

Ameliorative Effect of *Salvadora persica* (Miswak) on Cigarette Smoke Induced Anxiety and Depression in Rats

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ABSTRACT

Objectives: The aim of the study is to evaluate the anxiolytic and antidepressant activity of *Salvadora persica* in cigarette smoke-induced neuro-behavior changes in rats. **Methods:** The lyophilized decoction of *Salvadora persica* (*S. persica*) was administered daily for four weeks by oral route at the doses 50, 100 and 200 mg/kg to the cigarette smoke exposed rats. The depression and anxiety studies were done by forced swim test and elevated plus maze test, respectively. The serum levels of monoamine oxidase-A and relative brain weight were also determined. The results were analyzed statistically by one-way ANOVA followed by Duncans' multiple range tests. $p < 0.05$ was considered to indicate the significance of results. **Results:** The observation from the study indicated that exposure of cigarette smoke for eight weeks significantly ($p < 0.01$) enhanced the experimental parameters of depression and anxiety, besides increasing the monoamine oxidase-A and relative brain weight when compared with control animals. Administration of *S. persica* exhibited a dose-dependent inhibition in the neuro-behavioral parameters. *S. persica* at 200 mg/kg produced significant ($p < 0.01$)

antidepressant and antianxiety effects. The treatment was also found to reduce the serum monoamine oxidase-A and relative brain weight in the cigarette smoked animals. **Conclusion:** The data suggests that decoction of *S. persica* might possess antidepressant and anxiolytic properties in the cigarette smoke exposed animals. These actions could be related to its antioxidant and reversal in the neurocirculatory changes induced by the cigarette smoke.

Key words: Cigarette smoke, *Salvadora persica*, Antidepressant and antianxiety.

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INTRODUCTION

'Miswak' is a subtropical shrub commonly found in Arabian Peninsula, Egypt and India. The roots of the plant are referred by different names in different cultures such as chewing sticks, toothbrush tree, siwak and arak. The scientific name of the plant is *Salvadora persica* and it belongs to the family *Salvadoraceae*.¹ The plant is considered to be the oldest known natural substance for providing the oral hygiene and is popular among millions of people in Africa, South America, the Middle East and Asia. The roots are fibrous in nature and have excellent plaque removing properties.² The herb possesses significant antibacterial and antifungal potential which is an added advantage for maintaining the oral health.³

Studies conducted for the CNS activities indicated that the extracts of Miswak exhibited analgesic, anticonvulsant, sedative, antidepressant, anti-inflammatory activities.⁴ The bioactive components isolated for these effects include oleic acid, salvadouria, salvadorine, linoleic acid, trimethylamine, lignans, etc. The proposed mechanism for these actions include: presence of eugenol for analgesic activity, lignan glycosides, organic sulphur and urea alkaloids for anticonvulsant activity and prevention of apoptosis by the extract for antidepressant activity.^{4,5}

Cigarette (tobacco) smoking is common among both adults as well in adolescents. Cigarette smoking has been reported to contribute a wide range of health complications such as cancer, cardiovascular and respiratory diseases. Millions of deaths have been reported annually around the world due to smoking behavior.⁶ Data from these studies indicated that chronic cigarette smoke exposure results in several psychological disorders such as depression, anxiety, mood swings and sleep disturbance.

Besides, incidences of substance abuse were found to be more common among the people who are cigarette smokers.⁷

Depression is one of the most common psychiatric diseases and its prevalence is reported to be as high as 16% among the population. The symptoms of depression include change in appetite, change in sleep, low energy, low self-esteem, poor concentration or decision making, suicidal thoughts or plans.⁸ On the other hand, anxiety or anxiousness affects the way a person thinks, feel and behave and the symptoms include sweating, trembling, feeling of choking, nausea, abdominal distress, dizziness, feeling of losing control and or feeling of impending doom.⁹ These two psychiatric diseases have been reported to effect of quality of life among patients and can also hinder in the prognosis of the treatment. Hence, there is a global public health objective for effective treatment of these behavioral diseases thereby benefiting both patients as well to government exchangers responsible for providing the health care facilities.⁸⁻¹⁰

This study was designed with an aim to evaluate the antidepressant and anxiolytic properties of lyophilized decoction of *Salvadora persica* in chronic cigarette smoke exposed animals.

