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Effects of Amitriptyline and Ashwagandha on the Oxidative State and Acetylcholine Esterase Enzyme Activities in Rats

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ABSTRACT

Amitriptyline has a long history of effectiveness in treating depression. Due to its side effects, which include oxidative stress and anticholinergic effects, it is used less frequently. Ashwagandha is a substantial herb that has anti-depressant, antioxidant properties. The aim of study is to evaluate the effects of ashwagandha and amitriptyline on the oxidative state of acetylcholine esterase in rat salivary glands. Four groups of rats were created. Distilled water was given to group I (control), and group II received amitriptyline (10 mg/kg) orally. Ashwagandha root extract (200 mg/kg) was given orally to group III, while similar doses of ashwagandha root extract and amitriptyline were given in combination to group IV. Rats from each group were sacrificed at (7 and 30 days). A blood samples were collected to measure the total antioxidant capacity (TAC). For measuring acetylcholine esterase enzyme, salivary gland tissues were dissected. TAC after 7 days of oral administration showed a nonsignificant difference between groups while, after 30 days there is a significant decrease in TAC in group II and IV in comparison with that of the control group. Following oral dosing for seven days, acetylcholine esterase measurements revealed an increase in group II and a decrease in group IV as compared to the control group. While after 30 days, all groups acetylcholine esterase enzyme levels significantly decreased when compared with the control group. It can be Concluded that, Amitriptyline causes oxidative stress and temporarily inhibits acetyl cholinesterase, which results in anticholinergic action. Ashwagandha has acetylcholine esterase inhibitory characteristics and mild salivary gland antioxidant benefits.

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INTRODUCTION

Generation of reactive oxygen species (ROS) leads to oxidative stress **(Thanoon *et al.*, 2022).** ROS are regularly produced by the organism as a byproduct of various oxidative reactions and/or as a result of regular metabolic activity **(Pal *et al.*, 2017).** To maintain the best cellular functions, these species are detoxified by endogenous enzymatic and non-enzymatic antioxidant defenses. If the pro-oxidant-antioxidant equilibrium is not restored, oxidative stress caused by accumulations of free radicals may lead to DNA damage, protein oxidation, lipid peroxidation, enzyme inactivation, irreversible cellular dysfunction, and ultimately cell death **(Hajam *et al.*, 2022).** This oxidative stress has been related to a number of illnesses, including cancer, atherosclerosis, liver cirrhosis, diabetes and Alzheimer's disease which has reduced choline acetyltransferase (ChAT) activity, altered acetyl cholinesterase (AChE), and a lack of cholinergic innervation. The modulation of AChE is currently established and recognized therapeutic marker for the development of cognitive enhancers **(Singh *et al.*, 2019).** Through the scavenging of the reactive byproducts of lipid peroxidation, antioxidants are useful in the prevention and treatment of neurodegenerative disorders **(Taqa *et al.*, 2021).** For instance, antioxidants, such as medicinal plants, are organic, bioactive compounds that can be used to treat and prevent neurodegenerative diseases **(Ibrahem *et al.*, 2020).**

Solanaceae family plant ashwagandha is a well-liked herbal treatment for stress, rheumatoid arthritis, inflammation, and tuberculosis. It has been

proven that sitoindisides VII-X and withaferin-A, two of its main ingredients, have potent anti-stress and antioxidant capabilities. A thorough examination of this antioxidant spectrum is missing, despite the fact that the majority of Ashwagandha's anti-oxidant components are assumed to be responsible for its therapeutic effects. We've already written on the antioxidant properties and particular polyphenolic compounds of Ashwagandha root extracts **(Munir *et al.*, 2022).**

Amitriptyline, a tricyclic antidepressant, also used to treat migraines, chronic fatigue syndrome, and irritable bowel syndrome. Amitriptyline functions by preventing the reuptake of serotonin and norepinephrine. According to research, amitriptyline has negative effects that are caused by increased levels of lipid peroxidation and oxidative stress. Amitriptyline administration will result in oxidative stress, a rise in malonaldehyde levels, and a deficiency in coenzyme Q **(Rodick *et al.*, 2018).** Severe CoQ depletion may enhance oxidative stress, which may trigger the caspase-dependent death pathway **(Yousif et *al.*, 2022).** It has been reported that amitriptyline is dangerous due to mitochondrial dysfunction, neurotoxicity and oxidative stress in the mitochondria **(Abd Al Obaidi *et al.*, 2021; Laforgia *et al.*, 2021).**

This study aims to investigate antioxidant effects of ashwagandha and amitriptyline on acetylcholine esterase in salivary gland tissues and blood.

