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Running title: Melatonin ameliorates *Cannabis sativa*-induced oxidative stress in rats

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ABSTRACT

Cannabis sativa (CS) has been utilized for medicinal purposes since ancient times due to its phytochemical content, hence the quest to prevent its antioxidant effects in the body. This study investigated the effects of co-administration of melatonin and CS on oxidative stress (OS) in male (m) and female (f) Wistar rats. CS and melatonin were administered orally for three weeks. All the animals were provided with equal access to food and water and were sacrificed after the third week. OS markers were quantified following standard protocols. The results revealed a significant ($p<0.05$) increase in Lactate dehydrogenase (LDH) and malondialdehyde (MDA), with a significant ($p<0.05$) decrease in catalase, glutathione reductase (GSH), glutathione peroxide (GPx), total anti-oxidant capacity (TAC) and superoxide dismutase (SOD) was observed in the groups treated with high-dose of CS (6mg) with no significance differences observed in the low-doses (2 mg and 4 mg) treated groups when compared with the control in both sexes. However, Co-administration of CS and melatonin showed no significant differences in all the markers across the groups treated with both low and high-doses of CS in both sexes when compared with the control. This study concluded that co-administration of CS and melatonin could prevent OS associated with CS at high-dose. However, males exhibited more pronounced effects than females. Therefore, this study suggests that melatonin may be used as supplement to prevent CS-induced oxidative stress.

Key words: *Cannabis sativa*; Co-administration; High-dose; Low-dose; Melatonin; Oxidative stress

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INTRODUCTION

Cannabis sativa (CS) has been used medicinally for centuries, owing to its rich phytochemical composition [1]. This drives the interest in preventing its effect on the antioxidant defense system in the body. Globally, this substance is commonly abused as an illicit drug [2]. When cellular redox homeostasis is disturbed, reactive species (peroxides and free radicals) accumulate, damaging key biomolecules (proteins, lipids and genetic materials) [3].

Oxidative stress (OS) arises from a disequilibrium between pro-oxidants and antioxidants [4]. The balance can shift due to heightening reactive oxygen species (ROS) or impaired antioxidant protective mechanisms [5]. OS can also result from disequilibrium in the oxidizing system, comprising ROS, free radicals, and reactive nitrogen species (RNS) [6]. Antioxidant mechanisms are essential to mitigating free radicals, whose unchecked activity leads to harmful outcomes [7].

Melatonin is predominantly secreted at night, aligning with the dark period of the light/dark rhythm [8]. Studies have confirmed that it can scavenge free radicals effectively in multiple contexts, including hydrogen peroxide (H_2O_2), hydroxyl radical (OH^-), nitric oxide (NO), superoxide anion (O^{2-}), singlet oxygen (O), peroxynitrite anion ($ONOO^-$), hypochlorous acid (HOCl), among others [9-12]. Previous studies [13-14] revealed that CS has detrimental effect on oxidative stress. It has also been discovered that the effect of CS on oxidative stress is dose dependent and gender specific [15]. A study also revealed that melatonin could ameliorate the effect of CS on oxidative stress in female rats [10]. However, within my limit of research, how melatonin co-treatment with CS (at differences doses) influences gender-specific outcomes is still lacking. This study therefore aimed to bridge this area by examining the influence of CS in a cohort of male and female Wistar rats, so as to explore sex-related variations and investigate oxidative biomarkers(Lactate dehydrogenase (LDH), catalase, superoxide dismutase (SOD), glutathione reductase (GSH), glutathione peroxide (GPx), malondialdehyde (MDA) and total antioxidant capacity (TAC)),to assess the influence of co-administration of melatonin and CS, considering its dose dependent modulation in relation to OS. The selected oxidative stress markers were evaluated due to their ability to reflect the body's antioxidant defense status.

The objectives were to investigate the influence of co-administration of melatonin and CS on OS using male and female Wistar rats as subjects by considering its dose dependent modulation; and to evaluate the differential impacts of co-administration of melatonin and CS on OSin male versus female Wistar rats by considering its dose dependent modulation. The core hypotheses underpinning this study were: co-

administration of melatonin and CS would not affect OS in male versus female rats (null); and co-administration of melatonin and CS would affect OS in male versus female rats (alternative).

