Withaferin-A in dealing with second rate Alzheimer's disease patients: a 16-week placebo-controlled trial

Sonu sharma[1], Dr. Viney lather[1]*, Jyoti Gupta[2], Shilpa mamgain[2]

[1]Amity institute of pharmacy, Amity University, Noida, U.P.

[1]* Amity institute of pharmacy, Amity University, Noida, U.P.

[2]Galgotia College of Pharmacy, Greater Noida, U.P.

Correspondence Author*

Dr. **Viney lather**, Associate professor, vlather@amity.edu, Institute of Pharmacy, Amity University, Noida, 97299993350

First author[1]

Ms. Sonu Sharma, sonusharmapharma@gmail.com Institute of Pharmacy, Amity University, Noida,9891540303

ABSTRACT

What is identified:

Natural cures have been pushed off in the treatment of communicative and mental admonition indication of dementia with variable reaction. sativus Withaferin-A might forestall the collection of amyloid b in the human brain and consequently be worthwhile in cure of Alzheimer's sickness (AD).

Objective: The goal of this study was to determine the efficacy of Withaferin-A in the treatment of Alzheimer's disease.

Methods:

A total of 46 patients with potential Alzheimer's disease were screened for a 16-week, double-blind case study of patients with mild to moderate Alzheimer's disease. The psychometric trials, which included the AD assessment scale-cognitive subscale (ADAS-cog) and the medical dementia assessment scale-sums of boxes, were able to show the patients' overall perception and medical side. For a 16-week research, patients were randomly assigned to either capsule Withaferin-A (Group A) 30 mg per day (15 mg two times per day) or capsule placebo (two capsules per day).

Results:

After 16 weeks, Withaferin-A had a considerably better result on intellectual function than placebo (ADAS-cog: F = 3.11, d.f. = 1, P = 0.03; CDR: F = 3.21, d.f. = 1, P = 0.03) In the two trial sets, no significant changes or adverse events were found.

Keywords: Alzheimer's disease, psychometric trials, Withaferin-A

What is new and conclusion:
Withaferin appears to be both safe and beneficial in mild to moderate Alzheimer's disease, according to this double-blind, placebo-controlled trial. Larger randomised controlled trials are needed to corroborate the findings.

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia in people over the age of 65. (1). The onset of the sickness is deceptive, usually occurring beyond 55 years of age and increasing in frequency as one becomes older. At the age of 60, the probability of developing Alzheimer's disease is about 5%, increasing by a factor of two every five years. A continuous degradation in intellectual function, a deterioration in the ability to complete repetitious events of daily living, and ongoing changes in temperament and actions are all signs of scientific progress (1, 2) The formation of numerous amyloid plaques in the cerebral cortex is the pathophysiology of Alzheimer's disease (3).

The major component of amyloid plaques, as well as the amyloid precursor protein, is amyloid b. (APP). APP is found in both the brain and peripheral tissues (4, 5). NMDA-receptor antagonists and cholinesterase inhibitors are used to treat Alzheimer's disease, while there are still questions about their therapeutic efficacy (6).

Herbal treatments are utilised by over 80% of the world's population, particularly in developing nations, for primary health care (7, 8).The growing popularity of various ways of well-being care has sparked interest in the treatment of dementia with herbal drugs that may improve cognition (6). Herbal remedies are widely utilised in the treatment of communicative and psychological symptoms of dementia, however they have a variable effect (9). As a result, only a few plant kinds that have been employed in traditional medicine have an objectively discernible lack of toxicity (6).

An increase number of research are looking into the effects of extracts from some of these herbal plants. Those with an effect similar to that of approved medications, or an action that may be related to what is known or believed about Alzheimer's disease and vascular dementia, are of particular interest (6). Withania somnifera is a herbal treatment that has been used in China for many years to treat a number of ailments. An extract of Withaferin A has been used in numerous trainings to treat the symptoms and slow the progression of Alzheimer's disease (10). Withania somnifera has been shown to improve cognitive function and reduce anxiety in people with mild to moderate Alzheimer's disease (11, 12). Traditional medicine has utilised Withania somnifera, also known as ashwagandha, as an immune system booster, adaptogen, arthritic illness, cancer, stimulant, and anti-hypertensive agent (6, 13).

