PHARMACOLOGICAL STUDY ON THE ANTIDEPRESSANT ACTIVITY OF AVENA SATIVA

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Abstract:

The goal of this study is to evaluate antidepressant property of avena sativa (Oats) assessing in the treatment of initial stages of depression spectrum and management of major depressive disorder. In order to analyze how polyphenols of avena sativa affects psychological behavioral paradigm in mice predisposed to depression 2 methods were maneuvered. Forced swim test and tail suspension test were performed on depressed non fasting mice for a period of 8 weeks by dividing them into four equal groups per each method. Control was given normal saline, standard was given drug imipramine and extract 100mg and 200mg groups were given respective calculated doses. All the tests were significant when control mice were compared to that of standard and extracts. The onset of action of both the extracts was slower, however after 4th week onwards the results were more promising. As the week progresses the antidepressant activity of the extracts maintains efficacy to that of standard. The results inferred both the extracts of avena sativa have a substantial anti-depressant impact (of which 200mg has more than 100mg) by lowering immobility duration in both the behavioral models. The significant result postulates that avena sativa at both 100mg and 200mg dose extract possesses mood stabilizing and anti-depressant traits.

Index Terms: Anti-depressant, Avena sativa, forced swim test, tail suspension test

Abbreviations: Avena sativa extract dose 100mg/kg (ASED 100), Avena sativa extract dose 200mg/kg (ASED 200), two times a day (b.i.d), forced swim test (FST), Monoamine oxidase inhibitor B (MAO type B), orally / by mouth (p.o.), selective serotonin reuptake inhibitors (SSRIs), Tricyclic antidepressants (TCAs), tail suspension test (TST), major depressive disorder (MDD).

I. INTRODUCTION:

Depression is a consequential clinical disorder, dissimilar to sorrow or grief and with high pervasiveness to suicide [1]. The prevalence and solemnity of it intensified during the pandemic where the stats increased from 08.7% to 14.4% [2] and currently as of march 2023, 2.8×10^8 people across the globe suffers from depression[3]. It is defined by diagnostic and statistical manual of mental disorders, 4th edition, text revision (DSM-IV-TR) as persistent occurrence of following medical symptoms, every day for a span of more than 2 weeks, including uninterrupted sad thoughts, continuous depressed mood, anhedonia, unexplained tiredness or fatigue, excessive or no sleep state, irritation/agitation, sudden dietary and weight changes, perception of guilt and worthlessness and suicidal tendencies [4, 5] . Classified episodically as mild (2-3 symptoms per day), moderate (4-5 symptoms per day affecting life routine), severe but lacking psychotic condition (5 or more symptoms with suicidal tendencies) and major depressive disorder [6]. MDD apart from pentad of symptoms is often accompanied by psychotic symptoms of hallucination/delirium/psychomotor retardation and suicidal tendencies. The tendency for severity of depression and stress triggers varies in accordance to socio-economic-racial factors, trauma [7], genetics [8]and depression associated with terminal illness [9]. Continuous pharmacotherapy though beneficial brings forth adverse effect and dependence [10].

In consequence, dire needs for such potential pharmacological neutraceuticals are in research that can lessen the load in the management phase and govern as a remedial treatment of mild to moderate depressive disorders [11]. Avena sativa is such a versatile, potent pharmacologically beneficial plant. It has anti-oxidant, anti-diabetic, cholesterol reducing, weight reducing, anti-cancerous, anti-inflammatory, germicidal, antihypertensive and anti-atherosclerotic properties. The spectrum of its positive effects also includes its neuro-pharmacological effects in depression [12].

A. Avena sativa and its constituents as a formidable neutraceutical in mental health:

Avena sativa, a potent neutraceutical, commonly called as oats is the most consumed grain worldwide. Its cultivation history dates back to 2 millennia and is widely used for food, feeder, forage, health and cosmetology. It's a chief source of carbs, protein, fiber, minerals, lipids, vitamins and salient phytochemicals. The most pharmacologically significant phytochemicals are its alkaloids and polyphenols such as avenanthramides [13]. Food and mood goes hand in hand; neutraceuticals have positive impact on the neurotransmitters acetylcholine, dopamine, and serotonin involved in the enteric nervous system ergo there notable role in management and prevention of symptoms associated with mental health [14]. One of the etiologies of depression backed heavily by the massive success of conventional SSRIs and MAOIs, the monoamine hypothesis, precise the fact that the depletion of dopamine, serotonin and norepinephrine in the CNS expedite depression. Phytochemicals in plant aids in balancing these chemical transmitters of the CNS including polyphenols that decreases immobility phase in FST, saponins possessing anti-depressant property in animal models and alkaloids that inhibit the enzyme monoamine oxidase [15]. The alkaloids in avena sativa including indol group, flavonoids, organic acids, tocol, saponin, sterol and polyphenolic avenanthramides are possible contributors to its anti-depressant effects [16].

