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POST TRAUMATIC STRESS DISORDER AND THE TOXICOLOGY OF *CANNABIS SATIVA*

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Cannabis sativa, Post-traumatic stress disorder, Endogenous cannabinoids, N-Methyl D-Aspartate receptor, Hypothalamic-pituitary-thyroid axis, Adrenocorticotrophic hormone

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ABSTRACT: Many young men, women, and even the elderly are addicted to Cannabis intake abuse despite its predictable toxicological consequences. In this paper, we studied the toxic effects of oral administration of methanol extract of *Cannabis sativa* seeds using a total of forty male Wistar Rats. Animals were randomized into five groups (n = 8 rats) of approximately equal weight. Group 1 received 100 mg/kg of the extract, group 2 received 200 mg/kg of the extract, group 3 received 300 mg/kg dosage of the extract, group 4 received 2 ml of olive oil and group 5 received distilled water for 14 days. Result for AST was significantly ($p<0.05$) higher in groups 2 (57.00 ± 13.00 IU/L) and 3 (59.33 ± 10.53 IU/L), compared with normal control group 5 (31.33 ± 1.53 IU/L). Significantly ($p<0.05$) higher serum ALT was observed in groups 2 (50.00 ± 12.52 IU/L) and 3 (56.33 ± 10.21 IU/L). Results for kidney function, shows significantly ($p<0.05$) higher serum urea concentration in group 3 (13.75 ± 2.41 mg/dl) compared with the control group (8.75 ± 1.60 mg/dl). Serum creatinine concentration was significantly ($p<0.05$) higher in group 2 (2.25 ± 1.18 mg/kg) and group 3 (2.38 ± 1.57 mg/kg) when compared with the control group (1.09 ± 0.13 mg/kg). Significantly ($p<0.05$) higher SOD values was obtained in group 3 (72.64 ± 5.90 mg/kg) when compared with normal control group (19.62 ± 4.26 mg/kg). In conclusion, the study showed that oral administration of *Cannabis sativa* caused dose-dependent hepato-renal toxicity.

INTRODUCTION: Recent studies on cannabinoid chemistry are centered on understanding their mechanism of action and their role in alleviating chronically debilitating mental health conditions such as post-traumatic stress disorder (PTDS) and schizophrenia, and the role of the endogenous cannabinoid system in normal and diseased states of the brain, rather than establishing the threshold for the effects of the substance on the user.

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Post-traumatic stress disorder (PTDS) is the manifestation of symptoms following episodes of traumatic experiences such as fear, horror, and helplessness in an individual, which unlike normal experiences are more difficult for the brain to process [2]. During episodes of PTDS, the amygdale sends impulses to the hypothalamus which signals the sympathetic branch of the autonomic nervous system, endocrine system, and the neocortex, which is involved in memory processing [3].

Since, the amygdale is programmed to remember sensations such as smell and sound, such sensations associated with traumatic experience will be recalled and reinforced, when similar stimuli are perceived, causing the stimulation of the sympathetic nervous system to prepare the body for

danger [3]. Neuroendocrine dysregulation associated with PTDS includes abnormal regulation of the hypothalamic-pituitary-adrenal axis, which co-ordinates the neuroendocrine stress response systems in the brain [3]. The hypothalamic paraventricular nucleus within the hypothalamus responds to stress stimulus by stimulating the production and secretion of adrenocorticotrophic hormone (ACTH) from the anterior part of the pituitary gland [3]. The hormone, ACTH is transferred through the bloodstream to the adrenal cortex where it stimulates the secretion of glucocorticoids from the adrenal cortex [3]. Glucocorticoids in-turn activate the release of glutamate in the brain [3].

The neurotransmitter, glutamate binds to the N-Methyl D-Aspartate (NMDA) receptors that are located within the brain [3]. Dysregulation of the hypothalamic-pituitary-thyroid (HPT) axis of the brain is also noted as a possible consequence of PTDS [4]. Also, there is abnormal regulation of neurotransmitters such as catecholamine, serotonin, and amino acid/peptide neurotransmitters in the brain.

