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Effects of *Cannabis sativa* on the Neuromuscular System and Cognitive Behavior of Male Wistar Rats

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ABSTRACT

This research investigates the influence of *Cannabis sativa* on the neuromuscular system and cognitive behavior of male Wistar rats. Twenty rats were randomly allocated into five groups, with Group 5 serving as the control and Groups 1 to 4 receiving oral doses of *Cannabis sativa* at concentrations of 100 mg/kg, 200 mg/kg, 400 mg/kg, and 800 mg/kg, respectively. The study employs various behavioral tests, including the Beam Walking Test, Morris Water Maze, Tail Suspension Test, Open-Field Test, and Hand Grip Test, to assess the effects of *Cannabis* on Wistar rats. Results from the Beam walking Test suggest that the control group (Group 5) demonstrated the best neuromuscular performance, with Group 3, (receiving 400 mg/kg), following closely. In the Morris Water Maze, Groups 1 and 5 exhibited superior results, while higher doses had a negative impact. Tail Suspension Test outcomes revealed that Group 5 displayed non-depressive behavior, while Group 4 exhibited signs of depression. The Hand Grip Test demonstrated longer duration for Groups 2 and 4, suggesting a positive impact on muscle strength compared to the control, on Open Field Test, Group 1 spent the most of the time at the center, indicating lower anxiety, whereas other groups displayed increased anxiety with higher *Cannabis* doses. The study highlights complex and dose-dependent effects of *Cannabis* on neuromuscular and cognitive parameters. Caution is advised in interpreting these findings, and further research is recommended to elucidate underlying mechanisms and explore a broader range of doses.

Keywords: *Cannabis sativa*, cognitive function neuromuscular function

INTRODUCTION

Cannabis sativa, or marijuana, is a plant that has been used for millennia for both medical and recreational purposes. Cannabis plants contain a combination of Tetrahydrocannabinol (THC) and cannabidiol (CBD), which is the major active compound. It was not until the 1960s that THC was fully characterized and found to be the main psychoactive compound in *Cannabis*. The effects of *Cannabis sativa* is influenced by the ratio of these compounds. Although CBD, a non-psychoactive compound, may modulate the psychoactive effects of THC, potentially reducing anxiety and other adverse reactions. Tetrahydrocannabinol (THC) is a psychoactive compound found in *Cannabis sativa* and is responsible for the euphoric effects commonly associated with marijuana use [1]. The legal status of THC varies globally, with some countries legalizing its recreational or medicinal uses and others maintaining strict regulation. Its chemical structure is similar to endocannabinoids produced by the body, allowing it to interact with cannabinoid receptors in the central nervous system. *Cannabis sativa* contains compounds such as phytocannabinoids and plant sterols. Tetrahydrocannabinol (THC) is potent lipophilic antioxidants which stimulates appetite [2]; [3], it is the psychoactive ingredient in *cannabis*. It interacts with the body's endocannabinoid system to affect a number of physiological functions. There are worries about its effects on the neuromuscular system and cognitive behavior, even though it's therapeutic potential has been investigated. Marijuana is a complex plant material, which can elicit a variety of pharmacological and immunological effects and has been used for medicinal and recreational purpose [4]. Several modes of action have been proposed as accounting for the effects of THC on the neuromuscular system and cognitive behavior of man. In recent years, there has been a lot of discussion and controversy surrounding the use of *Cannabis*, more especially *Cannabis sativa*. Given that *Cannabis* is becoming more and more legal and

decriminalized globally. Many different mental functions, such as perception, attention, memory, learning, and decision-making, are included in cognitive behavior. The consumption of *Cannabis* has impaired verbal learning, memory and attention [5]. There are several effects that THC's interaction with Cannabinoid receptors can have on the neuromuscular system and cognitive activities. For instance, in animal models, THC has been demonstrated to impact muscle tone, motor coordination, and muscle strength. Furthermore, it may have an impact on cognitive functions like learning, memory formation, and attention. Previous research has shown that delta-9-tetrahydrocannabinol (THC), the primary psychoactive ingredient in *Cannabis*, interacts with particular receptors in the brain and peripheral nervous system [1]. These receptors, often referred to as cannabinoid receptors, are a component of the endocannabinoid system, which regulates a number of physiological functions. There are several effects that THC's interaction with cannabinoid receptors can have on the neuromuscular system and cognitive activities. For instance, in animal models, THC has been demonstrated to impact muscle tone, motor coordination, and muscle strength. Furthermore, it may have an impact on cognitive functions like learning, memory formation, and attention [6]. Cannabinoid receptors are proteins found on the surface of cells, particularly in the nervous system and immune cells. These receptors interact with endogenous cannabinoids (produced within the body), as well as external cannabinoids like those found in the cannabis plant. The two primary types of cannabinoid receptors are CB1 and CB2 [7].

