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ANTI-ANXIETY AND NOOTROPIC ACTIVITY OF *MORUS ALBA* EXTRACTS IN ALBINO WISTAR RATS

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Abstract:

The current investigation was planned to assess Anti-anxiety and Nootropic activity of aqueous and ethanol extracts of Morus Alba. in Albino wistar rats.

***Methods**: Anti-anxiety of aqueous and ethanolic extracts of Morus Alba was appraised by adaptogenic activity in rats through the forceful swimming and Biochemical parameters such as 6-β-OH-cortisol; urinary vanilly mandelicacid (VMA), homovanillic acid (HVA), ascorbic acid and 5-hydroxy indole acetic acid (5HIAA) were estimated to analyze the anti-anxiety activity. Aqueous and ethanolic extracts of Morus Alba were administrated orally at dose of 200 and 400mg/kg body weight 1h before the induction of anxiety to prevent anxiety-induced urinary biochemical changes in a dose dependent manner. However, non-significant changes in the urinary excretion of Homovanillic acid (HVA), urinary vanillymandelic acid (VMA), 6-β-OH-cortisol, 5-hydroxy indole acetic acid (5HIAA) and ascorbic acid was perceived when compared to basal levels in normal animals. Behavioral procedures of anxiety and cognitive-enhancing were assessed in rats. A ethanolic extract of M. Alba with dose ranges of 100, 200, and 400 mg/kg was given once a daily for 7 days via oral route and the efficacy was matched by those elicited by lorazepam (1 mg/kg, p.o.), imipramine (10 mg/kg, p.o.) and Withania somnifera (100 mg/kg, p.o.) for antianxiety, and nootropic studies, respectively. Standard drugs were given 1 time, 30 min preceding the behavioral trials.*

***Results**: Nevertheless, in all groups which were treated with aqueous and ethanolic extracts of Morus Alba, there was no statistically difference between level of 6-β-OH-cortisol, urinary vanillymandelic acid (VMA), homovanillic acid (HVA), ascorbic acid and 5-hydroxyindoleacetic acid (5HIAA) as compared to normal animals. One-way analysis of variance followed by Newman–Keuls multiple comparison test was employed to analyze the results. $P < 0.05$ was considered statistically significant as compared to control. MA at 400 mg/kg also induced an antianxiety activity similar to imipramine, in the behavioral despair, learned helplessness test, and tail suspension among selected doses of the MA. Moreover, MA at 400 mg/kg produced a significant nootropic effect.*

***Conclusion**: The study shows that among the different MA doses, MA at 400mg/kg possesses significant antianxiety and nootropic effects has therapeutic beneficial for the management of psychological ailments.*

***Keywords**: adaptogenic activity, Morus Alba, biochemical parameters.*

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INTRODUCTION:

Anxiety can be defined as the sum total of all the reaction of the body, which disorganise the normal physiological condition and result in a state of threatened homeostasis. Anxiety/stress is an internationally conceded phenomenon fortified by advancement of industrialization in a demanding civilization. Thus every individual is likely to face stressful situation in day to day life (Selye, 1998). Anxiety is a stimulus that activates the hypothalamic pituitary adrenal (HPA) axis and Sympathetic Nervous System (SNS) and begets a physiological change. Physiological responses to anxiety stimuli, including the increases in blood pressure, heart rate, body temperature and plasma concentration of adreno-corticotrophichormone (ACTH), can be related to the anxiety induced activation of the SNS. Anxiety prompts synthesis and release glucocorticoids (corticosterone and cortisol) and monoamines such as epinephrine, dopamine, norepinephrine and serotonin which are characteristic anxiety hormones (Carrasco et al., 2003). Adaptogens are the substances that help organisms to adapt to unfavourable stressful conditions, which could be physical, chemical, biological or mental conditions (Rege et al., 1999). The prevalent objective of adaptogenic therapy is due to diminish stress reactions during the alarm phase of the stress response, inhibitor retard the state of exhaustion and consequently issue a certain level of protection against long-term stress (Wagner et al., 1994). Morus alba belongs to family Moraceae commonly called as white mulberry. This plant has been used traditionally as anti-asthma, antidiabetic (Singabetal.,2005), hypotensive (Fukaiet al.,1985) and neuroprotective (Kangetal.,2006).The current investigation was carried out to assess the anti- anxiety activity of aqueous and ethanol extracts of Morus alba.