These neurotransmitters function in the mesolimbic dopaminergic pathway which is known to modulate the hypothalamic-pituitary-adrenergic axis in response to stress, while norepinephrine released from the sympathetic nerve endings in the locus ceruleus, mediates autonomic response to stress in the prefrontal cortex, amygdale, hypothalamus, periaqueductal grey, and thalamus, through a feed-forward mechanism that increases such response [3]. Also, there is sustained hyperactivity of the sympathetic nervous system as evidenced by elevations in the heart rate, blood pressure, and increased cerebrospinal fluid norepinephrine concentration.

Cannabis sativa contains several cannabinoids such as cannabigerol, cannabichromene, cannabidiol, cannabinol, and Δ9-Tetrahydrocannabinol, which function as neuromodulators when they bind on cannabinoid receptors to trigger the establishment of functional neural circuits and increased synaptic plasticity. These phytochemicals also have analgesic effects that help to alleviate pain through a mechanism that involves a cross-talk with opioid receptors at the molecular level, through G-proteins that are expressed in similar regions of the brain [3]. The cannabinoids also support the secretion of serotonin from serotonergic neurons in the dorsal and median raphe nuclei in the brain stem and also in the forebrain and prefrontal cortex [7]. They also cause the release of inhibitory neurotransmitters such as γ-aminobutyric acid (GABA), neuropeptide-Y and endogenous peptides. The neuroendocrine activity of serotonin includes analgesia, regulation of sleep, sexual activity, appetite, anxiety, circadian rhythm, motor activity, and cognitive function [3].

The main inhibitory neurotransmitter in the brain is γ-aminobutyric acid (GABA) [3]. It inhibits the corticotrophin release hormone/norepinephrine circuits involved in mediating stress responses through the GABA-A receptors that are localized with benzodiazepine receptors, which somewhat potentiate the inhibitory effects of GABA on postsynaptic neurons [3]. Neuropeptide-Y (NPY) inhibits the corticotrophin-releasing hormone/ norepinephrine circuits involved in stress and fear responses and also inhibits the release of norepinephrine from sympathetic neurons, this may be involved in promoting recovery from PTSD [6]. Endogenous opioid peptides such as endorphins and enkephalins, act upon the same opioid receptors which are activated by exogenous opioid molecules [3]. The body uses endogenous analgesic compounds such as opioid peptides like dynorphins, enkephalins, and β-endorphin, endocannabinoids and somatostatin, to alleviate long-lasting sensations of pain [3].

Endogenous opioid peptides, endogenous cannabinoids, and phytocannabinoids produce their analgesic effects in both the central nervous system and the peripheral nervous system through similar mechanisms that involve inhibition of ion-channels. This stops the release of excitatory neuropeptides such as noradrenaline and substance-P in nociceptive afferent neurons, thus preventing pain transmission [3].

Based on these somewhat beneficial neuromodulatory effects of cannabis, there has been a recent spike in the prescription of marijuana by general medical practitioners, to patients of PTSD, for the management of the disorder without prior knowledge of its toxic effects [6].

MATERIALS AND METHODS:

Materials:

Plant Material Sampling: The specimen, *Cannabis sativa* is a controlled substance in Nigeria, and so appropriate approval was taken from the security agencies before the sample was used in this study. The seeds of Cannabis sativa were bought in Oriugba market, Umuahia, Abia State. A voucher specimen of seeds and leaves were identified as *Cannabis sativa* (Cannabicea) by Dr. Garuba Omosun, a Taxonomist in the Plant Science Department of Micheal Okpara University of Agriculture Umudike, Nigeria. The seeds were removed after drying the plant. The dried seeds were milled into fine granules using a laboratory miller (ED-5, U.S.A) and stored in airtight container. The milled sample was soaked in methanol and mechanically agitated for 48 h to ensure complete extraction after which it was filtered using Whatman type-2 paper. After extraction, the solvent was completely evaporated over hot water bath leaving a viscous brown liquid that was dissolved in olive oil and stored in an amber colored reagent bottle and kept in the dark cupboard until it was used.