CB_1 Receptors is found in the central nervous system, including the brain and spinal cord and play a key role in modulating neurotransmitter release, affecting functions such as pain perception, mood, memory, and appetite. The psychoactive compound in Cannabis, THC (tetrahydrocannabinol) primarily binds to CB_1 receptors, leading to the characteristic effects of marijuana, including euphoria and altered perception. CB_2 Receptors is mainly found in the peripheral nervous system, immune cells, and various organs, including the spleen and gastrointestinal tract. It is associated with the regulation of immune function, inflammation, and peripheral tissue responses. CB_2 receptors are less prevalent in the central nervous system, and their activation is not typically associated with the psychoactive effects seen with CB_1 activation. It also increase appetite and Metabolic activities [8]. THC primarily binds to CB1 receptors, which are abundant in the brain and central nervous system. This binding leads to the activation of the endocannabinoid system, influencing neurotransmitter release and producing various physiological and psychological effects. THC is renowned for its psychoactive properties, which include euphoria, altered perception of time, enhanced sensory perception, and an increased sense of relaxation. These effects are the result of THC's impact on neurotransmitter release, particularly dopamine and gamma-aminobutyric acid (GABA) [9]. CBD is another major cannabinoid found in *Cannabis sativa* but differs from THC in that it is not psychoactive. It's chemical structure is distinct from THC, and it does not bind strongly to CB1 receptors, leading to its non-intoxicating nature [10]. CBD's mechanism of action is complex and involves interactions with various receptors, ion channels, and enzymes. Unlike THC, CBD does not directly bind to CB1 receptors but can influence them indirectly. CBD is well-tolerated, with few reported side effects. However, interactions with certain medications are possible. The legal status of CBD varies globally, with some regions allowing its use for medicinal purposes, while others permit it as a wellness product. Numerous studies to explored the cognitive effects of *Cannabis sativa* have been conducted on a series of behavioral tests on male Wistar rats, and found that chronic exposure to *Cannabis sativa* resulted in deficits in spatial memory and learning abilities. These findings indicate that *Cannabis sativa* can have a detrimental impact on cognitive function. The existing empirical studies suggest that Cannabis sativa can have negative effects on the neuromuscular system and cognitive behavior of male Wistar rats [11]. Chronic exposure to *Cannabis sativa* may lead to impaired motor coordination, muscle weakness, memory deficits, and attention impairments.

MATERIALS AND METHODS

In this study, a total of five independent groups of male Wistar rats were used, with each group housing four Wistar rats. Each group was assigned a different dose treatment of *Cannabis sativa*. The doses were administered orally and carefully controlled to ensure accuracy. *Cannabis sativa* extract was derived from it's leaves plant. A simple method called alcohol-based tincture was used, where the finely ground *Cannabis* was soaked in 70% ethanol at room temperature for 48hours. Then it was filtered through a whatman filter (No 1), the filtrate was collected and evaporated using rotary evaporator. It was further dried on a water bath. The extract was serially diluted to obtain concentrations of 100mg/ml/kg, 200mg/ml/kg, 400mg/ml/kg and 800mg/ml/kg, for groups 1-4 respectively while group 5 was used as the control. Beam walking test Beam walking test/ balance beam test is used to assess fine motor coordination and balance in rodents. The beam walking test was used to analyze the experimental animal's gait in an environment that challenges their ability to balance themselves to access their motor coordination and balance. The goal of this test was for the animal to stay upright and walk across an elevated narrow beam of 80cm to a safe platform [12].Time taken to traverse the beam, number of paw slips or missteps, coordination and balance during movement were recorded

Handgrip test

Hand grip test was conducted to assess grip strength and muscular endurance in adult male Wistar rats. The study aimed to investigate the potential impact of chronic exposure to *Cannabis sativa* on the rats' physical strength and the ability to maintain grip over time. These rats were individually subjected to the hand grip test apparatus, and their grip strength was measured by recording the force exerted on the grip sensor [13].

