Original Article

Anti-Infertility And Antioxidative Property Of Tiger Nut Milk On Oligozoospermia-Induced Infertility By Anti Hypertensive Drugs In Male Albino Rats

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ABSTRACT

Hypertension is a major public health concern. *Cyperus Esculentus* L (Tiger nut (TNM)) has been reported to be an anti-hypertensive. This research investigated the anti-infertility properties of tiger nut milk on oligozoospermia-induced infertility by anti-hypertensive drugs in male Wistar rats. A total of forty-eight male rats, weighing 200 – 240 g were divided into eight groups and were treated as follows: Group 1: Distilled water, Group 2: Amlodipine (0.07 mg/Kg), Group 3: Bisoprolol (0.07 mg /Kg B.W), Group 4: Amlodipine + Bisoprolol, Group 5: Amlodipine + (0.320 ul/100 g) TNM; Group 6: Isoprolol + (0.320 ul/100 g) TNM; Group 7: Amlodipine + Bisoprolol + (0.320 ul/100 g) TNM; Group 8: (0.320 ul/100 g) TNM. Biochemical parameters such as Catalase, Superoxide Dismutase, glutathione, and Malondialdehyde were determined in the Plasma, luteinizing hormone (LH) levels in testis using Spectrophotometer. Data was analyzed using one–way analysis of variance (ANOVA) followed by Tukey's Test with $p < 0.05$ considered significant. The result revealed that both antihypertensive drugs cause a significant ($p > 0.05$) decrease in LH in testis, CAT, SOD, and GSH in plasma. MDA level increased significantly in all the groups treated with amlodipine and bisoprolol. In conclusion, TNM extracts could mitigate infertility.

KEY WORDS: Antihypertensive drugs, Anti- oxidants, Oligozoospermia, Testosterone, Tiger nut milk.

INTRODUCTION

The increasing rate of hypertension in Africa is partly due to lifestyle changes caused by urbanization, especially in Nigeria, where half of the population now resides in urban areas[1]. Urbanization-related social and lifestyle shifts include reduced physical activity, high intake of salt and saturated fats, tobacco use, harmful alcohol consumption, poor stress management, overweight and obesity, and decreased consumption of fruits and vegetables[2,3]. In Nigeria, the prevalence currently estimates ranging from 22% to 44% depending on the region[4]**.** Hypertension refers to a condition where blood exerts excessive force against artery walls, characterized by systolic blood pressure of 140mmHg or higher and diastolic pressure of 90mmHg or higher[5]. It is a major risk factor for stroke, myocardial infarction, arteriosclerosis, and end-stage renal disease[6].

The treatment of hypertension with antihypertensive drugs seeks to help prevent the detrimental complications of high blood pressure, such as myocardial infarction and stroke. Antihypertensive medicines come in different classes; however, the ones that are most frequently used as initial therapy are: Thiazides Diuretics, Calcium channel blockers (CCB), Angiotensin converting enzyme inhibitors and Angiotensin II receptor blockers[7]. Except for patients with chronic kidney disease, whom Angiotensin converting enzyme inhibitors or Angiotensin II receptor blockers are advised as first line treatment. CCB are used as first-line treatment alone or in conjunction with other antihypertensive in all patients with hypertension regardless of age or race[7]. The CCBs selectively block the cellular inward flow of calcium through the calcium channels on cell membranes. The CCBs also have quite several therapeutic applications

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apart from hypertension such as in the treatment of supraventricular arrhythmias and angina. They bind to the L-type long-acting voltage-gated calcium channels in the heart, the pancreas and the vascular smooth muscles thereby blocking the inward movement of calcium. Two major categories of CCB exist; the dihydropyridines which have close to little or no effect on the myocardium. They are more often peripheral vasodilators which is one of the many reasons why they are used as therapy for hypertension, migraines, post-intracranial haemorrhage associated vasospasm[8].

The non-dihydropyridines, however, have inhibitory effects on the Sinoatrial, the slowing of cardiac conduction and contractility results in the atrioventricular nodes. This helps in reducing the demand of oxygen and allows for the treatment of hypertension. It also helps in controlling the rate in tachycardia rhythmias[8]. The CCBs decrease the amount of readily available intracellular calcium in the vascular smooth muscle and by doing so, they effectively cause smooth muscle relaxation. The CCBs help to decrease the systematic vascular resistance thereby reducing the arterial blood pressure by dilating the arterial resistance vessels. The most potent vasodilators, the dihydropyridines such as amlodipine and nifedipine, exhibit the greatest affinity to vascular smooth muscles and are thus the preferential agents for treating hypertension. Recent review, shows the CCBs have shown to prevent stoke and total cardiovascular syndromes when used as first-line for hypertension[9]. These drugs have been reported to be associated with the induction of infertility in the male gender via oligozoospermia[10].