Furthermore, it has been reported that Withaferin A extract or its active constituents have depressive, anticancer, anticonvulsant, and anti-inflammatory properties, as well as improving knowledge and recall and promoting oxygen transport in muscles (6, 13).

A number of recent clinical trials have revealed that Withaferin A is just as effective as imipramine in the treatment of depression (14–16). Due to their adaptive reactions to disease, responsiveness to many unrelated ailments, and production of broad-spectrum better confrontation to unfavourable properties of medicines (17–18), Ashwagandha and ginseng are considered adaptogens in Ayurveda. One of the most powerful characteristics of WS is its chemo preventive capability, which has been proven in numerous research (19-20).

Educations representing suppression of transplanted growths in mice (21–22) further underscore the role of WS as an anticancer medication. In rat copies, administration of WS r extracts (155 mg/kg/day) resulted in a 21–23% reduction in tumour problem and diversity of mammary malignancy, as convinced by methyl nitrosourea (23). Chemotherapy was thought to alleviate fatigue and toxicity in cancer patients (23). The presence of withanolides in WS is thought to be responsible for its anticancer properties (24). This essential withanolide is also found in a number of other plant species.

Table 1 lists the most prevalent medicinal plants that contain large amounts of WA. Molecular and pharmacological studies on WA have concluded that withanolides are linked to the beneficial benefits of WS (24). Because of the importance of WA, this review aims to describe the major pharmacological activities and related molecular mechanisms of WA, with a focus on anticancer characteristics.

METHODS

This was a 16-week double-blind trial of people in mild to moderate pain. A total of 46 patients with suspected Alzheimer's disease (AD) of mild to moderate severity were screened for trial participation. The diagnosis of Alzheimer's disease was confirmed using the Diagnostic and Statistical Guide for Neurological Disorders (25). According to the standards of the National Institute of Neurologic and Communicative Disorders and the Connected Illnesses Association, the focuses were categorised into legitimate AD ranks (26). For this experiment, patients had to give magnetic resonance imaging scans from less than a year ago to show time off from clinically significant dementia or dynamic cerebrovascular illness.

The presence criteria were age over 50 years and a reference line MMSE score of 20–30 (inclusive) on the mini-mental state examination (MMSE) (27). Patients with mild to severe Alzheimer's disease, as evidenced by risk factors such as hypertension, elevated cholesterol levels, and smoking, but who were in a stable state, were also eligible to participate in the trial. As part of the enclosure requirements, the patients had to have a knowledgeable and dependable caregiver accompany them to all test appointments and administer the test drugs. Patients were excluded if they showed signs of cardiovascular disease that could have harmed their ability to contribute to and complete the trial, or if they had other neurodegenerative diseases.

Any clinically severe hepatic, pulmonary, or endocrine problems; psychiatric, active peptic ulcer, urinary outflow blockage, or a history of epilepsy or serious alcohol misuse were also exclusion factors. Patients were excluded from the experiment because they had received cholinomimetic medication for AD during the previous 60 days, and the trial was eventually terminated for reasons other than trial enrollment persistence. Other antidementia medicines (e.g., oestrogen, chronic nonsteroidal anti-inflammatory drugs, selegiline) had to be phased out before the trial could begin. Psychotropic medications were stopped 48 hours before the cognitive exam. The Galgotias University of Pharmacy's Institutional Review Board (IRB) accepted the protocol.

The patients and their legally authorised representatives gave informed permission in compliance with the local IRB's protocols, and they were told they could leave the trial at any moment. The trial was conducted in conformity with the Helsinki Declaration and its subsequent revisions (28).

