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Histopathological Effects of Cannabis on the Heart and Brain of Winster Rats

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Abstract

Background: The central nervous system (CNS) physiological effects of *cannabis* have been extensively studied. However, very little is known about the histopathological changes in the heart and brain both in short time and chronic *cannabis* users. In this study, toxic effects of *cannabis* on the heart and brain of rat were investigated.

Aim: The study aimed to investigate any dose dependent toxic effects on the heart and brain of rats.

Methodology: Thirty (30) rats with average weights 150-200g were used for the study. The animals were divided into groups A, B, C and D. They were all acclimatized for 5 days and fed on the same feed. Animals in groups B to D were administered with different doses of *cannabis*-with Group D- the highest dose-40mg/kg/day, Group C-20mg/kg/day and Group B-l0mg/kg/day. These doses were chosen mainly from extensive literature review. Group A was used as the control. The *cannabis* substance was administered to the rats daily for 28 days in the laboratory in addition to their usual daily feeds and water. The animals from the different groups were sacrificed on days 7,14,2 1, and 28. The brain and heart were excised after dissecting the rats and the tissues were collected for histology.

Results: From the study, the animals were observed to have increased agitation, restlessness, and violent tendencies within 20-30 minutes after each administration which was dose dependent. Interestingly, gradual weight loss was observed in the experimental animals as against the Control group on the last week of the experiment. A dose dependent increased duration of sleep was also observed in the experimental animals but not in the Control group. No structural changes were observed in the heart while in the brain, inflammatory changes were observed.

Conclusion: This study showed no structural changes in the heart after administration of *cannabis* for the study period. This may suggest that although *cannabis* has been strongly associated with panic attack, it may not cause any structural damage to the heart membrane, musculature, and vasculature. However, the study has revealed that, in addition to issues of intoxication, *cannabis* can also produce histopathological damage to the brain. I therefore recommend that in addition to advice based on intoxication as reasons for abstinences, possible damage to brain tissues should also be given as reasons for abstinence and furthermore treatment of *cannabis* abuse should also involve possible investigations and treatment of brain damage.

Keywords: Histopathological; *Cannabis*; Heart; Brain; Rats

Abbreviations: CNS: Central Nervous System; CBG: Cannabigerol; CBC: Cannabichromene; CBD: Cannabidiol; THC: Tetrahydrocannabinol; CBL: Cannabicyclol; CBE: Cannabielsoin; CBN: Cannabinol; CBND: Cannabinodiol; CBT: Cannabitriol; GP: Globus Pallidus; CB1R: Cannabinoid 1 Receptor

Introduction

Cannabis is the second most commonly smoked substance after tobacco, with an estimated 160 million users (3.8% of the world's population of 15–64-year-olds) Adamson [1], Nsikak & Godwin 2019. Different plant substances produce specific pharmacological effects on humans Ashton [2], Berham [3]. Such effects may alter the normal physiological functions of the body, and even greater alteration at toxic levels Rajput [4]; Akinola [5]. Such alterations may include respiratory difficulty, changes in cardiac function, impaired renal functions and an altered perception. *Cannabis* consumption is also associated with a number of psychological effects in humans Thornicroft [6]; Borofka [7]; Louise [8]; Patton [9]; Odejide [10]; Stanley & Eneh [11]; MacFadden [12];

Zou & Kumar [13], although some researchers have argued about *cannabis* medicinal use Blanchard [14]; Gurley [15]; Hubbard [16]. Inspit of theses, the regulations for *cannabis* use have not been very effective Obot [17]. *Cannabis* specifically refers to the green, brown, or gray mixture of dried, shredded leaves, stems, seeds, and flowers of the *cannabis* plant; it's called *Marijuana* (Nsikak and Godwin, 2019). *Cannabis* exists in three forms: herbal *cannabis*, the dried leaves, and flowering tops Munro [18]. The resin of the *cannabis* is the pressed secretions of the plant, known as 'hashish' or 'charash Ujah [19]; Rajput & Kumar [4]. It contains diverse phytochemicals of biological activities and therapeutic influence, such as cannabinoids, terpenes, and phenolic compounds Hillig [20]. Cannabinoids is the most therapeutic compounds, because of its wide range of pharmaceutical effects in humans, including psychotropic activities Hillig [20]; Rajput & Kumar [4].