Morris water maze

The Morris water maze (MWM) is a test of spatial learning for rodents that relies on distal cues to navigate from start locations around the perimeter of an open swimming arena to locate a submerged escape platform. The Morris water maze (WM) is a widely used measurement of visuospatial learning that has been demonstrated to have high validity in identifying cognitive effects of various brain lesions and the effects of drugs used to treat cognitive deficits [14].

Open Field test

The Open Field test is a simple sensorimotor test used to determine general activity levels, gross locomotor activity, and exploration habits in rodent models of CNS disorders. One of the most commonly used anxiety assays is the Open Field Test (OFT), in which rodents are placed in an empty square or circular arena without a ceiling. Although the Open Field Test can also be used to measure other behaviors such as locomotion (total distance traveled), velocity, defecation, and latency to enter the center [15]. The experimental animals was placed in a square box and was observed, the fraction of time spent in the perimeter (thigmotaxis) was not recorded but the fraction of time spent at the center of the context was measured, using a range of six minutes.

Tail Suspension test

The tail suspension test (TST) was developed as a rodent screening test for potential (human) antidepressant drugs. It is based on the assumption that an animal will actively try to escape an aversive (stressful) stimulus. If escape is impossible, the animal will eventually stop trying [16]. The experimental animals were suspended from a lever by their tails and their behavior was recorded over a 6-minute time period. Naturally, the rats struggled to escape for a period of time before adopting a posture of immobility or continuous mobility. The test lasts for 6 min and the immobility time was measured during the final 4 minutes as nearly all rats attempt to escape in the first 2 minutes, so the immobility time was recorded after the first 2 minutes.

RESULTS

Beam Walking: The results graphically represented in fig 1, illustrates the performance of the control group and the treatment group exposed to *Cannabis* across multiple trials. Group 1, 2 and 5 show an increased performance, by consistently demonstrated a steady and efficient performance, with minimal time used to walk on the beam compared to other treatment groups. In contrast, group 3 and 4 exhibited an increased traversal time, suggesting an altered motor coordination and balance. During the beam walking trials, it was also observed that group 1, 2 and 5 exhibited smooth and coordinated movements, with no observable signs of imbalance or hesitation. While, rats in group 3 and 4 displayed signs of unsteady gait, hesitancy, and occasional loss of balance, which is an indication of impaired motor coordination. Statistical analysis revealed significant differences supporting the hypothesis that group 1, 2 and 5, has shown high coordination of ($p < 0.05$) showing a negative impact of high dosage of Cannabi*s* on motor coordination of group 3 and 4 (Table 1). Morris Water Maze: The results graphically represented in Fig 2 shows that groups with longer arrows signify a larger difference between data points, while short arrows suggest a smaller differences or indicate a decrease. The learning curves for the group 2 and 4 indicate a deterioration due to an increase escape latency after been administered with 200mg and 800mg of *Cannabis* across multiple trials. Group 1, 3 and 5 exhibited a progressive reduction in escape latency over consecutive trials, which is an indication of successful spatial learning. In contrast, group 2, and 4 displayed a slower learning curve, with comparatively higher escape latencies, suggesting impaired spatial memory acquisition. Statistical analysis confirmed significant differences ($p<0.05$) between group 3 (3.41 ± 0.78) and group 4 (42.63 ± 8.95), showing that an increased intake of *Cannabis* will increase escape latency with an adverse effects of *Cannabis* exposure on spatial learning and memory .(Table 2) Tail Suspension results illustrating the performance of the control group and the experimental group exposed to *Cannabis* during the tail suspension test (fig 3). Group 1, 2 and 5 exhibited a typical response to the tail suspension test, displaying a period of active struggling, followed by a gradual transition to immobility. While the groups 3 and 4 of 400mg/kg and 600mg/kg demonstrated an increase immobility time, suggesting a heightened vulnerability to stress-induced depressive-like behavior. Rats in group 3 and 4 displayed observable signs of depressive-like behavior, including a lack of escape-oriented behaviors, increased hanging passivity, and reduced attempts to free themselves from the suspended position. These behavioral alterations align with the interpretation of heightened depressive-like responses. Statistical analysis confirmed a significant difference between the high *Cannabis* intake and a reduced or no cannabis-exposed groups with mobility time ($p < 0.05$), indicating an impact of *Cannabis* exposure on the rats' response to the tail suspension stressor (Table 3).

