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(RESEARCH ARTICLE)

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Aphrodisiac, androgenic and libido enhancing activities of *Terminalia catappa* leaf extracts in Delta-9 tetra hydro carnnabinol induced erectile dysfunction in male Wistar rats

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Abstract

Introduction: Erectile dysfunction is the repeated inability to sustain erection firm enough for sexual intercourse while an aphrodisiac is an agent (food/drug) that arouses sexual activity. Various factors affect sexual performance in men, and include; psychological, hormonal abnormalities, aging, penile injury, chronic diseases, lifestyle, medications and radiation. However, the wide distribution of phosphodiesterase type 5 enzymes at various sites of the body led phosphodiesterase type 5 inhibitors to cause various unnecessary outcomes. Hence, it is vital to look for optional agents that could solve these limitations.

Material and Methods: In this present work, erectile dysfunction was induced by administering 30mg/kgbwt for 3days.Treatment given was as follows: A-Normal Control, B- Std control (THC+Viagra), C-Negative control (THC only), D- THC+ 200mg/Kgbwt ethanol leaf extract of Terminalia catappa (200mg/Kgbwt) E- THC + 400mg/Kgbwt ethanol leaf extract of Terminalia catappa for a succession of 14 days. Sexual behaviour parameters were monitored in the male rats on day 1,7 and 14 respectively after administration by pairing with a receptive female (1:1) thereafter, rats were sacrificed and serum was collected for some biochemical parameters using standard method. Cage side observation on the animals revealed prospective behaviours by the receptive female rats and precopulatory behaviours by the ethanol extract *Terminalia catappa* treated male rats.

Result: The extract at 200 and 400 mg/kg body weight significantly ($P<0.05$) increased the frequencies of mount and intromission. In addition, the ejaculation latency was significantly ($P< 0.05$) prolonged. The latencies of mount and intromission were reduced significantly ($P<0.05$) whereas ejaculation frequency increased. The extract also reduced the post- ejaculatory interval of the Wistar rats. Computed percentages of index of libido, mounted, intromitted, ejaculated and copulatory efficiency were significantly ($p<0.05$) higher in the extract- treated animals in a dosage dependent manner than the control whereas the inter copulatory interval decreased significantly. The extract also significantly ($p<0.05$) increased the serum testosterone, FSH and LH concentration but significantly($p<0.05$) reduced serum oestrogen, prolactin and progesterone of the treated groups when compared with the control. The extract also significantly ($p<0.05$) increased the sperm motility, total sperm count, and sperm viability but produced a significant ($p<0.05$) decrease in serum immobility when compared with the THC control.

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Conclusion: It can be logical to infer from this present work that extract of *Terminalia catappa* may elicit aphrodisiac, androgenic and libido enhancing activities in THC induced erectile dysfunction in a dosage dependent manner.

Keywords: Androgenic; Androgen binding protein; *Terminalia catappa*; Reproductive hormones; Spermatogenesis; THC

1. Introduction

Male reproductive system is a complex hormonal regulatory network that involve interplay of hormonal, neuropeptides, and mechanisms that regulate spermatogenesis, sperm motility, and erectile function. The hypothalamic-pituitary-gonadal (HPG) axis coordinates and governs testosterone production, which are essential for maintaining spermatogenesis, libido, and enhances nitric oxide (NO) signaling pathway that enhances penile erection (1). Disruptions in these pathways may leads to reproductive dysfunction such as erectile dysfunction (ED), and impaired sperm quality, both of which have significant implications for fertility (2). Erectile dysfunction (ED) is a prevalent condition characterized by the inability to achieve or sustain an erection sufficient for sexual performance. It can be influenced by psychological, neurological and socio-economic factors often linked to oxidative stress, inflammation, and disruptions of testosterone signaling pathways (3).

Tetrahydrocannabinol (THC), primary psychoactive component of *Cannabis sativa*, that has been associated with reproductive toxicity due to interference with cannabinoid receptors (CB_1 and CB_2) expressed in the testes, hypothalamus, and penile tissue (4). This psychoactive effect of Cannabis *sativa* may be modulated by the endocannabinoid system, particularly through cannabinoid receptor $_1$ (CB_1), which modulates nitric oxide (NO) production and penile smooth muscle relaxation (5). Long term exposure to THC suppresses testosterone synthesis, disrupts spermatogenesis, and impairs NO-mediated vasodilation, leading to reduced sperm count, motility, and erectile capacity in (6). These effects are mediated via oxidative stress, inflammation, and programmed cell death (apoptic effect) into testicular and penile tissues thereby inducing it reproductive sertoli cell damage and binding to testicular cell to enhance spermatogenesis (7,8). THC-induced reproductive dysfunction occurs through disrupting spermatogenesis by altering Sertoli and Leydig cell function, which are critical for sperm development and steroidogenesis respectively (8). Sperm profile alterations, including reduced viability and increased DNA fragmentation which are hallmarks associated with this condition, and are often accompanied by diminished libido and erectile capacity (9).

The oxidative stress in testicular tissue triggers lipid peroxidation of sperm membranes altering its spermatogenic potential by compromising fertility (10). Oxidative stress plays an importance role in erectile dysfunction as THC increases reactive oxygen species (ROS) production, that overcomes antioxidant defenses and causing lipid peroxidation in sperm membranes and penile smooth muscle cells (11), this oxidative imbalance increases inflammation and cellular damage thereby compromising reproductive function. Adjuvant treatments for ED, such as phosphodiesterase-5 (PDE-5) inhibitors (e.g., sildenafil) enhance vascular smooth muscle by increasing cAMP activities but yet fail to restore spermatogenic profile or reduces oxidative damage (12). THC-induced reproductive toxicity may be reverse due to antioxidant treatments like vitamin E but have limited therapeutic potential which necessitating interventions that focus on both sperm health and erectile function (13).

Terminalia catappa, also known as Indian almond plant, with pharmacological properties such as flavonoids, tannins, phenolic acids, and terpenoids which exhibit antioxidant, anti-inflammatory, cytoprotective effect, and aphrodisiac activities (14). These phytochemicals prevent reproductive toxicity by enhancing the repair of cellular damage and inhibiting pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-) and interleukin-6 (IL-6). They neutralize ROS activities in particularly by upregulate endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) and tannins stabilize cellular membranes integrity against oxidative stress induced THC-induced erectile dysfunction through the HPG axis and nitric oxide signaling pathways (15). According to Singh *et al*. (2023), the vaso-modulatory effects of *Terminalia catappa* increase blood flow to the penile via NO signaling, which is beneficial for both erectile function and spermatogenesis. The integration of plant-derived therapies into reproductive medicine requires evidence of efficacy, safety, and molecular targets (16). However, *Terminalia catappa* leaf extracts offer a holistic approach by targeting multiple pathways involved in THC-induced cellular damage, ROS scavenging, inflammation suppression, and hormonal restoration (17,8).

Advancements in phytopharmacology emphasize its therapeutic potential of natural compounds to complement or replace conventional treatments particularly in conditions involving oxidative stress and cellular tissue injury (18). The reproductive and protective effects of *Terminalia catappa* align with this paradigm, suggesting its natural intervention for THC-induced erectile dysfunction and sperm profile deficits (8). Therefore, this present research work was designed

to evaluate the effect of *Terminalia catappa* leaf extract on sperm profile following THC-induced erectile dysfunction in male Wistar rats.

2. Materials and Methods.

2.1. Plant Material

Terminalia catappa leaf was collected from UNICROSS community, Nigeria. The plant was identified at Department of Botany, University of Calabar, Calabar. The leaves were air dried until constant weight was obtained. The dried leaves were pulverized after which 200 g was macerated in 1000 ml (1:5 w/v) of 70 % ethanol for 72 hours with constant shaking using the electric shaker. This was later filtered using Whatman No.1 filter paper. The filtrate was then concentrated in water bath at 45ºC. The resulting slurry was weighed and reconstituted in distilled water to give the required dose.

2.2. Experimental animals

Twenty-five (25) male and female Wistar rats (200-250 g) was obtained from the Animal Holding Unit of Medical Biochemistry Department, UNICROSS, Okuku Campus. The animals were allowed to undergo acclimatization for seven days. The rats were housed in a plastic cage. The animal house was well ventilated and kept at room temperature and relative humidity of 29± 2 ºC and 70 % respectively with 12 hours natural light- dark cycle. Each rat was allowed free access to food and water *ad libitum*. Good hygiene was maintained by constant cleaning and removal of faeces and spilled feeds from cages daily. Oral route of administration was employed throughout the experimental period.

2.3. Methods:

Phytochemical analysis was determined by the method of (19). The male sexual behaviour test will be carried out by the methods of (20) as modified by (8). Serum testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels of extract treated male rats will be estimated using method of (21), sperm profile was determined by standard methods

2.4. Experimental design:

Erectile dysfunction was induced by administering 30 mg/kg bwt for 7 days. Treatment given was as follows: A-Normal Control, B- Std control (THC+Viagra), C-Negative control (THC only), D- THC+ 200mg/Kg bwt ethanol leaf extract of *Terminalia catappa* (200mg/Kg bwt), E- THC + 400mg/Kg bwt ethanol leaf extract of *Terminalia catappa* for a succession of 14 days.

3. Result

Thirty-five female proceptive and male precopulatory behaviour parameters were observed from the cage side when the extract-treated male rats were introduced to the receptive female rats. The proceptive behaviour displayed by the female rats included ear-wiggling characterized by a rapid antero posterior vibration of the ears, a short run where they suddenly stop and present their posterior to the male rats (darting) and a short jump with stiff legs followed by immobility and presentation (hopping).

The male rats, upon introduction, responded with immediate advances toward the females and displayed precopulatory behaviour such as chasing, anogenital sniffing which eventually culminated into mounting. The extract produced no sedative effect on the male rats since none of the animals showed any evidence of tiredness throughout the observatory period. Similarly, dot receptivity was not displayed by any of the female rats used in the study (8).