METHODOLOGY

Sampling procedure

CS leaves were provided by the National Drug Law Enforcement Agency (NDLEA), Nigeria, exclusively for research use.

Extraction of *Cannabis sativa* leaves

CS extraction was performed using Soxhlet apparatus, with 800g of dries CS leaves macerated in 98% ethanol for 48 hours. Following filtration, the filtrate was collected in a round-bottom flask mounted on a rotary evaporator under reduced pressure. The extract was concentrated to dryness via evaporation and cooled, affording 55 g of crude dried leaves of CS [15].

Experimental animals

Twenty male rats with mean weight (180g ± 1.89) and twenty female rats with mean weight (165g ± 1.23) used for this study were sourced from Temilade Animal Venture, Ogbomoso, Oyo State, Nigeria. They were housed at ambient temperature with ad libitum access to feed and water, under a standard 12-hour light/dark cycle. The principles of humane laboratory animal care (NIH publication No. 85-23, revised 1985) were followed throughout the study.

The experimental protocol was approved by Ethical Committee of University of Ilesa, Ilesa, Osun State, Nigeria with approval number (UNILESA/ERC/2026/016).

Experimental protocol

Following a 2-week period of acclimatization, male (m) and female (f) animals were separately randomized into four groups (n=5 per group per sex). Corresponding male (1m, 2m, 3m, and 4m) and female (1f, 2f, 3f, and 4f) groups received distilled water (control), 2 mg/kg body weight (bw) of CS, 4 mg/kg bw of CS, 6 mg/kg bw of CS, 4 mg/kg bw of melatonin, 2mg/kg bw of CS+4 mg/kg bw of melatonin, 4mg/kg bw of CS+4 mg/kg bw of melatonin, and 6mg/kg bw of CS+4 mg/kg bw of melatonin respectively, between 8:00 am to 10:00 am, orally, once daily for three weeks with free access to feed and water. Following the 21st daily dose, the rats were humanely sacrificed for experimental analysis.

Preparation of serum samples

Rats were humanely sacrificed using ketamine anesthesia (80mg/kg bw) via intraperitoneal injection. Blood samples were collected via cardiac puncture into experimental bottles. Blood samples were incubated for 30 min to clot followed by centrifugation at 625×*g* for 10 min in a Uniscope Laboratory Centrifuge (Model SM800B, Surgifield Medicals, Essex, England) to obtain the serum. The sera were transferred into plain bottles using a Pasteur pipette.

Prepared sera were immediately stored at -5°C and analyzed within 12 hours to preserve sample integrity.

Drug and assay kits

Lactate dehydrogenase (LDH) activity was determined spectrophotometrically (Spectramax Plus; Molecular Devices, Sunnyvale, CA, USA) according to the kit manufacturer's guidelines (product code BXC0243; Fortress Diagnostics, UK). Serum SOD concentration was measured using a colorimetric SOD colorimetric assay kit (Fortress Diagnostics Ltd., Antrim, UK; Product code: BXC0531), according to the kit manufacturer's guidelines. The amount of serum GPx was measured using GPx colorimetric assay kit (BioVision Inc., Milpitas, CA, USA), according to the kit manufacturer's guidelines. In line with the kit manufacturer's guidelines, total anti-oxidant capacity (TAC) in the serum was measured using a spectrophotometric microplate reader (Spectramax Plus, Molecular Devices, Sunnyvale, CA, USA) with the help of Oxi-Select TAC assay kit which involved the use of a single electron transfer mechanism (Cell Biolabs, Inc. San Diego, CA. cat no: STA-360). Catalase activity was measured using spectrophotometric reading [16]. The method used by [17] was adopted for GSH measurement. The assay procedure of [18], was used for Malondialdehyde (MDA) which was modified by [19].

Statistical analysis

Data was presented as the mean ± SEM. It was calculated using a two-way ANOVA, subsequently by the LSD post-hoc test to assess the level of significant in the samples with the help of graph pad, version 9.0. *P*-values less than 0.05 differences were considered statistically significant.

RESULTS

Table 1: Showing oxidative stress markers of rats (male (m) and female (f)) for control and treated (2.0 mg/kg bw CS, 4.0 mg/kg bw CS, 6.0 mg/kg bw CS, 4.0 mg/kg bw melatonin, 2.0 mg/kg bw CS + 4.0 mg/kg bw, 4.0 mg/kg bw CS + 4.0 mg/kg bw and 6.0 mg/kg bw CS + 4.0 mg/kg bw melatonin) groups.

