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Toxicological Effect of Ethanolic Extract of *Cannabis sativa* on Brain Serotonin in Adult Wistar Rats

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Abstract Studies have identified that *Cannabis sativa* (Marijuana) has been used recreationally and medicinally, this has resulted in an increase in the consumption of *Cannabis sativa* among young people. The aim of this study is to produce data on toxicological effect of ethanolic extract of *Cannabis sativa* on serotonin concentration and tissue histopathology in the brain of adult wistar rats. Rats were divided into 3 groups with each group consisting of 8 rats. Treated groups received ethanolic extract of *Cannabis sativa* 25mg/kg body weight and 10% ethanol. The treatments were administered orally within two weeks for short duration and five weeks for long duration. The brain tissues were used for histological assay; the brain serotonin level was determined. Results showed a significant alteration in the level of brain serotonin at two and five weeks administration compared to the control group. Histopathological alterations were also observed.

Keywords Cannabis sativa, Ethanol, Brain and serotonin

1. Introduction

Cannabis sativa, also known as marijuana is a hemp plant of 400 different identifiable chemical constituents, more than 60 of which are cannabinoids. The two main cannabinoids are delta-9-tetrahydrocannabinol (D9-THC) and cannabidiol (CBD) (Fusar-Poli *et al*., 2009). Cannabinoids exert their effect by interaction with specific endogenous cannabinoid (CB) receptors. *Cannabis Sativa* has been used recreationally and medicinally for thousand years (Arseneault *et al*., 2004) and there has been a steady increase in the consumption of cannabis in many countries, especially among young people (Solowij, 2004). *Cannabis sativa* is commonly used by physicians and pharmacists to treat a broad spectrum of ailments (Pacula *et al*., 2002). This rising prevalence has caused a global concern because the use of *Cannabis sativa* might lead to the use of other more harmful illegal drugs such as heroin and cocaine. Johnson (1990) reported that early and regular use of *Cannabis sativa* increases the risk of poor educational performance, early school drop-out, and depression, anxiety and psychosis in later life. Serotonin neurons, a neurotransmitter, originate in the lower brain stem raphe nuclei, including the dorsal and median, and it project to all regions of the brain (Tork, 1990).

There are several subclasses of serotonin receptors (5-HT1, 5-HTlb, 5-HT, 5-HT2, and 5-HT3) which researchers currently cannot directly measure serotonin concentrations in the human brain or within the synapses in laboratory animals. Roy *et al*. (1988) discovered that early onset of alcoholism is characterized by increase in impulsive behaviour and is associated with reduced serotonin turnover. Studies have shown that ethanol diffuses into the whole body and could potentially act on any tissue. The authors of this current research undertook this study to produce data on toxicological effect of ethanolic extract of *Cannabis sativa* on brain serotonin in adult wistar rats.

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2. Materials and Methods

2.1. Animals

Adult wistar rats weighing between 100–150g, bred by the animal house of the College of Medicine, University of Lagos, Idi-araba, were purchased and used for the study. The animals were given unrestricted access to water and standard laboratory rat pellets, produced by Ladokun Feed, Ibadan (Nigeria). The study was carried out in compliance with accepted principles for the use and care of laboratory animals as found in US guidelines (NIH publication/85-23, revised in 1985). The animals Rats were divided into 3 groups with each group consisting of 8 Rats.

2.2. Treatment and Chemical Analysis

Group A received 5 ml of physiologic saline supplied by Unique Pharmaceutical (Sango-Otta, Ogun State). Rats in the treatment groups were administered with ethanolic extract of *Cannabis sativa* (25mg/kg) and 0.5ml 10% ethanol

termed Groups B and C respectively. The route of administration was by oral administration for two weeks termed short duration and five weeks administration termed long duration. The brain tissues were used for histological assay; the brain serotonin level was also determined using High Performance Liquid Chromatography (HPLC) method.

2.3. Histological Examination of Tissues

The brain and liver tissues from the respective rats administered with marijuana, 10% ethanol, and saline were fixed in 10% formal saline for 72 hours. The organs were dehydrated in graded alcohol, cleaned in xylene and embedded in paraffin. The resulting blocks were exhaustively sectioned. The sections were randomized, while the selected sections were stained in haemotoxylin and eosin. The sliders were then examined at magnifications of X400 under microscope.

2.4. Statistical Analysis

The student's t-test and analysis of variance were used to analyze the data for significant difference. Graphpad prism 5.01 software was also utilized.