MATERIALS AND METHODS:

Plant material and Preparation of extracts

The fruits of Morus alba were collected from Chittor, Andhra Pradesh, India and authenticated by Department of Botany A.U College affiliated to Osmania University, Telangana, India, a voucher specimen (AUCP-PRJ-13/23) were preserved for future references. The fruits a material (1kg) were dried powdered and extracted with water and ethanol (60- 80oC) using soxhlet methods. The filtrate was evaporated at 70o C in a vaccum dryer to give final yield 40.5g.

Chemicals

Homovanillic acid (CAS 306-08-1), urinary vanillymandelic acid (VMA), 6-β-OH-cortisol, 5-hydroxyindoleacetic acid (5HIAA) and ascorbic acid was purchased from Sigma, ST Louis, MO, USA. Acetonitrile and methanol HPLC grade were supplied from Ganis Scientific & Surgicals Telangana, India. All other chemicals were analytical grade and obtained from local store of Ganis Scientific & Surgicals Telangana, India.

Animals

Albino Wistar rats (150-200gm) of either sex obtained from the NIN animal house, Hyderabad and were housed at room temperature in a well- ventilated animal house under 12hrs light/dark cycle in polypropylene cages (29"x22"x14") with stainless steel grill top, bedded with paddy husk. The animals were maintained under standard conditions in an animal house as per the guidelines of "Committee for the Purpose of C control and Supervision on Experiments on Animals" (CPCSEA) for at least one week prior to use. The rats had free access to standard rat chow and water ad libitum. The study protocol was approved by Institutional Animal Ethics Committee (IAEC), Anwarul Uloom college of Pharmacy. (Registration No: 173/2014, renewed in 2025).

Morus alba dose was selected on the basis of randomization and was administered in distilled water to Groups (II, III, and IV) at 100, 200 and 400mg/kg orally, once in a day for 7days. The control group (Group I) received an equal volume of distilled water. Standard drugs were also employed to Group V accordingly in each set of protocol and were dispensed orally to animals 1h before the experiments. On day7, animals were subjected to behavioral studies.

Nootropic Activity

Elevated plus maze -

The apparatus for elevated plus-maze test contained 2 open arms (50cm×10cm×40cm) and 2 closed arms (50 cm × 10 cm × 40 cm), for rats facing each other with an open roof that extends from a common central platform (10 cm × 10 cm).The maze was kept in a dimly lit room and elevated at a height of 50cm above the ground level. The rats were positioned in the center of the maze independently, facing one of the closed arms. Thereafter, a number of entries and time spent on the open and closed arms were documented throughout the 5 min observation period. An arm entry was defined when four paws of the rats were inside the arm. A neutral “blind” observer made observation(Vijayalakshmi,et.al).

Open field test-

The open field test apparatus was built of plywood (60cm×60cm×60cm) and was painted black. White marks of 6mm wide divide the floor in to sixteen

squares (15cm×15cm). The open field was lit with 16W bulb focusing on to the arena from a height of 100 cm excluding the open field; the whole room was kept dark throughout the experiment. Animals were positioned individually at the center of the test apparatus for 5min, and the following behavioral aspects were observed (Yadav et.al).

- Ambulation: Assessed in terms of the number of squares traversed by the rat.
- Rearings: Measured in terms of the number of times the rat raised on its rear limbs.
- Self-grooming: Measured in terms of the number of times The rat cleaned facial region and licked different body parts.
- Activity in center: Measured in terms of the number of Central squares traversed by the rat
- Fecal dropping: Measured in terms of the number of fecal droppings excreted during the observation.

Social interaction test-

The rodents were individually accommodated for 5 days prior investigation. The test device consists of a wooden box (60cm×60cm×35cm) located in a faintly illuminated room.On the 6thday, the rodents were individually positioned in the wooden box and offered two 7.5min familiarization sessions at 2 h time period. On the 7thday, based on sex and weight, rodents were paired and retained in the apparatus for 7.5min. The total time devoted by the rodent pair in "social interaction," included sniffing, biting, grooming, boxing, kicking, and crawling under or over the partner, was documented during 7.5min time, by a neutral blind observer.(File SE ET AL)

Anti-anxiety activity

Behavioral despair test-

Each animal was restrained in a cylinder (45cm×20cm) filled with water at a height of 38 cm (25°C ± 2°C) so that it could not contact with the bottom of the cylinder with its rear paws or mount over the edge of the cylinder. Dual swim sessions were performed, an early 15 min pretest followed by a 5 min test after 24h of drug administration. During the test session, the immobility period characterized by absolute cessation of swimming and performing necessary movement's essential to place its head beyond the aquatic level was observed. (Porsolt ET AL)