MATERIALS AND METHODS

Plant material and preparation of decoction

Fresh roots of the plant *Salvadora persica* grown in the Makkah region of Saudi Arabia was purchased. The plant material was authenticated by Dr. Hamdoon, Pharmacognosist in the Department of Phytochemistry

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and Medicinal Chemistry, College of Pharmacy, Qassim University and a voucher specimen was deposited in the herbarium.

The decoction was prepared as per the procedure described by Galati *et al.* 1999.¹¹ 100 g of dried powdered roots of *S. persica* was boiled with 1000 ml distilled water for 30 min. After filtration, the decoction was lyophilized. The quantity of lyophilized powder obtained from 100 g of drug was 12.6 g. The lyophilized powder was administered, in the morning, by oral gavage, at doses of 50, 100 and 200 mg/kg, dissolved in aqueous vehicle, in a volume of 0.5 ml/100 g of body weight.

Animals

Young adult rats of Wistar strain were used for the present study. Both male and female animals were utilized weighing 120-140 gm of body weight. The experimentation was conducted after obtaining the permission from the Institutional Animal Ethics Committee (Approval ID # 2019-CP-4). Animals were housed in the central animals house facility maintained under standard lab conditions. Animals were provided pelleted food and water *ad libitum* under 12 hr dark and light environment.

Experimental grouping

The experimental grouping of the animals was done as follows:

1. Control group: Normal saline (no exposure to cigarette smoke).
2. Positive control: Chronic exposure to cigarette smoke for six days in week for 8 weeks.¹²
3. Treatment group-1: *Salvadora persica* decoction (50 mg/kg, p.o, weeks)¹³ + Cigarette smoke.
4. Treatment group-2: *Salvadora persica* decoction (100 mg/kg, p.o, 4 weeks)¹³ + Cigarette smoke.
5. Treatment group-3: *Salvadora persica* decoction (200 mg/kg, p.o, 4 weeks)¹³ + Cigarette smoke.
6. Standard group: Ginseng (100 mg/kg, p.o, 4 weeks)¹⁴ + Cigarette smoke.

Experimental design

The experimental animals were exposed to the cigarette smoke in the chamber, a glass box in a cube shape (aquarium shape) with the size of 30 × 40 × 80 cm for keeping the rats and a hood over the aquarium-shaped box to evacuate the extra smoke from the environment (Figure 1) described by Ypsilantis *et al.* 2012.¹⁵ Animals were daily exposed to cigarette smoke (2-3 cigarettes) for total duration of 30 min (with intermittent exposure to fresh air for 2 min after every 10 min of smoke exposure). At the end of each week of exposure, the changes in the behavior were studied by using the forced swim test and elevated plus maze. Also, the changes in the body weight, general health condition, water and food consumption were monitored.

The animals were tested for depression and anxiety states after every week of cigarette smoke exposure and those exhibiting the neurobehavioral alterations were only included in the study. Once a significant level of depressive and anxiety states were observed in the animals (8th week), groups 3-6 were subjected to respective drug treatments for four weeks, simultaneously exposing the animals to cigarette smoke.

Behavioural studies

Forced swim test

In this test rats were forced to swim in a cylindrical transparent glass vessel (50 cm high and 21cm diameter), that contained fresh water to a depth of 26 cm at room temperature (27 ± 2°C). The total duration of immobility was measured during a 4 min test session. Rats were considered

immobile when they ceased struggling and remained floating in water except small movements necessary to keep their heads above the water. In addition, the number of climbing attempts and diving to locate the escape route were also recorded. The water was changed after each animal to avoid the influence of water temperature and substances left from the previous session.¹⁶

Elevated plus maze test

This test is one of the most commonly used models to assess anxiety in small rodents. Its design was similar to that originally described by Lister, 1987.¹⁷ The apparatus composed of two open (50 cm × 10 cm × 1 cm) and two enclosed (50 cm × 10 cm × 50 cm) arms that radiate from a central platform (10 cm × 10 cm) to form a plus sign. The plus-maze was elevated to a height of 50 cm above the floor level by a single central support. The parameters such as time spent in the arms, number of entries, headdips from open arm and defecation frequency were recorded for 10 min.