The effect of the extract of *Terminalia catappa* on sperm profile in THC induced erectile dysfunction in male Wistar rats. The extract significantly raised the pH of the spermatozoa of all the treated group to neutral pH range when compared with the normal control (fig1). The extract also significantly ($p<0.05$) increased the sperm motility, total sperm count, and sperm viability but produced a significant ($p<0.05$) decrease in serum immobility when compared with the THC control (fig2-5).

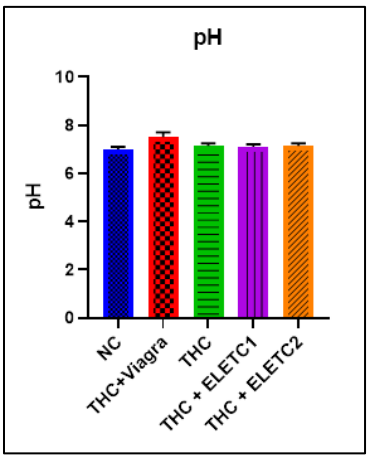
The sexual behaviour parameters (MF, IF, EF, ML, IL, EL and PEI) were monitored for both the controlled and *Terminalia catappa* treated groups but were observed to have varying latency and frequency (fig 6-26).

At day 1, the control group showed a decrease in IF, ML and increase in MF and PEI but no significant impact was observed in the other days (day7 and day14) compared to the extract-treated group .The extract-treated group at 200 and 400mg/kg body weight showed significant effect on the parameters in which IF and EF increased significantly ($p<0.05$) while ML and PEI decreased ($p< 0.05$) significantly at the days of observation compared to the controlled group and standard control(Fig 6-26).

The computed male rat's sexual behaviour parameters which include percentage (%) index of libido, mounted, intromitted, ejaculated and copulatory efficiency were significantly ($p<0.05$) higher in the *Terminalia catappa* extract-treated animals when compared to the control group (fig 27-32).

The ethanol extract of *Terminalia catappa* showed a significant ($p<0.05$) dosage increase in serum FSH, LH and testosterone but a significant decrease in prolactin, progesterone and oestrogen at 200 and 400 mg/kg body weight when compared with the control (Fig 33-38)

The ethanol extract of *T.C* showed a significant ($p<0.05$) increase in testicular catalase and SOD levels but there was a significant ($p<0.05$) increase in testicular MDA levels at 200 and 400 mg/kg body weight when compared with the control (Fig 39-42)



Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 1 The effect of *Terminalia catappa* extract on sperm pH profile following THC induced erectile dysfunction in male Wistar rats

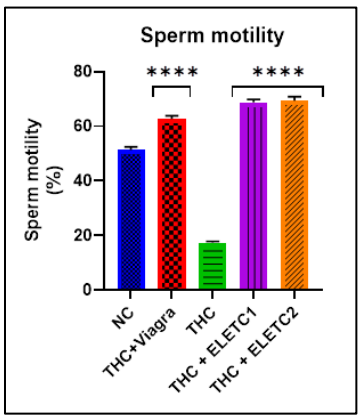


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Figure 2 The effect of *Terminalia catappa* extract on sperm motility following THC induced erectile dysfunction in male Wistar rats

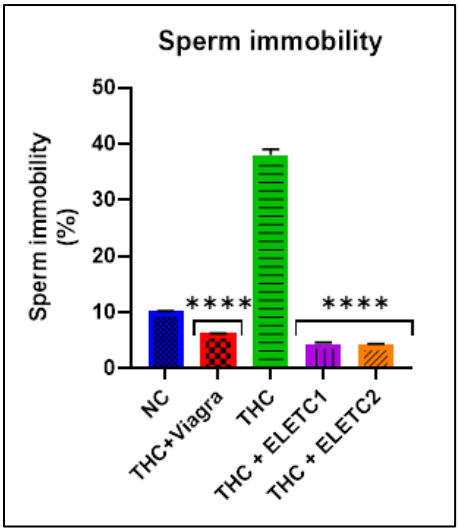

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Figure 3 The effect of *Terminalia catappa* extract on sperm immobility profile following THC induced erectile dysfunction in male Wistar rats

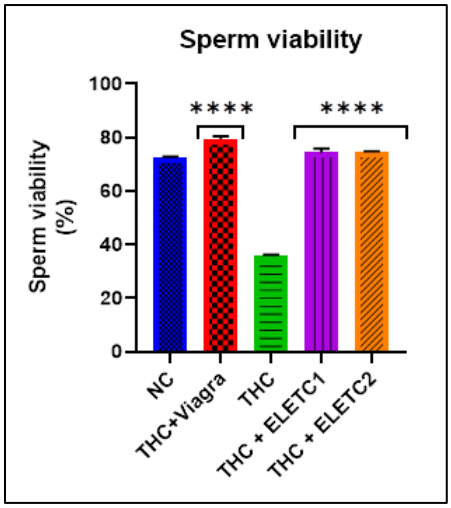

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Figure 4 The effect of *Terminalia catappa* extract on sperm viability profile following THC induced erectile dysfunction in male Wistar rats

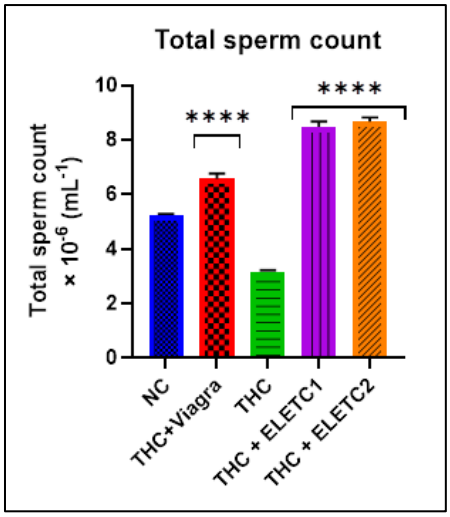

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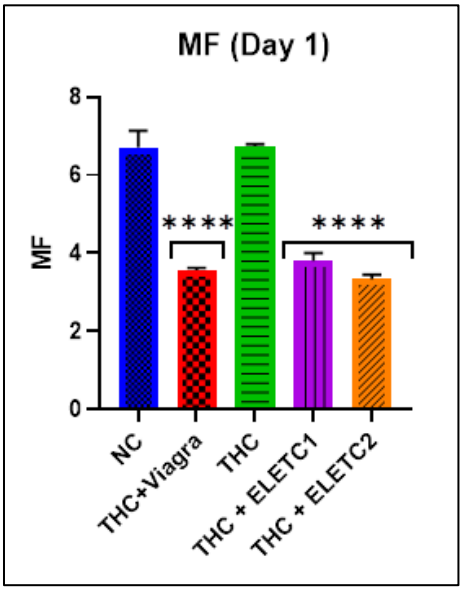
Figure 5 The effect of *Terminalia catappa* extract on sperm count profile following THC induced erectile dysfunction in male Wistar rats

The effect of *Terminalia catappa* leaf extracts on some sexual behaviour in THC induced erectile dysfunction in male Wistar rats on day 1



Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetrahydrocarnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 6 The effect of *Terminalia catappa* extract on mounting frequency following THC induced erectile dysfunction in male Wistar rats

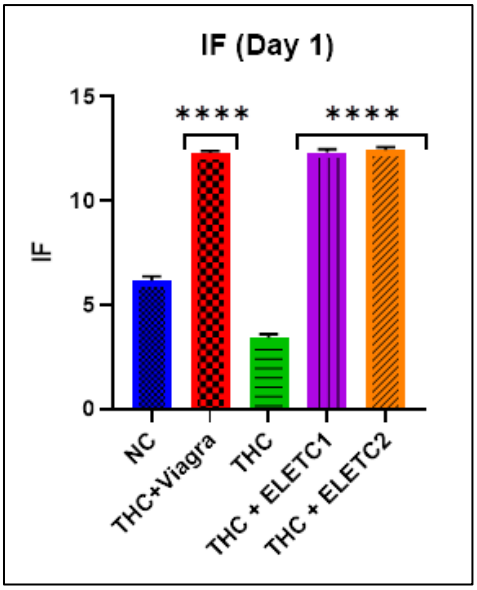


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Figure 7 The effect of *Terminalia catappa* extract on IF profile following THC induced erectile dysfunction in male Wistar rats

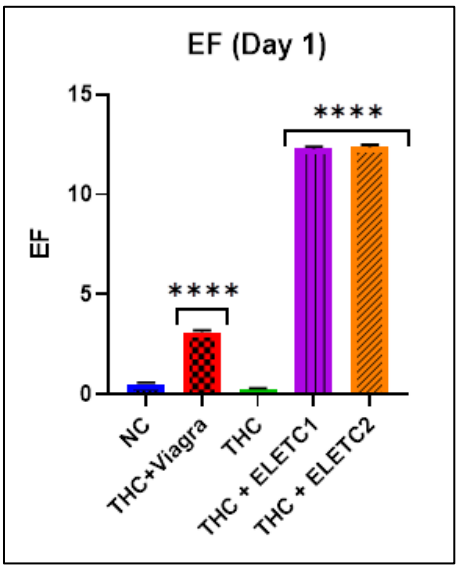

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Figure 8 The effect of *Terminalia catappa* extract on EF following THC induced erectile dysfunction in male Wistar rats