Tail suspension test

Each rat in the group was hanged by the tail (50 cm above the floor) with an adhesive tape to a cord in an upside down position so that its nostrils touch the water surface in a vessel. After the early escape-oriented actions, the rat rapidly turns out to be immobile, and the immobility period (the absence of initiating movements and includes passive swaying) was recorded during 5 min observation period. (Bourin M ET AL)

Learned helplessness test

Rats were exposed to a shock of 0.7 mA for 10 s every minute for 1h. The gadget was a box with dimensions of 30cm×45cm×30cm having grid floor. At an altitude of 20 cm above the base, a platform (7.5 cm × 7.5 cm) was introduced from one side wall to permit a jump-up escape reaction.The platform was not provided for the whole period of training. After the proper treatment, the rats were allowed for acquisition of a jump-up response. At the beginning of a trial, the platform was provided in the box, and a current of 0.7mA was introduced. The shock was ceased in 10s if the rat couldn't escape on to the platform within the specified period. If an escape retort ensued, the rat was permitted to stand on the platform for the length of 10s, and then reverted to the base. (Seligman ME ET AL)

Statistical analysis

The data were displayed as mean ± S.E.M. Statistical analysis was done by using student's paired t-test, where the difference was considered significant if $p < 0.05$.

RESULT AND DISCUSSION:

Anxiety is linked to many diseases such as heart disease, stroke, cancer, gastrointestinal problems, necrosis, etc[CottJ ET AL]. In view of the increasing investigation towards plants have non- specific resistance (adaptogens) activity towards anxiety, current research was considered to estimate the effect of aqueous and ethanol extracts of *Morus Alba* on non-invasive bio markers. Locus coeruleus in the centre and sympathetic nerves in the periphery release noradrenaline as the mediator(Sardessai ET AL).

Effect of the Morus alba Extract on Elevated Plus Maze

(200 and 400 mg/kg) treated rats exhibited a significant increase in entries made ($P = 0.0021$, $P < 0.001$) and time spent in open arms ($P=0.0063$,$P<0.001$) except at 100mg/kg ($P>0.05$).MA-treated rats exhibited a significant decrease in entries made ($P<0.001$,$P<0.001$) and time spent ($P=0.0218$,$P<0.001$) in enclosed arms at 200 and 400mg/kg, respectively. Lorazepam ($P < 0.001$) also produced significant anxiolysis and its effect was qualitatively comparable to that of MA. The results were summarized in Table-I.

Effect of the Morus alba Extract on Open Field Test

Rats treated with doses (100,200 and 400mg/kg) of MA showed a significant increase in open field ambulation (P=0.0221, P<0.001, and P<0.001), rearing (P>0.05,P<0.001, and P<0.001), activity in center (P>0.05, P>0.05, and P=0.0041), and self-grooming (P < 0.001, P < 0.001, and P < 0.001) when compared to vehicle-treated rats and produced comparable activity with lorazepam; indicating anxiolytic activity of MA. Simultaneously, a significant decrease in fecal droppings was observed at all doses of MA, except at 200 mg/kg (P > 0.05). Lorazepam (P < 0.001) also induced significant anxiolytic activity and its effect was also found to be qualitatively comparable to that of MA. The results were summarized in Table-II.

Effect of the Morus alba Extract on Social Interaction Test

Rats treated with MA spent significantly more time in social interaction as compared to control rats in a dose-dependent wise (P<0.001). Similarly, lorazepam-treated group exhibited a significant increase in social interaction (P<0.001) in rats and its effect was comparable to MA at all doses. The results were shown in Table-III.

Effect of the Morus alba Extract on Behavioral Despair Test

MA at 100mg (P=0.013), 200mg (P<0.001), and 400mg/kg (P<0.001) treated rats caused a significant dose-dependent decrease in immobility time. Imipramine also showed similar activity and effects were qualitatively comparable to that of MA (P<0.001). The results were summarized in Table-IV.

Effect of the Morus alba Extract on Tail Suspension Test in Rats

MA at 100(P=0.017), 200(P<0.001) and 400mg/kg (P<0.001) treated rats significantly reduced the immobility time dose- dependently, and MA at 400 mg/kg (P > 0.05) produced the equivalent effect as that of imipramine, a well-established antidepressant drug, which showed a significant reduction in immobility time. The results were summarized in Table-IV.