MATERIALS AND METHODS

1. Animals

A total of 40 male albino rats of 8–10 weeks, weighing 200-250g, were used in this study. The animals obtained from the Animals' House at the college of Veterinary Medicine/ University of Mosul, Iraq and maintained at a room temperature of 22±2C°, with a free access to water and food in 12 hours of light/dark cycles.

The study was confirmed by the Scientific Committee at the Department of Basic Dental Sciences/College of Dentistry/ Mosul University (UoM.Dent/A.L.56/22).

2. Experimental substances

Ashwagandha root extract was acquired from Roya pharma/Antalya, Turkey. Ashwagandha root extract was given daily at a dose of (200mg/kg) **(Khan *et al.*, 2015)** for 30 days. Amitriptyline was administered daily at a dose of (10mg/kg) for 30 days).

3. Experimental design

Four groups (each with 10 rats) were randomly assigned, five rats euthanized for each treatment period (7 and, 30 days) as follows:

Group I (Control) received (1.0ml/kg) of distilled water.
Group II (Amitriptyline) given Amitriptyline 10mg/kg orally.
Group III (Ashwagandha) ashwagandha root extract was orally administered at a dose of 200mg/kg.
Group IV (combination) received both amitriptyline and Ashwagandha root extract orally, with doses of 10mg/kg and 200mg/kg, respectively.

4. Specimen collection

At day 7 of administration, two hours after the last treatment, half the rats in every group were anesthetized with ether and sacrificed. Blood samples were collected from the plexus orbital fossa to measure total antioxidant capacity in the serum using Elisa kit, Salivary glands were extracted for measuring the tissue's acetylcholinesterase using the Acetylcholinesterase Elisa kit. Salivary glands were placed in buffered phosphate solution. After 30 days of administration, the same process was repeated for the remaining half of animals in each group.

5. Statistical analysis

Statistical Package for the Social Sciences version 21 was used for analysis. The data were expressed as Mean ± standard deviation. One-way analysis of variance and (Duncan's post-hoc test) were used to compare between the groups. P-values less than 0.05 were considered statistically significant.

RESULTS

Total antioxidant capacity

1. At day 7

The results in Fig.1 indicates that there are no significant differences in antioxidant capacity levels between the groups treated with Amitriptyline (1.03±0.3) Ashwagandha (1.58±0.66), and combination group (0.79±0.25) compared to that of the control group (1.21±0.08).

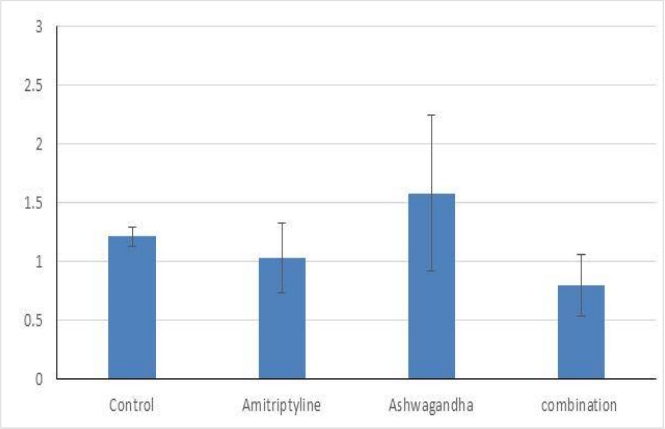

Fig.1: Serum total antioxidant capacity (U/L) at day 7.

1. At day 30

The results in Fig. 2 showed significant decrease in the levels of the total antioxidant capacity in groups treated with amitriptyline alone (0.87±0.06) and combination between amitriptyline and ashwagandha (0.58 ± 0.12), while ashwagandha treated group (1.25 ±0.12) had no substantial changes in the levels of the total antioxidant capacity in comparison with that of the control group (1.14±0.12)