The raw plant material contains essential fatty acids, nine essential amino acids, dietary fiber, enzymes, vitamins, minerals, flavonoids, carotenoids, terpenes, and Phyto cannabinoid acids a Hillig [20]; Ujah [19]; Rajput & Kumar [4]. Raw *cannabis* leaves, stems, stalks, and seeds can provide the body with almost all of the essential nutrients including carbohydrates, protein, fat, water, vitamins, minerals, trace amounts of calcium, sodium, potassium, and omega-3 fatty acids Audu [21], Ujah [19] reported presence of alkaloids, flavonoids, cardiac glycosides, resins, tenpins and steroids while the proximate composition had elevated levels of 6.87% moisture, 23% crude protein, 19.97% lipid and 11.8% Ash; 18.95% fiber and 39.70% NFE in the stem and 25.36% crude fiber content in seeds. C. sativa leaf contains 9 Essential Amino Acids (EAA), which have good concentration of methionine and lysine. Oladimeji & Valan [22] reported the presence of Alkaoid, flavonoids, cardiac glycosides, terpenes & steroids, and resins. Also, presents were Cannabigerol (CBG), Cannabichromene (CBC), Cannabidiol (CBD),'9-Tetrahydrocannabinol (THC), '8-THC, Cannabicyclol (CBL), Cannabielsoin (CBE), Cannabinol (CBN) and Cannabinodiol (CBND), Cannabitriol (CBT) Choudhary [23]. The most common route of consumption of *Cannabis* is smoking a cigarette (Nsikak and Godwin 2019). In contrast, others use it as an ingredient in foods, and are made available as beer. Two cannabinoid receptor systems; cannabinoid 1 receptor (CB1R) in the brain specific for Δ9-THC and cannabinoid 2 receptor (CB2R) are situated in the brain Onaivi [24]; Schweitzer [25]; Zou & Kumar [13]. The CB1Rs are located in the brain, particularly in the substantia nigra, the basal ganglia, limbic system, hippocampus, and cerebellum Pertwee [26]; Zou & Kumar [13]. The CB2Rs are expressed significantly in immune cells, spleen, and the gastrointestinal system, and to some extent in the brain and peripheral nervous system Chen [27]; Rodrigues [28]. A report revealed that *Cannabis* exposure result in impairments of executive function, including reversal learning, set shifting, and delayed match- and non-match-to-sample working memory tasks Chait & Zacny [29]; Gardner [30]; Ashton [2]; Berham [3]; Cohen & Weinstein [31].

Akinola [5] reported the neurobehavioral effects of daily oral ingestion of C. sativa and its modulatory changes in oxidative stress parameters in mice brain tissues in a study where neurobehavioral activities were assessed by observing animals rearing, grooming, ambulation, head dipping and freezing times. The animals fed with *cannabis*-diet displayed significantly reduced anxiety but statistically insignificant locomotory function, exploratory tendencies and neophilia, in a quantity dependent manner relative to the controls. *Cannabis* demonstrated both antioxidant and oxidative stress tendencies. Kim et al., (2019) reported that regular *cannabis* use can alter brain function, especially in networks that support working memory, attention, and cognitive control processing Chait & Zacny [29]; Gardner [30]; Ashton [2]; Berham [3]. The hippocampus and caudate nuclei specifically showed aberrant structural and functional coupling. These structures have high CB1 receptor density and may also be associated with changes in learning and habit formation that occur with chronic *cannabis* use. In addition to the physiological alteration, at normal or otherwise toxic levels, some zenobiotics can cause direct structural affectation and/or minor or major histological changes to tissue and organs of the body Awolabi [32]. Control/regulations for *cannabis* use is still relatively in effective in many countries Obot [17]. In spite of all these, a number of studies have laid claims to the medical usefulness of *cannabis* Blandchard [33]; Hollister [34]; Hubbard [16]. *Cannabis* is a genus of flowering plant that belongs to the kmgdom-plantae, division *magnolioghyta*, class *magnohopsidea*, order *Rosales*, family-*cannabareae* Hangman [35]. *Cannabis* has three *putative species, cannabis sativa Linnaeus subsp. Indica L., Cannabis sativa subsp. Sativa, L.* (*cannabis sativa* information, 2008), and *Cannabis* ruderalis Janiseh Berham [3]; Booth [36]; Audu [21]. These three Texas are indigenous to central Asia and surrounding regions. *C. Rucleralis* is commonly described as 'auto-flowering and may be day-neutral. Various strains of *cannabis* have been identified and although there are hundreds of strains of *cannabis* in existence, there are also many rumors and urban legends (Hirsch et at., 1997; Short D.J. 1990).

