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AMLODIPINE –INDUCED ALTERATIONS IN MALE REPRODUCTIVE HORMONES OF ALBINO RATS: BENEFICIAL ROLES OF TIGER NUT MILK

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ABSTRACT

Hypertension is a leading risk factor for cardiovascular disease and premature death worldwide. This has led to the increased clinical prescription of antihypertensive medications especially calcium channel blockers (CCBs) that have been implicated in male fertility by altering hormone secretion. To investigate the role of Tiger nut milk in amlodipine isomers-induced male reproductive hormones alterations, forty-two male albino rats (150g -170g) were randomly segregated into six groups (n=7) for a six week experiment: Group 1 (control), group 2 (amlodipine 0.07mg/kg), group 3 (S-amlodipine 0.035mg/kg), group 4 (amlodipine + Tiger nut milk), group 5 (S-amlodipine + Tiger nut milk), and group 6 (Tiger nut milk 3.5ml/kg). Blood samples for hormonal assays were collected into EDTA coated tube after four weeks, to confirm alterations in male reproductive hormones, before commencing Tiger nut milk treatment for a further two weeks. The experimental rats were euthanized; blood samples were collected and centrifuged to obtain plasma for luteinizing hormone and testosterone assays. A significant reduction ($p<0.05$) in the plasma luteinizing hormone and testosterone levels were recorded for amlodipine-treated male albino rats compared with the control, while a milder effect was observed for the hormonal levels of groups treated with S-amlodipine. Feeding with Tiger nut milk, showed favorable mild reversal of the hormonal decrements. This study thus suggests that, consumption of Tiger nut milk may be beneficial in cases of prescribed amlodipine-induced male reproductive hormone alterations.

Keywords: Antihypertensive drugs, Calcium Channel Blockers, Amlodipine, S-amlodipine, Testosterone, Luteinizing hormone, Tiger nut milk.

INTRODUCTION

Hypertension is the leading preventable risk factor for cardiovascular disease (CVD) and mortality worldwide (Wang *et al.* 2023, Stanaway *et al.*, 2018). As at 2010, a total of 1.38 billion people (31.1% of the global adult population) had hypertension, defined as systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg (Mills *et al.*, 2016). The prevalence of hypertension is rising globally owing to ageing of the population and increases in exposure to lifestyle risk factors including unhealthy diets (i.e. high sodium and low potassium intake) and lack of physical activity (Tripathi *et al.*, 2022). The increased risk associated with blood pressure (BP) elevation can be greatly reduced by treatment with antihypertensive drugs that lower both BP and related target organ damage (Verdecchia *et al.*, 2022).

Calcium channel blockers (CCB) are one of the most commonly prescribed medications for hypertension and cardiovascular diseases. The transmembrane changes of the Ca2+ ion initiate many physiological events; thus, the blockage of calcium channels by CCB has several potential clinical indications (Dolphin, 2018). Calcium channel blockers are drugs prescribed for lowering blood pressure. They work by slowing the movement of calcium into the cells of the heart and blood vessel walls (Zohny *et al*., 2023).

Calcium Channel Blockers are classified into two main clinical categories based on their physiological effects: dihydropyridines (eg, amlodipine, nifedipine, felodipine, nicardipine) and non-dihydropyridines (eg, verapamil and diltiazem) (Chakraborty and Hamilton, 2023). Dihydropyridines have a greater affinity for peripheral vascular smooth muscle cells, while non-dihydropyridines have a greater affinity for cardiomyocytes (Chakraborty and Hamilton, 2023).

Amlodipine is commonly used in the control of angina and hypertension (Wang *et al*., 2023). Formulations of amlodipine (AML) may contain its different salts such as besylate, mesylate, or maleate. These salts are considered interchangeably and the strength of the dosage form is determined in terms of the parent molecule, that is, amlodipine (Angeli *et al*., 2018). Amlodipine is an oral dihydropyridine CCB that inhibits the transmembrane infux of calcium into cardiac muscle and vascular smooth muscle, hence resulting in prolonged efficacy (Bulsara *et al*., 2024). The antihypertensive effect of AML is due to peripheral vasodilation and subsequent reduction in systemic vascular resistance (Schettini *et al*., 2023). Amlodipine has a half-life of 30–50 hours, which allows for once-daily administration (Bulsara *et al*., 2024).