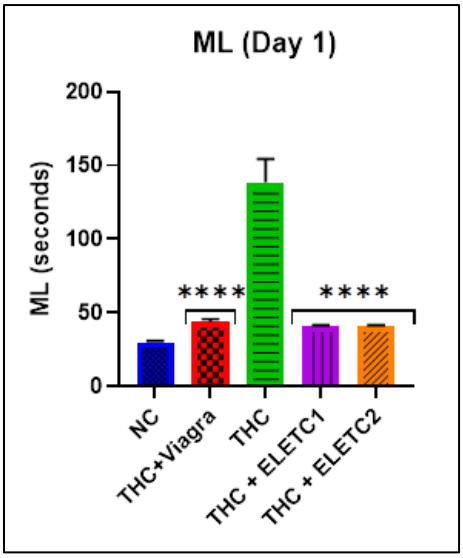

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Figure 9 The effect of *Terminalia catappa* extract on ML following THC induced erectile dysfunction in male Wistar rats

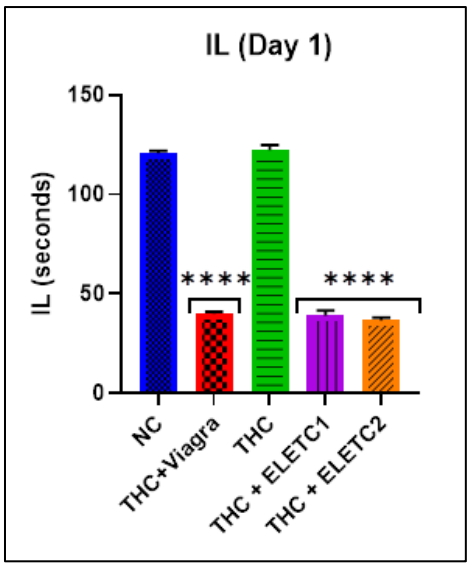

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Figure 10 The effect of *Terminalia catappa* extract on IL following THC induced erectile dysfunction in male Wistar rats

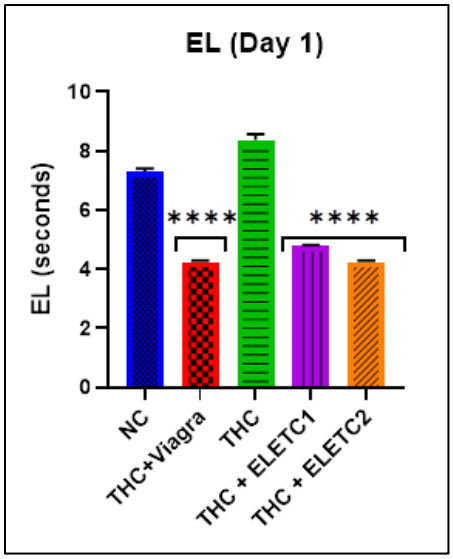

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Figure 11 The effect of *Terminalia catappa* extract on EL following THC induced erectile dysfunction in male Wistar rats

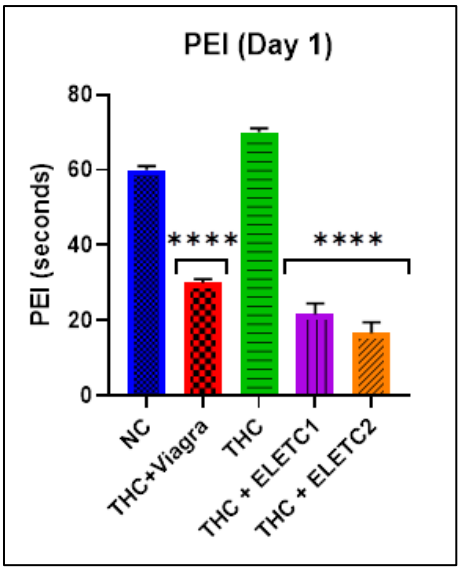

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Figure 12 The effect of *Terminalia catappa* extract on PEI following THC induced erectile dysfunction in male Wistar rats

The effect of *Terminalia catappa* leaf extracts on some sexual behaviour following THC induced erectile dysfunction in male Wistar rats on day 7

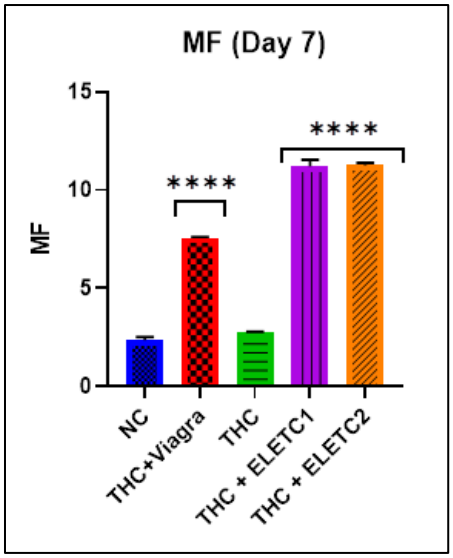

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Figure 13 The effect of *Terminalia catappa* extract on sperm MF following THC induced erectile dysfunction in male Wistar rats

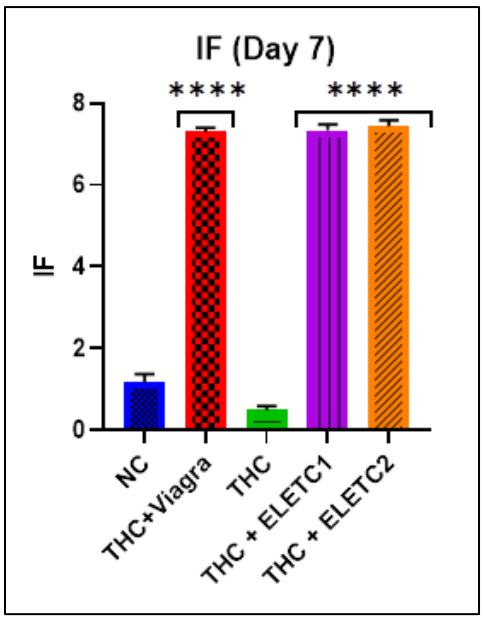

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Figure 14 The effect of *Terminalia catappa* extract on IF following THC induced erectile dysfunction in male Wistar rats

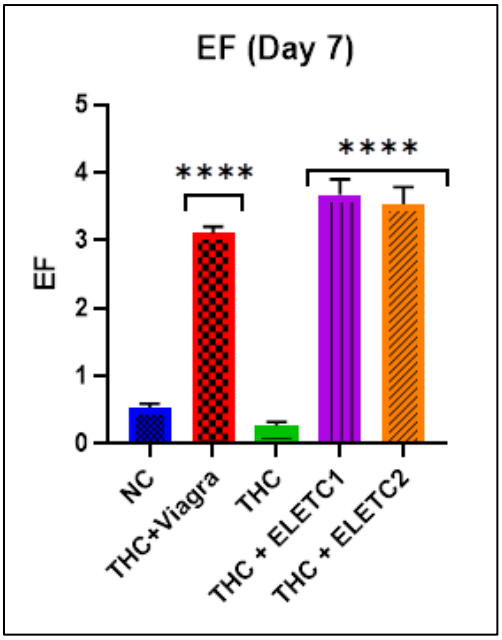

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Figure 15 The effect of *Terminalia catappa* extract on EF following THC induced erectile dysfunction in male Wistar rats

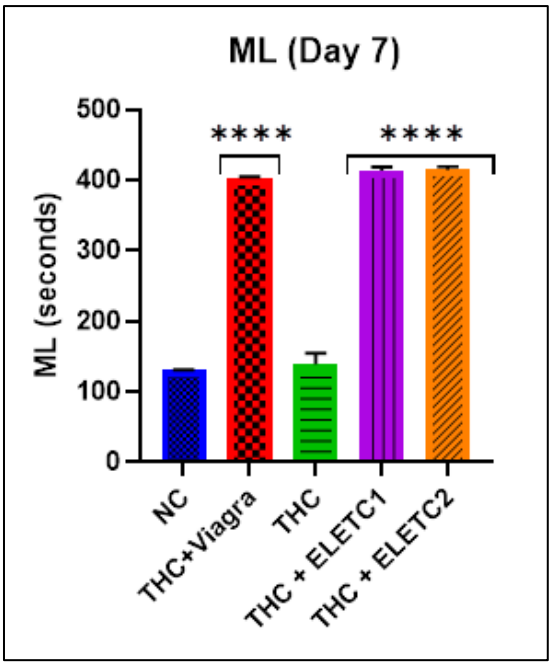

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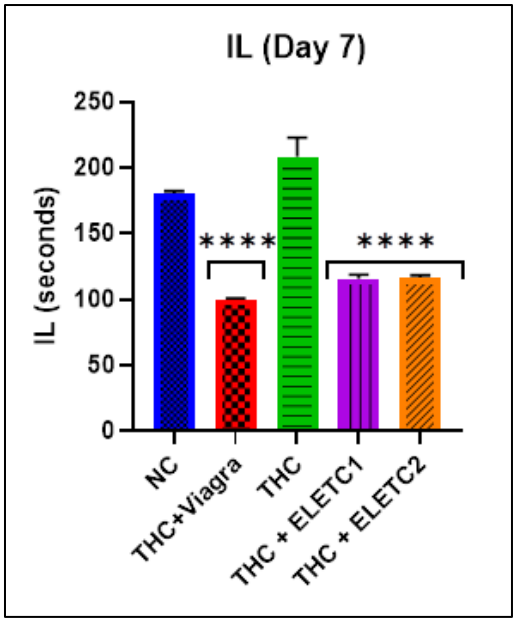
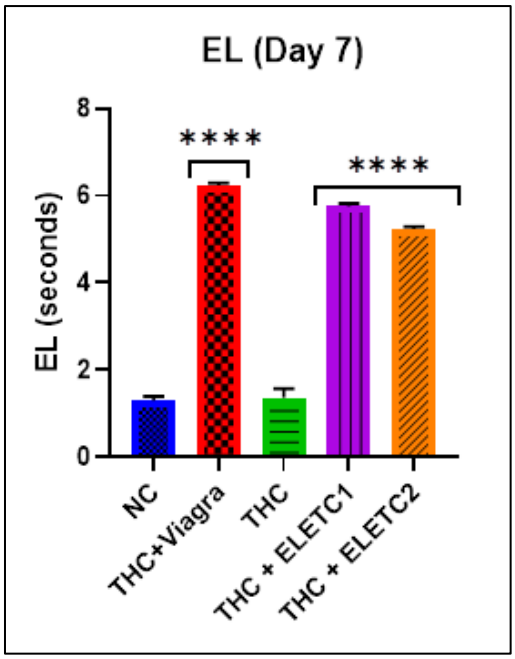
Figure 16 The effect of *Terminalia catappa* extract on ML following THC induced erectile dysfunction in male Wistar rats