3. Result

Result in Table 1 shows that administration of adult wistar rats with ethanolic extract of *Cannabis sativa* resulted in significant alteration of the serotonin levels in the brain. Also, 10% ethanol significantly decrease ($p<0.05$) serotonin level at 2 weeks and 5 weeks compared to the control.

Table 1. Brain serotonin level in wistar rat

	GROUP A	GROUP B	GROUP C
Week 2	20.66 ± 2.90	17.66 ± 1.20	16.00 ± 0.57*
Week 5	21.66 ± 4.33	19.33 ± 1. 45	19.00 ± 1.73*

Values are means ± Standard deviation of eight animals per group.
* Significance at $p< 0.05$.

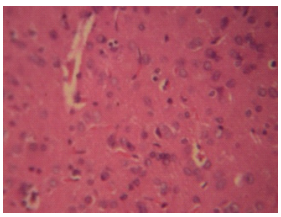

Figure 1. 2 weeks administration of normal saline showing normal brain tissue

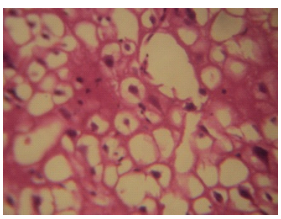

Figure 2. 2 weeks administration of ethanolic extract of *Cannabis sativa* showing mild cerebral edema

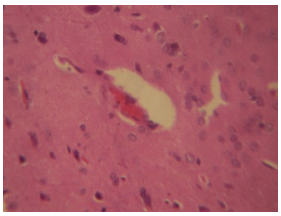

Figure 3. 2 weeks administration of 10% ethanol showing severe and diffuse distortion by strained vacoulisation and edema

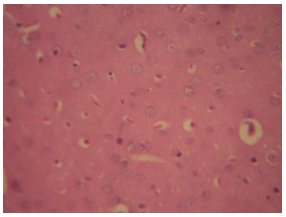

Figure 4. 5 weeks administration of normal saline showing normal brain tissue

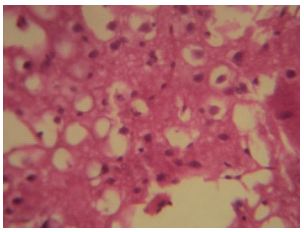

Figure 5. 5 weeks administration of ethanolic extract of *Cannabis sativa* showing mild cerebral edema

After 5: weeks administration of ethanolic extract of cannabis sativa

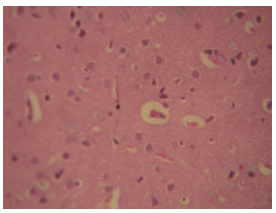

Figure 6. 5 weeks administration of 10% ethanol showing severe and diffuse distortion by strained vacuolization and edema

Figure 1 to 6 shows the photomicrographs of brain of adult wistar rats treated with ethanolic extract of *Cannabis sativa* and 10% ethanol.

The result of the tissue histopathology revealed that the brain tissue of the *Cannabis sativa* treated rats displayed a mild cerebral edema after 2 weeks and 5 weeks of administration but 10% ethanol treated group displayed a severe and diffuse distortion by strained vacoulisation and edema after 2 weeks and 5 weeks of administration.

4. Discussion

In this study, one major observation is that 10% ethanol had significant decrease ($P<0.05$) on serotonin level in the brain of the group C compared to the control. This is in agreement with the observation of McBride *et al.* (1993)

suggesting that decreased serotonin release after acute alcohol exposure has been observed in brain regions that control the consumption or use of numerous substances, including many drugs of abuse. However, many of alcohol's effects on the brain probably arise from changes in the interactions between serotonin and other important neurotransmitters. Also, the ethanolic extract of *Cannabis sativa* decreased brain serotonin level remarkable. It was not until 1990s that cannabinoid receptors in the brain responding tetrahydrocannabinoids were discovered. *Cannabis sativa* affects the brain primarily through cannabinoid receptors. These two receptors CB1 and CB2 interact with other neuron components resulting in the decrease in serotonin. The toxic effect of *Cannabis sativa* has been attributed to the tetrahydrocannabinoids it contains. The histopathological alterations observed in this study is similar to those recorded in the study of Tijani *et al*. (2012) in which the sections of superior colliculus of the animals treated with *Cannabis sativa* showing vacuolation of neurons and stroma.

5. Conclusions

It can be concluded that *Cannabis sativa* causes serotonin level to decrease in experimental rats compared to the control subjects. Histological findings suggest inflammatory changes in the brain tissues of adult wistar rats.

6. Recommendations

More studies need to be carried out in human to evaluate the effect of prolonged exposures to *Cannabis sativa* on brain.

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