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Clinical Research Review

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# Adaptogens Relieve Fatigue and Pain of Recent Long COVID

## Efficacy of adaptogens in patients with long COVID-19: a randomized, quadruple-blind, placebo-controlled trial

Karosanidze I, Kiladze U, Kirtadze N, Giorgadze M, Amashukeli N, Parulava N, et al. Pharmaceuticals. 2022 Mar 11;15(3):345.

A trial performed in Georgia, Europe enrolled patients with a confirmed COVID-19 diagnosis based on a positive SARS-CoV-2 test and the presence during the last 30 days of at least three of the long COVID-19 symptoms (fatigue; headache; respiration problems; sweat; cognitive disorders [poor attention or memory, anxiety, depression]; loss of smell and taste; cough; pain in joints, muscles and chest). Patients had been discharged from a COVID hotel isolation, intensive care unit or online clinics. Those experiencing long COVID symptoms for more than 3 months were excluded. Patients were under observation or admitted to a controlled facility or hospital and received placebo or herb combination for 2 weeks. Based on the average strength of the extracts, the combination provided approximately 0.68 g/day of *Rhodiola rosea* dried root, 2.10 g/day of *Schisandra chinensis* dried fruit and 3.67 g/day of *Eleutherococcus senticosus* dried root. Patients were assessed at baseline, weeks 1 and 2, and one week after finishing the treatment (follow-up visit). The trial was quadruple-blinded, as the participants, care provider, investigators and outcomes assessor did not know which patients were given the herb combination or placebo.
At baseline, the average age of the 100 patients was 48.85 years, and 85% were women. Ninety-nine patients completed the trial.

- Compared to placebo, the herb combination significantly decreased the duration of fatigue and pain in 50% of patients (by approximately 1 and 2 days, respectively).
- The number of patients with pain and fatigue was significantly less in the herb group than in the placebo group on days 9 and 11 (*see table for results*).
- Significant relief of severity of all long COVID symptoms over the course of treatment and the follow-up period occurred in both groups of patients, particularly for anxiety, depression, cognitive performance (attention) and daily walk time. However, significant differences between herbal treatment and placebo were observed for cough and daily walk time. The longer duration of walking compared to placebo is likely to correlate with the decrease in pain and fatigue brought about by the herbs.
- At the end of follow-up, interleukin-6 in the blood was significantly lower in the herb group (while it non-significantly increased in the placebo group), and there was a significant difference between the two groups for creatinine. Those receiving the herb combination had significantly lower blood creatinine compared to the results for the placebo group, suggesting the herbs may help prevent progression of kidney damage.
- There were no significant differences between the groups for the blood markers of inflammatory response (C-reactive protein) and blood coagulation (D-dimer).
- Only one adverse event (allergic conjunctivitis) was recorded – in a patient taking the placebo.

**Key Finding**

A combination of adaptogens (Rhodiola, Schisandra and Eleutherococcus) improved fatigue and pain in patients with long COVID symptoms of less than 3 months.

| | Adaptogen Combination | Placebo | |
|---|---|---|---|
| patients with pain on day 9 | 39% | 57% | p=0.0019 |
| patients with fatigue on day 11 | 28% | 43% | p=0.0157 |
| duration of cough (days) | 8.1 | 6.3 | p=0.0219 |

## Licorice Gargle Soothes and Heals Mouth Ulcers

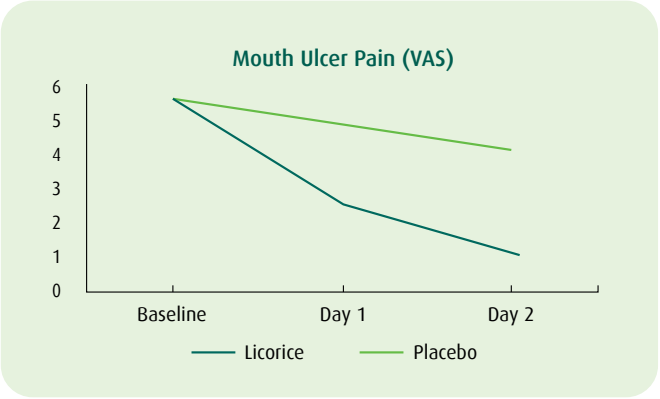
Effective licorice gargle juice for aphthous ulcer pain relief: A randomized double-blind placebo-controlled trial.