All known strains of *cannabis* are wind-pollinated Clark et al, 1991; Ainsworth [37] arid produce 'feed' that are technically called achenes. Most strains of *cannabis* are short day plant (Clark et al., 1991) with the possible exception of *Cannabis sativa* subsp. Saliva var. *Spontanea* (=C. ruderalis). *Cannabis* is an annual dioecious, flowering herb. The leaves are palmately comp and, with serate leaflets. The quality and potency of *cannabis* depend on a number of factors; the part of the plant, the planet, the soil Cultivation and method of preparation Pertwee [26]; Ujah [19]; Oladimeji & Valan [22]. The psychoactive potency of *cannabis* plant is approximately as follows (descending order), Trichomes, Female flowering buds, Male flowering buds, new shoots, leaves from flower buds, leaves in ascending order of size, Stems of leave (petioles) in ascending order of size, Stem in ascending order of size, Roots and seeds. The potency of herbal *cannabis* decreases over time in storage and is affected by what parts of the plant have been included in the product Chen [26]; Zou & Kumar [12]. Hence,

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a user has little guarantee about the intensity of the high Anthony and Heizer [38]; Beautrais [39]; Higuera-Matas et al, 2009; Ujah [19]; Broyd [40]; Cohen [41]; Cohen & Weinstein [31]; Choudhary [23]. The central nervous system (CNS), particularly the limbic system constitutes the center of emotion and appears to be the pharmacodynamic target of *cannabis*. The pirncipal component of *cannabis* is A9 THC, however, the cannabis plant contains more than 400 chemicals, of which about 60 are chemically related to A9 THC. In humans, A-THC is the metabolite that is active in the central nervous system (CNS). Specific receptors for the cannabinols have been identified, cloned and characterized Friedman H [42]. The distribution of cannabinoid receptors in rats is similar to that of humans Munros S [18] The receptor is densely present in the hippocampus, globus pallidus (GP), basal ganglia, the perventricular nucleus, the substantial nigra, pars reticulata, and the cerebellum. Binding of tritiated ligand is moderate in the cerebral cortex and the caudate, putamen and sparse in the brainstem and spinal cord. This probably explains the reduced tendency of *cannabis* to cause respiratory depression even with an intoxicating dose as well as reduced cardiac effects. Studies in animals have shown that the cannbinoids affect the monoamine and y-aminobutyric acid (GABA) neurons.

When *cannabis* is smoked, the euphoric effects appear within minutes, peak in about 30 minutes, and last 2 to 4 hours. Some motor and cognitive effects last 5 to 12 hours. *Cannabis* can also be taken orally when it is prepared in food, such as brownies and cakes. About two to three times as much *cannabis* must be taken orally to be as potent as *cannabis* taken by inhaling its smoke. Many variables affect the psychoactive properties of *cannabis*, including the potency of the *cannabis* used, the route of administration, the smoking technique, the effect of pyrolysis on the cannbainoid content, the setting, the user's past experience, the user's expectations, and the user's unique biological vulnerability to the effects of cannabinoids. Apart from its blood vessels and some neuroglial elements, the whole of nervous system is derived from the ectoderm. The part of the ectoderm that is determined to give origin to the brain and spinal cord. The limbic system which constitutes the centre of emotion appears to be the pharmacodynamic target of *cannabis*. This system (the rewards system of the brain) is not precisely defined anatomically and has been implicated in functions such as emotion and memory. This definition includes the following cortical areas (the limbic cortex) the cingulate, parahippocampal and subcallosal gyri These structures surround the upper brain stem Subcortical nuclear groups embraced in this system include the amygdaloid body (nucleus) and the septal area. The central nervous system (CNS) physiological effects of *cannabis* have been extensively studied Higuera-Matas et al, 2009; Ujah [19]; Broyd [40]; Cohen [41]; Cohen & Weinstein [31]. However, very little is known about the histopathological changes in the brain and other important organs of both short time and chronic *cannabis* users Awolabi [32]. In this study, toxic effects of *cannabis* on the heart and brain of rat were investigated. This study therefore aimed to investigate any dose dependent toxic effects on the heart and brain of rats.

Objectives

a) To examine the possible histopathological effect of *cannabis* on the brain and heart of rats.

b) To determine any dose dependent effects of *cannabis* on these tissues.

c) To find out any alteration in the histological architecture of the brain and heart of rat using histopathological examination.

Methodology

Thirty (30) rats with average weights 150-200g were used for the study. The animals were divided into groups A, B, C and D. They were all acclimatized for 5 days and fed on the same feed. Animals in groups B to D were administered with different doses of *cannabis*—with Group D— the highest dose—40mg/kg/day, Group C—20mg/kg/day and Group B—l0mg/kg/day. These doses were chosen mainly from extensive literature review. Group A was used as the control. The cannabis substance was administered to the rats daily for 28 days in the laboratory in addition to their usual daily feeds and water. The animals from the different groups were sacrificed on days 7,14,2 1, and 28. The brain and heart were excised after dissecting the rats and the tissues were collected for histology.

Results

Effect of *Cannabis* on Weight

From the study, it was observed that the rats gained weight in the first and second weeks, but most of the rats lost some weight in the last week of the experiment. The later observation was not noticed in the rats in group C that receive the lowest dose as well as in the control animals.