Hand Grip Test: Group 2, 3 and 4 exhibited consistent and strong peak grip strength, reaching a plateau value indicates the rats' maximal muscular force. Group 1 and 5 displayed a noticeable reduction in peak grip strength, suggesting a potential positive impact of *Cannabis* exposure on muscular strength. During the sustained grip phase, group 2, 3 and 4 that was administered 200mg /kg, 400mg/kg and 800mg/kg maintained a relatively stable force output, indicating good muscular endurance. While, those of 0mg/kg and 100mg/kg exhibited a decline in force over time, pointing towards reduced endurance and possibly impaired muscle function. Rats in the group 1 and 5 displayed an observable sign of impaired grip, such as early release of the grip apparatus, increased paw trembling, and a less sustained effort to maintain grip. These signs align with the interpretation of diminished muscular strength and endurance associated with *Cannabis* exposure. Statistical analysis (236.91±11.45, 173.15±51.89, 186.00±57.02) confirmed a significant difference between the high dosage and reduced or no *Cannabis* exposure groups with $p<0.05$, supporting the hypothesis that cannabis exposure positively impacts grip strength and endurance (Table 4).

Open Field Test: The graphical representation of this test is seen in Fig 5. Group 1 exhibited a consistent level of exploratory behavior, covering a moderate distance across the open field. The other groups displayed a reduced total distance traveled especially group 4, suggesting a decreased overall locomotor activity, possibly associated with altered motor coordination. Group 1 demonstrated a higher proportion of time spent in the center zone, indicating a reduced anxiety-like responses. Conversely, group 4 spent less time in the center zone, suggesting heightened anxiety-related behavior such as decreased exploration of the central area, increased freezing behavior, and reduced engagement in exploratory activities, further supporting the interpretation of heightened anxiety-like responses. Statistical analysis confirmed significant differences between the group 1 (100mg/kg) and group 4 (800mg/kg) of *Cannabis sativa*, (23.11 ± 7.95) and (6.42 ± 2.65) respectively indicating the impact of chronic cannabis exposure on both locomotor activity and anxiety-related behavior. (Table 5)

Cumulative mean weight result indicates the growth pattern of the animals and how *Cannabis sativa* influence their rate of feed consumption and the corresponding weight gain per group over the experimental period. (Table 6). The rats were weighed weekly in their different groups using a digital scale, their mean weight increased from (44.52 ±3.86, 46.03± 2.78, 46.83± 3.23, 49.35 ± 2.24, 46.05± 2.17) respectively at week 1 to this (90.9 ± 2.31, 88.68± 7.95, 67.65±24.10, 98.00±33.54, 79.90± 4.97) at week 4, indicating an increased in weight due to *Cannabis* intake which led to an increase in their appetite and feed consumption.

Table 1	**Result of beam walking test**				
	trial 1	trial2	trial3	trial4	trial5
grp1	13.26 ± 1.57	10.71 ± 2.13	9.31 ± 1.31	7.06 ± 1.26	6.39 ± 1.38
grp2	12.72 ± 3.07	6.90 ± 1.71	8.77 ± 2.56	5.60 ± 1.46	8.86 ± 3.56
grp3	13.73 ± 2.03	11.51 ± 4.17	13.27±5.94	11.49±2.89	12.47±6.16
grp4	9.91 ± 1.72	7.53 ± 2.59	9.32 ± 3.89	9.48 ± 2.39	10.18±5.63
GRP5	18.02 ±2.98	14.54 ± 1.85	11.41±3.09	8.52 ± 2.28	7.69 ± 1.86