Liu HL, Hsu PY, Chung YC, Lin CH, Lin KY. Pak J Pharm Sci. 2022 Sep;35(5):1321-1326.

A randomized, double-blind, placebo-controlled trial involving 54 patients with acute mouth ulcers was conducted in Taiwan at a dental clinic. The study excluded patients with known systemic diseases, those who had received other treatments and patients with chronic ulcers (existing for more than five days). Participants received mouthwashes to be gargled for 10 to 20 seconds, four times daily. The herbal mouthwash was made as a decoction (40 g of Licorice root boiled for 30 minutes in one liter of water). The herb was obtained from a traditional Chinese herb shop.* The placebo mouthwash contained xylitol, and both mouthwashes contained a drop of natural coloring (caramel). A 10-point visual analog scale (VAS) was used to evaluate the self-assessed pain levels before and after treatment. VAS scores represent pain, rated from 0 (no pain) up to unbearable pain (10). The demographic and basic clinical characteristics of the patients were similar, and not statistically different at baseline, although there were more patients with major ulceration in the Licorice group than the placebo group: 26.7% vs 8.3%, respectively, with most patients having minor ulceration (66.7% vs 91.7%), and a few with herpetiform (very small and grouped ulcers; 6.7% vs 0%).

- The Licorice group had significantly less pain compared with the placebo group at day 1 and day 2 ($p<0.001$ for both; *see graph*).
- The mean size of the ulcers was markedly reduced by the action of Licorice on both days, and the results compared to placebo were statistically significant.
  - For example, at day 2, the ulcer size was 1.33 mm from a baseline of 5.00 mm for those gargling with Licorice. For the placebo group, the ulcer size was 3.83 mm from a baseline of 4.17 mm.
- There were no reports of serious adverse effects.

**Reviewer's Note:** The species may have been *Glycyrrhiza glabra*, *G. uralensis* or *G. inflata*, as these are used as medicinal Licorice in traditional Chinese medicine. The authors refer to Licorice 'juice', including mention of the classic clinical research carried out in the 1940s where Licorice juice was used to treat gastric and duodenal ulcers. In these earlier publications, the prescribed preparation was succus liquiritiae, and although a succus often refers to the expressed juice of a fresh plant, this is not the case with Licorice – succus liquiritiae is a concentrated aqueous extract. A suitable gargle can be made using 5 mL of a high quality 1:1 liquid extract added to 70-80 mL of saline (or approximately 1 teaspoon in 2.5 fl oz).




**Key Finding**

Licorice gargle relieved pain and promoted the healing of acute mouth ulcers.

## Boswellia Assists Cognitive Function in Brain Injury – Again

Effect of a boswellia and ginger mixture on the memory dysfunction of the mild traumatic brain injury patients: a randomized, double-blind controlled trial.

Yousefi O, Ghazi Mirsaiid S, Azami P, Karimi G, Mani A, Niakan A, et al. Bull Emerg Trauma. 2022 Oct 1;10(4):157-64.