Effects of *Cannabis* on the Histology of the Brain

Figure1 & Figure 2a,b,c below show the photomicrographs of the brain of animal from test group D (Highest dose) on the day 7 of the experiment, showing infiltration of the outer cortex by acute inflammatory cells and around blood vessels. Similar observation was made in group C on day 14. See Figure 3a,b,c Interestingly, no abnormality of changes was seen on the histology of the heart throughout the experiment.

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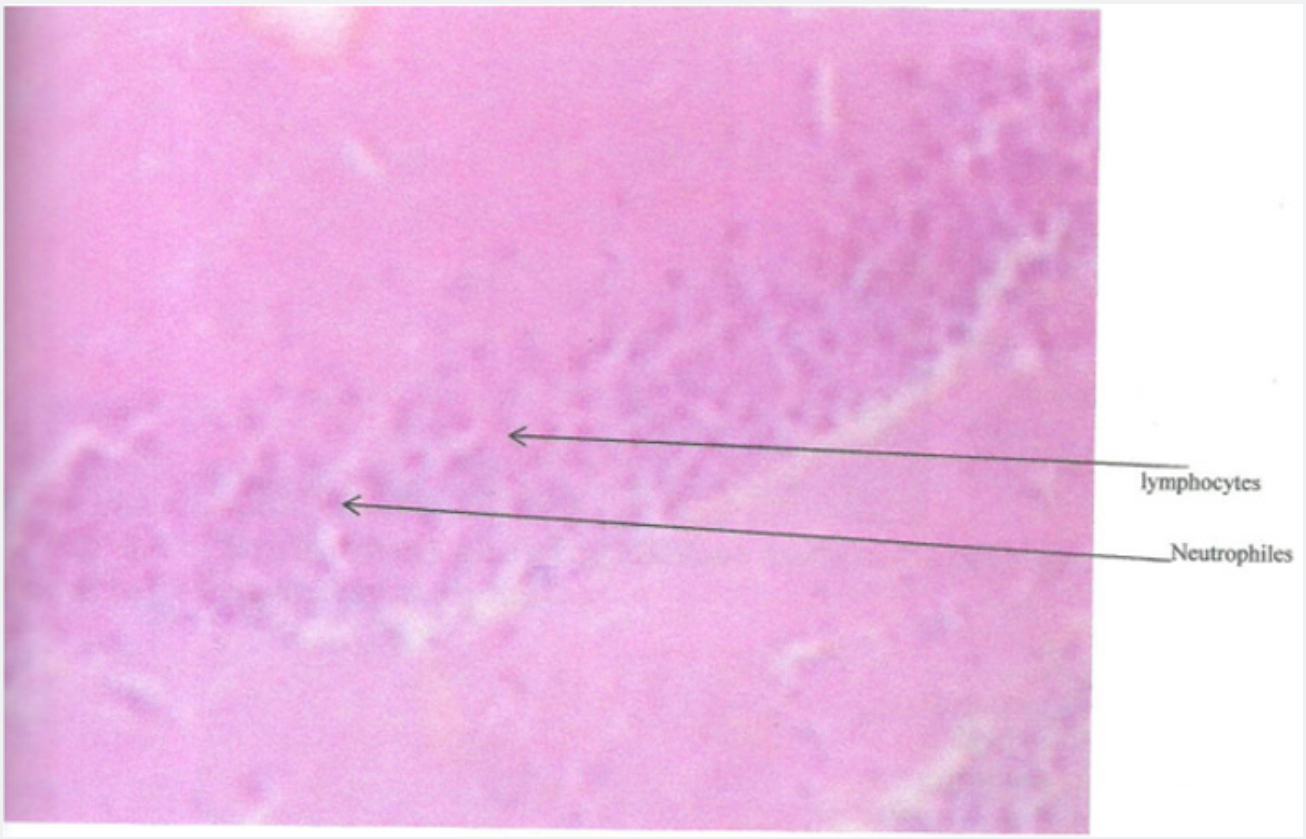

Figure 1: Below shows a photomicrograph of the brain of the control group rats showing normal architecture.

