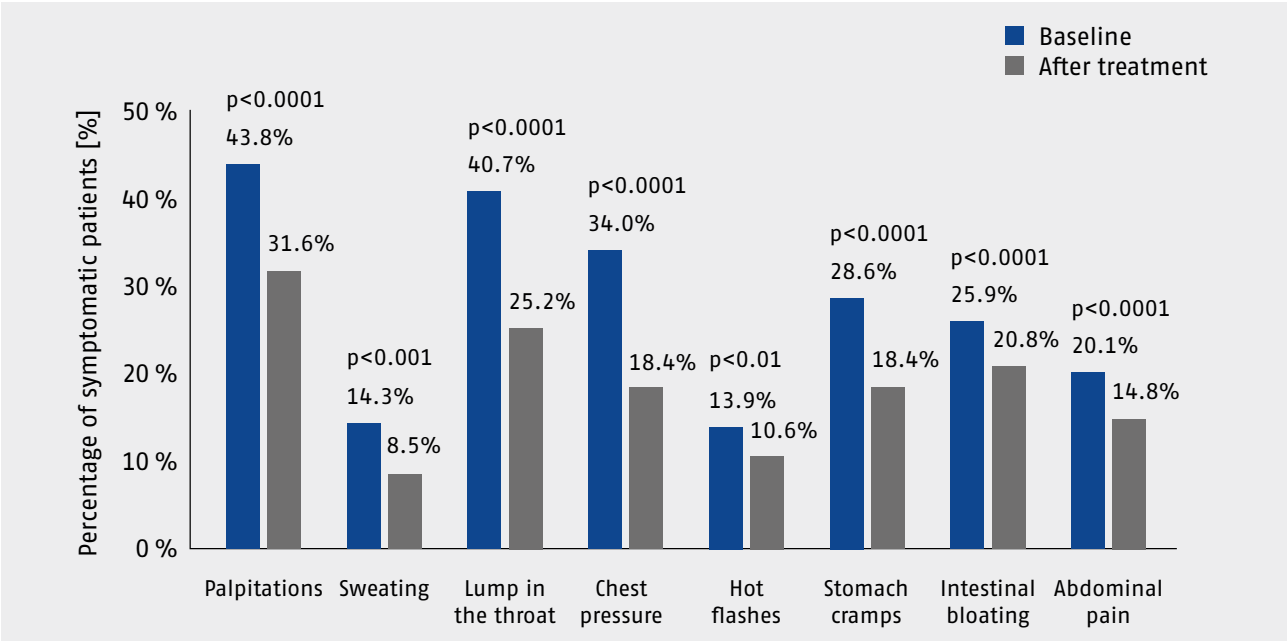

Fig. 2. Changes in somatic symptoms

symptoms of their patients on an eight-point scale [4]. The mean stress level at the time of inclusion was 50 ± 9 on the PSM-9 scale and 84.8% of patients had an elevated stress level defined according to the scale, with a score of ≥40. The mean PSM-9 score was 39 ± 11 after the 15-day treatment, resulting in a significant mean reduction of about 20% ($p < 0.0001$). The percentage of patients with an increased stress level (PSM-9 score >40) decreased to 44.4% compared to 84.8% before treatment ($p < 0.0001$) (**Fig. 3**).

Sleep disturbances were assessed with the Athens Insomnia Scale (AIS), a scale validated in several languages that assesses eight sleep factors on a four-point scale [5]. A score above 6 can be used to diagnose insomnia. The average AIS score of the study participants was 12.0 ± 4.7. 88.2% of the participants had a score of more than 6, and thus demonstrably a sleep disorder.

After 15 days of treatment, the mean AIS score was 7.7 ± 5.0, resulting in an improvement in sleep of 34.7% ($p < 0.001$). The proportion of patients with confirmed sleep disturbances (AIS score >6) decreased from 88.2% before treatment to 55.6% ($p < 0.05$) (**Fig. 3**).

The assessment of the changes after 15 days of taking the study medication in the nine individual symptoms of the PSM-9

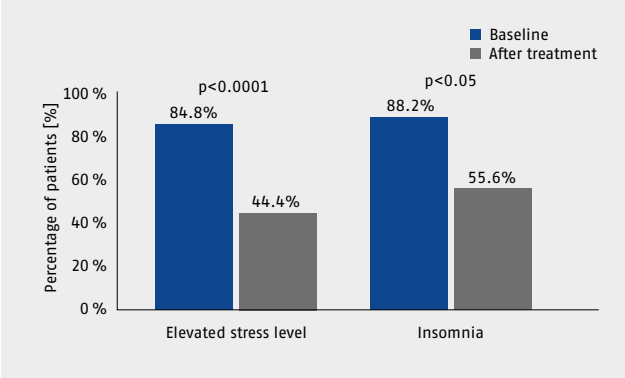

Fig. 3. Change in the percentage of patients with increased stress levels (PSM-9 >40) or confirmed sleep disorders (AIS >6)

showed a comparable improvement in all nine axes (**Fig. 4**).

These clinical improvements were also reflected in the patients' quality of life. The effects on daily life were determined with a visual analogue scale (VAS) (0 = no effect; 100 = intensive effect) (**Fig. 5**).

Placebo-controlled volunteer study: Proven benefit also under defined psychological and physiological stress situations

Complementing the non-interventional observational study, a randomised, placebo-controlled, double-blind trial was presented in a cross-over design in 2020 [6]. Healthy adults (n = 27), without anxiety and mood disorders received either the quadruple herbal combination or placebo for 14 days, switching treatments after a 28-day wash-out period.

Two tablets were taken three times a day. The aim of the trial was to investigate the effects of taking the phytopharmaceutical for two weeks on relevant psychological and physiological stress parameters.