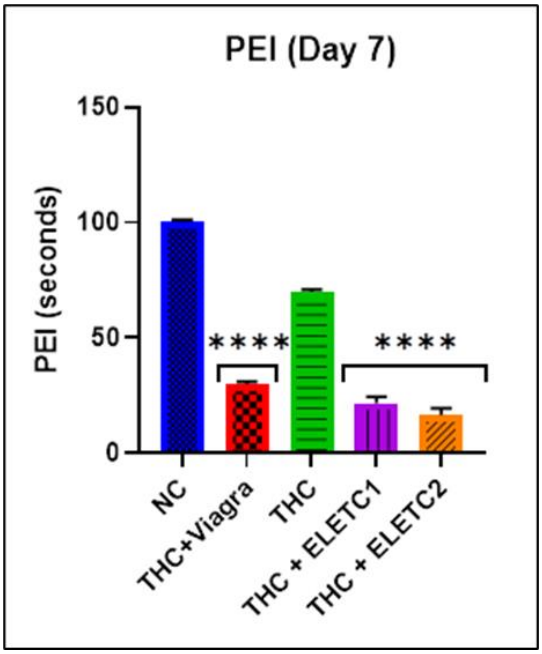
Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 17 The effect of *Terminalia catappa* extract on IL following THC induced erectile dysfunction in male Wistar rats



Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

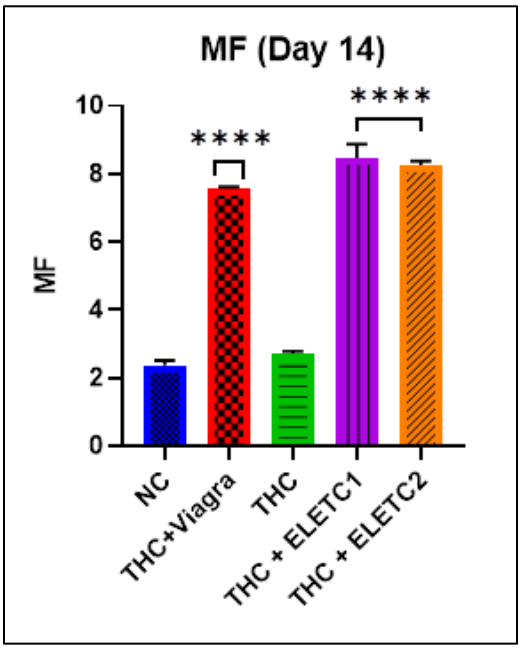
Figure 18 The effect of *Terminalia catappa* extract on EL profile following THC induced erectile dysfunction in male Wistar rats



Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

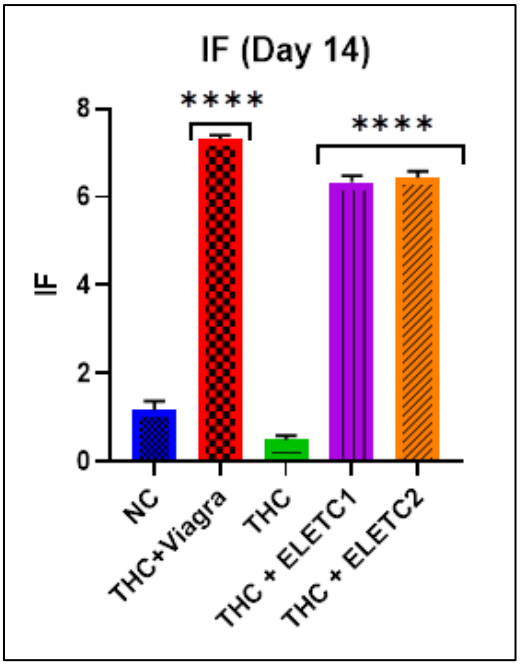
Figure 19 The effect of *Terminalia catappa* extract on PEI following THC induced erectile dysfunction in male Wistar rats

The effect of *Terminalia catappa* leaf extracts on some sexual behaviour following THC induced erectile dysfunction in male Wistar rats on day 14



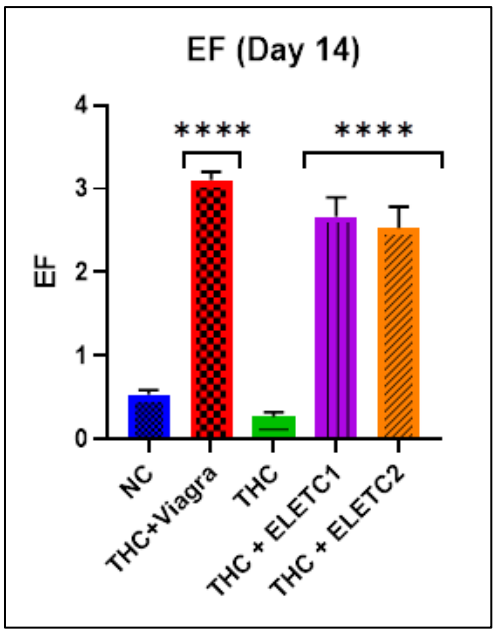
Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 20 The effect of *Terminalia catappa* extract on MF following THC induced erectile dysfunction in male Wistar rats



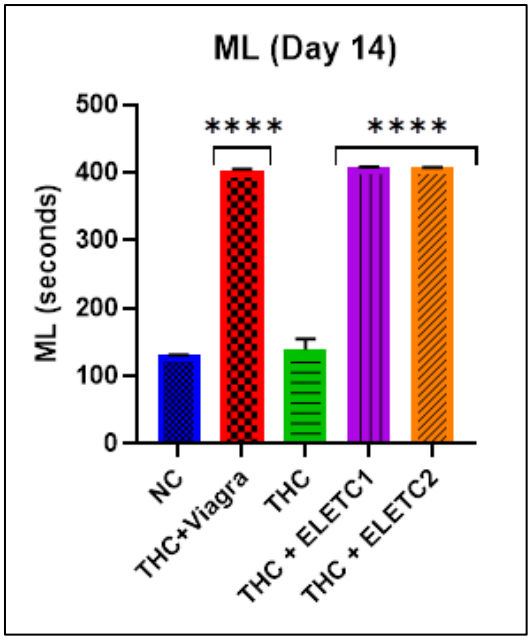
Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 21 The effect of *Terminalia catappa* extract on IF following THC induced erectile dysfunction in male Wistar rats



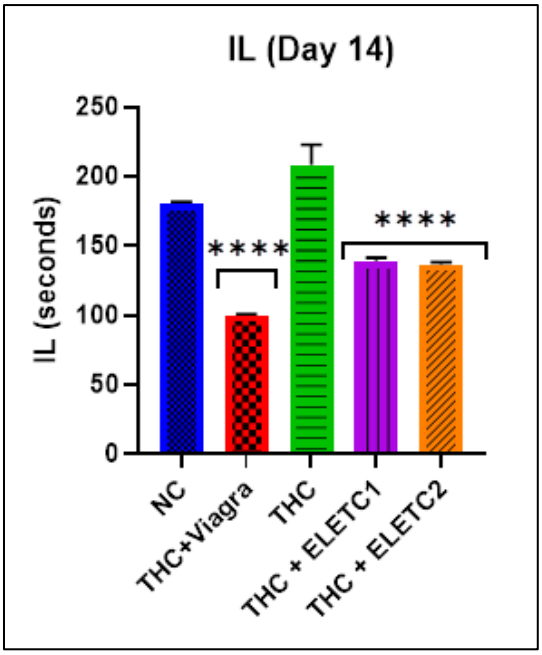
Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 22 The effect of *Terminalia catappa* extract on EF following THC induced erectile dysfunction in male Wistar rats



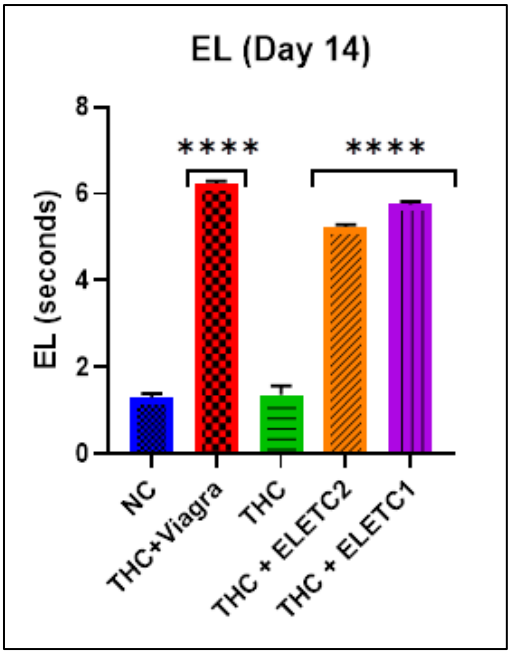
Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 23 The effect of *Terminalia catappa* extract on ML following THC induced erectile dysfunction in male Wistar rats