Treated groups	LDH (u/l)	MDA (umol/l)	Catalase, (u/l)	GSH (u/l)	GPx (mmol/l)	TAC (umol/l)	SOD (U/L)
Control (m)	600±15.01	22.34±1.05	29.00±1.12	100.00±2.76	3.50 ±0.34	85.21±1.64	180.00±6.43
Control (f)	500±19.76	20.13±1.21	26.34±0.97	60.00±2.16	2.50 ±0.51	75.41±1.08	150.00±4.08
2mg/kg CS (m)	650±11.76	23.27±3.11	27.12±2.11	95.00±2.54	3.20 ±1.01	80.41±1.92	175.00±4.61
2 mg/kg CS (f)	550±8.94	21.00±1.52	25.87±1.67	57.00±1.54	2.4±0.10	72.21±0.96	140.00±2.95
4 mg/kg CS (m)	670±16.43	23.98±1.23	27.79±0.56	90.00±2.15	3.10 ±1.32	78.31±1.05	172.00±1.74
4 mg/kg CS (f)	580±21.32	22.67±2.01	24.78±1.59	61.00±1.75	2.20 ±0.84	63.32±1.23	137.00±3.74
6 mg/kg CS (m)	980±25.75#	28.00±1.97#	18.65±1.32#	62.00±1.89#	1.20±0.04#	52.98±1.84#	145.00±4.21#
6 mg/kg CS (f)	850±22.76#	26±3.11#	16.98±0.79#	40.00±3.21#	0.40±0.13#	45.39±0.98#	115.00±4.01#

4mg/kg melatonin (m)	600±15.01	22.34±1.05	29.00±1.12	100.00±2.76	3.50 ±0.34	85.21±1.64	180.00±6.43
4mg/kg melatonin (f)	500±19.76	20.13±1.21	26.34±0.97	60.00±2.16	2.50 ±0.51	75.41±1.08	150.00±4.08
2 mg/kg CS + 4 mg/kg melatonin (m)	580±12.25	21.86±1,13	28.20±1.52	98.50±3.15	3.47 ±0.42	80.22±1,72	170.76±4.45
2 mg/kg CS + 4 mg/kg melatonin (f)	495±15.76	19.75±1.32	25.00±1.02	59.00±1.98	2.28 ±0.86	74.34±1.63	148.00±4.11
4 mg/kg CS + 4mg/kg melatonin (m)	576±10.65	19.08±1.25	28.19±1.42	98.12±1.96	3.42 ±1.01	80.21±1.75	167.00±6.12
4mg/kg CS + 4 mg/kg melatonin (f)	486±13.75	19.43±1.20	25.00±1.20	57.45±2.63	2.14 ±0.48	72.98±0.75	145.00±4.42
6 mg/kg CS + 4 mg/kg melatonin (m)	980±25.75#	28.00±1.97#	18.65±1.32#	62.00±1.89#	1.20±0.04#	52.98±1.84#	145.00±4.21#
6 mg/kg CS + 4 mg/kg melatonin (f)	850±22.76#	26±3.11#	16.98±0.79#	40.00±3.21#	0.40±0.13#	45.39±0.98#	115.00±4.01#
Values were expressed as mean ± SEM; *P< 0.05 vs control and other treatment groups (M and F); #P< 0.05 vs CS-treated groups (M and F)							

The results obtained are presented in Table 1. There was a significant ($p<0.05$) increase in Lactate dehydrogenase (LDH) and malondialdehyde (MDA), with a significant ($p<0.05$) decrease in catalase, glutathione reductase (GSH), glutathione peroxide (GPx), total anti-oxidant capacity (TAC) and superoxide dismutase (SOD) was observed in the groups treated with high-dose of CS (6 mg) with no significance differences observed in the low-doses (2 mg and 4 mg) groups when compared with the control in both sexes. However, co-administration of CS and melatonin showed no significant differences in all the markers across the groups treated with both low and high-doses of CS in both sexes when compared with the control.