Currently, a number of long-term pharmaceutical treatments could pose a clinical problem. Researchers have demonstrated a link between various antihypertensive medications and a decrease in male fertility[11,12]. Particularly, beta blockers and CCBs tend to have a negative effect on male fertility, leading to azoospermia and/or oligozoospermia in a number of cases. It has been shown in the mouse model that CCBs, such as amlodipine, can reduce testosterone, luteinizing hormone (LH), and follicular stimulating hormone (FSH), which in turn affects spermatogenesis and sperm parameters[13,12]. Antihypertensive drugs have a lot of side effects such as dry cough among others[14].

Herbal medicines are used for primary health care by roughly 75% to 80% of the world's population due to its superior compatibility with the human body, cheaper costs than modern pharmaceuticals and fewer side effects[15]. One of such substances that possess promising herbal therapeutic properties is Tiger nut (TN).

Tiger nut (*Cyperus Esculentus*) is a perennial plant that belongs to the sedge family (Cyperacea)[16]. In Nigeria, the Hausas call it “Aya”, Yorubas “imumu”, the Igbos “ofio”. TN is a tuber that is rich in nutrients including carbohydrates, essential amino acids and vitamins as well as other phytochemicals that possess beneficial antioxidant properties. They protect the body against aging and diseases like cancer and heart diseases[17]. TNM is good for the heart because it contains high amount of monounsaturated fats[18].Monounsaturated fat rich diets are associated with lower low-density lipoprotein (LDL) and higher high-density lipoprotein (HDL) cholesterol levels. They have a lower risk of having a heart attack, stroke and dying from heart disease[19,20]. TN contains a lot of minerals, oleic- acids and it also gives energy and due to this, it has been used for years as a healthy plant. TNM contains very high arginine content that is responsible for liberating the hormone that produces insulin, it also contains carbohydrates that have a base of sucrose and starch[21]. Tiger nut milk (TNM) has also been reported to have some preventive effects against cardiovascular diseases and cancer due to its vitamin E content which also plays a role in red blood cell formation and function[22]. Another vitamin present in TNM is vitamin C which serves as a good antioxidant, which supports iron absorption and assists the maintenance of vitamin E levels which is essential for tissue preservation and the immunological system[23]. The high vitamin B1 content in TNM helps in adjusting the central nervous system and it promotes the body's adaptation to stress[24]. The dietary fibre content in TN is also very high and it is very effective in the prevention and the treatment of a good number of diseases like coronary health disease, colon cancer, obesity, diabetes, just to mention a few[25]. The vitamin E present in tiger nut milk (TNM) promotes the delay of aging, the increase of skin elasticity and it also helps in relieving the appearance of wrinkles. It is also required for fertility in both males and females[26]. Despite the diverse potential of TN, it has remained an underutilized and neglected plant in the world[18]. It is therefore very necessary to make known the importance of this crop in order to propagate its development and improve its use in various parts of the world. This study was designed to investigate the ameliorative effect TNM on antihypertensive drugs induced infertility in male albino rats.

MATERIALS AND METHODS

Chemicals

Rat LH (luteinizing hormone) ELISA KIT obtained from ELK Biotechnology, located at 1312 17th Street #692 Denver, CO 80202 USA and Rat Testosterone, T BT-LAB ELISA Kit purchased from Bioassay Biotechnology Laboratory, located at 501 Changsheng S Rd, Nanhu Dist, jiaxing, zheijiang, China. Pyrogallol, distilled water, ammonium molybdate, trichloroacetic acid, hydrogen peroxide, EDTA, glutathione, sodium hydroxide, hydrochloric acid, acetone, TBARS, DTNB, sodium azide, potassium hydroxide, Amlodipine All chemicals and reagents were of analytical grade.

Preparation of tiger nut milk

TN was purchased from local vendors from the market and identified by a taxonomist. Bad nuts were separated from the good ones. The nuts were washed with distilled water and 200g of nuts was weighed using a weighing balance. Two hundred gram (200g) of nut was blended in 200mls of distilled water using a stainless-steel industrial blender. The milk was extracted from the blended nut using a sieve and the TNM was refrigerated and kept in a cool temperature.