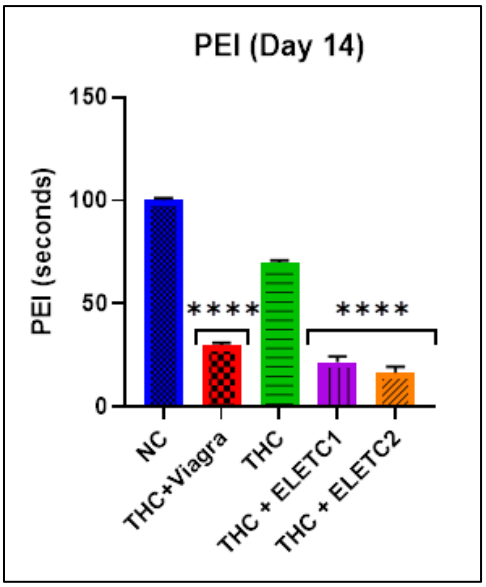
Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 24 The effect of *Terminalia catappa* extract on IL following THC induced erectile dysfunction in male Wistar rats



Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

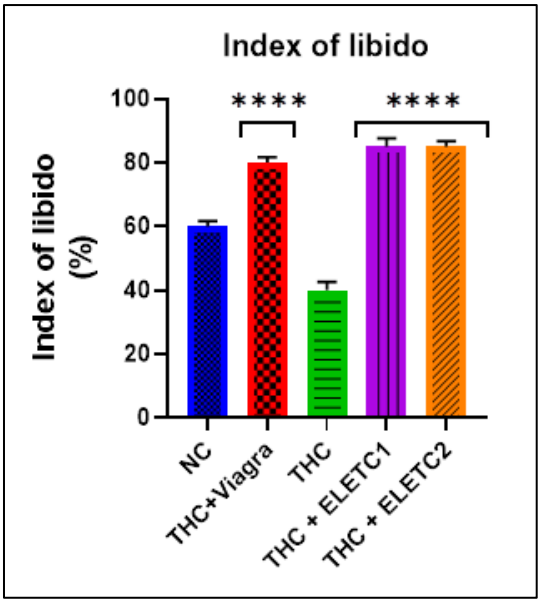
Figure 25 The effect of *Terminalia catappa* extract on EL following THC induced erectile dysfunction in male Wistar rats



Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

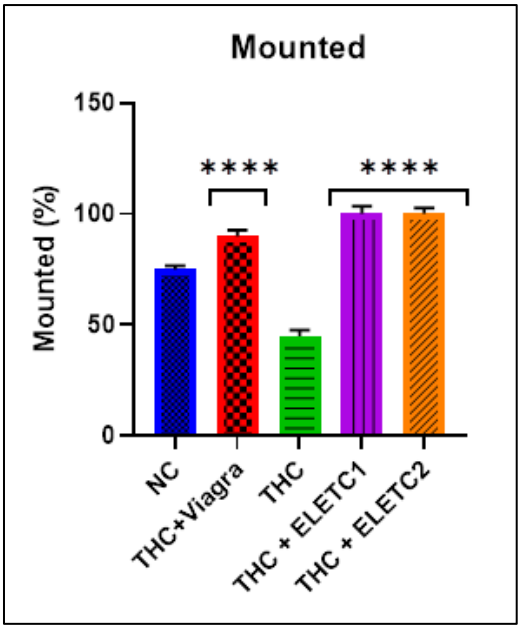
Figure 26 The effect of *Terminalia catappa* extract on PEI following THC induced erectile dysfunction in male Wistar rats

The effect of *Terminalia catappa* leaf extracts on some computed parameters of sexual behaviour of male Wistar rats



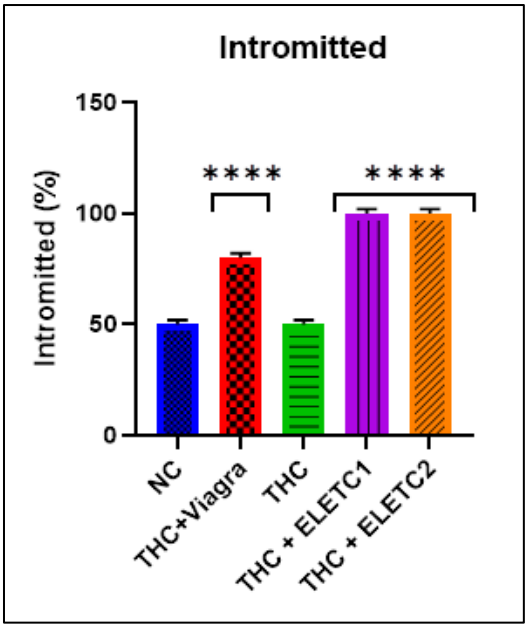
Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 27 The effect of *Terminalia catappa* extract on index of libido following THC induced erectile dysfunction in male Wistar rats



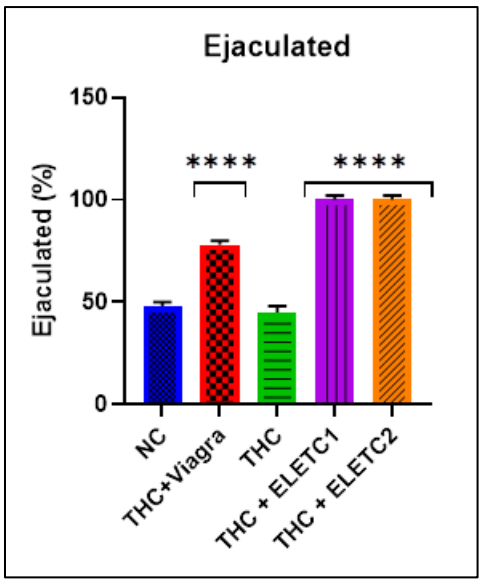
Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 28 The effect of *Terminalia catappa* extract on % mounted following THC induced erectile dysfunction in male Wistar rats



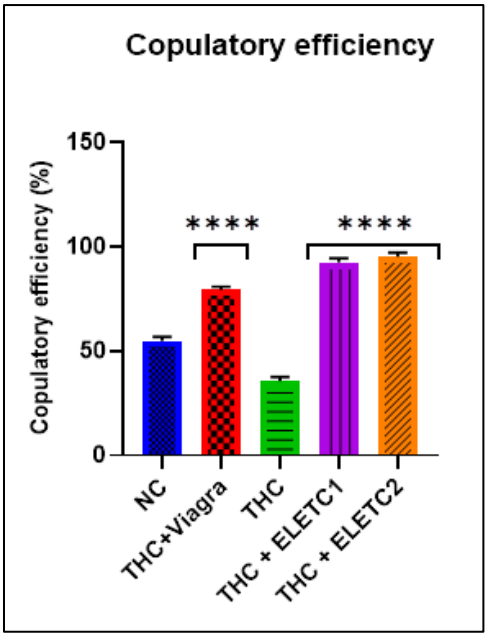
Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 29 The effect of *Terminalia catappa* extract on % intromitted following THC induced erectile dysfunction in male Wistar rats



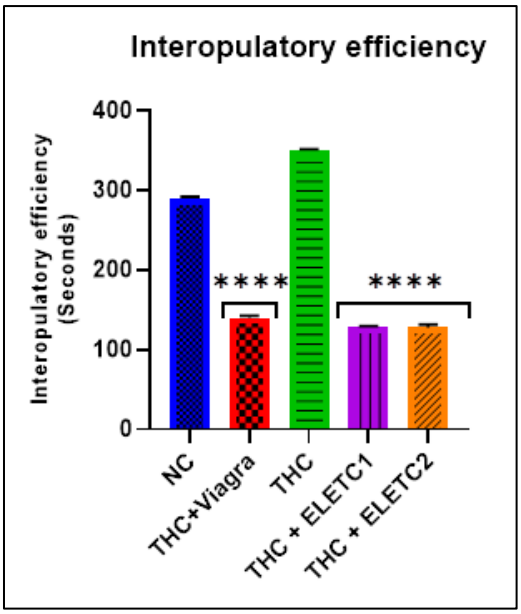
Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 30 The effect of *Terminalia catappa* extract on % ejaculated following THC induced erectile dysfunction in male Wistar rats



Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

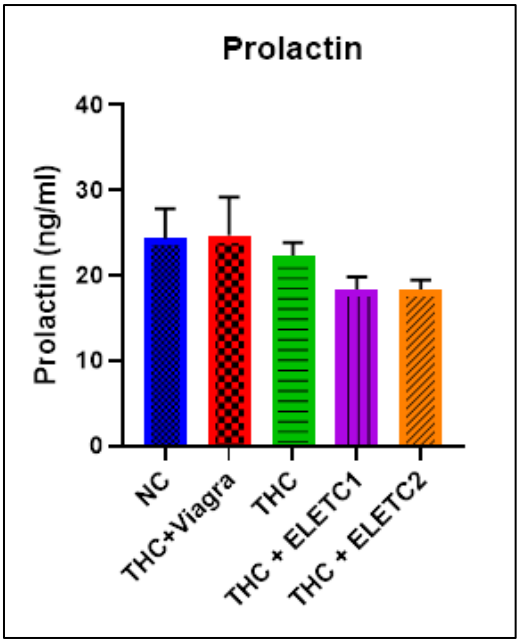
Figure 31 The effect of *Terminalia catappa* extract on copulatory efficiency following THC induced erectile dysfunction in male Wistar rats



Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

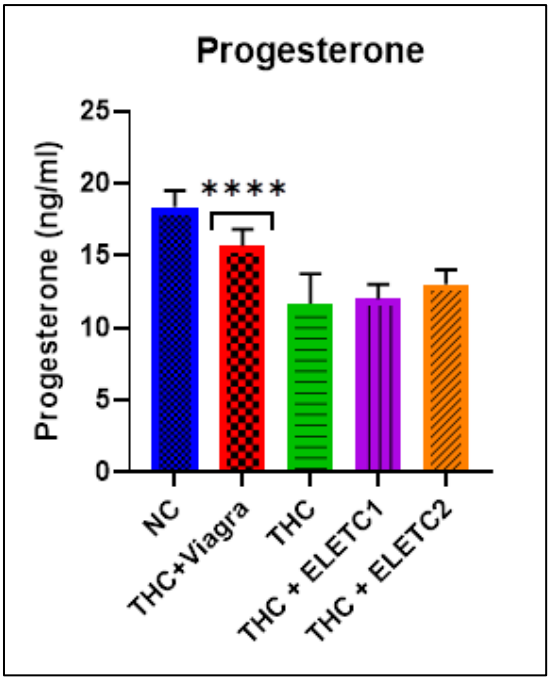
Figure 32 The effect of *Terminalia catappa* extract on intercopulatory following THC induced erectile dysfunction in male Wistar rats