Estimation of serum monoamine oxidase levels

The principle of monoamine oxidase-A enzyme estimation by ELISA kit is based on a competitive enzyme immunoassay system. The assay was done as per the procedure described in the users' manual (Cloud Clone Corp, USA); the 96 well plate are coated with IgG, to which standard dilutions or samples were added for competitive immune-reaction. After incubation and plate washing, the enzyme activity was determined by 3,3',5,5'-tetramethylbenzidine (TMB) and the concentration of monoamine oxidase-A was calculated by measuring the optical density at 450 nm and from the standard concentration vs optical density curve.¹⁸

Relative brain weight

The influence of various treatments was determined from the variation in the mass of the brain with respect to the body weight and is referred as relative brain weight.¹⁹

Statistics

The results obtained were expressed as mean ± SE. The data was analyzed using one-way analysis of variance and Duncan's multiple range tests. In all cases, $p < 0.05$ was considered to indicate significance.

RESULTS

Effect of *Salvadora persica* decoction on the depressive parameters in chronic cigarette smoke exposed rats by using forced swim test

The observation from the Table 1 indicated that eight weeks of cigarette smoke exposure significantly increased the time of immobility ($p < 0.001$) in rats and also reduced the number of climbing attempts ($p < 0.01$) and dives ($p < 0.05$) compared to the control. The administration of *S. persica* at 50 mg/kg did not alter significantly the time of immobility, number of climbing attempts and dives compared to the cigarette smoke exposed animals. However, when the dose of *S. persica* was tested at 100 mg/kg, a significant ($p < 0.05$) reduction in the immobility duration and number of dives were increased when compared to the challenge group. These changes were found to be further significantly altered when *S. persica* was tested at 200 mg/kg. The immobility time was reduced ($p < 0.01$), the climbing attempts were increased ($p < 0.05$) and the dives were enhanced ($p < 0.05$) compared to cigarette smoke exposed group. On the other hand, ginseng at 100 mg/kg produced a significant ($p < 0.01$) decrease in the time of immobility and enhanced the climbing attempts and number of dives compared to the smoke exposed animals.

Effect of *Salvadora persica* decoction on the anxiety parameters in chronic cigarette smoke exposed rats by using elevated plus maze test

The elevated plus maze test indicated that cigarette smoke exposed animals showed significant alteration in the anxiety parameters such as time spent in the open arm ($p < 0.001$), number of entries to open arm ($p < 0.05$), number of entries to close arm ($p < 0.05$), number of head-dips ($p < 0.05$) and defecation frequency ($p < 0.05$) as compared to the control group. The administration of *S. persica* showed a dose-dependent reversal in the parameters characterized for the anxiety. At 50 mg/kg, *S. persica* did not produced a significant change but at 100 mg/kg, a significant ($p < 0.05$) increase in the duration of time spent in the open arm was observed compared to the cigarette smoke group. *S. persica* at 200 mg/kg exhibited a significant increase in the time duration in the open arm ($p < 0.01$), number of entries to open arm ($p < 0.05$) and number of head-

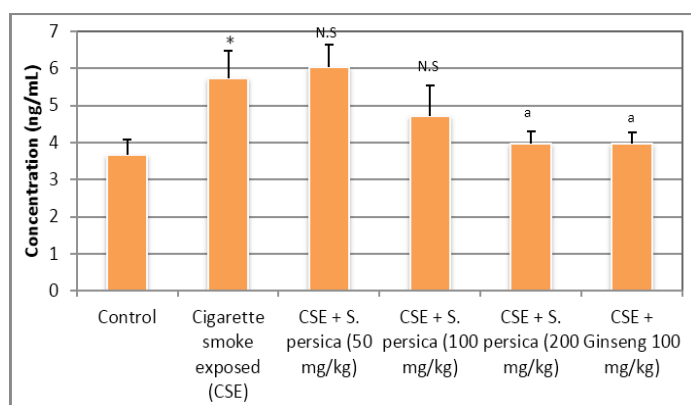


Figure 1: Effect of *S. persica* on serum MAO-A level in cigarette smoked animals.