Experimental design

Forty (40) male albino Wistar rats weighing between 200-240g were purchased from the College of Veterinary

Medicine, Federal University of Agriculture, Abeokuta (FUNAAB) for this study. The animals were acclimatized for two weeks before the commencement of the experiment and they were fed with standard rat chow and drinking water ad libitum. The animals were housed in small cages with good ventilation in the animal house of the Department of Chemical Sciences, Augustine University, Ilara-Epe, Lagos State. After the two weeks of acclimatization, all the experimental rats were randomly segregated into eight (8) groups consisting of four (5) rats in each group. Group 1: Distilled water; Group 2: Amlodipine (0.07mg/Kg body weight [B.W]); Group 3: Bisoprolol (0.07mg/Kg B.W); Group 4: Amlodipine + Bisoprolol (1:1, 0.07mg/Kg B.W); Group 5: Amlodipine + TNM; Group 6: Bisoprolol + TNM; Group 7: Amlodipine + Bisoprolol + TNM; Group 8: TNM alone (0.320ul/100g).

Sample Collection

Groups 2, 3 and 4 were exposed to hypertensive drugs for two weeks. Treatment with TNM commenced for another two weeks. The experimental animals were placed on an overnight fast, and they were sacrificed on the next day. The blood samples were collected via cardiac puncture into clean heparinized and Eppendorf tubes. The blood samples were centrifuged for 10 minutes at 3,500 rpm to obtain the plasma. The supernatants were then collected into well-labelled Eppendorf tubes and refrigerated until assayed. The livers, kidneys, testes and spleens of the rats were harvested, rinsed in normal saline, weighed and stored in the refrigerator at freezing temperature. The testes were selected at random and preserved in 10% formalin and sent out for biochemical analysis (Histopathology).

Biochemical Analysis

Determination of rat testosterone

The kit used for this assay is a Competitive ELISA kit and it is used for the quantification of Testosterone (T) in serum, plasma, cell culture supernatants, ascites, tissue homogenates and other biochemical fluids.

Superoxide Dismutase (SOD) Activity Assay

Superoxide dismutase (SOD) activity was determined according to the method described by Marklund[27] using a spectrophotometer at 420nm

Catalase Activity

The activity of catalase was determined spectrophotometrically at 405nm according to the method described by Shangari [28].

Assay of reduced Glutathione (GSH) Level

Glutathione in whole blood was determined using the spectrophotometric method described by Ellman[29] at 420nm within 20 minutes.

Determination of rat luteinizing hormone concentration

The levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone were measured by using enzyme- linked immunosorbent assay (ELISA) according to the methods described in Manafa *et al.*[30].

Statistical Analysis

Values were expressed as Mean Sstandard Error Mean (SEM). The level of homogeneity among the results of groups was tested using analysis of variance (ANOVA) $p<0.05$ was considered significant. Where heterogeneity occurred, the groups were separated using Duncan and Turkey's Multiple Range Test (DMRT). All analysis was done using Statistical Package for social sciences (SPSS) version1.7

RESULTS

Proximate composition of tiger nuts

Figure 1 shows the proximate composition of fresh tiger nuts contained in every 100g of the sample. Moisture content of the tiger nut tubers obtained was 42.40%, crude protein 8.51%, ash 1.18%, crude fat 17.00%, crude fibre 13.10% and carbohydrate 17.82%.

Effects of TNM on LH levels of rats induced anti-hypertensive drugs.

Figure 2 shows the effects of tiger nut milk on LH levels of rats induced anti- hypertensive drugs. All the group exposed to hypertensive drugs had a significant decrease ($p<0.05$) in LH level compared with control. Treatment with TNM increased the hormonal level.

Effects of TNM on testosterone levels of rats induced anti-hypertensive drugs

Figure 3 shows the effects of tiger nut milk on testosterone level of rats induces anti- hypertensive drug. From the graph, there was a significant reduction ($p<0.05$) in testosterone level in all the group when compared with the control and the group treated with tiger nut milk only.

