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RESEARCH ARTICLE

ALSUntangled #74: Withania Somnifera (Ashwagandha)

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Abstract

ALSUntangled reviews alternative and off-label treatments on behalf of people with ALS (PALS) who ask about them. Here, we review withania somnifera (WS) commonly known as ashwagandha or winter cherry. WS has plausible mechanisms for slowing ALS progression because of its effects on inflammation, oxidative stress, autophagy, mitochondrial function, and apoptosis. Preclinical trials demonstrate that WS slows disease progression in multiple different animal models of ALS. Of the five individuals we found who described using WS for their ALS, two individuals reported moderate benefit while none reported experiencing any significant side effects. There is currently one clinical trial using WS to treat PALS; the results are not yet published. There are no serious side effects associated with WS and the associated cost of this treatment is low. Based on the above information, WS appears to us to be a good candidate for future ALS trials.

Keywords: *Withania somnifera, Ashwagandha, Winter cherry*

Introduction

ALSUntangled reviews alternative and off-label treatments for ALS on behalf of people living with ALS (PALS). Here we review Withania somnifera (WS), commonly known as ashwagandha or winter cherry. WS is one of the ingredients in a supplement combination we previously reviewed (1), but here we focus specifically on the therapeutic potential of WS for PALS which is currently being advertised on multiple Internet websites (2, 3). The claims made on these websites have not been verified by our team.

Background

Withania somnifera (WS) is an herb used in traditional (ayurvedic) medicine (4). It is composed of a variety of withanolides with possible functions ranging from the modulation of mitochondrial function to anti-inflammatory, antioxidant, anti-apoptotic, and neuro-protective properties (4–6). WS is sometimes used as an over-the-counter supplement to treat anxiety and insomnia (7), but it has not been approved by the FDA or EMA for any indication. As is often the case with over-the-counter supplements, the exact concentrations of

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potentially active ingredients in WS supplements may not be reliable or available.

Mechanisms

Anti-inflammatory

Upregulation of neuroinflammatory markers including NF-kB (a protein complex that regulates apoptosis and induces the expression of inflammatory genes) occurs in preclinical ALS models and PALS and has been noted even before the onset of symptoms (8–10). WS treatment can inhibit NF-κB transcription in isolated cancer cell lines and in the blood and synovial fluid of patients with rheumatoid arthritis, thereby decreasing neuroinflammation (11, 12). Additionally, WS treatment can reduce the expression of a pro-inflammatory astrocyte activation marker, GFAP, in a mouse model of Parkinson's disease (13). While these mechanisms are theoretically promising, we have not yet found any proven treatment for ALS that works via inhibition of NF-kB or GFAP.

Antioxidant

Oxidative stress is caused when there is an increase in reactive oxygen species (ROS) relative to the intrinsic biochemical reducing system and antioxidants (14). Oxidative stress is clearly happening in PALS (14). One FDA-approved treatment for ALS is believed to work as an antioxidant (15). A human study showed that WS treatment over a 3-month period significantly decreased the presence of ROS in semen from infertile men (16). We have not yet found evidence that WS decreases markers of oxidative stress in the central nervous system of humans (Table 1).

Table 1. Table of evidence for WS.

	Grade	Explanation
Mechanisms	B	WS has potentially beneficial effects on inflammation, oxidative stress, autophagy, mitochondrial function, and apoptosis; only its anti-inflammatory and antioxidant effects have been measured in humans and these were in peripheral fluids and cells, not central nervous system ones
Preclinical	A	WS treatment showed benefits in multiple studies done by different groups in pre-clinical models of ALS
Cases	C	One verified "ALS Reversal" had his motor improvements start while taking a product containing WS along with other ingredients.
Trials	U	No published clinical trials of WS in ALS.
Risks	B	Less than 10% of patients in trials across many indications other than ALS show only rare, non-serious side effects

Autophagy induction

Autophagy is defined as the process through which cells recycle their damaged organelles (17). Autophagy dysregulation has been proposed as a driver of progression in multiple neurodegenerative diseases, including ALS (reviewed in 17). Three groups using different compounds to stimulate mitochondrial autophagy showed benefits in the G93A mutant SOD1 (mSOD1^{G93A}) mouse model of ALS (reviewed in 17). Another group administered WS to this same mouse model of ALS and demonstrated enhanced markers of autophagy, better-preserved spinal cord motor neuron counts and improved lifespan (18). We have not yet found an effective ALS treatment that works in PALS by improving autophagy.

Modulation of mitochondrial function

Mitochondria are cellular organelles responsible for energy metabolism, calcium homeostasis, and apoptosis (19). A large body of literature suggests that mitochondrial dysfunction occurs early in ALS with effects on energy production, calcium metabolism and apoptotic signaling (reviewed in 19). Several groups have targeted mitochondrial dysfunction in trials; while some benefits were seen with this approach in ALS animal models, there have yet to be convincing benefits from this strategy in humans (reviewed in 19). Given this, we believe caution is warranted in considering the translatability of a study in which WS treatment given to a human SOD1 overexpression (hSOD1) fly model of ALS improved mitochondrial function, climbing behavior and survival (20).