Reports exist suggesting that Calcium channel blockers, despite exhibiting substantial cardiovascular selectivity, may have anti-reproductive effects in males on long-term treatment (Ghomeshi *et al*., 2023). The underlying mechanism of CCBs in etiology of infertility is still under investigation. Although there are evidences that CCBs possess antiproliferative activity, which may interfere with fertility (Salvio *et al*., 2022).

Sexual dysfunction has an increased preponderance among hypertensive men (Bager *et al*., 2023). Manifestation of dysfunction comprises of reduced libido, inability to obtain or maintain an erection (impotence), and premature or retarded ejaculation (Bertelli *et al*., 2022). These symptoms are often first reported by patients while receiving antihypertensive therapy, which has led to a widespread belief that sexual dysfunction is caused by a specific antihypertensive agent rather than by hypertension itself (Al Khaja *et al*., 2016). Hernández-Cerda *et al*. (2020) reported a rising order of prevalence of erectile difficulties in normotensive subjects (7%), untreated hypertensive men (17%), and treated hypertensive men (25%). Sexual dysfunction is a significant side effect of many antihypertensive agents, and consequently is a major reason for noncompliance with therapy (Al Khaja *et al*., 2016). It then becomes pertinent to seek foods or supplements that might protect and or mitigate the growing concerns of CCBs induced alterations in reproductive hormones which might lead to male infertility in unsuspecting individuals, particularly of reproductive age.

Tiger nut (*Cyperus esculentus L.*) belongs to the

sedge family: *Cyperaceae* and is known by other names like chufa, yellow nutsedge, earth almond and ground almond. It is a perennial crop cultivated extensively in Asia, west African Countries including Nigeria and Ghana, parts of Europe particularly Spain as well as in the Arabian Peninsula (Omeje *et al*., 2022; Abdelkader *et al*., 2017). In Nigeria, Tiger nut is called "Ofio" by the Yorubas, "Akiausa" by the Igbos and "Aya" by the Hausas. It is cultivated for its edible tubers, called earth almonds, as a snack food and for the preparation of horchata de chufa, a sweet, milk-like beverage (Ogbuagu and Airaodion, 2020).

Tiger nuts are rich in minerals such as phosphorus, potassium, calcium, magnesium, and iron; vitamins including A, B, C and E; amino acids such as valine, leucine, phenylalanine, lysine, histidine, tryptophan cysteine and glycine; as well as monosaccharides including glucose, fructose and mannose (Omeje *et al*., 2022; Maduka and Ire, 2018). The Tiger nut milk is very nutritive and serves as a good source of energy (Oyetoro *et al*., 2019). Also, Tiger nut milk neither contains lactose casein nor cholesterol and is therefore, an ideal drink for people who do not tolerate gluten or cow's milk (Bamishaiye and Bamishaiye, 2011). In Spain, Tiger nut tubers can be made into a refreshing beverage to make a kind of milk called "Horchata" (Mohdaly, 2019). Previous studies have revealed that Tiger nut help to prevent heart problems, thrombosis and activate blood circulation; it also helps in preventing and treating urinary tract and bacterial infection and assist in reducing the risk of colon cancer when eaten (Adejuyitan *et al.* 2009). It was also reported to be helpful as an antidotal nutritional remediation against nuerobehavioural deficits (Enye *et al*., 2024) Tiger nut is essential for fertility in both men and women, and it helps to promote normal menstruation and is a potent aphrodisiac (Edo *et al*., 2023). The aim of this study is to ascertain the beneficial effect of Tiger nut milk on amlodipine-induced alterations in rat's testosterone and luteinizing hormone levels.

MATERIALS AND METHODS

Chemicals and reagents

Amlodipine, S-amlodipine, testosterone ELISA kit (Calbiotech science company; 1953 Cordeli Ct., El Cajon, CA92020 USA) and rat luteinizing hormone ELISA kit (Elabscience Biotechnology Inc. USA). All chemicals and reagents used for this study were of analytical grade.