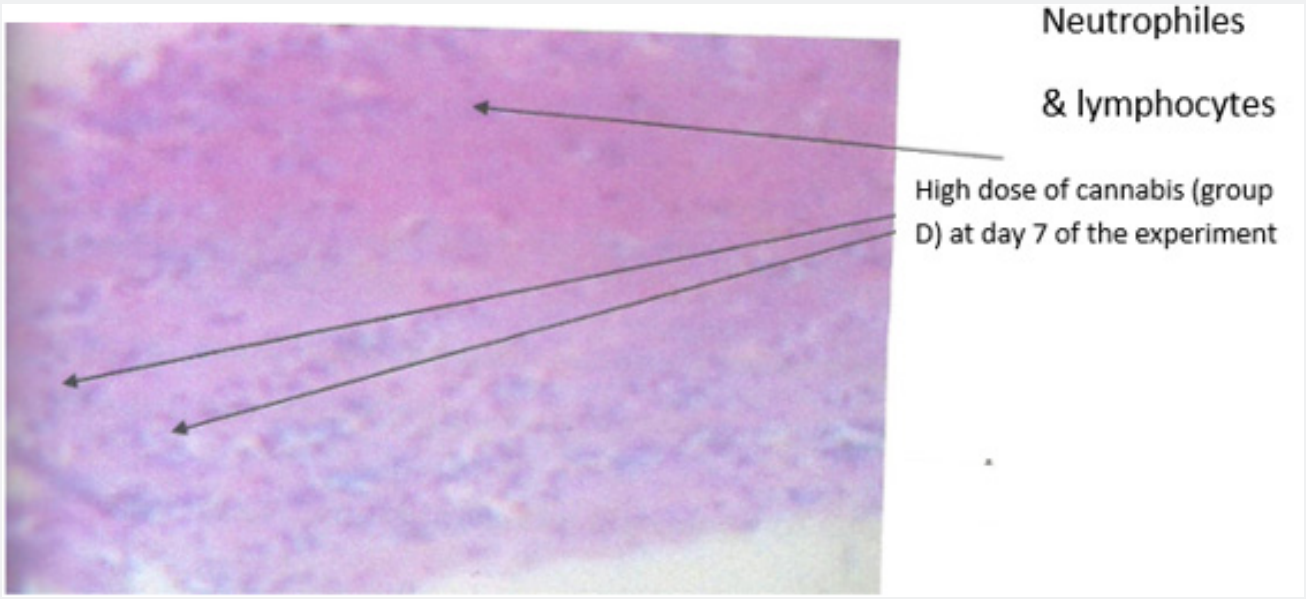

Figure 2a: Showing infiltration of the outer cortex by acute inflammatory cells and around blood vessels.

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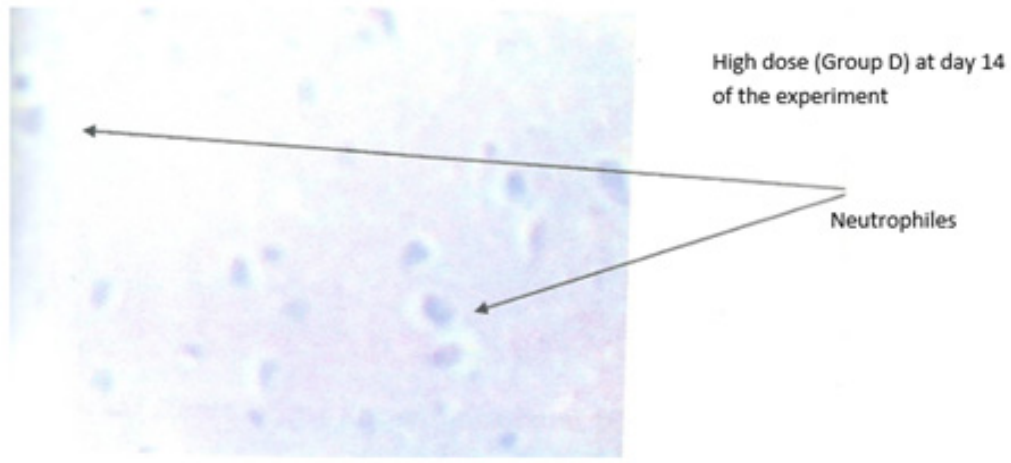

Figure 2b: Brain of rat showing diffuse inflammatory cells (neutrophiles and lymphoctes).