Measurements

The psychometric trials included the MMSE, which was later followed by the AD Assessment Scale-cognitive subscale (ADAS-cog) (29), as well as the clinical dementia rating scale–sums of boxes (CDR-SB) (30), which were all completed to reveal the individuals' overall cognitive and clinical profiles. All trials were calculated at the start and every two weeks while the treatment was ongoing.

Intervention

Patients were randomly assigned to receive a withaferin A capsule or a placebo tablet in a 1: 1 ratio, and a computer-generated code was utilised to determine whether they received a twice-daily Withaferin capsule or a placebo capsule. During the trial, no individual participant randomization code was revealed. After the database was locked at the end of the trial, treatment codes were unblinded. The placebo and Withaferin tablets had the same appearance. Patients were randomly randomised to receive Withaferin 30 mg per day (15 mg twice per day) (Group A) or placebo capsules (two capsules per day) for a 16-week research in this double-blind, multicentre investigation.

Preparation of capsule of withaferin A

The experimental parameters of W. somnifera supercritical fluid extraction were optimized in the first step using a central composite design (CCD). The herbal extract was then micronized utilizing a new, reproducible, and robust process of carbon dioxide supercritical solvent expansion. The Draper-Lin tiny composite designs were also used to optimize the experiment's parameters. Furthermore, we discovered Withaferin. Liquid chromatography–mass spectrometry (LC–MS) was used to identify a nanoparticle in the extracted materials, and field emission scanning electron microscopy was used to characterize the precipitates (FESEM).

Safety evaluation

At each visit, all adverse occurrences were recorded, whether they were reported or observed. At each visit, a routine physical examination was performed. At week 0, week 8, and week 16, complete physical examinations were performed, including 12-lead ECG recordings.

Statistical analysis

Using the last observation carried forward approach, the primary efficacy analysis employed data from the intention-to-treat population, which was defined as all patients randomly assigned to treatment who received at least one dose of study medication. A two-way repeated measures analysis of variance (time–treatment interaction) was used by the researchers. The between-subjects component (group) was defined as the difference between the two groups, whereas the within-subjects factor (measurement) was defined as the difference between the nine measures recorded throughout treatment (time). This was done for both the ADAS-cog and CDR-SB

scores. The reduction in score on the ADAS-cog and CDR-SB scales at week 16 compared to baseline was assessed using an unpaired two-sided Student's t-test. Fisher's exact test was used to compare baseline data and the frequency of adverse events between treatments.

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RESULTS

The preliminary profile is shown in Figure 1. Between January 2006 and June 2008, 82 individuals were evaluated for the preliminary, with 46 of them being randomly assigned to either the Withaferin A or the false therapy instance. In January 2009, the most recent agreement concluded the concentrate. There was no difference in benchmark variables such as orientation, age, length of illness, or educational level (Table 1). The number of dropouts in the Withaferin and false treatment groups was 1, 3, and 1, respectively.

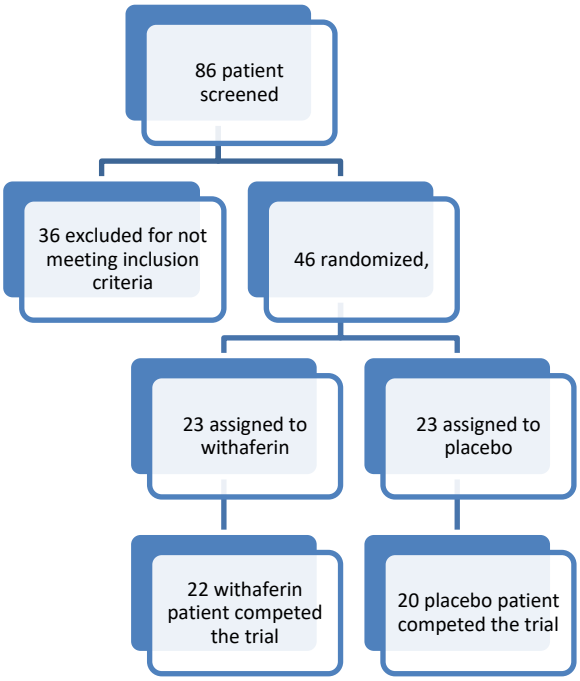

Fig. 1. Trial profile.