Tiger nuts collection and Tiger nut milk extraction

Fresh Tiger nut tubers were purchased from Eleweran market, Abeokuta, Ogun state. The tubers were sorted, and taken to a botanist at the Department of Botany, Federal University of Agriculture, Abeokuta for identification- voucher number: FHA-4286. The fresh tubers were first sorted and thoroughly washed in running tap water and then soaked in distilled water for 24 hours and kept in the fridge. The tubers was then ground using an industrial electric grinder (smart home 29CCW, USA.), the milk was extracted using a muslin cloth and was preserved in the refrigerator at 40C before usage.

Animals and experimental design

Forty-two healthy male albino rats (150 – 170 g) used for this study were obtained from the animal house facility, College of Veterinary Medicine, Federal University of Agriculture, Abeokuta, Nigeria. They were housed in wire-floored cages under standard ambient laboratory conditions of 12 hours light-dark cycle, room temperature. Animals

were daily supplemented with standard pelleted diet and were given water *ad libitum*. The animals were acclimatized to laboratory conditions for two weeks preceding the commencement of the experiment. Handling of the experimental animals is consistent with international principles on the care and use of experimental animals (National Research Council (US) committee, 2011). Animals were segregated into six groups each comprising of seven rats. Control group received water for six weeks, Group 2 received 0.07 mg/kg amlodipine for four weeks, Group 3 received 0.035 mg/kg S-amlodipine for four weeks, Group 4 received 0.07 mg/kg amlodipine for four weeks and Tiger nut milk for two weeks, Group 5 received 0.035 mg/kg S-amlodipine for four weeks and Tiger nut milk for two weeks, Group 6 received Tiger nut milk for two weeks. All treatments were orally administered via oral gavage.

Biochemical evaluations

The plasma testosterone was assayed using testosterone Enzyme-Linked Immunosorbent Assay (ELISA) kit (Calbiotech science company; 1953 Cordeli Ct., El Cajon, CA92020 USA) according to the procedure described in the kit's manual. Plasma luteinizing hormone was determined according to the method described in the rat-specific luteinizing hormone Enzyme-Linked Immunosorbent Assay (ELISA) kit (Elabscience Biotechnology Inc. USA).

Statistical Analysis

Data were analyzed by one-way analysis of variance (ANOVA), followed by Duncan test for multiple comparisons among the groups of rats using Statistical Package for the Social Sciences Version 16. The data were expressed as mean ± standard error of the mean. P values < 0.05 were considered statistically significant.

RESULTS

Plasma luteinizing hormone concentration of the experimental male albino rats

Four weeks of amlodipine (0.07 mg/kg) and S-amlodipine (0.035 mg/kg) administration caused a significant reduction in the luteinizing hormone level of the groups orally fed amlodipine and S-amlodipine, compared to the control group. However, treatment with Tiger nut milk significantly increased the plasma luteinizing hormone levels in fed groups (Figure 1).

Plasma testosterone concentration of the experimental male albino rats.

Four weeks of amlodipine (0.07 mg/kg) and s-amloipine (0.035 mg/kg) administration caused a significant reduction in the testosterone levels of the groups given amlodipine and S-amlodipine compared to the control group. However, Tiger nut milk significantly increased the plasma testosterone levels in orally administered groups (Figure 2).