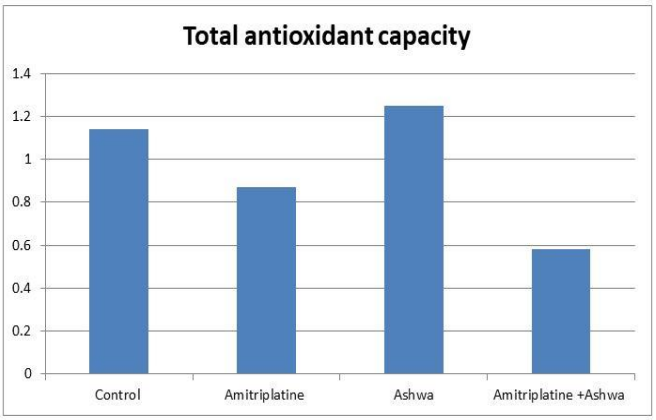

Fig.2:Serum total antioxidant capacity (U/L) at day 30

Acetylcholine esterase enzyme measurement in salivary glands

1. At day 7

The results in Fig.3 showed significant increase in acetylcholine esterase in the amitriptyline group (5.9 ±0.4)* compared with groups treated combination of amitriptyline with Ashwagandha (3.44±0.22) , Ashwagandha group (4.76 ± 0.55) and control group (4.82±0.26) at p value ≤0.05, as shown in Fig. 3.

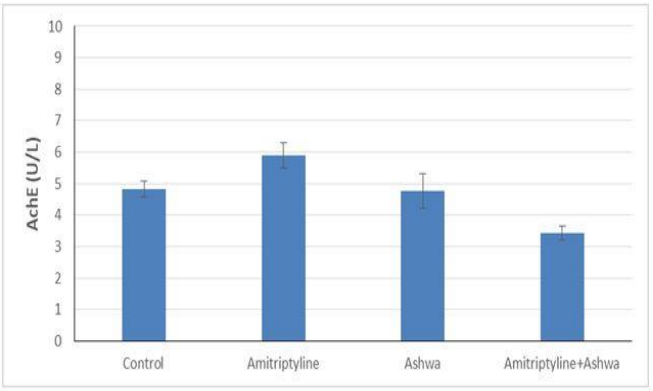

Fig.3: The levels of Acetylcholine esterase enzyme(AchE) at day 7 measured in (U/L).

1. At day 30

The results showed significant decrease in acetylcholinesterase in group treated with Amitriptyline (2.76±0. 64), ashwagandha (3.18±0.28) and combination of ashwagandha with amitriptyline (1.77±0.36) in comparison to the control group (4.49±0.78) at p-value ≤0.05, as shown in Fig. 4.

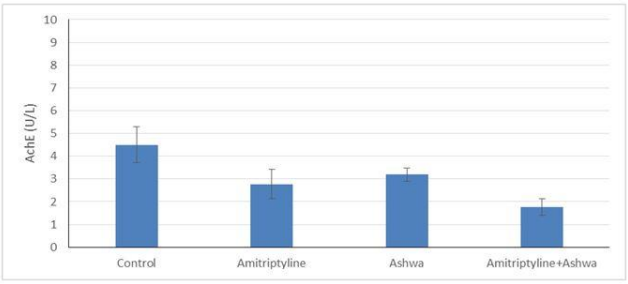

Fig.4: Acetyl cholinesterase enzyme (AchE) levels (U/L) at day 30.

DISCUSSION

The current study revealed ashwagandha administration protects salivary glands from oxidative stress through its antioxidant effect and a decrease in the acetylcholine esterase levels. Amitriptyline administration results in oxidative stress, which is shown by a decrease in total antioxidant capacity and an increase choline esterase enzyme in blood and salivary gland tissues. This result is consistent with the findings of other research that suggests ashwagandha has neuroprotective properties **(Zahiruddin *et al.*, 2020).** Ashwagandha has been used to treat a variety of neurological problems, including cognitive impairments, anxiety, and depression, according to preclinical and clinical research **(Durg *et al.*, 2015).** The reason for neuroprotective effect can be due to withanolides, glycowithanolides and sitoindosides and how they prevent lipid peroxidation (LPO) and increase antioxidant levels **(Paul *et al.*, 2021).**

The findings of this study concur with research demonstrating that Withanolide-A, a compound isolated from the roots of Ashwagandha, may restore synapses and regenerate neurites in severely injured neurons (**Kuboyama *et al.*, 2005,. (Mandlik and Namdeo 2021).** By raising the concentrations of total proteins and antioxidant enzymes like superoxide dismutase **(Cojocariu *et al.*, 2020)** and raising the amounts of several antioxidant enzymes, ashwagandha will lessen the production of free radicals in the affected cells. Withanamides, has been shown to remove free radicals generated during the onset and development of neurodegeneration **(Barua *et al.*, 2020).** Withanone, an active component of ashwagandha, protected NMDA-induced neuron-like cells by lowering the levels of malondialdehyde as indicators of DNA damage, according to research by Dar et al. (2017) **(Dar *et al.*, 2017).** The protective properties of ashwagandha are shown in decreasing glial activation and nuclear factor kappa B phosphorylation **(Dutta *et al.*, 2018).** After 7 days, Ashwagandha-treated group had a decrease in AChE. This finding in agreement with a study demonstrated the administration of Ashwagandha for the treatment

of Alzheimer's disease caused a decrease in acetylcholine esterase due to the herb's ability to reduce amyloid **(Sanka *et al.*, 2018).**