In relation to this beta glucan of avena sativa stimulate and regulate the growth of gut microbiome (Bifidobacteria, Faecalibacterium prausnitzii, Akkermansia, Roseburia and muciniphila) [17]. This property is in direct proportion to regulating cognitive functioning and alleviating depression through promoting healthy bidirectional connection along the gut-microbiota-brain axis pathway. One of the medical symptoms of depression is stress-induced sudden weight gain or obesity [14] and avenanthramides and beta glucan in avena sativa when consumed acts as a weight reducer thereby managing the disease[18].

B. Avena sativa as an antioxidant barrier against depression and in enhancing cognition:

One of the most prevalent attributes to MDD is oxidative stress emerging due to the imbalance between the antioxidant defense network of body and excessive pool of reactive oxygen specie. The failure to balance the scale results in the initiation of proinflammatory cytokine cascade advancing to stage of necrotic cells. It is a well-established fact that human brain is susceptible to oxidative stress as it requires more oxidative metabolic activity and has high concentration of membrane lipids. An imbalance or increased oxidative stress victimizes the brain yield MDD [19]. Avena sativa's extract and supplementation works against oxidative stress. This can be a targeted cure against MDD and promoting mental health [20].

Contrary to depression that hinders concentration and cause cognitive fatigue and distortion, avena sativa enhances focus and mental alertness during strenuous cognitive load. Possible mechanism for this attribute is may be due to avenanthramides inhibiting nitric oxide that inhibits activation of nuclear factor kappa B suppressing inflammatory cytokines. These eventually cause cerebral vasodilation [21], a behavior analogous to SSRIs [22]. Phytic acids, vitamin E and flavonoids found in avena sativa also contribute to its antioxidant property[23].

C. Avena sativa as a mood stabilizer in depression:

A study infers that its extract has mood stabilizing property as seen by the positive interpretations after subjecting the rats to FST and shock avoidance learning. In that particular study 36 animal subjects were administered a low dose extract 10 g/kg + food, a high dose extract 100g/kg + food and were then compared with each other and the control group. Both the extract and specifically the lower dose showed less despair and enhanced motivation characterized by increased in mobility time, a behavioral marker of FST. The subjects also provided an active response to stress and negative stimuli; a major precursor of depression [24]. This may be due to avena sativa's ability to augment neurotransmitter dopamine levels and reduce serum hormonal cortisol level there within decreasing stress and exerting perception of motivation, pleasure and reward [25].

Similar claim has been established by a commercial avena sativa extract of hammering stress in synchrony with agitation as well as improving circadian rhythm sleep[26]. The occurrence of insomnia associated longer sleep latency and maintaining deeper sleep is a serious clinical symptoms of depression, along with excessive or daytime sleep [27]. Intervention improving sleep quality in inadvertently uplifts mood treating and managing depression[28]. Subsequently, European herbal tea infusions of avena sativa are prescribed b.i.d.; for 3 to 6 months daily, to act as a mood stabilizer in relieving stress and promoting healthy sleep cycle[29].

D. Possible mechanism underlying the antidepressant action of avena sativa:

The first line therapy for depression is MAOIs and TCAs follow suit by SSRIs and serotonin and norepinephrine reuptake inhibitors. The conventional drugs take 3-4 weeks to relieve clinical symptoms and overall 6-12 weeks for effective therapeutic antidepressant action [30]. Theoretically avena sativa is said to mimic the action of antidepressants. Popular mechanism pinpoints around the hypothesis of avena sativa's ability to inhibit MAO type B enzyme thereby accumulating dopamine at the synapse henceforth prolonging cerebral effects of positive mood, concentration, learning, memory, motivation and organizational thoughts. Apart from nitric oxide mechanism, another theory highlights its constituent avenacins to be a major cerebral performance booster modulating neurotransmission and inhibiting acetyl choline esterase enzyme in accordance with inhibition of MAO type B. Polyphenols of avena sativa are also Phosphodiesterase4 inhibitor, thereby they possibly aid in strengthening the long-term memory [31], augmenting intelligence and in protecting and generating neurons [32].