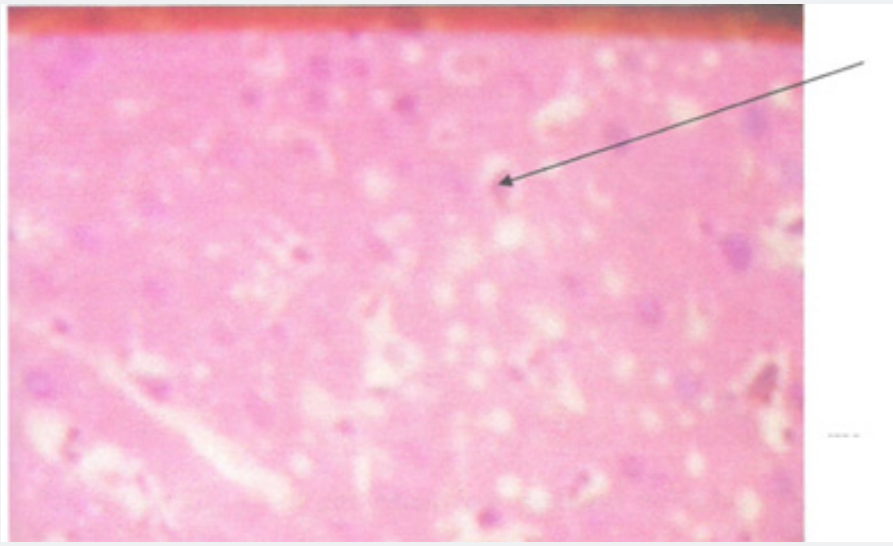

Figure 2c: Brain showing infiltration of outer cortex by acute inflammatory cells-Neutrophiles.

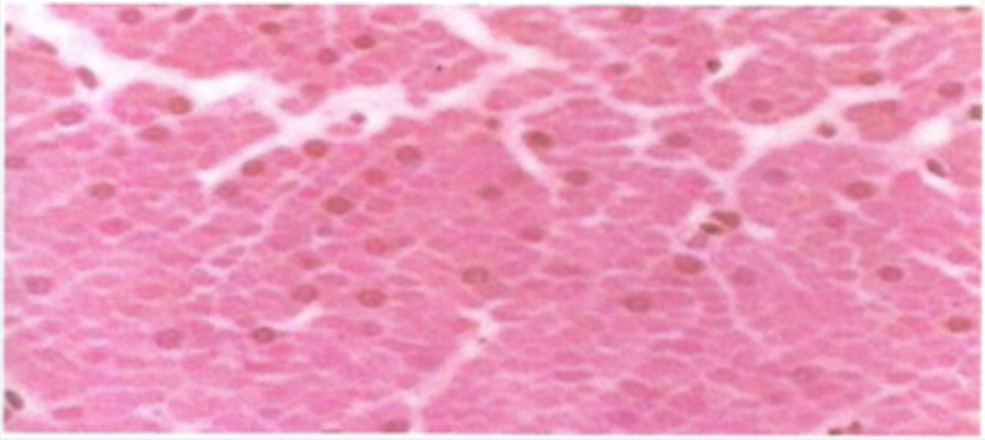

Figure 3a: Heart of rat showing normal histology on day 7.

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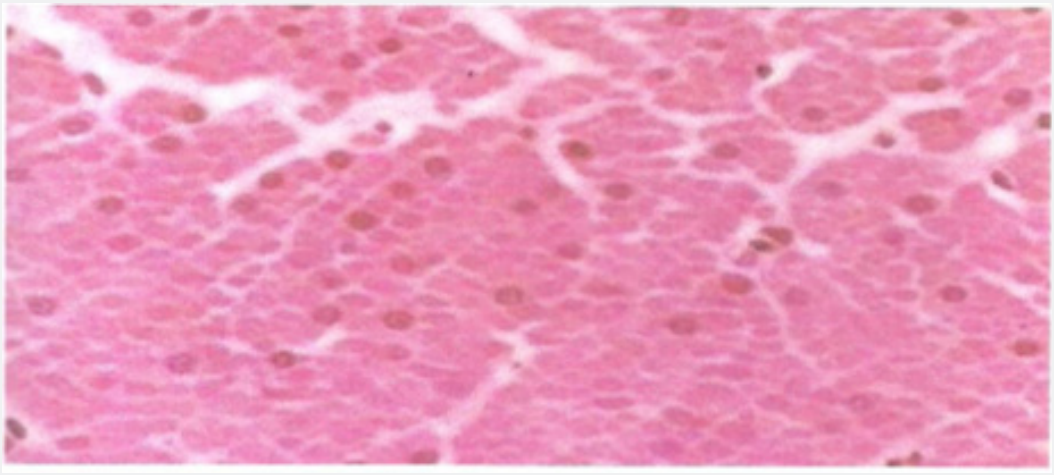

Figure 3b: Below shows the photomicrograph of the heart of the test group A on day 14 of the experiment.