Values are expressed as Mean \pm SE, N.S = Not significant, $n=6$

Statistics: One-way Anova followed by Duncans' multiple range tests

* $p < 0.05$ compared with control group

a $p < 0.05$ compared with the cigarette smoke exposed group

Table 1: Effect of *Salvadora persica* decoction on the depressive parameters in chronic cigarette smoke exposed rats by using forced swim test.

Treatment	Time of immobility (sec)	Number of climbing attempts	Number of dives
Control	104.33 \pm 6.68	12.85 \pm 1.54	8.04 \pm 0.65
Cigarette smoke exposed (CSE)	174.01 \pm 8.45***	6.92 \pm 1.06**	3.29 \pm 0.78*
CSE + <i>S. persica</i> (50 mg/kg)	179.43 \pm 7.89 N.S	7.67 \pm 0.87 N.S	2.98 \pm 0.91 N.S
CSE + <i>S. persica</i> (100 mg/kg)	146.70 \pm 7.21a	7.74 \pm 1.24 N.S	5.79 \pm 0.90 a
CSE + <i>S. persica</i> (200 mg/kg)	132.47 \pm 6.36 b	10.60 \pm 1.28 a	6.17 \pm 0.86 a
CSE + Ginseng 100 mg/kg)	128.37 \pm 7.83 b	11.86 \pm 1.12 b	7.11 \pm 0.69 b

Values are expressed as Mean \pm SE, N.S = Not significant, $n=8$

Statistics: One-way Anova followed by Duncans' multiple range tests

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared with control group

a $p < 0.05$, b $p < 0.01$ compared with the cigarette smoke exposed group

Table 2: Effect of *Salvadora persica* decoction on the anxiety parameters in chronic cigarette smoke exposed rats by using elevated plus maze test.

Treatment	Time spent in open arm (sec)	Number of entries to open arm	Number of entries to close arm	Number of head-dips from open arm	Defecation frequency
Control	190.10 \pm 10.27	11.30 \pm 2.41	6.29 \pm 2.13	17.89 \pm 3.98	0.54 \pm 0.12
Cigarette smoke exposed (CSE)	94.34 \pm 6.22***	4.68 \pm 1.69*	14.61 \pm 3.21*	8.12 \pm 1.27*	3.41 \pm 0.77*
CSE + <i>S. persica</i> (50 mg/kg)	107.57 \pm 8.34 N.S	6.67 \pm 1.58 N.S	15.32 \pm 3.99 N.S	10.34 \pm 3.86 N.S	3.62 \pm 0.47 N.S
CSE + <i>S. persica</i> (100 mg/kg)	121.78 \pm 8.72 a	6.39 \pm 1.73 N.S	12.56 \pm 2.67 N.S	12.79 \pm 2.99 N.S	3.72 \pm 0.58 N.S
CSE + <i>S. persica</i> (200 mg/kg)	140.29 \pm 9.60 b	9.34 \pm 1.88 a	12.37 \pm 4.08 N.S	14.83 \pm 2.79 a	2.02 \pm 0.86 N.S
CSE + Ginseng 100 mg/kg)	138.07 \pm 10.55 b	9.75 \pm 1.52 b	12.74 \pm 3.50 N.S	15.52 \pm 2.33 a	1.26 \pm 0.26 a

Values are expressed as Mean \pm SE, N.S = Not significant, $n=8$

Statistics: One-way Anova followed by Duncans' multiple range tests

* $p < 0.05$, *** $p < 0.001$ compared with control group

a $p < 0.05$, b $p < 0.01$ compared with the cigarette smoke exposed group

dips ($p < 0.01$) compared to the smoke exposed group. The administration of ginseng showed similar action on the time spent in open arm ($p < 0.01$) but further increased the number of entries to open arm ($p < 0.01$). The drug also increased the number of head-dips ($p < 0.05$) and reduced the defecation frequencies ($p < 0.05$) compared to the challenge group. However, none of the treatments in the tested doses altered significantly the number of entries to the close arm (Table 2).