The effect of Boswellia and Ginger on mild traumatic brain injury (mTBI) was investigated in a clinical trial conducted in Iran. Patients who were admitted to the emergency room, diagnosed with mTBI and who complained of memory dysfunction in the first follow-up session after the hospitalization (held after one week) were included. They received either capsules containing placebo or Boswellia resin (1.08 g/day) plus Ginger (108 mg/day).* Ninety-three patients completed the one-month trial. They were assessed using the auditory-visual learning test (AVLT) questionnaire, at baseline, at one month and two months after treatment. There were no

| Tests | |
|---|---|
| AVLT | A series of tests assessing memory function, comprised of two different lists of 15 words. The test is repeated 5 times, and recall is tested each time. In the sixth step, the second list of words is read and the patient is asked to recall these words, then they are asked to recall the words from the first list. After a pause of 20 minutes (without reading the list), patients are asked again to mention words that they recalled from the first list – this is the seventh step. From this data, the individual parameters are obtained (*four listed below*), and an increase in the number indicates a better response. |
| total learning | The total number of words from the first list that a patient recalls during the first five repetitions. The range is 0 to 75. |
| retroactive interference score | The difference between the number of recalled words at the sixth step and the number recalled after the fifth step. It is used to determine the degree to which new information prevents the retrieval of old information, and the score can be between -15 and 15. |
| forgetting rate | Evaluates long-term memory. The difference between the number of recalled words between the seventh and fifth steps of the first word list. The score ranges from -15 to 15. |
| net positive score | The difference between the number of words that were said wrongly and the number said correctly from the first word list. |

| Results: Changes from Baseline† | | | | |
|---|---|---|---|---|
| | Boswellia and Ginger | Placebo | Boswelia and Ginger | Placebo |
| | At one month | | Two months after treatment | |
| total learning | 7.46 | 3.90 | 14.42 | 9.08 |
| retroactive interference score | 1.54 | 0.32 | 2.00 | 0.72 |
| forgetting rate | 0.78 | -0.40 | 2.04 | 0.52 |
| net positive score | 2.26 | 0.76 | 4.14 | 1.86 |

**Table 3. ALTV parameters (reported as the score differences) for which the differences between the two groups achieved statistical significance.**
**Abbreviations:** AVLT: Auditory Verbal Learning Test
**Note:** † Baseline values for herb and placebo groups, respectively: total learning: 32.66 and 32.24; retroactive interference score: 3.12 and 3.02; forgetting rate: 4.08 and 3.80; net positive score: 2.20 and 2.40

statistically significant differences in the scores of the AVLT parameters between the two groups at baseline.

- All patients recorded some improvement at the end of the one-month treatment and two months later.
- However, there were significantly better scores for some parameters in those treated with the herbal combination at both time periods compared to placebo – specifically for total learning, retroactive interference score, forgetting rate and net positive score (*see Table 3*). The improvements in word span and hit parameters were not significantly different.

**Reviewer's Note:** Product information obtained from the internet, and a previous research publication (Int J Prev Med. 2012 Jul;3(7):499503), defines the composition as *Boswellia serrata* resin and *Zingiber officinalis* dried rhizome. A previous randomized, double-blind, placebo-controlled trial that administered a higher dose of Boswellia was discussed in *Clinical Research Review* No. 15, September 2022.

**Key Finding**

A combination of Boswellia and small amount of Ginger significantly improved memory function in patients with traumatic brain injury.

## Ashwagandha Supports Female Sexual Function

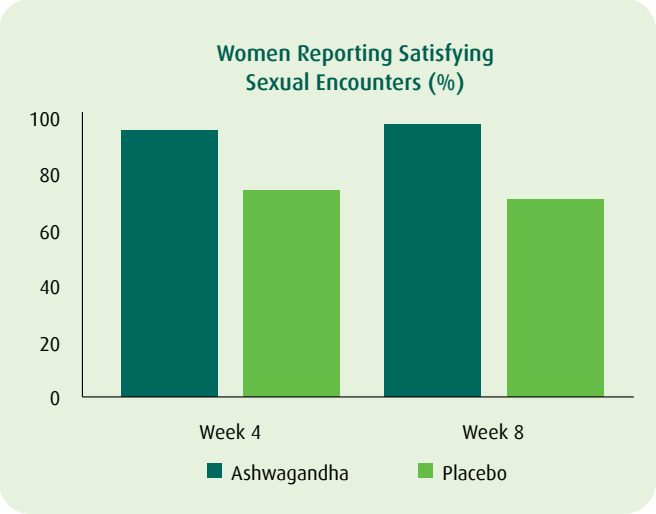
Efficacy and safety of ashwagandha (*Withania somnifera*) root extract for improvement of sexual health in healthy women: a prospective, randomized, placebo-controlled study.