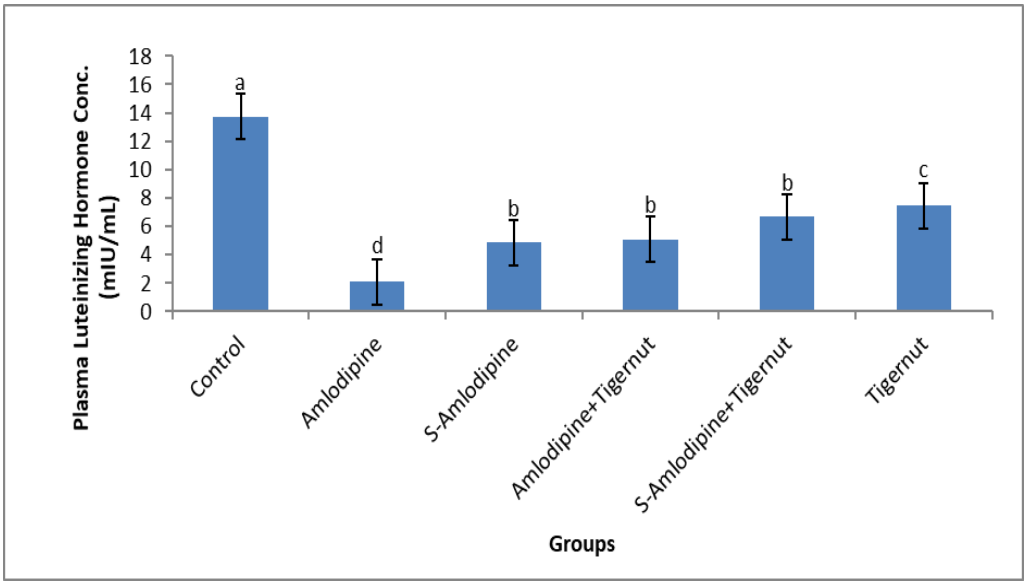

Figure 1: Effects of Tiger nut milk on plasma luteinizing hormone concentration of rats exposed to amlodipine and S-amlodipine. Results are presented as mean ± SEM, p < (0.05). Similar letters indicates no significant difference.

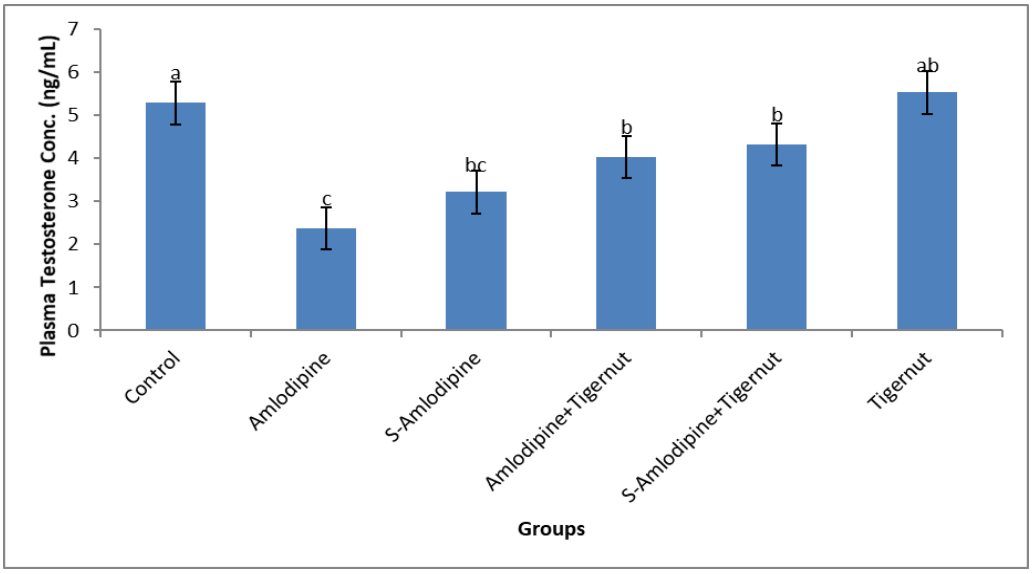

Figure 2: Effects of Tiger nut milk on plasma testosterone concentration of rats exposed to amlodipine and S-amlodipine. Results are presented as mean ± SEM, p < (0.05). Similar letters indicates no significant difference.

DISCUSSION

The increased clinical prescription of anti-hypertensive medications especially calcium channel blockers (CCBs), among which is amlodipine and its S-amlodipine isomer, may be most beneficial in addressing increased clinical cases of hypertension amongst all affected ages (Wang *et al*., 2023). However, the growing concern of CCBs implication in male infertility (Ghomeshi *et al*., 2023) requires scientific attention, particularly because of unsuspecting individuals who have been placed on CCBs and are within the active reproductive age. Calcium ions are important for many biological processes such as excitation-contraction coupling, excitation-secretion coupling, fertilization and regulation of gene expression. It has been established that calcium plays an important role in the synthesis, release and functioning of several hormones. Therefore, the administration of calcium channel blockers may affect endocrine glands and hormones secreted by the latter (Rimple *et al*., 2014). Calcium channel blockers (CCB) produce their effects mainly by blocking the calcium channels, thus altering the calcium concentrations across the cells. Hence, administration of calcium channel blockers may alter the activity of calcium in promoting steroidogenesis and/or spermatogenesis consequently resulting in hindered production and or secretion of testosterone and ultimately, compromised sperm production (Rimple *et al*., 2014).