Effects of TNM on plasma SOD activity of rats induced anti- hypertensive drugs

Figure 4 shows the effects of tiger nut milk on plasma SOD activity of rats induced anti – hypertensive drugs. From the graph, rats exposed to Amlodipine alone showed a significant increase in SOD activity compared with control. The synergistic administration of both antihypertensive drugs (Amlodipine and Bisoprolol) was shown to significantly increase SOD activity more than the mono-therapeutic effect. However, TNM treatment reduce the SOD activity, tending it towards the control level.

Effects of TNM SOD activity in testis of rats induced with anti- hypertensive drugs

In figure 5, group exposed to Amlodipine and bisoprolol showed a significant increase in SOD activity compared with control and the group administered TNM alone. Tiger nut milk was able to reduce the effect of amlodipine as seen in group 5

Effects of TNM on Catalase activity in plasma of rats induced with anti- hypertensive drugs

Figure 6 shows the effects of tiger nut milk on catalase activity in plasma of rats induced with anti – hypertensive drugs. From the graph, there was a significant increase ($p<0.05$) in CAT activity in group exposed to amlodipine

and amlodipine + bisoprolol alone as compared with control TNM treatment was able to reduce the effects caused by both hypertensive drugs.

Effects of TNM on Glutathione Peroxidase (GP_X) activity in plasma of rats induced with anti-hypertensive drugs

Figure 7 shows the effects of glutathione peroxidase activity in plasma of rats induced with anti- hypertensive drugs. From the graph, it shows that group administered with TNM alone showed a significant increase in GPx activity compared with control. Amlodipine and bisoprolol reduced the GPx activities in the experimental rats.

Effects of TNM on Glutathione Peroxidase (GP_X) activity in testis of rats induced with anti- hypertensive drugs

Figure 8 shows the effects of glutathione peroxidase activity in testis of rats induced with anti – hypertensive drugs. From the graph, it shows that there was a significant decrease in GPx activities in the testis in groups exposed to anti-hypertensive drugs. Treatment with TNM extract was able to increase the activities but not significant as compared with group treated with TNM alone and control.

Effects of TNM on Lipid peroxidase and peroxidation in plasma of rats induced with anti- hypertensive drugs

Figures 9 shows the effects of tigernut milk on lipid peroxidation in plasma of rats induced with hypertensive drugs. The graph shows that there was a significant increase in peroxidation in groups exposed to Amlodipine and bisoprolol compared to control. TNM treatment was able to slightly reduce the peroxidation.

Effects of TNM on lipid peroxidation in testis of rats induced with anti- hypertensive drugs

Figure 10 and 11 show the effects of tiger nut milk on lipid peroxidation in testis of rats induced with hypertensive drugs. The graph shows that there was a significant increase in peroxidation in all the groups exposed to antihypertensive drugs. Treatment with TNM reduced the lipid peroxidation but significant except in group exposed to Bisoprolol treated with TNM.

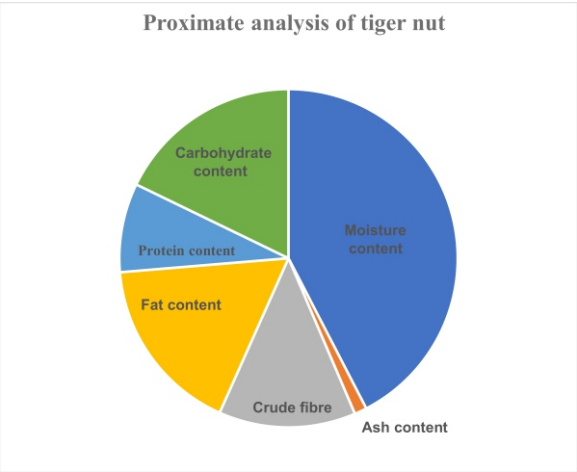

Figure 1: Shows the proximate analysis of tiger nut

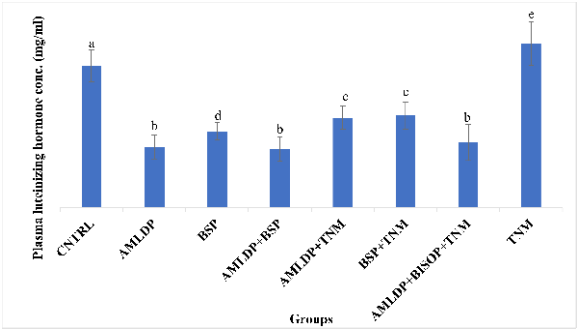

Figure 2: Plasma LH concentrations in rats treated with tiger nut milk after exposure to antihypertensive drugs. Values are presented as mean+/- S.E.M, n =8. Values with different superscripts along the same row are significantly different at $p<0.05$.