The purpose of this study is to validate the theory of possible antidepressant action of avena sativa and to acquire assistance from its antidepressant role in therapy drug management phase of MDD and in curing mild to moderate depression. As management is a key feature of healing neuropsychiatric disorders and their relapse, avena sativa's substantial play can also aid in lessening the load of adverse effects, drug abuse and economic cost of prolonged treatment.

II. STATISTICAL RESULTS:

All subjects were divided into four treatments/groups/variables per each method for FST and TST; Control (given distilled water 10ml/kg p.o), standard (given Imipramine 25mg/kg p.o), ASED 100 (avena sativa extract dose 100mg/kg) and ASED 200 (avena sativa extract dose 200mg/kg). They were depressed for 2 weeks using similar tests, preceding research that prolonged for 8 weeks consecutively with dose being administered orally for 3 days per week. The results were analyzed and interpreted using IBM SPSS software.

A. Results for FST: post hoc test:

Multiple Comparisons

Tukey HSD

Dependent Variable	(I) Treatment of drug	(J) Treatment of drug	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Mobility time in seconds	Control	Standard	-133.167*	12.433	.000	-165.70	-100.63
		ASED 100	-57.125*	12.433	.000	-89.66	-24.59
		ASED 200	-92.375*	12.433	.000	-124.91	-59.84
	Standard	Control	133.167*	12.433	.000	100.63	165.70
		ASED 100	76.042*	12.433	.000	43.51	108.57
		ASED 200	40.792*	12.433	.008	8.26	73.32
	ASED 100	Control	57.125*	12.433	.000	24.59	89.66
		Standard	-76.042*	12.433	.000	-108.57	-43.51
		ASED 200	-35.250*	12.433	.028	-67.78	-2.72
	ASED 200	Control	92.375*	12.433	.000	59.84	124.91
		Standard	-40.792*	12.433	.008	-73.32	-8.26
		ASED 100	35.250*	12.433	.028	2.72	67.78
Immobility time in seconds	Control	Standard	133.167*	12.500	.000	100.46	165.87
		ASED 100	57.083*	12.500	.000	24.38	89.79
		ASED 200	90.167*	12.500	.000	57.46	122.87
	Standard	Control	-133.167*	12.500	.000	-165.87	-100.46
		ASED 100	-76.083*	12.500	.000	-108.79	-43.38
		ASED 200	-43.000*	12.500	.005	-75.71	-10.29
	ASED 100	Control	-57.083*	12.500	.000	-89.79	-24.38
		Standard	76.083*	12.500	.000	43.38	108.79
		ASED 200	33.083*	12.500	.046	.38	65.79
	ASED 200	Control	-90.167*	12.500	.000	-122.87	-57.46
		Standard	43.000*	12.500	.005	10.29	75.71
		ASED 100	-33.083*	12.500	.046	-65.79	-.38

The mean difference is significant at the 0.05 level.

i. A highly significant difference is seen in the mobility and immobility time of control compared to all three treatments.

ii. A highly significant difference is seen in the mobility time and immobility time of standard compared to control and dose 100mg. Significant difference is also seen when individually both the dependent variables of standard are compared with that of dose 200mg. This postulates that all treatments have unequal means.

iii. Taking both the dependent variables in consideration, it was found that the dose 100mg is statistically significant to control, standard and 200mg.

iv. A highly significant difference is seen in the mobility and immobility time of dose 200mg and control concluding that the means are unequal. When both the dependent variables of dose 200mg are compared individually with the standard significant difference is seen. The difference in the mobility time of dose 200mg with dose 100mg is also significant. When comparing the dependent variable immobility time of dose 200mg with dose 100mg slight significant difference is seen (0.046). However it is still less than 0.05 stipulating that it is indeed significant as well.