Amyloid aggregation can speed up the onset and progression of neurodegeneration due to accelerating the production of ROS by activating NMDA receptors. ROS can also speed up the development and aggregation of amyloid and its phosphorylation and polymerization **(Iova *et al.*, 2014).** The development of amyloid-B plaques will lead to a reduction in the cholinergic neurotransmitter acetylcholine, may be caused by ROS. This could affect synaptic transmission, which could trigger inflammatory reactions and cell death **(Omar *et al.*, 2021).** These results are in agreement with those of **Birla *et al.*, (2019),** which showed how W. somnifera's neuroprotective benefits mitigated the behavioral abnormalities brought on by Bisphenol through its anti-oxidative properties by raising levels of endogenous antioxidants **(Birla *et al.*, 2019).** Inhibiting AB synthesis, NF-kB activation, maintaining synaptic function, lowering apoptotic cell death, reversing the decline in cholinergic indicators, and enhancing antioxidant benefits via Nrf2 migration to the nucleus are some of the ways that ashwagandha exerts positive impacts on the body. Nrf2 enhances antioxidant enzyme activation in a manner similar to this. It's recommended that WA triggers Nrf2 to go to nucleus, where transcription factor increases the expression of neuroprotective heme oxygenase-1 proteins **(Farooqui *et al.*, 2018; Dutta *et al.*, 2020).**

Withanamides, present in ashwagandha root extract have impact on amyloid beta-induced neurotoxicity **(Dar *et al.*, 2017)**. Ashwagandha could shield the brain from the toxicity of amyloid plaques, according to research by Tiwari and colleagues **(Tiwari *et al.*, 2018).** These findings suggest that withanamides can increase the generation of soluble APP, decreasing the amount of amyloid and can bind to the active site of amyloid-B to protect cells from amyloid-B toxicity and prevent the development of fibrils **(Roy, 2018).** After 30 days of testing, the amitriptyline and ashwagandha combination group's biochemical analysis showed a reduction in antioxidant capacity because amitriptyline's effects on oxidative stress are exacerbated by the production of free radicals by iron, which present in sufficient amounts in ashwagandha to initiate the fenton reaction and cause a continuous oxidation reduction reaction that results in the generation of free radicals **(Qiu *et al.*, 2015).** Ashwagandha ability to reduce the levels of Acetylcholinesterase suggests that ashwagandha increase salivation and counteracts the anticholinergic side effect of amitriptyline which causes xerostomia after one week of treatment. This result is consistent with studies showed withanolide-A effective treatment for Alzheimer's disease by inhibiting acetylcholinesterase. Withanolide-A is essential for correcting the incline in cholinergic indicators like choline acetyltransferase and acetylcholine (ChAT) **(Roy, 2018; White *et al.*, 2018).**

Ashwagandha inhibited BuChE and AChE enzymes in vitro experiment **(Behl *et al.*, 2016).** Rats treated with ashwagandha had higher levels of ACh, choline acetyltransferase (ChAT), and other cholinergic markers. Ashwagandha also increases muscarinic M1 receptor binding **(Bhattacharya *et al.*, 1995).** After being treated with ashwagandha the cell lines' toxicity brought on by Amyloid-B was reversed by inhibition of acetyl cholinesterase **(Kurapati *et al.*, 2013).** The two distinct effects of amitriptyline on the acetyl cholinesterase during the study's two different administration periods of 7 and 30 days may be explained by the fact that acetylcholine stimulates the five muscarinic receptor subtypes M1 to M5, each of which activates different subfamily of G protein **(Santiago and Abrol, 2019).**

CONCLUSION

Amitriptyline induces oxidative stress, inhibits acetylcholinesterase momentarily, and has a fleeting anticholinergic effect. Ashwagandha root extracts possess antioxidant and acetylcholinesterase inhibitory properties.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the research data and tools used with this study.

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