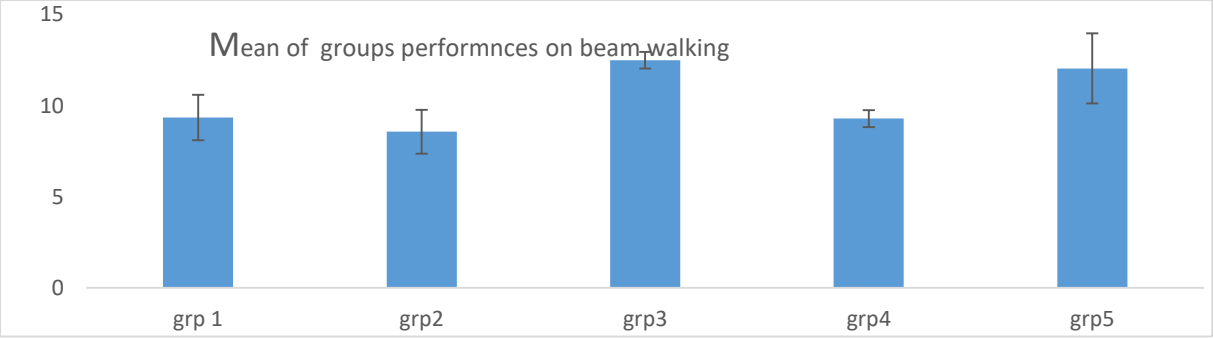

Fig.1 Mean of group performance on Beam Walking Test

Table 2: Result of different groups trials on morris water maze test					
	trial 1	trial2	trial3	trial4	trial5
grp1	8.35 ± 3.13	3.41 ± 0.78	9.28 ± 1.89	11.59 ± 1.75	5.35 ± 1.58
grp2	5.48 ± 1.34	66.39± 19.04	10.34± 3.49	8.08 ± 3.91	6.51 ± 1.67
grp3	23.45± 4.59	18.63 ± 9.95	18.06± 7.80	18.03± 11,59	21.6± 12.20
grp4	42.63 ±8.95	12.81 ± 2.98	13.05± 3.33	9.65 ± 2,79	6.48 ± 1.72
GRP5	9.80 ± 1.88	5.08 ± 0.69	5.95 ± 1.65	10.28± 2.23	6.94 ± 1.34

Statistical analysis indicating significant differences ($p<0.05$) between group 3 (3.41 ± 0.78) and group 4 (42.63 ±8.95), showing that an increased intake of *cannabis* will increase escape latency with an adverse effects of *cannabis* exposure on spatial learning and memory (Table 2).