The effect of *Terminalia catappa* leaf extracts on some serum hormones following THC induced erectile dysfunction in male Wistar rats



Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 33 The effect of *Terminalia catappa* extract on prolactin profile following THC induced erectile dysfunction in male Wistar rats



Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 34 The effect of *Terminalia catappa* extract on progesterone profile following THC induced erectile dysfunction in male Wistar rats

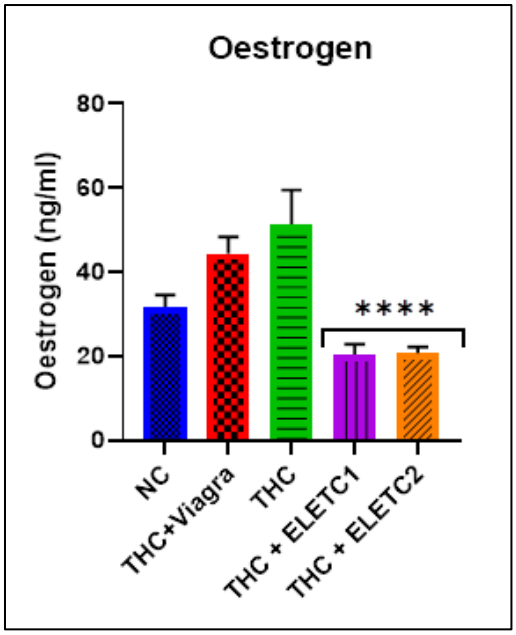


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Figure 35 The effect of *Terminalia catappa* extract on oestrogen profile following THC induced erectile dysfunction in male Wistar rats

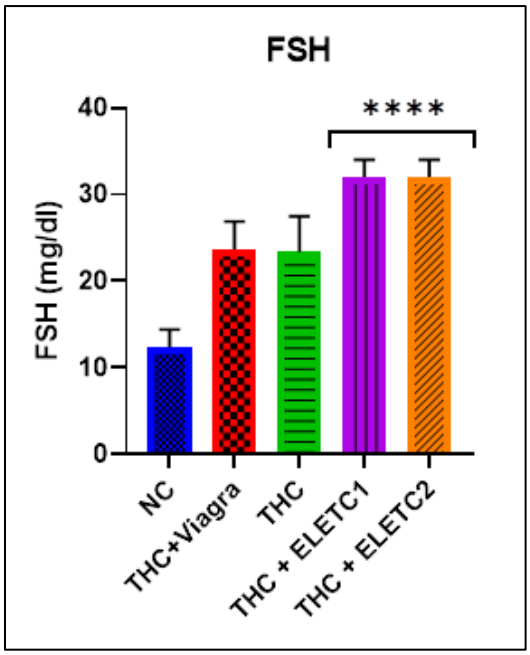

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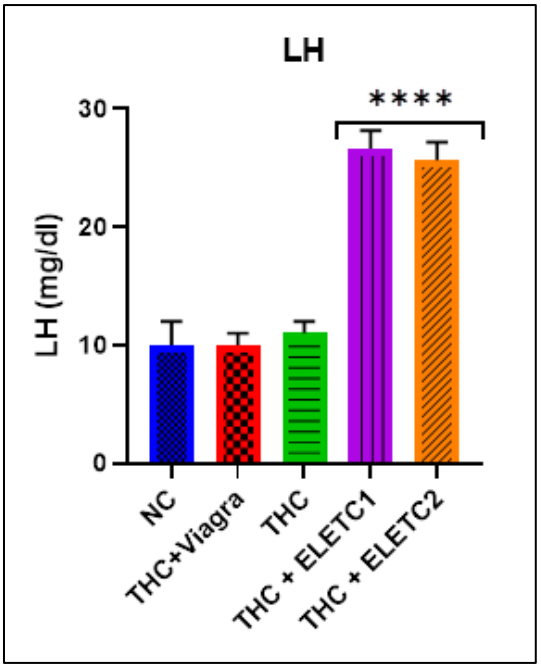
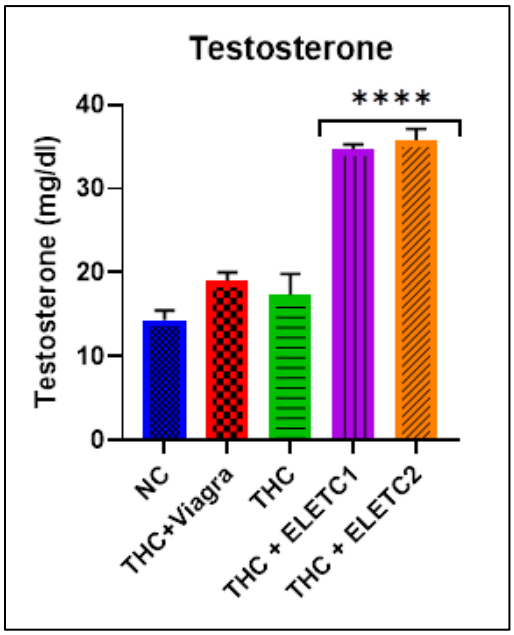
Figure 36 The effect of *Terminalia catappa* extract on FSH profile following THC induced erectile dysfunction in male Wistar rats



Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

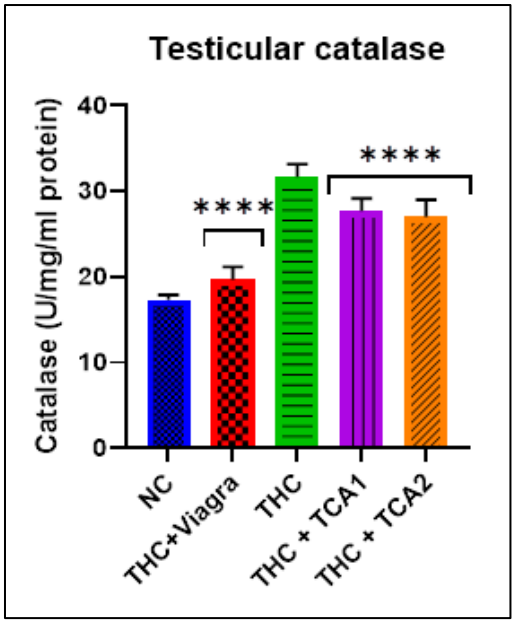
Figure 37 The effect of *Terminalia catappa* extract on LH profile following THC induced erectile dysfunction in male Wistar rats



Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

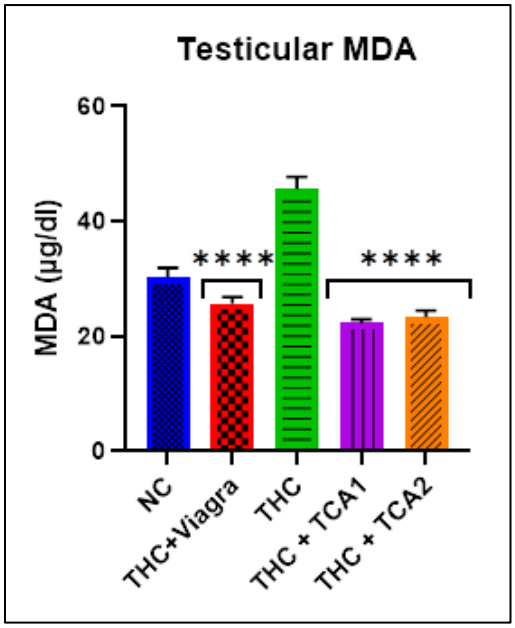
Figure 38 The effect of *Terminalia catappa* extract on testosterone profile following THC induced erectile dysfunction in male Wistar rats

The effect of *Terminalia catappa* leaf extracts on testicular oxidative biomarkers of male Wistar rats



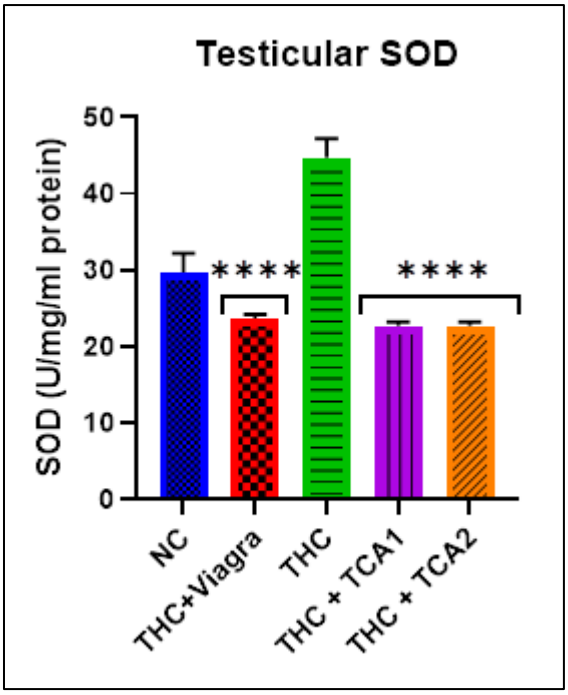
Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 39 The effect of *Terminalia catappa* extract on testicular catalase following THC induced erectile dysfunction in male Wistar rats



Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 40 The effect of *Terminalia catappa* extract on testicular MDA following THC induced erectile dysfunction in male Wistar rats



Key: NC: Normal Control, THC+Viagra: Δ^9 tetra hydro carnnabinol + Viagra, THC: Δ^9 tetra hydro carnnabinol, THC + ELETC1: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (200mg/Kgbwt) THC + ELETC2: Δ^9 tetra hydro carnnabinol + Ethanol leaf extract of *Terminalia catappa* (400mg/Kgbwt).