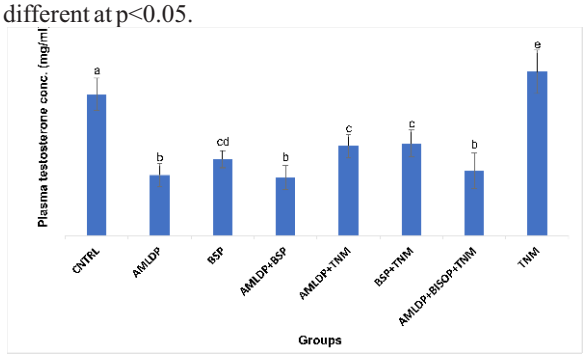

Figure 3: Plasma testosterone concentrations in rats treated with tiger nut milk after exposure to antihypertensive drugs. Values are presented as mean+/- S.E.M, n =8. Values with different superscripts along the same row are significantly different at $p<0.05$.

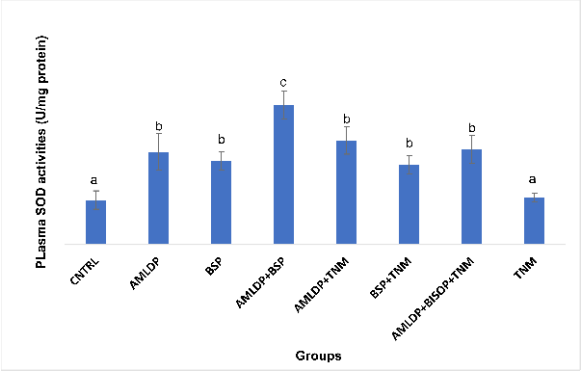

Figure 4: Effect of two weeks TNM treatment on SOD in plasma of male albino rats. Values are presented as mean+/- S.E.M, n =8. Values with different superscript along the same row are significantly different at $p<0.05$.

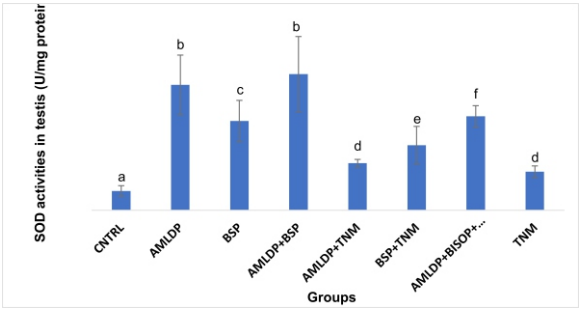

Figure 5: Effect of two weeks TNM treatment on SOD in testis of male albino rats. Values are presented as mean+/- S.E.M, n =8. Values with different superscript along the same row are significantly different at p<0.05.

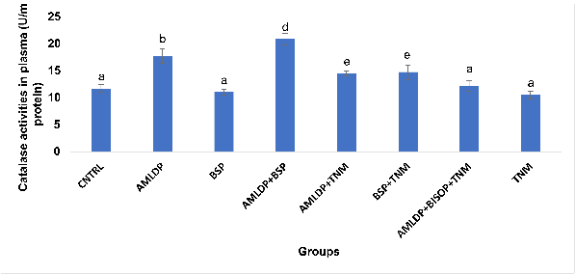

Figure 6: Effect of two weeks TNM treatment on CAT in the plasma of male albino rats. Values are presented as mean+/- S.E.M, n =8. Values with different superscripts along the same row are significantly different at p<0.05.

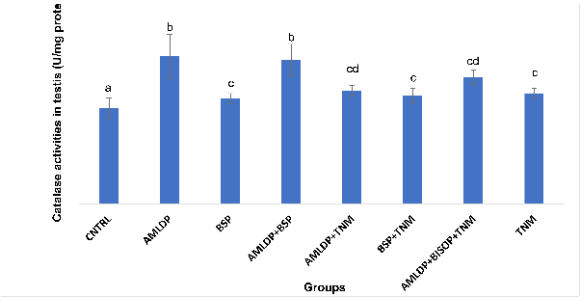

Figure 7: Effect of two weeks of TNM treatment on CAT in the testis of male albino rats. Values are presented as mean+/- S.E.M, n =8. Values with different superscripts along the same row are significantly different at p<0.05.