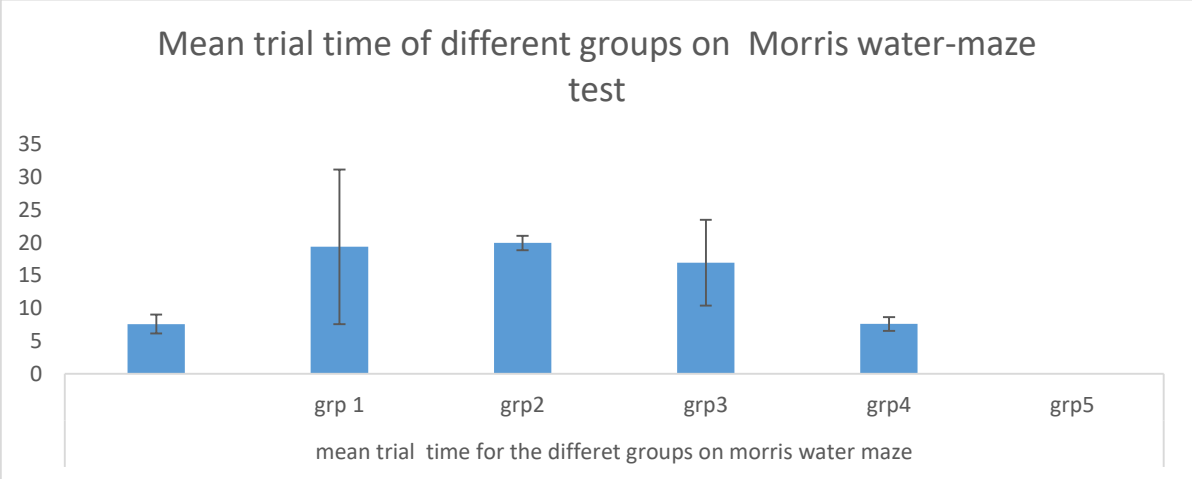

Fig.2: Mean of group performance on Morris water maze test

Table 3 Result of different groups trials on suspension test					
	trial 1	trial2	trial3	trial4	trial5
grp1	12.98 ± 2.22	9.98 ± 1.55	18.20 ± 6.54	10.36 ±2.00	13.91 ± 2.22
grp2	22.68 ± 2.74	11.65 ± 1.83	16.98 ± 3.99	20.34 ±2.74	14.94 ± 4.74
grp3	65.48 ± 40.34	26.10 ± 11.03	16.96 ± 11.74	12.06 ±9.99	17.96 ± 8.72
grp4	13.36 ± 2.39	17.50 ± 3.83	9.30 ± 5.03	3.31 ± 1.95	3.67 ± 2.15
grp5	95.35 ± 10.49	87.07 ± 7.63	90.70 ± 8.44	92.85± 1.00	86.41 ± 4.47

Statistical analysis confirmed a significant difference ($p < 0.05$) between the high *Cannabis* intake and a reduced or no cannabis-exposed groups with mobility time indicating an impact of *Cannabis* exposure on the rats' response to the tail suspension stressor (Table 3)

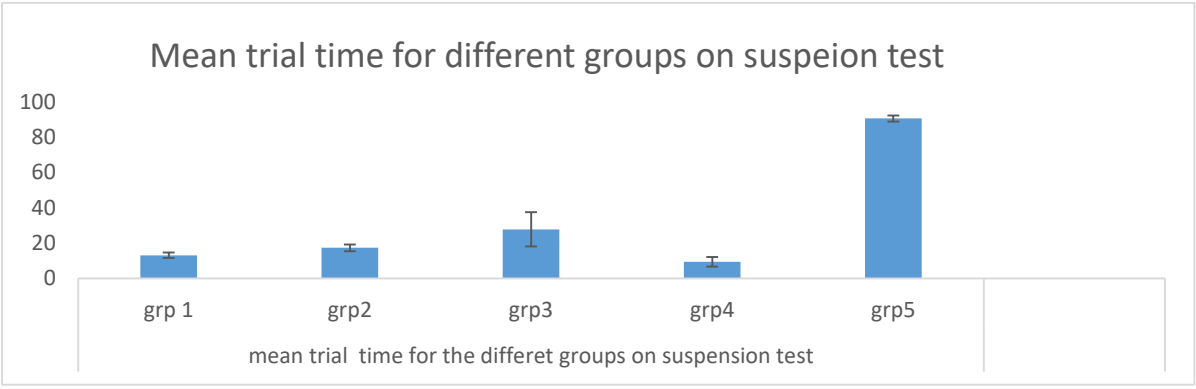

Fig.3 Mean of group performance on Tail Suspension Test

Table 4: Result of different groups trials on handgrip tests					
	trial 1	trial2	trial3	trial4	trial5
grp1	13.64 ± 6.14	6.32 ± 0.36	12.78 ± 12.66	5.66 ± 2.12	11.66 ± 7.30
grp2	20.08 ± 7.77	134.46 ±27.48	173.15 ± 51.89	186.00±57.02	79.85 ± 22.00
grp3	23.95 ± 6.02	30.30 ± 7.00	21.58 ± 6.98	16.95 ± 7.66	112.03 ± 32.67
grp4	78.95 ± 43.38	236.91 ± 11.45	74.10 ± 44.34	64.51 ± 21.02	143.43 ± 35.68
GRP5	72.65 ± 17.80	81.93 ± 11.76	84.03 ± 14.54	70.66 ± 11.73	51.37 ± 6,09