Figure 41 The effect of *Terminalia catappa* extract on testicular SOD following THC induced erectile dysfunction in male Wistar rats

4. Discussion

Advancements in phytopharmacology emphasizes on the therapeutic potential of natural compounds to complement or replace conventional treatments particularly in conditions involving oxidative stress and cellular tissue injury THC-induced erectile dysfunction (18). The reproductive protective effects of *Terminalia catappa* align with this paradigm, suggesting its natural intervention for THC-induced erectile dysfunction and sperm profile deficits.

This present study was designed to evaluate the effect of *Terminalia catappa* leaf extract on sperm profile following THC-induced erectile dysfunction in male Wistar rats. This research aimed to elucidate the underlying mechanisms by evaluating key parameters of sexual behaviour, including mount frequency (MF), intromission frequency (IF), ejaculation frequency (EF), mount latency (ML), ejaculation latency (EL), post-ejaculatory interval (PEI), as well as sperm bio-oxidative markers parameters and reproductive hormone levels.

The seminal pH, essential for sperm capacitation and motility of sperm, and it is tightly regulated within 7.2–8.0 by the bicarbonate buffer system that may be mediated by carbonic anhydrase, and prostatic secretions containing citrate and zinc (22). The THC+Viagra treated group exhibits a significant increase in pH, possibly due to sildenafil's inhibition of phosphodiesterase-5 (PDE5) by increasing cyclic GMP (cGMP) levels, which may activate protein kinase G (PKG) and enhances CFTR chloride channel-mediated bicarbonate influx ion channels, leading to alkalization (23). This disrupts proton gradients that may be required for sperm hyperactivation via a calcium-dependent process via CatSper channels. Contrastingly, the THC group shows a marked pH decline attributable to CB_1 receptor activation by THC, which modulates G-protein-coupled inwardly rectifying potassium (GIRK) channels and impairs V-ATPase proton pump function that disrupts pH homeostasis (24). The significant increase in pH stability at both 200 and 400 mg /kg body weight of T.catappa treated groups. This suggests that *Terminalia catappa* may enhances the antioxidant defense system, potentially through its phenolic compounds which in turns stabilize membrane-bound ion transporters and carbonic anhydrase activity mitigating THC-induced acidosis which aligns with the work of (25), who reported that phytochemicals from *Terminalia catappa* mitigate pH dysregulation under oxidative stress, possibly by scavenging free radicals that may impair ion channel function.

Sperm motility, are essential for fertilization which depends on ATP production through mitochondrial oxidative phosphorylation and glycolysis with dynein ATPase driving flagellar movement (26). The significant reduction in

motility (below 40%) and viability in the THC+Viagra and THC groups indicating oxidative damage induces by THC. THC activates CB_1 receptors by upregulating NADPH oxidase and increasing reactive oxygen species (ROS) such as superoxide (O_2^-) and hydrogen peroxide (H_2O_2), which peroxidize sperm membrane lipids rich in polyunsaturated fatty acids (27). Viagra enhances this by enhancing vasodilation and oxygen delivery, that potentially overwhelming endogenous antioxidants such as glutathione and vitamin E. The significant increase in testicular catalase and SOD levels at 200 and 400 mg/kg body weight suggests that *Terminalia catappa* may enhance the antioxidant defense system which it is in agreement with the finding of Mandal and Das (2009). However, catalase decomposes H_2O_2 into water and oxygen ($2H_2O_2 \rightarrow 2H_2O + O_2$), while SOD converts superoxide into H_2O_2 and oxygen ($2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$), preventing lipid peroxidation and mitochondrial DNA damage. Therefore, this antioxidant of *Terminalia catappa* surge to preserves mitochondrial membrane potential ($\Delta\Psi m$) and ATP synthase activity, explaining the motility recovery to 70–80% in treated groups. Immobility, inversely correlated with motility, peaks at 40% in the THC group due to impaired flagellar axonemal integrity but drops below 20% at 400 mg /kg body weight *T.catappa*, suggesting that *Terminalia catappa* may restore microtubule dynamics through its flavonoid or exodant content, such as quercetin which may stabilize cytoskeletal proteins.

Viability declines sharply with THC+Viagra and THC (below 40%) due to ROS-induced endoplasmic reticulum stress triggering the unfolded protein response (UPR) and caspase-3-mediated apoptosis (28). The significant increase in viability to 80% in the group treated with 400mg/kg body weight of the extract suggests that *Terminalia catappa* may exert an anti-apoptotic effect, possibly via upregulation of Bcl-2 or inhibition of Bax translocation according to (29). This protection may involve *Terminalia catappa* tannins, which has been reported to activate sirtuin-1 (SIRT1), a regulator of mitochondrial biogenesis under oxidative stress, a mechanism explored in sperm cryopreservation (30).

Moreso, the significant reduction in total sperm count in the untreated groups (below 4×10^6/mL) reflects spermatogenic impairment. THC suppresses the hypothalamic-pituitary-gonadal (HPG) axis by inhibiting gonadotropin-releasing hormone (GnRH) pulsatility, reducing luteinizing hormone (LH) and testosterone levels, which are essential for spermatogonial proliferation and spermiogenesis (31). Testosterone regulates genes like c-kit (promoting spermatogonial survival) and Stra8 (inducing meiotic entry) while Sertoli cells, reliant on androgen signaling pathway support spermatid maturation through lactate provision (32). Viagra may increase this by altering testicular microcirculation and or by increasing hypoxia-inducible factor-1α (HIF-1α), and triggering germ cell apoptosis. Therefore, the significant increase in sperm count to 8×10^6/mL in the group treated with 400mg/kg body weight suggests that *Terminalia catappa* may enhance the antioxidant defense system, potentially through its ellagitannins which stimulate LH secretion via hypothalamic modulation or protect the blood-testis barrier by upregulating tight junction proteins such as occluding (30,8), who demonstrated that *Terminalia catappa* extracts mitigate spermatogenic damage under oxidative stress, possibly by scavenging ROS and supporting steroidogenesis.

Mating behaviour metrics reveal a biphasic response driven by neurochemical and hormonal shifts. The N group shows baseline activity, while Viagra treated group significantly increases MF, IF, and EF, attributable to sildenafil's enhancement of nitric oxide-cGMP signaling by activating guanylate cyclase (sGC), increasing cGMP, and relaxing cavernosal smooth muscle via PKG, thus boosting penile erection and copulatory frequency (33,8). THC alone depresses these metrics, consistent with CB1 receptor-mediated inhibition of dopamine release in the nucleus accumbens, reducing sexual motivation, and anxiogenic effects via increased amygdala activity according to finding of Fattore & Fratta (2018). The significant increase in testicular catalase and SOD levels in the extract treated groups suggests that *Terminalia catappa* may enhance the antioxidant defense system, mitigating THC-induced neuroinflammation by reducing microglial ROS production, as noted by (34). This restores dopaminergic tone, that justify the recovery of MF, IF, and EF to near-normal levels, potentially through *Terminalia catappa* phenolic acids, which inhibit cyclooxygenase-2 (COX-2) and reduce prostaglandin-mediated inflammation in neural circuits.

Latencies (ML, IL, EL) and PEI are significantly prolonged with THC, reflecting reduced sexual motivation and extended refractory periods due to THC's activation of μ-opioid receptors in the paraventricular nucleus, inhibiting oxytocin release and endocannabinoid suppression of glutamatergic signaling pathway (35). Therefore, significant decrease in latencies and PEI in the extract treated groups suggests that *Terminalia catappa* may enhance synaptic plasticity, potentially via its flavonoids upregulating brain-derived neurotrophic factor (BDNF) or reducing proinflammatory cytokines (e.g., TNF-α) which is in agreement with (36). The sustained improvement on Day 7, with EF nearing baseline, indicates a cumulative effect due to involvement of *Terminalia catappa* tannins mediating epigenetic modifications such as histone deacetylase (HDAC) inhibition in dopaminergic neurons, as reported by (37). However, antioxidant surge to prevents lipid peroxidation in neural membranes, preserving neurotransmitter vesicle release.

The mating behavior metrics on Day 7 showed significant variations across treatment groups. The control group exhibits baseline sexual activity with MF, IF, and EF at moderate levels, while THC+Viagra significantly increases these

frequencies due to sildenafil's enhancement of nitric oxide-cGMP signaling pathway. This may activate guanylate cyclase (sGC) by increasing cGMP and relaxing cavernosal smooth muscle via protein kinase-G (PKG) thus promoting penile erection and copulatory behavior (25). However, THC alone depresses MF, IF, and EF, consistent with CB1 receptor-mediated inhibition of dopamine release in the nucleus accumbens thereby reducing sexual motivation and anxiogenic effects via increased amygdala activity (38). Therefore, the significant increase in MF, IF, and EF in the THC+ELET and THC+ELET+C2 groups suggests that *Terminalia catappa* may enhance the antioxidant defense system according to report of (39). Furthermore, this antioxidant surge by *Terminalia catappa 's* phenolic compounds like gallic acid, mitigates THC-induced neuroinflammation, restoring dopaminergic tone and sexual motivation, as supported by (34).