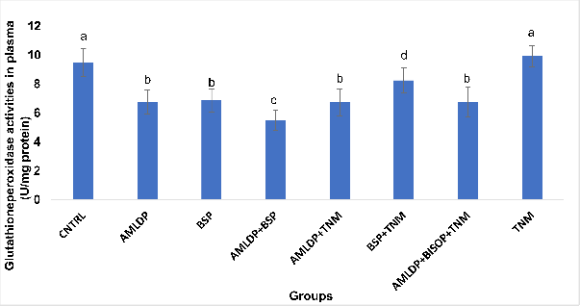

Figure 8: Effect of two weeks of TNM treatment on GPx in plasma of male albino rats.
Values are presented as mean+/- S.E.M, n =8. Values with different superscripts along the same row are significantly different at p<0.05.

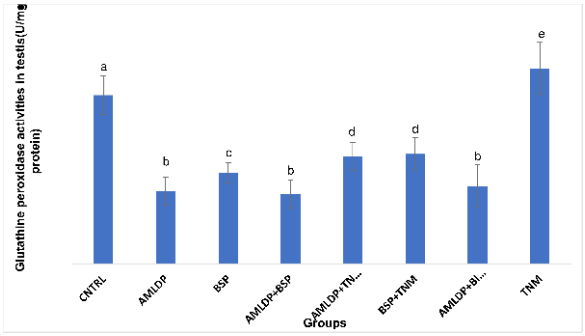

Figure 9: Effect of two weeks of TNM treatment on GPx in the testis of male albino rats. Values are presented as mean+/- S.E.M, n =8. Values with different superscripts along the same row are significantly different at p<0.05.

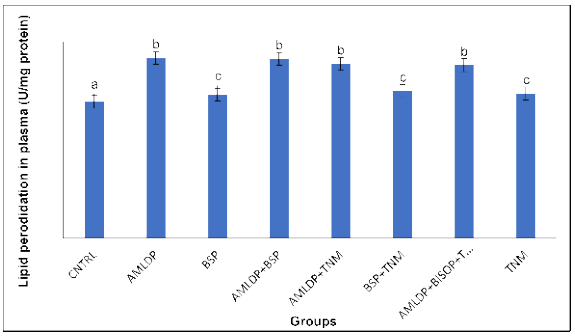

Figure 10: Effect of two weeks of TNM treatment on peroxidation of lipids in plasma of male albino rats. Values are presented as mean+/- S.E.M, n =8. Values with different superscripts along the same row are significantly different at p<0.05.

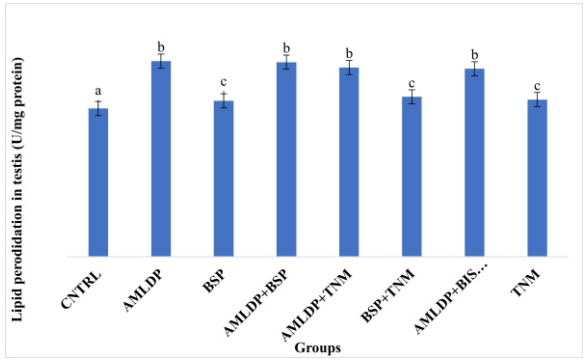

Figure 11: Effect of two weeks TNM treatment on Lipid Peroxidase in testis of male albino rats. Values are presented as mean+/- S.E.M, n =8. Values with different superscript along the same row are significantly different at p<0.05.

DISCUSSION

The outcome of the proximate composition of TN showed the various components in a decreasing order of moisture, carbohydrate, crude fat, crude fiber, crude protein, and ash contents. This implies that TN are high in moisture, carbohydrate, fat and fiber content[33].

This research shows that amlodipine causes a decrease in the levels of luteinizing hormone and testosterone in males Wistar rats. The reduction of these essential reproductive hormones in males suggests low libido and erectile dysfunction, leading to reduced spermatogenesis, hence causing oligozoospermia [11,34]. However, beta blockers' anti-hypertensive drugs have been reported to have adverse effects on spermatogenesis[35]. This study also corroborates the research carried out by Erem[36] with the suggestion that beta-adrenergic receptor blockers have adverse effects on spermatogenesis, specifically propranolol and carvedilol, which are non-selective.