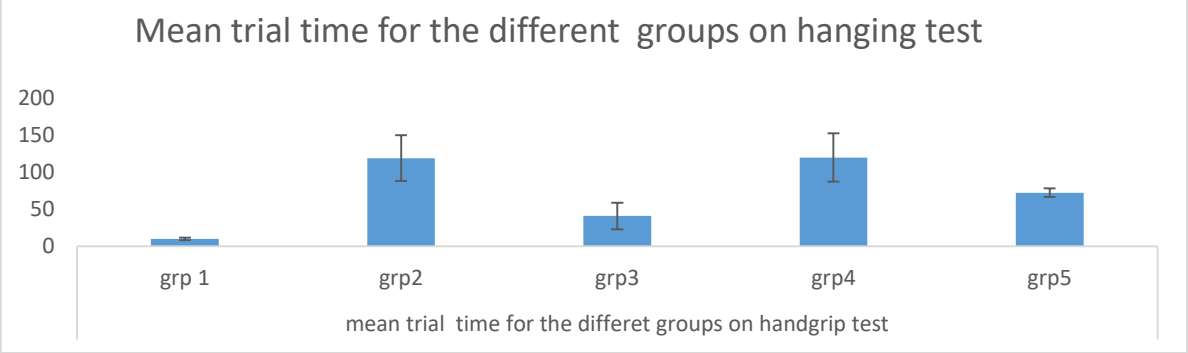

Fig.4 Mean of group performance on Handgrip Test

Table 5: Result of different groups trials on open field test					
	trial 1	Trial 2	Trial 3	Trial 4	Trial 5
grp1	23.11 ± 7.95	23.31 ± 8.63	19.035 ± 6.84	17.93 ±5.00	15.97 ± 2.63
grp2	46.06 ± 24.74	25.76 ± 4.92	15.88 ± 6.04	10.90 ±1,67	22.87 ± 6.27
grp3	18.83 ± 9.12	27.21 ± 3.55	21.61 ± 3.03	16.76 ±5.80	38.17 ± 6.05
grp4	8.312 ± 3.13	9.15 ± 3.11	9.32 ± 1.78	6.42 ± 2.65	12.52± 1.69
GRP5	24.21 ±4.99	33.81 ± 13.03	14.53 ± 4.44	19.72 ±5.52	13.45 ± 7.33

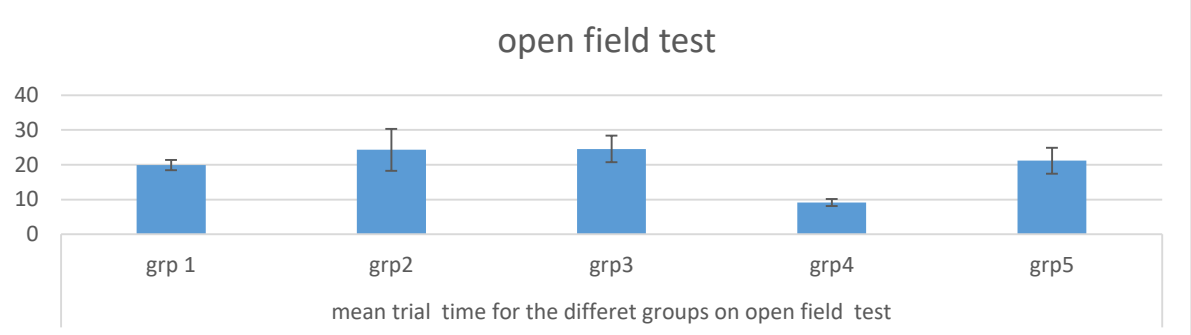

Fig.5: Mean of group performance on Open Field Test

Table 6: Result of different groups of animal weights within treatment period

	Animal weights within the treatment period				
	GRP1	GRP2	GRP3	GRP4	GRP5
wk1	44.52 ±3.86	46.03± 2.78	46.83± 3.23	49.35 ± 2.24	46.05± 2.17
wk2	63.15 ±3.38	52.70± 6.04	50.98 ± 4.05	57.7 ± 19.72	55.35± 2.64
wk3	83.78 ±3.48	71.93 ±9.10	64.73±22.79	82.8 ± 30.65	59.68± 2.21
wk4	90.9 ± 2.31	88.68± 7.95	67.65±24.10	98.00±33.54	79.90± 4.97