Latencies (ML, IL, EL) and PEI on Day 7 show a contrasting trend. THC significantly prolongs these metrics, reflecting reduced sexual motivation and extended refractory periods, possibly due to CB1 receptor activation in the paraventricular nucleus by inhibiting oxytocin release and endocannabinoid suppression of glutamatergic signaling (35). The significant decrease in ML, IL, EL, and PEI in the *Terminalia catappa* treated groups suggests that *Terminalia catappa* may enhance the antioxidant defense system possibly by reducing microglial ROS production and preserving synaptic plasticity. Therefore, *Terminalia catappa 's* flavonoids such as quercetin, may upregulate brain-derived neurotrophic factor (BDNF) and reduce proinflammatory cytokines (e.g., TNF-α) enhancing neural signaling as reported by (36). The antioxidant protection likely prevents lipid peroxidation in neural membranes, ensuring efficient neurotransmitter vesicle release and reducing refractory periods.

By Day 14, the mating behaviour metrics showed long-term effects in the *T.catappa* treated groups. The THC group show suppressed MF, IF, and EF, reflecting persistent neurochemical imbalance. In similar manner, the significant increase in MF, IF, and EF at both 200 and 400 mg/kg body weight of *Tatappa* groups suggests that *Terminalia catappa* may enhance the antioxidant defense system according to finding of (39). Catalase and SOD mitigate oxidative stress by neutralizing ROS, preventing damage to dopaminergic neurons in the mesolimbic pathway, which is critical for sexual motivation*. Terminalia catappa 's* ellagitannins may also inhibit constitutive induced cyclooxygenase-2 (COX-2) by reducing prostaglandin-mediated inflammation in neural circuits which is in conjunction with (25). Therefore, the sustained improvement on Day 14 suggests a cumulative potentially involving *Terminalia catappa 's* tannins mediating epigenetic modifications, such as histone deacetylase (HDAC) inhibition in dopaminergic neurons by enhancing gene expression related to synaptic plasticity (37).

Latencies (ML, IL, EL) and PEI on Day 14 follow a similar to Day 7, with THC showing a prolong metrics, while groups treated with both 200 and 400 mg/kg body weight showed significant reductions. However, the significant decrease in latencies and PEI suggests *that Terminalia catappa* may enhance the antioxidant defense system by protecting neural membranes from lipid peroxidation and preserving glutamatergic and oxytocinergic signaling cascade. Therefore, *Terminalia catappa 's* phenolic acids may also modulate serotonin levels by reducing anxiogenic effects and improving copulatory efficiency explored by (34). Similarly, the consistent improvement over 14 days showed that *Terminalia catappa 's* potential for long-term neuroprotection.

The index of libido, percentage mounted, and percentage intromitted showed a holistic view of sexual behavior. The THC group shows a significant decline in these metrics, reflecting reduced libido and mating success due to THC's suppression of testosterone via the hypothalamic-pituitary-gonadal (HPG) axis, as well as dopamine inhibition (40). The significant increase in the index of libido, percentage mounted, and percentage intromitted in the THC groups treated with *T.catappa* suggests that *T catappa*. may enhance the antioxidant defense system, according to finding with (39). Therefore, Catalase and SOD neutralize ROS by protecting Leydig cells from oxidative damage and supporting testosterone synthesis which is critical for libido via *Terminalia catappa 's* flavonoids that enhance nitric oxide bioavailability and improving penile erection and mating success as supported by (30). In like manner, the high percentages in the *T.catappa* group indicate a synergistic effect by potentially involving *Terminalia catappa 's* tannins upregulating androgen receptor expression, enhancing sexual behaviour.

Ejaculatory function increased to approximately 100% in both groups treated with 200 and 400mg/kg body weight, compared to around 50% in the Viagra treated group, and only 20% in the THC-only group. This observed significant increase indicate that *Terminalia catappa* , through its bioactive compounds in *extract of T.catappa*, enhances the neurochemical pathways involved in ejaculation and copulation potentially by modulating dopamine and serotonin levels in the brain, which are very essential for sexual behavior (41). Dopamine facilitates ejaculation by acting and binding on D2 receptors in the medial preoptic area (MPOA) of the hypothalamus region that is involved in male sexual behavior (42). The poor performance of THC alone aligns with (43), research indicating that high doses of THC impair sexual function by over-activating CB1 receptors, leading to desensitization of reward pathways. However, the significant increase suggests that *Terminalia catappa* may suggest its counter effect against desensitization possibly through the antioxidant and anti-inflammatory properties of its tannins and flavonoids, which could enhance

downstream signaling pathways such as cyclic AMP (cAMP) production, often suppressed by THC (44), and have shown that *Terminalia catappa* leaf extracts possess potent antioxidant activity, which may protect dopaminergic neurons from oxidative stress induced by THC (45).

Intercopulatory efficiency, shows a drastic increase in the THC group (around 300 seconds) compared to NC and THC+Viagra (both around 150 seconds) with 200 and 400mg /kg body weight of *T.catappa* showing intermediate values (around 100 seconds). This indicate that THC alone prolongs the time between intromissions potentially due to altered serotonin signaling in the brainstem, as serotonin delays ejaculation by acting on 5-HT1A receptors (33). However. reduction in inter copulatory efficiency with extract of *T.catappa* indicates a normalization of this timing and this significant increase suggests that *Terminalia catappa* may balance serotonin and dopamine levels or enhance nitric oxide (NO) production which facilitates penile erection and intromission (34). The report (46), who demonstrated that CB_1 receptor modulators can influence NO synthase activity in penile tissue thereby affecting intromission frequency. *Terminalia catappa* is known to contain triterpenoids and phenolic compounds that may upregulate endothelial NO synthase (eNOS), supporting this mechanism (47,8).

Hormonal profiles profile shows the biochemical mechanisms underlying these behavioural changes. Prolactin levels are relatively stable across the treatment groups ranging from 20–30 ng/mL with no significant differences. How ever, unexpected changes in prolactin often shows a rises post-ejaculation and can inhibit sexual behavior by suppressing dopamine release (48), this lack of change may indicate that the treatments do not significantly alter prolactin-dopamine feedback loops or that the timing of sample collection missed peak prolactin surges.

Progesterone in males modulates GABAergic signaling which can inhibit sexual behavior by reducing neuronal excitability in the MPOA (49). However, the reduction in progesterone with treatment with *T.catappa* , where this significant increase suggests that *Terminalia catappa* may decrease GABA-mediated inhibition, could allow for greater dopaminergic activity, enhancing sexual behavior and *Terminalia catappa 's* flavonoids such as quercetin are known to modulate GABA receptors effect (50).

The significant increase oestrogen in males may occurs as the result aromatization of testosterone by the enzyme aromatase and high oestrogen levels which are associated with reduced libido and erectile dysfunction (51). The THC-induced increase in oestrogen may contribute to its detrimental effects on sexual function, and a similar significant increase *Terminalia catappa* indicate that treatment with *T.catappa* may mitigate this by inhibiting aromatase activity or enhancing oestrogen clearance level (52). Therefore, *Terminalia catappa* extracts shown to possess anti-aromatase activity, which could this reduction.

FSH and LH are essential for spermatogenesis and testosterone production by acting on Sertoli and Leydig cells in the testes (8,53). This significant increase suggests that *Terminalia catappa* enhances hypothalamic-pituitary-gonadal (HPG) axis activity possibly by upregulating gonadotropin-releasing hormone (GnRH) release or reducing negative feedback from oestrogen and testosterone loop. Therefore, *Terminalia catappa 's* steroidal saponins may stimulate GnRH release supporting this effect by (54).

Testosterone serves a primary reproductive hormone that drives male sexual behavior by acting on androgen receptors in the brain and periphery to enhance libido, erection, and ejaculation (42). However, this significant increase suggests that *Terminalia catappa* enhances testosterone production contributing to the improvements in ejaculatory and copulatory efficiency, as well as the normalization of interopulatory efficiency which aligns with recent findings of (55), who reported that *Terminalia catappa* extracts can enhance testosterone production by reducing oxidative stress in Leydig cells thereby improving steroidogenesis.

The significant increase in testicular catalase and SOD levels suggests that exodant of T.C enhance the antioxidant defense system in the testes which was in agreement with (39). Catalase and SOD are essentially antioxidants enzymes that mitigate oxidative stress thereby neutralizing reactive oxygen species (ROS). Catalase decomposes hydrogen peroxide (H_2O_2) into water and oxygen, while SOD converts superoxide radicals into H_2O_2 and oxygen, thus preventing cellular damage that may be induce by THC. The marked increase in these enzymes indicates a protective response against oxidative stress, likely induced by THC exposure, as THC is known to generate ROS and cause testicular damage (56). The THC group, in contrast, shows lower levels of catalase and SOD compared to the CA1 and CA2 groups, suggesting that THC alone does not effectively bolster antioxidant defenses, potentially exacerbating oxidative stress in the testes there by mimic the recovery phase by upregulating antioxidant defenses, potentially through antioxidants mechanisms that counteract THC-induced ROS production (57). Therefore, this increase in plant exodant (T.C) suggest its therapeutic potential effects or long-term impacts that sustained elevation of SOD and catalase (CAT) could disrupt normal redox signaling in the testes, which is essential for spermatogenesis.

In similar manner, the significant increase in MDA in the *T.catappa* treated group may suggest that extract might offer a more balanced protective effect against lipid peroxidation, possibly due to a different phytochemicals ingredient that may mitigates oxidative cellular damage thereby suggesting its potential as therapeutic agents to counteract THC-induced oxidative stress (8).

5. Conclusion

It can be inferred from this present work that extract of *Terminalia catappa* may improve and or prolonged sexual drive in THC induced erectile dysfunction in a dosage dependent manner.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there is no conflict of interest related to this work.

Statement of ethical approval

Ethical approval for the study was obtained from the Faculty of Basic Medical Science Animal Research Ethical Committee of Cross River University of Technology, Calabar, Nigeria (approval number FBMS/UNICROSS/24/022).

Author's contribution:

All authors contributed substantially to the conception, design, and interpretation of data presented in this review. They were actively involved in the analysis of existing literature, drafting of the figures, writing of the manuscript, and critical revision of its intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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