DISCUSSION

Oxidative stress (OS)is the disequilibrium between the reactive ROS and the ability of a biological system to rapidly neutralize reactive species and mitigate their harmful effects [20]. When a cell's redox equilibrium is disturbed, peroxides and free radicals are generated. These molecules destroy the biomolecules (proteins, lipids, and DNA), and other parts of the cell resulting in harmful outcomes [21]. OS, generated via oxidative metabolism, causes lesions in DNA strands and base pairs [22]. ROS which includes hydrogen peroxide (H_2O_2), hydroxyl radical (OH), and superoxide radical (O^{2-}) majorly cause base damage indirectly [23]. Earlier studies have identified melatonin as a pro-oxidant role [24, 9-10, 25-26, 11, 27-29].

Melatonin's critical role includes acting as a free radical scavenger, mitigating OS [30].

OS is implicated in the development of the listed conditions: Alzheimer's disease, myocardial infarction, infectious diseases, heart failure, fragile X syndrome, Parkinson's disease, lichen planus, autism, cancer, atherosclerosis, and chronic fatigue syndrome [31, 11].

Previous studies revealed that CS induced OS by disrupting the antioxidant defense system [13-14]. Additionally, it was found that the effect of CS on OS was dose dependent and also depends on gender differences since the effect was more obvious in male than in female [15]. Consistent with earlier findings, it was observed that melatonin could ameliorate the effect of CS on OS in female rats by obstructing the binding of CS with its receptors [10].

In this study, co-administration of melatonin and CS at both low and high-doses abolished the effect of CS on OS in both male and female rats. This suggests that melatonin has the antioxidant potential to mitigate OS induced by CS. This aligns with findings from [10, 32] who reported decrease in oxidative stress following co-administration of melatonin and CS in animals. An increase in the LDH observed in this study after CS was administered could be due to high-dose of CS and this was consistent with the findings of [11, 28] who reported that administration of CS stimulated OS by increasing LDH in both sexes. This may be attributed to LDH's key role in producing nicotinamide adenine dinucleotide phosphate (NADPH), an intermediate that fuel ROS generation [33]. However, melatonin was able to mitigate the effect of CS on OS (LDH) at both low and high-doses. This was in line with the findings of [10, 15] who observed decreased in LDH level in male and female rats CS followimg administration of melatonin.

Additionally, results also showed increase in MDA levels in both sexes at the high-dose of CS but not at low-doses. These findings correspond to those of [14, 34] who both observed an increase in MDA level following administration of CS in rats. This finding suggests that CS if not well treated may induce lipid peroxidation of polyunsaturated fatty acids, which are degraded by ROS [35]. More so, findings from this study also indicated a decrease in GSH, catalase, and GPx, TAC and SOD levels at high-dose for both male and female rats. This may result from elevated lactate dehydrogenase activity in these animals, driving the ROS buildup in them. These were in line with the findings of [15, 36] who both observed a decrease in antioxidant enzymes following administration of CS in rats at high-dose. However, the oxidative stress caused by CS in the groups treated with high-dose was ameliorated by melatonin possibly by acting as a hormone, neutralizing free radicals via directly and/or indirectly pathways [37-38], also enhancing the capacity of antioxidant enzymes to neutralize most of the ROS generated [39]. Generally, this study revealed that there were gender differences in response to the effect of co-administration of melatonin and CS on OS

which were more pronounced in males than in females. These could be due to various factors. One of the factors could be via the expression of cannabinoid receptor and signaling pathway. Cannabinoid receptors are more abundant in males compare to females [40]. CS may also induce epigenetic changes via altered global deoxyribonucleic acid (DNA), potentially driving cannabis-induced immunosuppression, and particularly in the male blood cells [41]. The study limitations are, it is not known whether administration is done in the afternoon or evening could produce different results compared to the time (morning) the administration was done in this study; it is also not known whether melatonin produced by the body at night could interfere with the administered melatonin.

Conclusion

Co-administration of melatonin and CS appeared to attenuate CS-associated OS at high-dose. The observed effects were more pronounced in males compared to females, indicating a sex-dependent response. Therefore, this study suggests that melatonin may be used as supplement to prevent CS-induced oxidative stress.

Complementary human studies are also required to broaden the understanding and explore therapeutic potential of cannabinoid-melatonergic systems in modulating OS.

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