Effect of *Salvadora persica* decoction on the serum monoamine oxidase-A level in chronic cigarette smoke exposed rats.

The serum monoamine oxidase estimation indicated that when the animals were chronically exposed to cigarette smoke the level of the enzymes significantly ($p < 0.05$) increased compared to the control animals. Administration of *S. persica* at 200 mg/kg significantly ($p < 0.05$) reduced the enzyme levels compared to cigarette smoked animals, while lower tested doses of *S. persica* did not induce significant alteration. The administration of ginseng (100 mg/kg) also produced a significant ($p < 0.05$) reduction in the level of MAO-A level compared to the challenge group (Figure 1).

Effect of *Salvadora persica* decoction on the relative brain weight in chronic cigarette smoke exposed rats

The studies conducted to find the effect of various treatments on the relative brain weight indicated that after chronic exposure of cigarette smoke the weight of the organ increased significantly ($p < 0.05$) compared to the control group. The administration of *S. persica* at 50 and 100 mg/kg did not exhibit significant change in the relative weight of brain however, when the dose was increased to 200 mg/kg, a significant ($p < 0.05$) reduc-

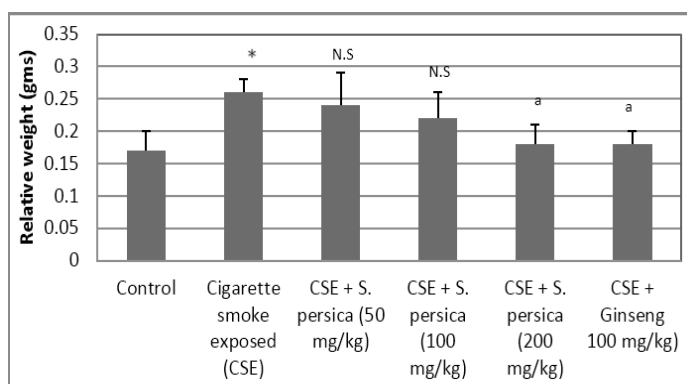


Figure 2: Effect of *Salvadora persica* decoction on the relative brain weight in chronic cigarette smoke exposed rats.

Values are expressed as Mean \pm SE, N.S = Not significant, $n=8$

Statistics: One-way Anova followed by Duncans' multiple range tests

* $p<0.05$ compared with control group

a $p<0.05$ compared with the cigarette smoke exposed group

tion was observed compared to the cigarette smoked animals. Similar findings were noted when ginseng was tested at 100 mg/kg in the cigarette smoke exposed animals (Figure 2).

DISCUSSION

The results from this study indicated that chronic exposure of rats to cigarette smoke significantly ($p<0.01$) altered those parameters that are suggestive of depression and anxiety, when compared with the control. The relative brain weight and serum monoamine oxidase-A level were found to be elevated after cigarette exposure. Administration of decoction of *Salvadora persica* exhibited a dose-dependent reversal in these changes. It alleviated the parameters of depression and anxiety at the highest dose (200 mg/kg), besides reducing the relative brain weight and serum monoamine oxidase-A level. Similar antidepressant and anti-anxiety effects were found when ginseng was tested as a standard agent (Table 1 and 2, Figure 1 and 2).