Experimental Animals: Forty-eight male Wistar rat of the albino strain weighing 150-200g obtained from the Animal House of College of Veterinary Medicine, Micheal Okpara University of Agriculture Umudike, were used in this study. On arrival, the initial weights of the rats were taken. The rats were acclimatized for one week before the experiment was started. The animals were exposed to the normal 12 h light and dark cycles under tropical weather conditions, and all rats were allowed free access to a standard diet and tap water.

Experimental Design:

Animal Grouping and Treatments: The rats were randomly placed into 5 groups of 8rats each as follows:

Group 1: Treatment Group 1: Animals were exposed to 100 mg/kg body weight of test sample dissolved in virgin olive oil and given normal rat feed and water for 14 days *ad libidum*

Group 2: Treatment Group 2: Animals were exposed to 200 mg/kg body weight of the test sample, dissolved in virgin olive oil and given rat feed and water for 14 days *ad libitum.*

Group 3: Treatment Group 3: Animals were exposed to 300 mg/kg body weight of the test sample dissolved in virgin olive oil and given normal rat feed and water for 14 days *ad libitum.*

Group 4: Vehicle Control Group: Animals received 2 ml virgin olive oil ad normal rat feed and water for 14 days *ad libitum.*

Group 5: Normal Control Group: Animals received normal rat feed and water for 14 days *ad libitum.*

Animal Sample Collection and Preparation: After the period of treatment, the animals were fasted overnight and sacrificed by cervical dislocation after being anesthetized with chloroform. Blood was collected into an EDTA anticoagulant bottle from the heart through the sharp cardiac puncture, using a syringe needle for hematological assays. The blood sample for other biochemical studies was collected in a plain bottle and allowed to clot, after which the plasma was obtained by centrifuging at 3000 rpm for 5 min. The serum was collected after centrifuging using micro-pipette. The liver and kidney were excised and drained of blood using clean, sanitary paper. The organs were placed in a bottle containing 10% formaldehyde buffered saline.

RESULT:

Proximate Composition of *Cannabis sativa*: Proximate composition showing the actual amount of nutrients present in the sample analyzed.

TABLE 1: PROXIMATE PROPERTIES OF *CANNABIS SATIVA* SEEDS

Parameters	Concentration (%)
Moisture content	6.69 ± 0.14
Dry matter	80.91 ± 0.14
Crude protein	19.10 ± 0.01
Ash content	11.84 ± 0.02
Crude fiber	18.87 ± 0.01
Crude fat/lipid	19.33 ± 0.00
Carbohydrate	43.04
Oil absorption capacity	1.87 ± 0.00
Water absorption capacity	2.20 ± 0.00

Values are means ± standard deviation of duplicate determinations

As shown above in **Table 1,** *Cannabis sativa* seeds contain high concentrations of lipid, carbohydrates, and dry matter, when compared with other components of the examined sample.

Quantitative Phytochemical Screening of *Cannabis sativa* Seeds: Phytochemicals are naturally occurring, biologically active compounds that are found in the vegetative parts of plants.

TABLE 2: PHYTOCHEMICAL CONTENT OF *CANNABIS SATIVA* SEEDS

Phytochemical	Concentration (mg/100g)
Alkaloid	3.15 ± 0.01
Flavonoid	2.82 ± 0.01
Saponin	6.10 ± 0.01
Tannin	2.14 ± 0.01
Cyanogenic glycosides	0.10 ± 0.01
Phenol	0.27 ± 0.01

Values are the mean ± standard deviation of duplicate determinations

As shown in **Table 2**, the concentration of saponin, flavonoid, tannin, and alkaloid was high when compared with the other anti-nutrients such as phenol and cyanogenic glycosides

Mineral Composition of *Cannabis sativa* Seeds: Minerals are naturally occurring element present in plant and animal products in different amounts.