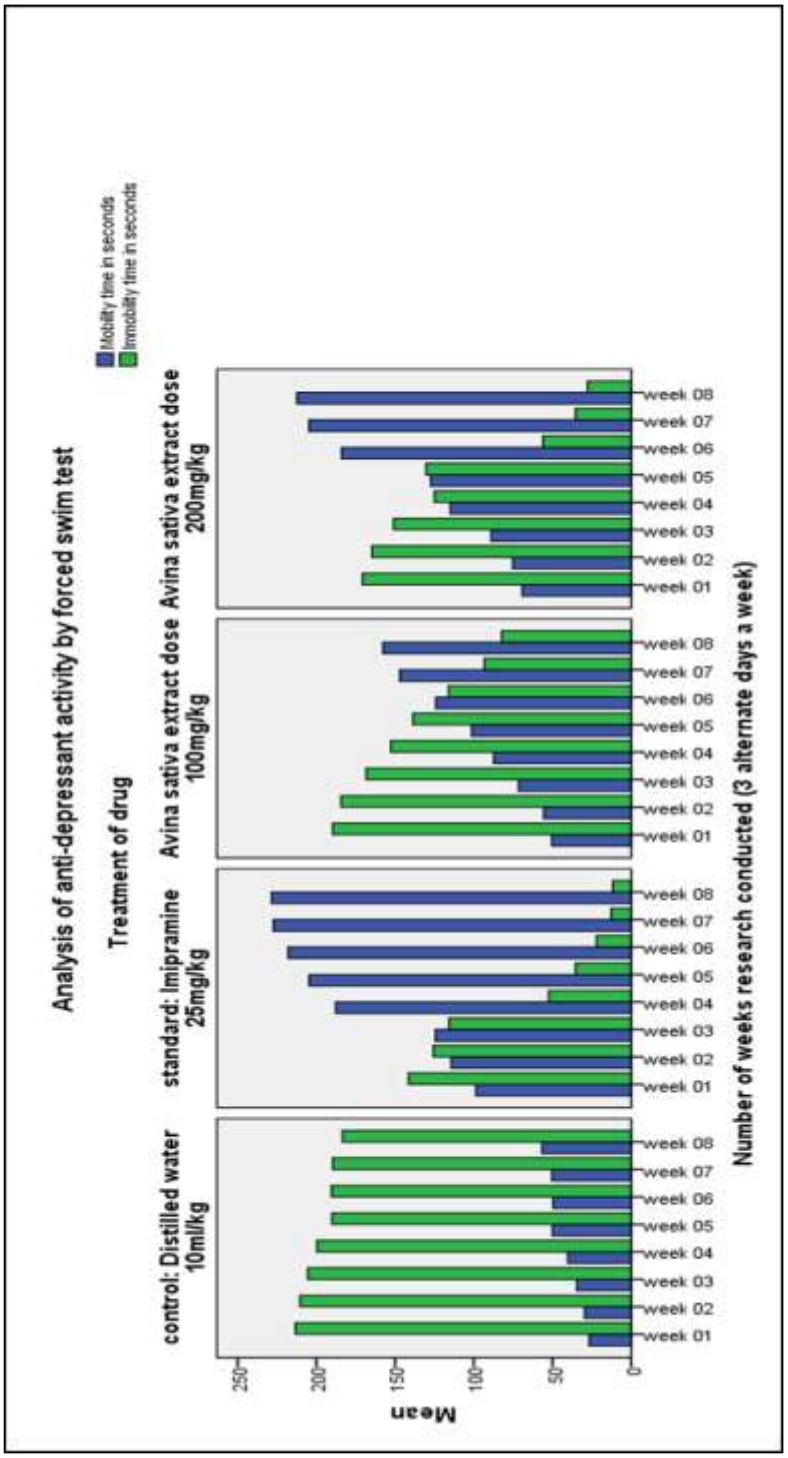

Figure 1: Bar graph of anti-depressant activity parameters (Mobility and immobility time) of all 4 groups during 8 weeks via FST