Exposure to cigarette smoke is reported to cause several diseased conditions that affect almost all the systems of body. Cigarette smoke contains complex mixtures of various chemicals. Some of them are gases (carbon monoxide, hydrogen cyanide), liquid-vapor portion of smoke aerosols (formaldehyde, acrolein, benzene, nitrosamines) and submicron-sized solid suspended particles (nicotine, phenol, polyaromatic hydrocarbons).⁶

The higher incidences of mental illness and smoking habits has emerged as one of the major concern specially among the middle aged population since it accounts for much of the reduction in the life expectancy. The data available in the literature indicates that the severity of the disease increases with duration and frequency of tobacco smoking.^{7,9} It was observed from the present study that when animals were exposed to cigarette smoke for chronic duration of time there was a significant increase in the depressive and anxiety parameters (Table 1 and Table 2). The mechanism suggested is that tobacco smoke affects the neurocirculatory system of an individual. The prolonged exposure of nicotine is reported to dysregulates the hypothalamic-pituitary-adrenal system, resulting in hypersecretion of cortisol and alterations in the activity of associated monoamine neurotransmitter system, whose function is to regulate reactions to various types of stressors.²⁰

Administration of *S. persica* reduced the depressive and anxiety parameters in the cigarette smoke exposed animals. Similar results were observed when ginseng was treated to tobacco smoke exposed rats (Table 1 and Table 2). Earlier studies on the ginseng revealed that administration

of this natural substance corrected the hypothalamic-pituitary-adrenal (HPA) axis defects. It corrected the sympathetic nervous system pathway that was involved in defective regulation of neurotransmitters controlling the emotional, behavior and various types of stresses.²¹ From these data, it can be suggested that daily gavage of decoction of *S. persica* might have exhibited similar mechanism in preventing the neurocirculatory changes in HPA responsible for psychological disorders. However, none of the treatments in the tested doses significantly reduced the number of entries to the closed arm (Table 2). It can be suggested that increasing the duration of treatment might produce significant reduction since the administration of drugs found to minimize the locomotory actions of the animals in the closed arm.

Further, the modifications in the neurotransmitters levels can be correlated from the studies on the monoamine oxidase-A level in the serum. Our results indicated that cigarette smoke exposed animals has significantly elevated the levels of enzymes that destroys the monoamines such as serotonin, dopamine, norepinephrine.²¹ The administration of decoction of *S. persica* as well as the ginseng significantly reduced these enzymes when they were tested at 200 mg/kg and 100 mg/kg, respectively (Figure 1).

The noxious chemicals present in the cigarette smoke are known to produce deleterious effects to organs including brain. The agents have the tendency to damage the delicate cells of nervous system and can contribute in various types of inflammatory responses.²² Our study indicated that cigarette smoked animals had significant higher relative brain weight compared to the normal animals (Figure 2). Administration of ginseng significantly reduced the relative weight of brain. Ginseng is reported to contain natural antioxidants called ginsenosides and contribute in potent anti-inflammatory action.²³ *Salvadora persica* also reported to possess anti-inflammatory and antioxidant properties due to the presence of flavonoids and phenolic compounds.^{4,5} Presence of these phytochemicals could be related to reduction in the relative weight of the brain in cigarette smoke exposed animals.

CONCLUSION

The observation from the study indicated that chronic exposure of cigarette smoke altered the neurobehavioral parameters in rats besides increasing the monoamine oxidase-A and relative brain weights. Administration of *Salvadora persica* decoction minimized these changes suggesting its antidepressant and anxiolytic properties. The treatment also reduced the monoamine oxidase-A and relative weight of brain indicating that the decoction might correct the neurotransmitter alterations and brain injuries. More studies in this direction are suggested to reveal the precise mechanism of action of Miswak on neurobehavioral diseases.

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CONFLICT OF INTEREST

There is no conflict of interest with this research.

ABBREVIATIONS

S. persica: *Salvadora persica*; **p.o:** per oral; **min:** minutes; **ELISA:** Enzyme linked immunosorbent assay; **IgG:** Immunoglobulin G; **TMB:** Tetra methyl benzidine; **S.E:** Standard error; **MAO-A:** Monoamine Oxidase-A; **HPA:** Hypothalamic-pituitary-adrenal.

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