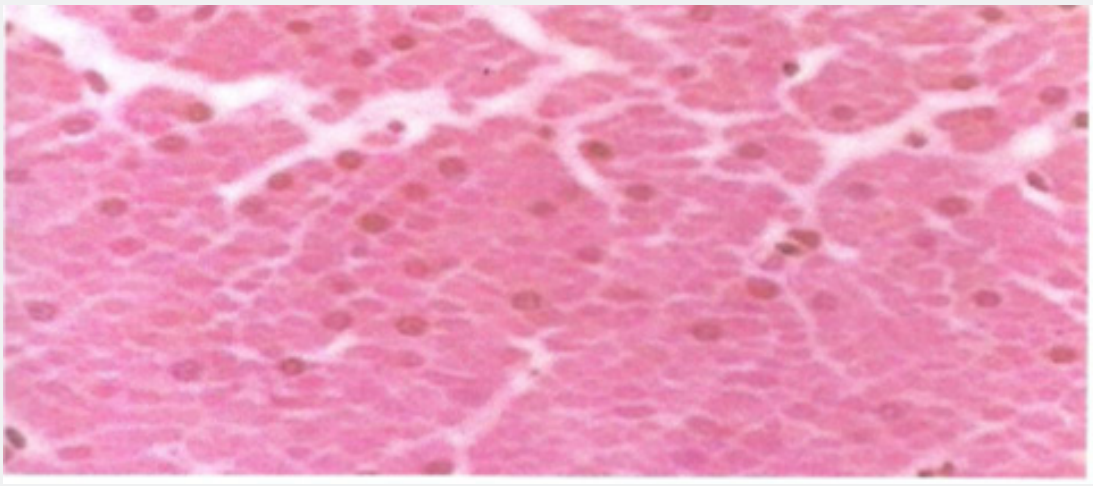

Figure 3c: Hear of rat showing normal cellular architecture on day 28.

Discussion

This study was undertaken to determine, if in the addition to the usual intoxication, euphoria, and the feeling of "high" experienced by the users of *cannabis*, there are other structural changes caused by substance in some organs in the body and also to find any associated dose dependency effects. The organs studied include the brain, heart, liver and kidneys. Surveys have shown that marijuana is the most commonly used illicit drug world-wide (Kessler et al.1994). Several studies done on the effects of *cannabis* used have limited themselves mainly to the central nervous system (CNS) effects of this psychoactive substance. Despite the overwhelming results of the CNS effects such as changes in mood, perception, motivation, the "high" and "mellowing out", incordination, impairment in learning and memory, there is as yet no convincing evidence that marijuana use damages brain cells or produces any permanent functional changes, Hubbard [16] although there are animal data indicating impairments of maze learning that persists for weeks after the last dose. (The Report of the National Commission on Marijuana Drug Abuse; Effect of long-term *cannabis* use, 2007). In this study, the oral route was preferred to inhalation because of dosage administration. Also in humans, oral ingestion of *cannabis* has been found to cause episodes of anxiety particularly panic and hallucination in about 50% to 60% than smoked marijuana Smoking produces a rapid onset of action and permits the set regulation of dose according to effect Also oral method of *cannabis* use seems to be increasing as most people use it to cook various dishes. The results of this study show that the animals which received *cannabis* showed increased aggression, violence and restlessness within- 30 minutes to 1 hour after intake of drugs. This effect was directly proportional to the dose of *cannabis* and declined to marked slowness and sluggish signs and excessive sleepiness in the last one week of the study. This suggests probably the onset of the most controversial a motivational syndrome.

This finding is consistent with the work of Tenant and Groesbeck. (Tenant S, Groesbeck D, 1972; Hall et al, 1994; Andrews J, 2001). The limbic system controls emotions (aggression, violence, anger, and rage) m human and it bears great deal of similarity with

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that of rat Stimulation of this centre therefore by engaging CBI and CB2 by the *cannabis* substance is thought to be responsible for the observed aggression, violence, restlessness, intoxication and the "high" that were observed in these animals Same explanation goes to similar effects seen in humans who consume *cannabis* and most other psychoactive substances like cocaine, PCP, LSD, opoid etc. Previous findings from Broyd [40]; Cohen [41] also revealed that impairment of executive function in synthetic cannabinoid users compared with recreational users of *cannabis* and non-users. Yucel et al. (2016) reported a decrease in hippocampal volumes following *cannabis*. Report from Beale [43] reported restorative effect of CBD on the subventricular and CA1 subfields in current *cannabis* users, especially those with greater lifetime exposure to *cannabis*. Awolabi [32] reported that *cannabis* exposure results in altered individual neurons morphologies and the spatial distribution of the cells in the Cornu Ammonis and dentate gyrus at higher concentration. Despite, numerous studies on *cannabis* on cognitive and hippocampus architectures, there are limited study on the effect of *cannabis* on the hippocampus on animal model in this research sphere. The study revealed increased appetite in the experimental animals with corresponding weight gains See Table 1. This is consistent with several studies (Binitie A, 1988; Odejide AO, 1980; Odegide AO, Sanda OA, 1976). However, it was observed that there was a progressive weight loss in the experimental animals in the last one week of the experiment. This may probably suggest that with prolonged use of *cannabis*, despite the munchies, there is gradual reduction in the rate of weight gains.