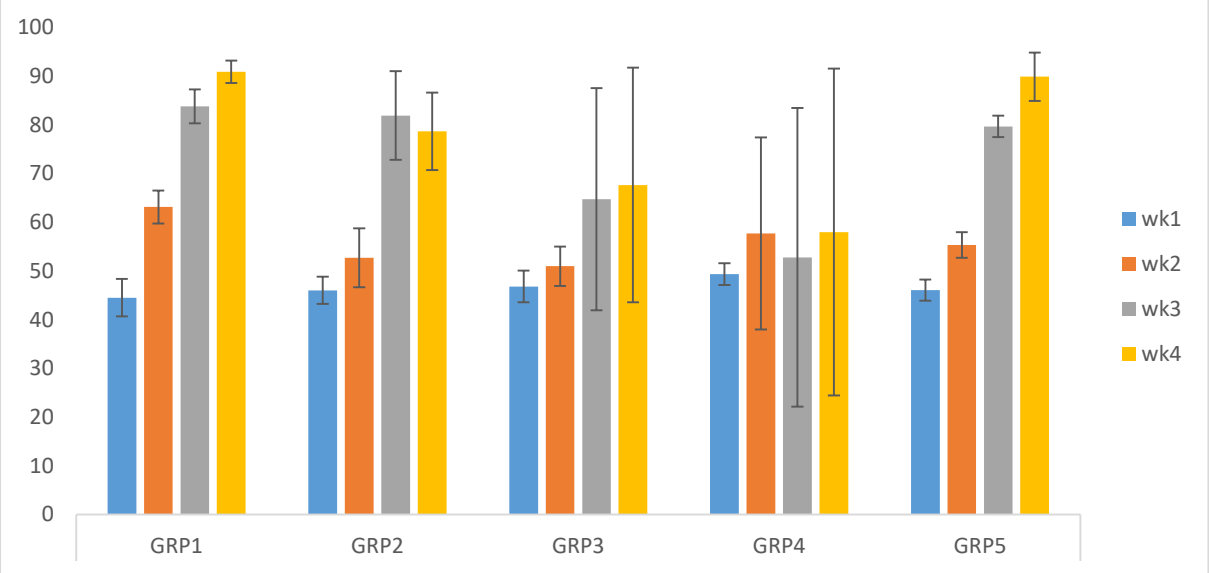

Fig. 6. Result of different groups of animal weights

DISCUSSION

The results suggest that chronic exposure to *Cannabis sativa* will adversely affects motor coordination and balance in a rat model, as evident by prolonged traversal times, increased foot slips, and observable signs of impaired coordination during the beam walking test. These findings align with existing literature on the psychomotor effects of cannabinoids and underscore the importance of considering motor function in the evaluation of increased dose of *Cannabis*. The impairment in spatial memory retention during the probe trial on Morris water maze test further underscores the potential detrimental consequences of *Cannabis sativa* , indicating that a small dose of *Cannabis sativa* can alter the spatial learning and deteriorated the rat performance on Morris water maze test. *Cannabis sativa* increases susceptibility to depressive-like behavior in rats, as indicated by prolonged immobility during the tail suspension test. These findings align with existing literature on the potential impact of cannabinoids on mood-related behaviors and emphasize the importance of considering emotional outcomes in the evaluation of high dose of Cannabis exposure. The results suggest that the exposure to *Cannabis sativa* has an impact on grip strength and muscular endurance in rats, as it is evident by increased peak grip strength and ability to sustain grip over time. These findings align with existing literature on the mechanisms of endocannabinoid modulation of dopamine release in reward and addiction showing that an increased dose can increase the physical performance, muscular endurance and strength of the rats. The results of Open Field test suggest that an increased dose of Cannabis sativa induces anxiety-like responses and alters locomotor activity in rats, as evident by reduced exploration of the central area and decreased overall distance traveled in the open field. These findings align with existing literature on the anxiogenic effects of *cannabidiol* this evaluation shows that a low dose of *Cannabis* exposure give a positive impact but an increased dose of *Cannabis sativa* on Wistar led to anxiety

CONCLUSION

The results of the study test suggest that *Cannabis*, particularly at a dosage below 200 mg/kg, have a positive influence on the neuromuscular coordination and balance on memory and non-depressive behavior and anxiety of male Wistar rats. Additionally, the control group (Group 5) demonstrated comparatively lower poor responses in these parameters. It was also observed that higher doses expressed negative responses in some of

the parameters. This highlighting the potential benefits of *Cannabis* on cognition neuromuscular coordination, memory and depressive behaviours.

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