Effect of the Morus alba Extract on Learned Helplessness Test

The escape failure significantly decreased in rats treated with the dose of MA 400mg/kg (P<0.001). In addition, the number of avoidance response also significantly increased, respectively, with the same dose of MA (P < 0.001). Imipramine (P <0.001) also showed significant reduction of learned helplessness and its effect was qualitatively comparable to that of MA at 400 mg/kg. The results were summarized in Table-IV.

Table-I : Effect of the Morus alba extract on elevated plus- maze test in rats

Treatment	Time spent on (s)		Entries on	
	Enclosed arms	Open arms	Enclosed arms	Open arms
Control	224.36±3.26	47.72±1.93	2.66±0.04	2.23±0.37
CF(100mg/kg)	221.19±4.82	43.23±1.01	2.82±0.04*	2.62±0.12
CF(200mg/kg)	206.91±4.03*	62.97±2.43*,$	2.48±0.03*,$	3.47±0.21*,$
CF(400mg/kg)	197.66±3.69*,$	82.26±3.24*,$,#	1.91±0.03*,$,#	4.67±0.16 *,$,#
Lorazepam(1mg/kg)	179.45±2.43*,$,#,¥	98.02±2.97*,$,#,¥	1.96±0.02*,$,#	5.16±0.25*,$,#

Values are expressed as mean±SEM (*n*=6).*P<0.05 significant as compared to vehicle, $$P$<0.05 significant as compared to MA (100mg/kg), #P<0.05 significant as compared to MA (200 mg/kg), ¥P<0.05 significant as compared to MA (400 mg/kg), statistical test employed is one-way ANOVA followed by Tukey's multiple comparisons test. MA: Morus alba, SEM: Standard error of mean, ANOVA: Analysis of variance

Table-II: Effect of the Morus alba extract on open field test in rats

Treatment	Ambulation	Rearings	Self-groomings	Activity in center	Fecal droppings
Control(vehicle)	32.07±1.03	8.75±1.97	3.70±0.09	0.41±0.03	3.68±0.12
CF(100mg/kg)	39.45±1.22*	17.08±2.25	4.84±0.05*	1.47±0.07	4.17±0.15*
CF(200mg/kg)	46.67±1.54*,$	21.62±2.82*	5.28±0.15*,$	2.01±0.04	3.79±0.06
CF(400mg/kg)	52.23±1.81*,$	26.47±1.46*,$,#	6.08±0.13*,$,#	3.52±0.97*	1.88±0.08*,$,#
Lorazepam(1mg/kg)	56.61±1.63*,$,#,¥	31.81±2.31*,$,#	7.12±0.15*,$,#,¥	4.02±0.89*,$	1.34±0.02*,$,#,¥

Values are expressed as mean±SEM (n=6).*P<0.05 significant as compared to vehicle, $$P$<0.05 significant as compared to MA (100mg/kg),#P<0.05 significant as compared to MA (200 mg/kg), ¥P<0.05 significant as compared to MA (400 mg/kg), statistical test employed is one-way ANOVA followed by Tukey's multiple comparisons test. MA: Morus alba, SEM: Standard error of mean, ANOVA: Analysis of variance

Table-III: Effect of the Morus alba extract on social interaction test in rats

Treatment	Social interaction time(s)
Control (vehicle)	63.33±1.38
CF (100mg/kg)	91.83±1.42*
CF (200mg/kg)	107.16±1.92*,$
CF (400mg/kg)	151.83±1.01*,$,#
Lorazepam(1mg/kg)	163.5±1.43*,$,#,¥

Values are expressed as mean±SEM (n=6).*P<0.05 significant as compared to vehicle, $$P$<0.05 significant as compared to MA (100 mg/kg); #P<0.05 significant as compared to MA (200 mg/kg), ¥P<0.05 significant as compared to MA (400 mg/kg), statistical test employed is one-way ANOVA followed by Tukey's multiple comparisons test. MA : Morus alba , SEM: Standard error of mean, ANOVA: Analysis of variance

Table-IV: Effect of the Morus alba extract on behavioral despair test, tail suspension test, and learned helplessness test in rats