Table 1: Effect of Cannabis on Weight.

Group	Day0 (g)	Day 7 (g)	Day 14 (g)	Day 21(g)	Day 28 (g)
Control (A)	155±5	180±20	200±20	125±5	135±5
10mg/ kg/day	160±5	200±5	190±5	195±5	195±5
20mg/ kg/day	170±5	210±5	210±10	195±10	180±5
40mg/ kg/day	170±5	210±5	220±10	185±10	175±5

The mechanism of weight gain is thought to be due to stimulation of the CB 1 receptors in the ventrornedial area of the hypothalamus. Receptor desensitization may be responsible for the weight loss observed later in the experimental animals. Note that this was marked in the experimental animals on the highest dose of *cannabis* (40mg/kg/day), indicating a possible dose dependency effect. A dose dependent intoxication effect was observed in the experimental animals following each administration of *cannabis* probably due to the high". This is consistent with many other earlier works that administration or consumption of large doses of *cannabis* causes acute intoxication (Andrew J.,2001). The histological findings revealed, in the animal that were dissected abnormality in the brain of the experimental animal which was chattered by infiltration of the outer cortex, meninges, choroids plexuses and blood vessels with acute inflammatory cells. This finding, however, was not consistent as it was only seen in about 0.2% of the experimental animals. It is thought that the impairment in cognitive function may be due to this inflammation. There is no literature on histological alteration of the brain with *cannabis* use, however, some of the toxicological studies have indicated that brain damage characterized by enlarged ventricles, damage to hippocampus and amygdale may all occur (Gbose D 1978) [44]. It has been suggested that most of the symptoms seen with cannabis psychosis like hallucinations and paranoia may be due to these structural changes. Also, Gbanai et al in 2008 noted that the wide therapeutic index is largely due to the fact that *cannabis* can bind with mirage of receptors, has prolonged half - life and can also accumulate in the tissue for a long time. Although the physiological functions of the CB receptors and their endogenous legends are incompletely understood, they are likely to mediate most of the CNS effects of *cannabis* [45,46]. This is because they are widely distributed with high densities in the cerebral cortex, hippocampus, striation and cerebellum (Iversen, 2003). For instance the effect on the hippocampus and other parts of the limbic systems produce the impaired memory and learning and possibly "high" and intoxication.

Although there is in obvious *cannabis* induced movement disorder, the subtle incoordination and a staggering movement which may accompany intoxication supports the wide receptor distribution in the cerebral cortex, striatum and the cerebellum. These are areas in the brain that control both voluntary and involuntary movement [47,48]. Specific CB antagonists have been developed and are in controlled clinical trials. One of these, rimonabant, has been reported to reduce relapse in cigarette smokers and to produce weight loss in obese patients (Gilman and Goodman, 2008 ed). An attempt to investigate any toxic effect of *cannabis* on the histology of the heart was born out of established strong relationship between *cannabis* use and panic disorder and because the later has been associated with various cardiac abnormalities particularly mitral valve prolapse. However, many people have argued that it may be the panic attack itself due to the hyper dynamic states it induces. In the study, no histological abnormality was found in the heart of all the animal that received *cannabis*. This may probably support earlier claims that cardiac abnormalities are most likely at high prolonged doses of *cannabis*. (Stimmel, B., 1979).

Conclusion

This study showed no structural changes in the heart after administration of *cannabis* for the study period. This may suggest that although *cannabis* has been strongly associated with panic attack and other cardiovascular effects, it may not cause any structural damage to the heart membrane, musculature and vasculature. However, the study has revealed that, in addition to issues of intoxication, *cannabis* can also produce histopathological damage to the brain [49,50]. It is therefore recommended that in addition to advice based on intoxication as reasons for abstinences, pos-

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sible damage to brain tissues should also be given as reasons for abstinence and furthermore treatment of *cannabis* abuse should also involve possible investigations and treatment of brain damage.

Recommendations

From the observations and results from this study, it's become appropriate to make the following recommendations.

i. Abusers of *cannabis* should abstain from the psychoactive substance as it is capable of causing structural damage(s) to such organs like the brain, liver, and kidney.

ii. In treatment of patient with *cannabis* abuse should necessarily involve appropriate investigations and treatment of these organs studied may be unique to the patient.

iii. The health sector, government as well as nongovernmental organizations should increase awareness and advocacy campaign about the inherent danger as well as the need to abstain from *cannabis* consumption.

iv. Such campaign should be focused on at-risk group like the youth, motor park drivers, secondary as well as university students.

v. The already existing legislations by the NDLEA and other law enforcement agencies, prohibiting the cultivation, handling and supply as well as smoking of *cannabis* should be well structured.

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