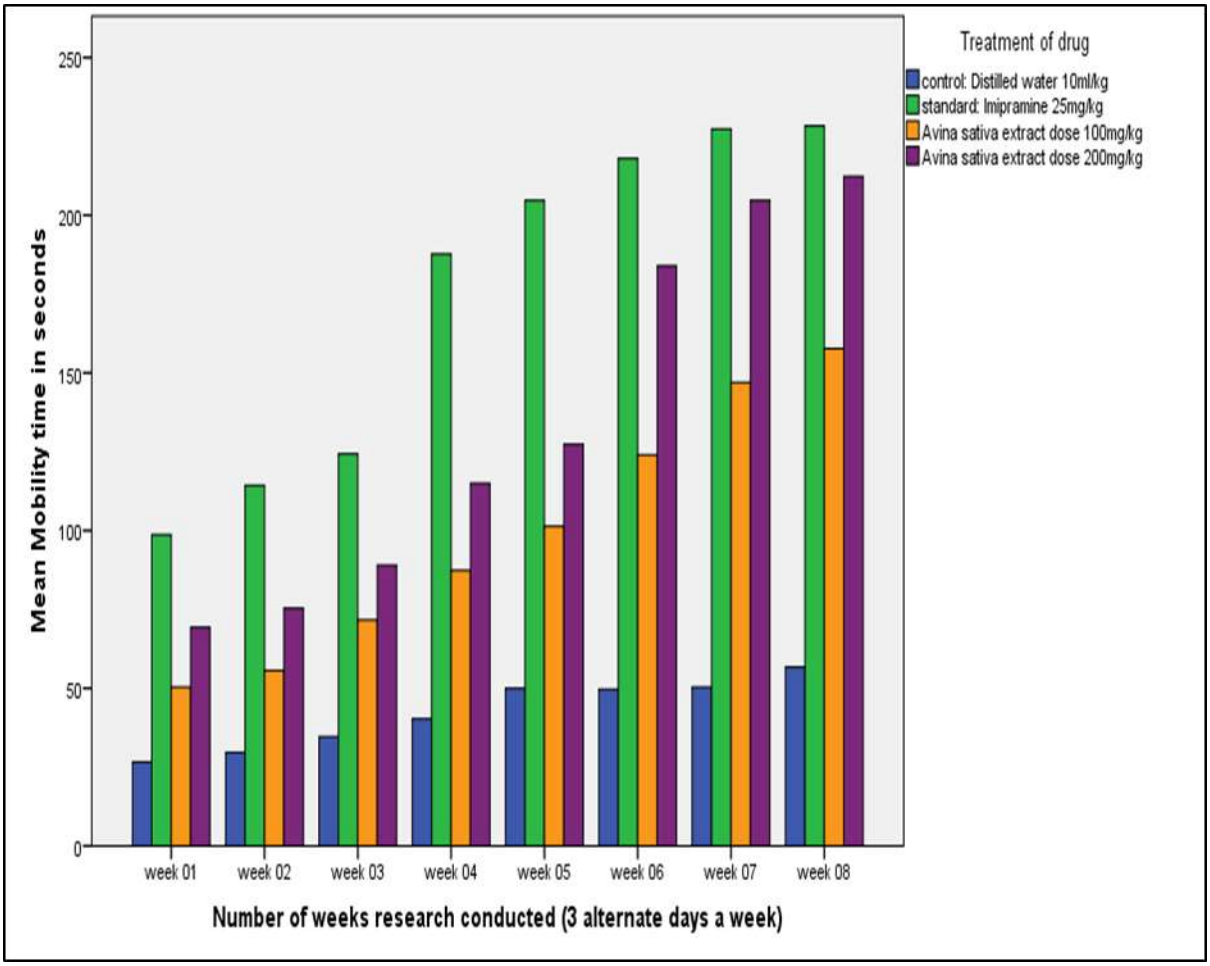

Figure 2: Single parameter assessment: Bar graph of mean mobility time by all 4 groups during 8 weeks via FST

B. Results for TST: post hoc test:

Multiple Comparisons

Tukey HSD

Dependent Variable	(I) Groups or treatments of drug	(J) Groups or treatments of drug	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Mobility time in seconds	Control	Standard	-84.875*	8.423	.000	-106.92	-62.83
		ASED 100	-50.083*	8.423	.000	-72.12	-28.04
		ASED 200	-75.542*	8.423	.000	-97.58	-53.50
	Standard	Control	84.875*	8.423	.000	62.83	106.92
		ASED 100	34.792*	8.423	.000	12.75	56.83
		ASED 200	9.333	8.423	.686	-12.71	31.37
	ASED 100	Control	50.083*	8.423	.000	28.04	72.12
		Standard	-34.792*	8.423	.000	-56.83	-12.75
		ASED 200	-25.458*	8.423	.017	-47.50	-3.42
	ASED 200	Control	75.542*	8.423	.000	53.50	97.58
		Standard	-9.333	8.423	.686	-31.37	12.71
		ASED 100	25.458*	8.423	.017	3.42	47.50
Immobility time in seconds	Control	Standard	84.875*	8.423	.000	62.83	106.92
		ASED 100	50.083*	8.423	.000	28.04	72.12
		ASED 200	75.542*	8.423	.000	53.50	97.58
	Standard	Control	-84.875*	8.423	.000	-106.92	-62.83
		ASED 100	-34.792*	8.423	.000	-56.83	-12.75
		ASED 200	-9.333	8.423	.686	-31.37	12.71
	ASED 100	Control	-50.083*	8.423	.000	-72.12	-28.04
		Standard	34.792*	8.423	.000	12.75	56.83
		ASED 200	25.458*	8.423	.017	3.42	47.50
	ASED 200	Control	-75.542*	8.423	.000	-97.58	-53.50
		Standard	9.333	8.423	.686	-12.71	31.37
		ASED 100	-25.458*	8.423	.017	-47.50	-3.42