Longer-term effects were assessed with various psychological questionnaires, and acute psychological and physiological effects were determined in response to an artificial psychosocial stress situation in the laboratory (observed multitasking stressor, OMS).

In addition, mood, sleepiness and cognitive functions were assessed via a mobile app (Cognimapp) on days 7 and 14 of the intervention period.

After 14 days of taking the trial drug, the participants reported a reduced subjective feeling of anxiety, assessed with the POMS questionnaire (POMS = Profile of Mood States, dimension: tension/anxiety). In response to the psychosocial stressor (OMS), they showed an attenuated response,

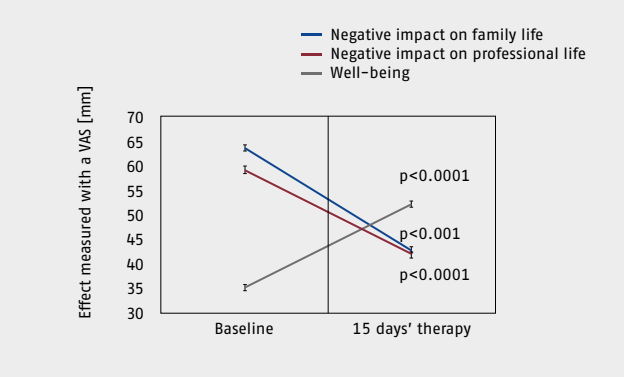

Fig. 5. Negative impact on professional and family life and change in general well-being before and after 15 days of therapy. Data points show the mean ± SEM in mm of a visual analogue scale (0 = no effect; 100 = intensive effect)

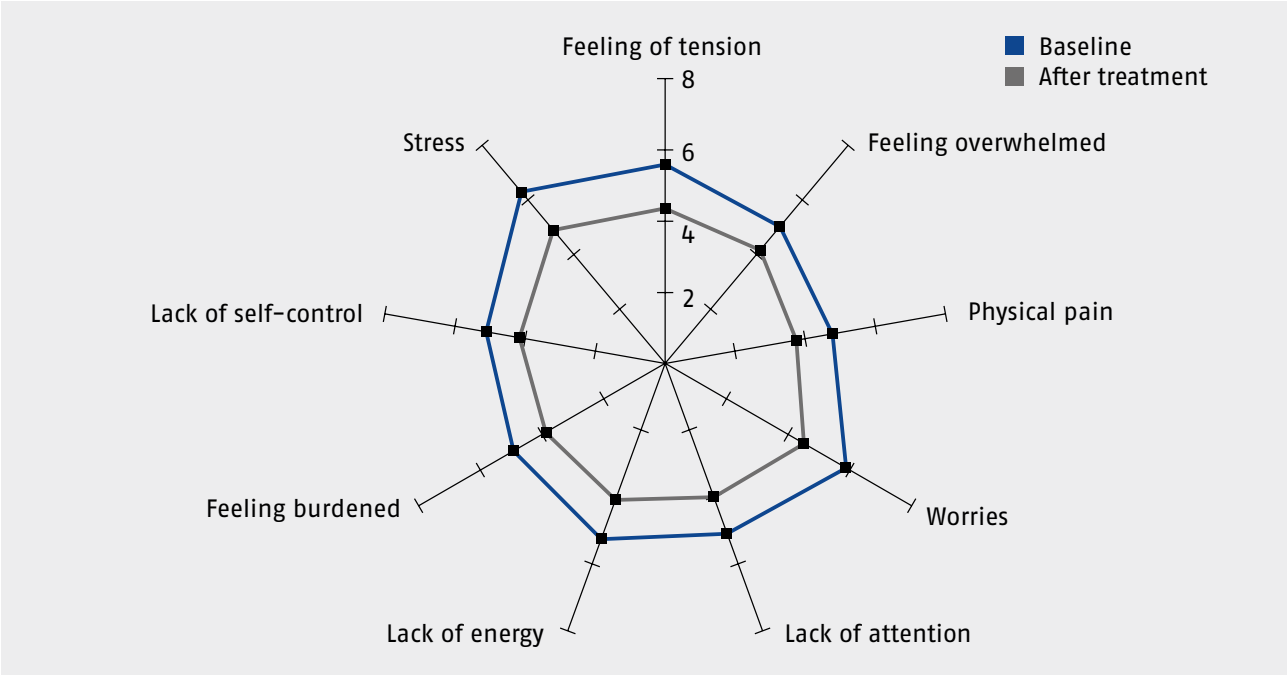

Fig. 4. Change in the different axes of the PSM-9 under treatment with the quadruple herbal combination

evidenced by a lower α-amylase level in saliva and a reduction in electrodermal skin conductance (measured as galvanic skin response). No negative effects were observed on subjective arousal or cognitive performance assessed via the app. Thus, compared to the placebo, the phytopharmaceutical even led to significantly fewer false alarms in sustained attention (RVIP task, Rapid Visual Information Processing).

Phytopharmaceutical product as first-line treatment for stress symptoms

The results of the studies demonstrate the benefit of the quadrupal herbal combination as a first-line treatment for stress-related symptoms such as mild insomnia, anxiety, tension and nervous restlessness. Positive effects on psychological as well as somatic stress symptoms and an improvement in quality of life were shown in real-life data and were supported by a placebo-controlled volunteer study.

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Conflict of interest: Heba Aziz-Kalbhenn and Christiane Kolb are employees of Steigerwald Arzneimittelwerk GmbH, Darmstadt.

Disclosure: Medical writing and publication funded by Steigerwald Arzneimittelwerk GmbH, Darmstadt.

Information regarding manuscript

Submitted on: 14.12.2021
Accepted on: 15.02.2022
Published on: 27.02.2022