TABLE 3: RESULTS FOR THE MINERAL CONTENT OF *CANNABIS SATIVA* SEEDS

Mineral	Concentration (mg/100g)
Potassium	13.73 ± 0.01
Phosphorus	10.00 ± 0.02
Sodium	17.52 ± 0.01
Calcium	14.65 ± 0.01
Magnesium	09.67 ± 0.01
Zinc	2.00 ± 0.01
Iron	1.00 ± 0.01

Values are the mean ± standard deviation of duplicate determinations

As shown above, in **Table 3,** potassium, phosphorus, sodium, calcium, and magnesium were present in higher concentrations in the sample than other minerals such as zinc and iron.

TABLE 4: BIOCHEMICAL AND TOXICOLOGICAL EFFECTS OF ORALLY ADMINISTERED METHANOL EXTRACTS OF *CANNABIS SATIVA* SEEDS ON SOME KIDNEY FUNCTION PARAMETERS IN MALE WISTAR ALBINO RATS

Groups	Creatinine (mEq/dl)	Urea (mg/dl)	Bicarbonate (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)
Group 1 100 (mg/kg) + oil	2.37 ± 1.13	13.00 ± 1.91	24.10 ± 4.10	4.00 ± 1.02	37.53 ± 2.14
Group 2 200 (mg/kg) + oil	2.25 ± 1.18*	12.10 ± 0.75	26.40 ± 4.38	3.68 ± 0.62	39.20 ± 4.40*
Group 3 300 (mg/kg) + oil	2.38 ± 1.57*	13.75 ± 2.41*	27.43 ± 4.28	3.70 ± 0.24	47.38 ± 7.80*
Group 4 0.0 (mg/kg) + oil	1.10 ± 0.15	10.85 ± 1.56	29.48 ± 4.12	3.03 ± 0.32	33.43 ± 4.50
Group 5 0.0 (mg/kg) only normal control	1.09 ± 0.13	8.75 ± 1.60	30.03 ± 4.07	4.05 ± 1.05	18.63 ± 2.90

Values are mean ± standard deviation for n = 5. *significant difference from the normal group at ($p<0.05$)

Compared to the normal control, the rats in group 2 (200 mg/kg + oil) and group 3 (300 mg/kg + oil) had significantly ($p<0.05$) higher serum urea concentration. The difference (0.31 mg/dl) between the serum bicarbonate ion concentration observed in groups 2 and 3, was not significant ($p<0.05$) when compared with the difference between each of them and the normal control group. Compared to the normal control; there was no significant ($p<0.05$) change observed in the serum potassium concentration. There was a significant ($p<0.05$) higher serum chloride ion concentration observed in group 2 and 3 when compared with the normal control group.

TABLE 5: BIOCHEMICAL AND TOXICOLOGICAL EFFECTS OF ORALLY ADMINISTERED METHANOL EXTRACT OF *CANNABIS SATIVA* ON SOME LIVER FUNCTION PARAMETERS IN MALE WISTAR ALBINO RATS

Groups	AST (U/L)	ALT (U/L)	SOD (U/L)	Blood glucose (mg/dl)	Total protein (mg/dl)
Group 1 100 (mg/kg) + oil	46 ± 6.56	41.00 ± 2.65	60.01 ± 5.03	91.33 ± 3.06	3.36 ± 0.25
Group 2 200 (mg/kg) + oil	57.00 ± 13.00	50.00 ± 12.52*	67.68 ± 3.43	90.00 ± 3.10	4.47 ± 0.61
Group 3 300 (mg/kg) + oil	59.33 ± 10.53	56.33 ± 10.21*	72.64 ± 5.90	80.33 ± 3.12	6.28 ± 0.56
Group 4 0.0 (mg/kg) + only	30.33 ± 2.52	36.00 ± 1.00	22.25 ± 4.72	98.00 ± 4.17	6.28 ± 0.56
Group 5 0.0 (mg/kg) only normal control	31.33 ± 1.53	37.00 ± 1.00	19.62 ± 4.20	93.67 ± 4.20	5.63 ± 0.27

Values are a mean ± standard deviation for n=5. *significant difference from the group at ($p<0.05$)