Ajgaonkar A, Jain M, Debnath K. Cureus. 2022 Oct 28;14(10):e30787.

A double-blind, placebo-controlled study randomized 80 women, with hypoactive sexual desire disorder who did not have any hormonal disturbances, to receive either capsules containing

standardized extract of *Withania somnifera* root[1] or identical placebo for eight weeks. Sexual function was assessed using questionnaires: FSFI (Female Sexual Function Index) containing 19 items, and subdivided into 6 domains: desire, arousal, lubrication, orgasm, satisfaction and pain; and FSDS (Female Sexual Distress Scale), a 12-item survey that measures sexually related personal distress during the previous 30 days. Secondary outcomes were the change in quality of life explored using the General Health Questionnaire (GHQ-28) and a record of sexual activity consisting of total sexual encounters and satisfying sexual encounters (SSEs). HSDD is defined as per the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition as a persistent or recurrent absence of sexual fantasies and desire for sexual activity, causing marked personal distress or interpersonal difficulties. Participants had a FSFI total score of less than 26 and/or a FSDS score of greater than 11.[2] The average age of the herb group was 29.1 years, and 29.9 years for the placebo group. Eight participants were excluded due to follow-up loss or failure to take the capsules. The final efficacy analyses were done on the per-protocol dataset of 72 women (37 in the herb group, 35 in the placebo group), whereas the safety analysis used the intention-to-treat dataset of all 80 women.

- There were statistically significant improvements in FSFI total scores from baseline for those taking Ashwagandha compared to placebo at weeks 4 and 8 ($p<0.0001$ for both).
  - At week 8, the mean total score for Ashwagandha increased from 14.20 to 22.62; for placebo the score increased from 14.17 to 19.25.
  - The improvements were statistically significant in five of the domains: arousal, lubrication, orgasm, sexual satisfaction and pain.
- There were also greater improvements in the FSDS scores in the Ashwagandha group compared to placebo at weeks 4 and 8 ($p<0.0001$).
- There was a greater improvement in total GHQ-28 score at the end of the trial with Ashwagandha compared to placebo, although not statistically significant.
- There were no differences in the total number of sexual encounters between the groups over the course of the study. The number of successful sexual encounters (SSEs) increased in the herb group at week 8, but decreased in those taking placebo.
- There was a significantly greater number of women taking Ashwagandha reporting SSEs at week 4 ($p=0.017$) and week 8 ($p=0.002$) as compared to placebo (*see the graph*).
- Adverse events were comparable in the two groups (nausea and drowsiness; three women in each group). They were mild, self-limiting and according to the authors, were not associated with the treatments (herb or placebo).




**Reviewer's Notes:**

1. Information about the extract from the supplier and defined in two published articles (Phytomedicine. 2019 Jul;60:152881; J Ethnopharmacol. 2021 Jan 10;264:113276), reveals it to be between 12:1 and 15:1 in strength and contain at least 5% withanolides. This suggests the 600-mg dose of extract was equivalent to about 7.2-9 g/day of dried root, and provided 30 mg/day of withanolides.

2. The FSFI total score ranges from 2 to 36, with higher scores indicating better sexual function. The cutoff score for normal sexual function is 26.5. The 12-item FSDS has a maximum score of 48 points, and a decreasing score indicates decreasing personal distress regarding sexual function.

**Key Finding**

A fairly high dose of Ashwagandha root extract, standardized for withanolides, improved sexual function in women with low sexual desire.

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