*. The mean difference is significant at the 0.05 level.

i. A highly significant difference is seen in the mobility and immobility time of control compared to all three treatments therefore we conclude that the mean of both the dependent variables (mobility time and immobility time) of all three groups have unequal means.

ii. A highly significant difference is seen in the mobility time and immobility time of standard compared to control and dose 100mg postulating that they have unequal means.

iii. Taking both the dependent variables in consideration, it was found that the dose 100mg is statistically highly significant to control, standard and 200mg.

iv. A highly significant difference is seen in the mobility time and immobility time of 200mg dose to control group.

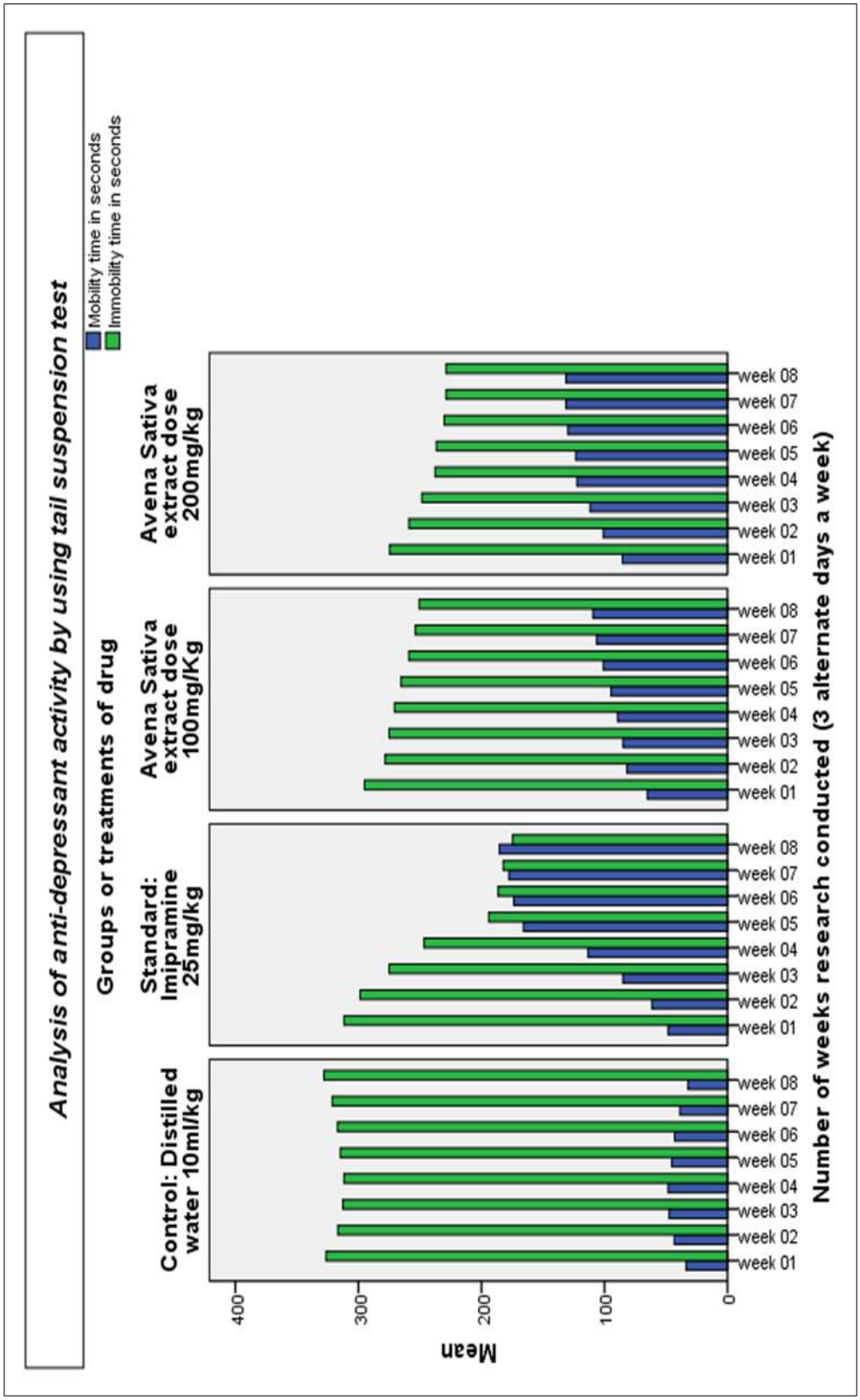

Figure 3: Bar graph of anti-depressant activity parameters (mobility and immobility time) of all 4 groups during 8 weeks via TST

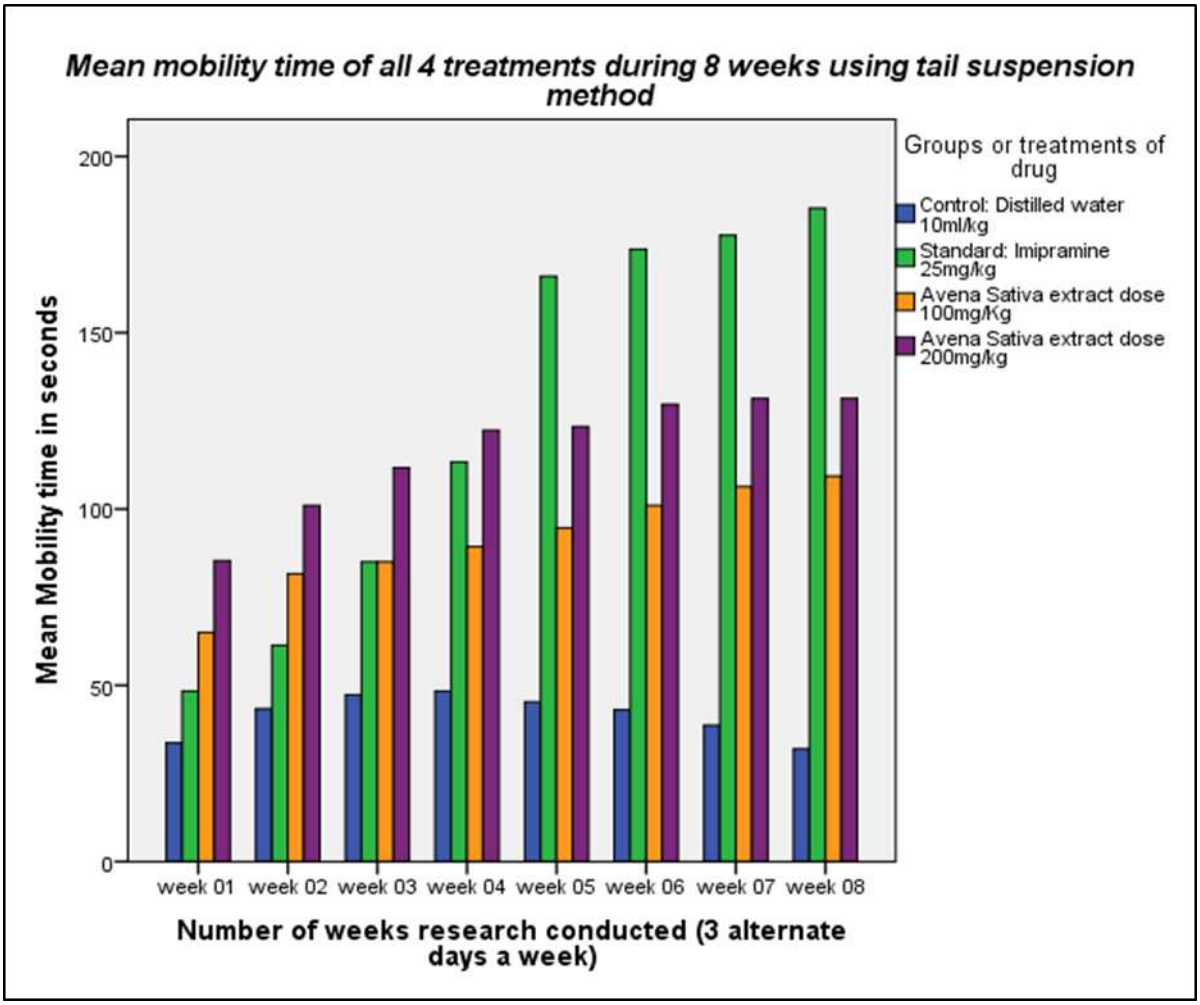

Figure 4: Single parameter assessment: Bar graph of mobility time of all 4 groups during 8 weeks via TST