The result showed a significant ($p<0.05$) higher serum AST activity in group 1 (100 mg/kg + oil), group 2 (200 mg/kg + oil), and group 3 (300 mg/kg + oil) when compared with the normal control group. Significantly ($p<0.05$) higher serum ALT activity was observed in groups 2 and 3 when compared with the normal control group. There was a dose-dependent elevation of SOD activity: group 3>group 2>group 1, which were significantly ($p<0.05$) higher than in group 4 (0.0 mg/kg + oil) and group 5 (0.05 mg/kg only). There was a slight significant ($p<0.05$) difference in blood glucose concentration between treatment and control groups, implying that the test sample does not affect glucose metabolism. There was no significant ($p<0.05$) difference in total serum protein concentration of all groups when compared with the normal control group.

TABLE 6: BIOCHEMICAL AND TOXICOLOGICAL EFFECTS OF ORALLY ADMINISTERED METHANOL EXTRACT OF *CANNABIS SATIVA* SEEDS ON SOME HEMATOLOGICAL PARAMETERS IN MALE WISTAR ALBINO RATS

Groups	Hb (g/dl)	PCV (%)	WBC ($\times10^9$/L)	RBC ($\times10^{12}$/L)	MCV (*fL*)	MCH (ρg)	MCHCH (g/dl)
Group 1	8.67	42.67	13.60	6.32	66.00	12.53	21.03
100 mg/kg + Oil	± 0.24	± 7.57	± 0.71	± 0.15	± 0.81	± 0.15	± 0.50
Group 2	7.87	46.00	14.32	6.83	64.38	11.82	16.89
200 mg/kg + oil	± 1.21	± 9.17*	± 0.81	± 2.36	± 0.54	± 5.04	± 0.46
Group 3	8.93	43.67	14.40	6.99	65.09	12.78	20.46
300 mg/kg + oil	± 0.61	± 1.53	± 0.93	± 0.24	± 0.94	± 0.75	± 0.28
Group 4	8.90	47.33	8.07	7.57	65.42	10.55	16.89
0.0 mg/kg + oil	± 0.75	± 3.12	± 2.13	± 0.51	± 0.94	± 0.95	± 0.32
Group 5	9.67	43.67	11.48	6.99	65.09	13.84	22.14
0.0mg/kg only	± 0.12	± 1.53	± 1.73	± 0.24	± 0.94	± 0.38	± 0.61

Values are mean ± standard deviation for n=5, *significant difference from the normal group at ($p<0.05$)

The result shows no significant ($p<0.05$) difference in hemoglobin concentration between treatment groups and the control groups. This implies that the treatment did not affect heme formation. There was a slightly significant ($p<0.05$) increase in hematocrit value for treatment group 2 (200 mg/kg + oil) when compared with the normal control group (0.0mg/kg only), implying a fairly normal population of red cells in the blood of animals that received this dosage. There was a slightly significant ($p<0.05$) decrease in the population of white blood cells in the treatment groups when compared with the normal control group, implying that the treatment slightly suppressed the production of white blood cells in the treatment groups, this may be due to an inflammatory response or the activation of CB2 receptors found in the bone marrow which induces the synthesis of myeloid-derived suppressor cells that cause immunosuppression by inhibiting the production of T-cells. No significant ($p<0.05$) difference was recorded in mean cell volume, mean cell hemoglobin concentration values across the groups, compared with the normal control group.

DISCUSSION: *Cannabis sativa* is an annual tropical plant commonly used in the preparation of folk medicine due to its hallucinogenic potentials [8]. This study aimed to evaluate the biochemical and toxicological effects of orally-administered methanol extract of *Cannabis sativa* using selected biochemical parameters in male Wistar albino rats.