Reproductive hormones are crucial for sexual development, fertility and reproductive cycle (Davidge-Pitts and Solorzano, 2022). Testosterone is the primary male sex hormone which is produced by the Leydig cells within the testes. The production of testosterone is regulated by the hypothalamic-pituitary-testicular axis. Hypothalamus release gonadotropin-releasing hormone (GnRH), which stimulates the pituitary to release luteinizing hormone (LH) which in turn stimulates the Leydig cells to produce testosterone that is critical for reproductive function. Testosterone is important for the development of male reproductive organs and secondary sexual characteristics. It is very essential for sperm production and libido (Manocha *et al*., 2018)

The findings of this study showed that amlodipine treatment was associated with significant decrease in the plasma luteinizing hormone and testosterone concentrations. This might be due to amlodipine interference with the role of calcium in steroidogenesis, since calcium acts as a second messenger and regulate the synthesis of steroid hormones such as testosterone. Calcium regulates steroidogenesis in Leydig cells, which are responsible for testosterone production. S-amlodipine, an enantiomer of amlodipine did not show a significant reduction in the levels of these hormones when compared to Tiger nut milk treated group. However, there was a significant reduction in the levels of the studied male sex hormones compared with those of the control rats.

This study showed that groups fed Tiger nut milk had increased luteinizing hormone and testosterone concentrations. It thus seems Tiger nut enhance calcium metabolism in favour of sex hormone production. Allouh *et al.* (2015) had earlier reported that it may have acted directly on testicular cells and not through the hypothalamus-pituitary testicular axis, since no variations in FSH and LH levels were observed due to Tiger nut treatment. Increment in sex hormones levels translates to production of sperms. Ogbuagu and Airaodion, (2020) and Gbotolorun *et al.* (2022) in their earlier studies, reported that

Tiger nut milk increased luteinizing hormone and testosterone concentrations which resulted in increased sperm count, quality and motility, hence boosted fertility in male rats.

Tiger nut is relatively available locally and cheap. Hence, it seems to be a tuber consumed by the poor. The underestimation of its nutritional components has resulted in its underuse for health benefits (Adenowo and Kazeem, 2020). Tiger nut is rich in zinc and magnesium. Zinc plays crucial role in steroidogenesis, particularly in the testes by modulating steroidogenic enzymes and impacting testosterone production as well as protecting against CCB induced testicular damage. Zinc is involved in the regulation of luteinizing hormone which stimulates the testes to produce testosterone, adequate zinc level support the normal functioning of this hormonal pathway. Zinc is also associated with increased sensitivity of testosterone receptor in target tissues enhancing the effectiveness of the available testosterone.

Magnesium which is also a mineral content of Tiger nut plays a tangible role in maintaining overall hormonal balance within the body imbalances in hormones can negatively impact testosterone level, magnesium helps in preventing such disruption. The motility of sperms needs the joint presence of cAMP and Mg ATP. It was found that the formation of ATP, as well as, cAMP is a magnesium intensive process. It was also found in vivo that magnesium increases the sperm motility, while the sperm production increases up to 80%. Chandra *et al.* (2013) had earlier reported that magnesium has beneficial effect on male gonadal system. Tiger nut contains fructose, a major source of energy for sperm cells (Omeje *et al.*, 2022).

CONCLUSION

This study supports earlier study reports that calcium channel blockers particularly amlodipine, may be associated with reproductive dysfunctions. The dysfunctions may be via altering the levels of reproductive hormones including luteinizing hormone and testosterone as observed in male Wistar rats. The result of this study suggests that Tiger nut milk may be beneficial in reversing the deleterious effect of amlodipine and S-amlodipine, thereby, providing respite for unsuspecting patients in their active reproductive age that have been clinically placed on amlodipine for treatment of hypertension.

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