Groups	Immobility time(s)		Learned helplessness test	
	Behavioral despair test	Tail suspension test	Escape failure	Avoidance response
Control(vehicle)	106.50±1.92	133.83±4.95	21.33±1.08	8.46±1.08
CF(100mg/kg)	94.83±2.16*	114±5.36*	18.94±0.56	10.40±0.56
CF(200mg/kg)	84.33±2.63*	102±1.15*	18.26±0.70	12.13±0.70
CF(400mg/kg)	64.50±2.59*,$,#	83.16±4.13*,$	11.43±0.33*,$,#	17.16±0.55*,$,#
Imipramine (10mg/kg)	48.16±2.30*,$,#,¥	80.83±4.60*,$,#	10.76±0.88*,$,#	18.36±1.16*,$,#

Values are expressed as mean±SEM (n=6).*P<0.05 significant as compared to vehicle,$$P$<0.05 significant as compared to MA (100mg/kg);#P<0.05 significant as compared to MA (200 mg/kg), ¥P<0.05 significant as compared to MA (400 mg/kg), statistical test employed is one-way ANOVA followed by Tukey's multiple comparisons test. MA: Morus alba, SEM: Standard error of mean, ANOVA: Analysis of variance

DISCUSSION:

Anxiety represents reactions of the body to a stimulus that tends to modify home stasis (Selye,1998). Stress hormones are synthesised during stress condition for example the catecholamines (epinephrine and norepinephrine) produced by the SNS, and corticosteroids, produced by the ACTH stimulated

adrenal cortex and glucocorticoid stimulated increase in serotonin are the major anxiety/stress hormones (Uresinetal., 2004). In the current investigation, VMA as the peripheral metabolite of NA, 5-HIAA as the main metabolite of serotonin,6-β-OH cortisol as metabolite of cortisol, HVA as the predominant metabolite of dopamine and ascorbic acid as a metabolite of glucose (in rats) were taken as an non-invasive biomarkers to display the increase in peripheral sympathetic activity during anxiety/stress to assess the anti-anxiety activity of aqueous and ethanol extracts of *Morusalba*. The data indicated that VMA,5- HIAA, 6-β-OH cortisol, HVA and ascorbic acid were excreted in urine daily at certain levels (basal values)as metabolites of NA, 5-HT, cortisol, DA and glucose respectively. The stress affected on the neurotransmitter levels and increased VMA,5-HIAA,6-β-OH cortisol, HVA and diminished ascorbic acid excretion. When aqueous and ethanol extracts of *Morusalba* administered to normal animals did not change VMA, 5-HIAA, 6-β-OH cortisol, HVA and ascorbic acid in comparison with basal values but prior administration of aqueous and ethanol extracts of *Morusalb a*t o anxiety/stress induced rats

Exhibited the reduction in urinary VMA, 5-HIAA, 6-β-OH cortisol, HVA and increased the ascorbic acid levels in dose dependent manner. The previous phytochemical evaluation of *Morus alba* divulged the presence of phenolic compounds such as flavonoids (Quercetin, rutin), tannin which could be expected to be responsible for anti-anxiety activity (Ayoola et al., 2011). As VMA is a metabolite of norepinephrine (NE) and NE is synthesized by dopamine. Previous reports exhibited that these phytochemicals can bind to the $GABA_A$-BZDS complex, consequently, enhance GABA level and decline dopamine and decrease plasma corticosterone level that lead to reduce level of VMA and 6-β-OH cortisol repectively (Patiletal.,2006). Phenolic compounds such as flavonoids showed the affinity towards D_2 receptor; hence they can block the dopamine receptor and decrease the serotonin which causes to decrease level of HVA(Samsonetal.,2006). These active compounds can prevent activity of tryptophan hydroxylase enzyme which is involved in the biosynthesis of 5-HT,thus they can reduce level of 5HIAA ultimately (Singhetal.,1990). Ascorbic acid is also utilized as a co-factor in the biosynthesis of NE from DA may also attribute to low concentration of ascorbic acid in urine. Hence, effect of these bioactive compounds on reduction of dopamine synthesis that can influence on the increase of urinary level of ascorbic acid

CONCLUSION:

The current appraisal exhibited that aqueous and ethanol extracts of *Morus Alba* have anti-anxiety potential due to impede the anxiety induced increase of adrenergic, serotonergic, cortisol and dopaminergic mechanism. Future evaluations can assess on the levels of neurotransmitters in different regions of brain, as there is limited data that examines the correlation of CNS and urinary neurotransmitters in animals.The present investigation manifest that aqueous and ethanol extract of Morus alba have anti-anxiety activity due to normalization of monoamines and glucocorticoids homeostasis by acting on HPA axis and SNS.

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