III. DISCUSSION:

Depression requires patient compliance and prolonged duration of treatment to be beneficial. To add to worry anti-depressant therapy related adverse effects and drug abuse are a challenge in managing depressive episodes. This has lead science to search for potential neutraceuticals that have similar neuro-protective property to aid in the treatment of this fatal illness [33].

In this study the forced swim test (FST) and tail suspension test were used as behavioral paradigm of antidepressant activity [34] . Encapsulating FST results, significant difference was found amongst all variables that is control, standard, ASED 100 and ASED 200. The mobility time of the Standard had the peaked effect amongst all variables and remained the highest each consecutive week. Second to that, is ASED 200 that initially progressed tardily but after week 05 showed substantial results almost corresponding to the standard. Comparatively ASED 100 antidepressant activity was also latent in initial weeks however it too continued to progress each week. The conventional standard imipramine is effective in the treatment of depression giving immediate effect [35]. This expeditious effect lacks in both the extracts. As seen in the study the week 04th of imipramine antidepressant activity is equivalent to week 06th of ASED 200 and week 08th of ASED 100. Nevertheless the extracts though slowed paced continued to show antidepressant traits.

Innumerable variables of struggling and climbing (sudden motion of only front paws breaking the water's surface tension) were also observed during the research [36]. This antidepressant trait was initially visible only in standard mice howbeit similar conduct started showing in ASED 200 mice from the 03rd week onwards and ASED 100 mice from 4th week onwards. In terms of the swimming parameter Standard mice were active swimmers from 2nd week whereas ASED 200 mice and ASED 100 showed similar behavior from the 3rd and 5th week onwards while in contrast control group continued despondency.

Whilst conducting research using 2nd method, TST, parameter that account for true mobility was kept uniform overall as well. The vigorous convulse and shaking of the body as well as trying to escape or run or climb using both the front and hind paws was considered true variables of mobility. Slight motion confined to only using either front paw without the hind paws did not account for mobility. Consequently oscillatory back and forth pendulum motion biased either due to gravity or due to momentum attained by the mice prior to preceding movement did not account as mobility variable as well [37]. Interpreting its result, significant differences were evident in all 4 groups/treatments/variable between the groups that is comparatively with each other and within the group that is individual weekly advancement. The mobility time of standard culminated after 04th week whereas ASED 200 and ASED 100 showed these effects after 5th week. The study also highlights both the extracts although does not give prompt antidepressant effect yet they sustain their pharmacological effects after prolong continuous usage. Managing the effects of depression mimicking conventional drug imipramine highlights Avena sativa's extract role as promising antidepressant agent.

This characteristic of Avena sativa as a potent neuro-pharmacological plant is may be due to constituting polyphenols that have antidepressant and mood stabilizing effect. The theory that its long term consumption results in decreasing stress, a major mediator in depression ergo proved[38]. However, as witnessed in the study, the positive cognitive dose mediated response is not immediate. Possible mechanisms involve in the antidepressant effects are the inhibition of MAO type B, acetyl cholinesterase and PDE type 4 enzymes. Inhibition of the former increases the dopamine in the synapse thereby treating despair whereas inhibition of the later boost cognition, uplifts the mood and enhances the memory[39] all of which if inverse are elemental targets of depressive symptoms[40].

IV. CONCLUSION:

The purpose of this research is to evaluate antidepressant effects of Avena sativa on mice. Significant research results of dose extracts, both individually and comparatively with the control and standard infers that avena sativa possesses anti-stress and mood stabilizing traits. Although their efficacies are governed slowly as compared to standard imipramine, promising results are witnessed in the 4th week, after which a continuous streak of positive result of anti-depressant effects are interpreted each successive week in which ASED 200 response being quicker than ASED 100.

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CONFLICT OF INTEREST:

The above article has no conflict of interest.

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