Base line data

	Withaferin group	Placebo group
Gender	Male = 14	Male = 13
	Female = 11	Female = 12
Age (mean ± SD)	72.65 ± 3.89 (Year)	73.13 ± 4.7 (Year)
	Under diploma=13	Under diploma=14
	Diploma= 8	Diploma= 8
	Higher diploma= 5	Higher diploma= 3
Time (since diagnosis)	18.30 ± 8.21 (month)	18.17 ± 8.31 (month)

Number of patient with adverse events

Adverse events	Withaferin	Placebo	P
dizziness	3 (12.04)	1 (5.34)	0.6
Fatigue	2 (9.63)	2 (9.63)	0.38
Hypomania	2 (9.63)	0	0.46
Dry mouth	1 (5.34)	1 (5.34)	0.49
Nausea	2 (9.63)	3 (12.04)	1.0

Efficacy measures

ADAS-cog. Figure 2 shows the mean SEM scores of the two groups of individuals. On the ADAS-cog rating scale, there were no significant differences between the two groups at week 0 (baseline) (t = 007, d.f. = 44, P = 094). The effect of group, the between-subjects factor (F = 412, d.f. = 1, P = 004) revealed a substantial difference between the two groups. Over the course of the experiment, the two treatments behaved differently (groups-by-time interaction, Greenhouse–Geisser correction; F = 20443, d.f. = 363, P 00001). At week 16 (endpoint), the difference between the two groups was significant (t = 416, d.f. = 44, P 00001).

CDR-SB. Figure 3 shows the mean SEM scores of two groups of individuals. Between the two groups, there were no significant difference.

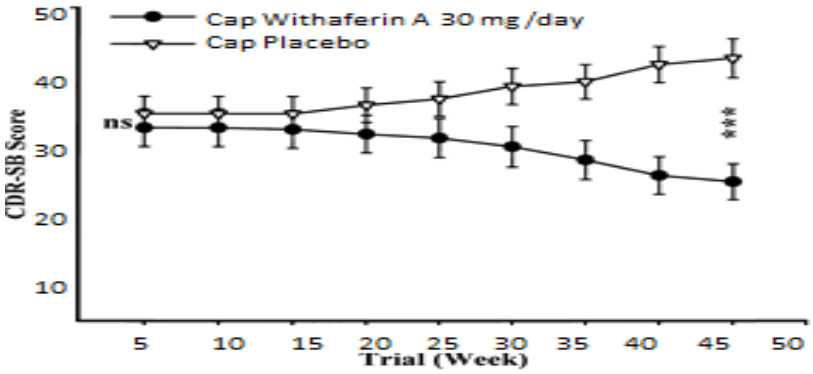

Fig. 2. Mean ± SEM scores of the two protocols on the ADAS-cog score. ns, non-significant.

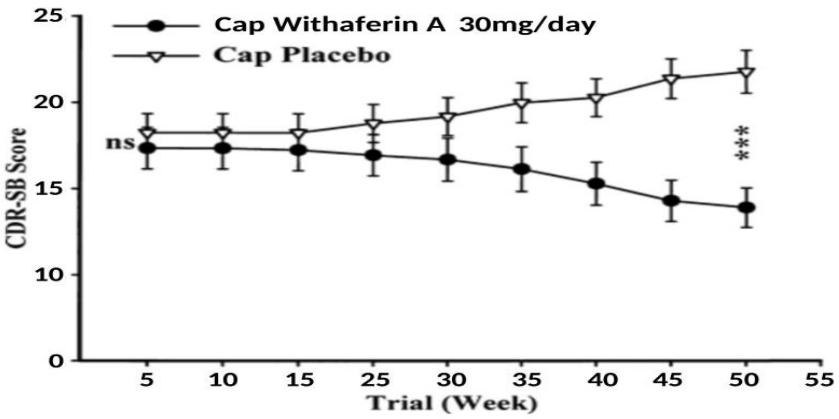

Figure 3 shows the mean SEM scores of the two methods on the CDR-SB score.