From the results in **Table 1**, the moisture content (6.69 ± 0.14%) is slightly higher than the value (5.9%) reported by Audu (1) from their study on *C. sativa* leaves and (4.5 ± 0.15%/100g) reported by Audu (1) from their study on opium poppy seeds (*Papaver samniferum*). This implies that the moisture content of the flour sample can be influenced by the method of flour preparation and also *Cannabis sativa* seeds contain more moisture than opium poppy seeds. From this study, dry matter content (80.91 ± 0.14%) is lower than the value (98.88%) reported by Audu (1) for marijuana, but higher than the value (58.0 ± 0.15g/100g) reported by Audu (1) for the seeds of opium poppy (*Pappaver somniferum*), suggesting that *Cannabis sativa* seeds and leaves may be a better source of crude fiber than opium seeds. The protein content (19.10 ± 0.01%) is lower than the value (20.19%) reported by Audu (1), from their study, but higher than (16.5 ± 0.15g/100g) reported by Audu (1), from their study on opium poppy

seeds. Protein enhances the repair and replacement of worn-out tissues and also play a vital role in the immune system [8]; hence the seeds and leaves of Cannabis sativa may support this role but may not be a good source of protein, due to the low crude protein recorded from this study. It further suggests that the changes in AST and ALT activities **Table 4** were not of immunologic causes. **Table 6**, shows the effects of an orally administered extract of the sample on some liver function parameters. The result recorded shows significantly ($P<0.05$) higher serum AST activity in treatment groups 1, 2 and 3 when compared with the normal control group, suggesting that the extract may be toxic at increasing concentrations, most probably due to an inflammatory response that results in increased leakage of the enzyme. The observed significant ($p<0.05$) increase in serum ALT levels in treatment group 2 (50.00 ± 12.52 U/L) and group 3 (56.33 ± 10.21 U/L) when compared with the normal control group (37.00 ± 1.00 U/L) shows a dose-dependent toxicity and hence caution should be taken in ingesting high doses of the drug.

Significantly ($p<0.05$) higher SOD activity was recorded in treatment group 3 (72.64 ± 5.90 U/L) when compared with the normal control group (19.62 ± 4.26 U/L), this may be due to the increase in the levels of superoxide dismutase activity as a result of increasing levels of free radicals induced by the treatment at this dosage. There was no significant ($p<0.05$) difference in the blood glucose levels between treatment and controls. This implies that the test substance did not affect glucose metabolism. No significant ($p<0.05$) difference was obtained in total serum protein concentration of all the treatment groups when compared with the control groups. This implies that the treatment did not affect protein metabolism. This further suggests that the observed high levels of liver enzymes (AST, ALT, and SOD) were not of immunogenic causes.

Table 7 shows the effects of an orally administered extract of the sample on selected hematological parameters. The results showed no significance ($p<0.05$) difference in hemoglobin concentration between treatment groups and control groups. This implies that the treatment did not affect heme formation. There was a slight significant ($p<0.05$) higher hematocrit value for the treatment group 2, when compared with the normal control groups. This suggests that there was a fairly normal population of red blood cells in the blood of the animals that received this dosage. There was a slightly significant ($p<0.05$) decrease in population of white blood cells in the treatment groups when compared with the normal control group, implying that the treatment slightly suppressed the production of white blood cells in the treatment groups. This may be due to an inflammatory response or the activation of CB2 receptors in the bone marrow, which induces the synthesis of myeloid-derived suppressor cells that cause immunosuppression by inhibiting the production of T-cells. No significant ($p<0.05$) difference was recorded in mean cell volume, mean cell hemoglobin and mean cell hemoglobin concentration values across the groups.

CONCLUSION: This work has elucidated the toxic effects of oral ingestion of Cannabis sativa extract as being a dose-dependent elevation of biomarkers for liver and kidney, congestion of the central vein due to portal inflammation in the liver and immunosuppression due to the observed difference in white blood cell count between treatment groups and the normal control groups.

RECOMMENDATION: The study proved the potentially toxic effects of *Cannabis sativa*. Care must be taken in prescribing the drug to patients of post-traumatic stress disorder to avoid addiction that may result in the consumption of higher doses of the drug, to the detriment of the user.

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CONFLICT OF INTEREST: There is no conflict of interest.

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