Role in apoptosis

Apoptosis is defined as programmed cell death (17). Deregulation of apoptosis may play a role in ALS pathogenesis (reviewed in 17). Data are conflicting as to whether WS might inhibit apoptosis (13) or induce it (21, 22).

In summary, while WS has several mechanisms that might be helpful in ALS, its anti-inflammatory and antioxidant effects are the only ones that hav been measured in humans and these were in peripheral fluids or cells. It is not clear that WS can accomplish any of its mechanisms in the central nervous system of patients with ALS. Therefore, we assign a TOE "Mechanisms" grade of B.

Pre-clinical models

WS and its derivative Withaferin A (WA) have been studied in multiple pre-clinical models of ALS including the mSOD1^{G93A} mouse (18, 23), G37R mutant SOD1 mouse (mSOD1^{G37R}, 23), hSOD1 fly (20), and mutant TDP-43 mouse (24,

25). These were small but otherwise well-designed studies that showed better-preserved motor neuron counts in the spinal cord (18, 23) as well as improved motor function (18, 20, 24) and/or survival (18, 23).

Based on these multiple well-designed studies demonstrating benefits from WS treatment in different pre-clinical models of ALS, we assign a TOE "Preclinical" grade of A.

Cases

In the online community PatientsLikeMe, we found 18 individuals who reported taking WS for their ALS (26). Of these 18, five completed detailed treatment evaluations:two individuals self-reported moderate effectiveness while three self-reported no or indeterminate effectiveness. Of the two individuals who self-reported moderate effectiveness, one took it along with "Normast" (a dietary supplement reported to have anti-inflammatory and neuroprotective effects, 27) and that sometime after beginning WS, they were able to say a few words aloud again for the first time since losing that function. This gain in function was unable to be verified due to the passing of this individual before the creation of this review. This individual took a dose of 4 grams daily. Since small, transient improvements in PALS can be part of the natural history of the disease (28), this report is not proof of benefit from WS. The other individual who self-reported moderate effectiveness commented that they switched to another treatment which they found to be better, though they did not elucidate how or why. We reached out to inquire about their experience and did not hear back. This individual did not provide dosing information. Both individuals reported an adherence level of "always" but we have no way to verify this reported adherence, nor can we determine the duration of use. The three individuals who found no benefit took doses of 670 mg daily, 1300 mg daily, and 1300 mg daily with adherences of always, usually, and usually, respectively (26).

We previously described one person with ALS who had significant motor improvements start while taking a product containing WS along with other ingredients (1). Based on this, we assign a TOE "Cases" Grade of C. Of course, associations such as these do not prove causality.

Clinical trials

There is one interventional phase 2 clinical trial for WS in ALS that is currently listed to be in its recruiting phase, however, the listed estimated study completion date is September of 2022 and no results have been posted (29). According to the online description, this is a randomized, double-blind, trial testing WS at 2 doses (1088mg daily and 544mg daily) versus placebo over 8 weeks (29). We reached out to the study coordinators in the summer and fall of 2023 to inquire on the estimated date of completion and were informed on both occasions that the study has concluded but the results have not yet been finalized. Therefore, we assign a TOE "Clinical Trials" grade of U.

Dosing, risks, and costs

The highest dose of WS that we found used in any human study was 5 g/day (30). The active trial in PALS is using 1088mg daily and 544mg daily (29). The optimal dose (if any) for treating ALS is currently unclear.

The 5 patients using WS for ALS in the online community PatientsLikeMe self-reported no side effects (26). This is currently the only available safety and tolerability data from PALS. A review of 30 human trials using WS for other conditions concluded that it had an excellent safety profile (31). No serious adverse events were reported in any of these trials. The following rare side effects were described: loose stools, somnolence, epigastric pain/discomfort, giddiness, drowsiness, hallucinations, nausea, constipation, vertigo, rhinitis cough, cold, decreased appetite, dry mouth, hyperactivity, cramps, blurring of vision, hyperacidity, skin rash and weight gain. Since these occurred in less than 10% of treated patients, we assign a TOE "Risks" grade of B. Again, we caution that PALS may experience different side effects compared to patients with these other conditions.

PatientsLikeMe users self-reported a cost of less than $25 per month (26). WS can be purchased without a prescription. The purity of different brands of WS has not been established.

Conclusion

WS appears reasonably safe, has plausible mechanisms by which it might slow ALS progression and has promising data obtained in multiple different preclinical models of ALS. While there are also some interesting self-reports from PALS, and one verified ALS reversals on a compound containing WS, these must be interpreted with caution because of the variable natural history of ALS progression. We conclude that WS is a reasonable compound for ALS trials, and we look forward to the results of the one trial that is underway.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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