On the CDR-SB at week 0 (baseline) (t = 052; d.f. = 44; P = 060). The effect of group, the between-subjects factor (F = 412, Table 2) revealed a substantial difference between the two groups and the number of patients that experienced unpleasant effects.

The behavior treatments were not similar over the trial period (groups-by-time interaction, Greenhouse–Geisser correction; F = 113.26, d.f. = 5.39, P < 0.0001). The difference between the two groups was significant at week 16s (endpoint) (t = 5.32, d.f. = 44, P < 0.0001). The changes at week 16 compared with baseline were: –0.57 ± 18 (mean ± SD) and –0.57 ± 18 for Withaferin A and placebo, respectively. A significant difference was observed on the change of scores of the CDR-SB at week 16 compared with week 0 in the two groups (t = 13.13, d.f. = 42, P < 0.0001).

Safety

In any case, Withaferin A is safe and effective in the treatment of mild to moderate Alzheimer's disease, according to this study. To further confirm this herbal medicine, larger and longer randomised controlled trials are needed. One death occurred in the placebo group due to a myocardial infarction. Over the course of the trial, five adverse events were observed. The difference in the frequency of adverse events between the *Withaferin A* and placebo groups was not significant (Table 2). None of the negative incidents were serious enough to warrant a drop-out.

DISCUSSION

Alzheimer's disease is a critical public health problem that affects patients and has a huge negative impact on caregivers and loved ones (1, 4). As a result, a great deal of effort has been put into developing new and effective treatments. A vast range of treatments aiming at diverse targets are available to treat Alzheimer's disease.

Because the existing licensed medications are often useless, alternative remedies, particularly herbal therapy, may have a place in treating Alzheimer's disease (6). Herbal medicine is still the cornerstone of therapy for roughly 75–80 percent of the world's population, primarily in developing countries, in basic health care, due to higher cultural acceptance and often better

side-effect profiles. However, in the industrialised world, their use has skyrocketed in the last ten years (31).

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Withaferin in low doses in the passive avoidance task, A counteracted scopolamine-induced performance losses, and in the object recognition test, it antagonised the extinction of recognition memory (18).

The results of this study corroborate those of previous studies (18, 21–24), as well as the antioxidant and antiamyloidogenic properties of a Withaferin A stigma extract (21). In Alzheimer's disease, behavioural symptoms are common and contribute considerably to disease morbidity (32). In Alzheimer's disease, depression has been linked to accelerated cognitive loss, increased caregiver burden, higher patient-care expenditures owing to early institutionalisation, increased medication use, more frequent negative side effects, and more extensive institutional staffing needs (32).

Various basic studies and recent published clinical trials (14–16, 33) have found withaferin A to be antidepressant, with side effects comparable to placebo groups. In our study, adverse events ranged from moderate to severe, and no subjects withdrew out as a result of them. The current study had some limitations, including a small number of patients and a short follow-up period. More randomized controlled trials should be done as a result. Herbal medicines should be compared to current pharmacological treatments in the treatment of Alzheimer's disease. As a result, comparing donepezil to anticholinesterase inhibitors would be fascinating.

CONCLUSIONS

In any case, Withaferin A is safe and effective in the treatment of mild to moderate Alzheimer's disease, according to this study. To further confirm this herbal medicine, larger and longer randomised controlled trials are needed.

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