TNM treatment was able to remediate the effects caused by antihypertensive drugs by slightly increasing the LH level by 48 % and 52 % compared with anti-hypertensive drugs alone. Luteinizing hormone is needed to aid spermatogenesis; however, its reduction could result in the induction of oligozoospermia. The elevation of LH with treatment with TNM alone suggests that the TN tuber possesses phytochemicals that have the potentials to elevate the levels of LH[37].

Testosterone, on the other hand, was significantly reduced by Amlodipine, and a very slight decrease was caused by Bisoprolol. The synergistic administration of these antihypertensive drugs also lowered the testosterone level significantly. The result shows that amlodipine could reduce the processes of spermatogenesis[38]. This antihypertensive drug, amlodipine, has shown its potential to cause the onset of oligozoospermia, thereby causing erectile dysfunction and decreased libido, which is a factor of infertility[39]. Lower testosterone means lesser sperm production, which in turn means a depreciation in the fertility of men. TNM was able to reverse the testosterone levels of the groups that were administered amlodipine and Amlod + Bisop. This treatment was able to cause a slight increase to the level of testosterone. High concentration of arginine present in TNM, which is very essential for spermatogenesis, could be responsible for its ameliorative effect on infertility caused by the use of antihypertensive drugs, specifically amlodipine[40]. The effect of TN on testosterone showed that there was a significant rise in testosterone levels following TNM administration to animals that had induced infertility. This finding on testosterone hormone is, however, consistent with other research findings [41,42,43,44]. The exact mechanism by which TN boosts testosterone levels is not entirely clear. However, it may be assumed that TNM may act directly on testicular cells, and not through the hypothalamus-pituitary axis. This speculated mechanism is possible[45] on the phytochemistry of TN that showed the presence of several components (quercetin, Vitamins E and C and the mineral Zinc) which may positively contribute to testosterone synthesis and as such, improve the reproductive function.

From the present research, we observed a significant increase ($p<0.05$) in SOD and CAT activities in the testis and plasma of all the rats with antihypertensive drugs, only when compared with the control group. The group administered TN shows a significant reduction in the activities of SOD and CAT. An elevated SOD and CAT activity may indicate that the body is trying to protect testicular cells from oxidative stress, which can cause damage to DNA and proteins in the cells. This can lead to infertility and other health issues. Oxidative stress is caused when free radicals are not properly eliminated from the body. SOD is an enzyme that helps to protect cells from damage caused by free radicals. SOD and CAT activities may increase to neutralize these harmful molecules. Results from previous investigations indicated that TN is essential for male reproductive health because it enhances male reproductive parameters and defends them from harm. This might be a result of the chemical and phytochemical makeup of TNM, but they also give tissues antioxidant activity[46,47,48].

Reduced glutathione activity at significant levels ($p<0.05$) was observed in rats that were administered antihypertensive drugs as compared to the control group. Low glutathione activity in plasma indicates that the body is not able to neutralize harmful oxidants and free radicals effectively, which can lead to oxidative stress and inflammation. This is caused by various factors such as poor nutrition, exposure to toxins or chronic diseases with the use of certain dugs. Low level of glutathione activity has been linked to infertility in some studies which correspond to our recent findings. Glutathione is an important antioxidant that helps to protect sperm cells from oxidative stress caused by free radicals. Low level of glutathione in the body could lead to decreased sperm motility, poor sperm quality and infertility. TNM has been used in the relief of diarrhea, dysentery, and indigestion since it contains numerous antioxidants, including vitamin E, Vitamin C, and Quercetin as well as minerals such as Zinc, potassium, and phosphorus. C. esculentus is known to boost sexual competence and also increase male fertility by increasing libido and sexual performance, as well as restore sexual abnormalities[44].

Lipid peroxidation increased significantly ($p<0.05$) in the plasma and testis of rats that were administered antihypertensive drugs as compared to the control group. Various researchers have also recorded increase in lipid peroxidation due to intake of antihypertensive drugs especially amlodipine[49,50,51,52,53]. Lipid peroxidation can lead to the damage of sperm cells and affect their motility and quality. High level of lipid peroxidation has also been linked to female infertility. Oxidative stress can damage oocytes and affect their quality which can lead to problems of fertilization and implantation. The mechanism by which the TNM was able to protect against oxidative stress in rat model may be due to the level of phenolic compounds present in the plant. A variety of polyphenols are known to have the ability to inhibit testosterone 5alpha reductase activity and so prevent the development of BPH[54].

CONCLUSION

This study justified that Amlodipine and Bisoprolol can causes infertility in men, reducing the synthesis of sperm and thus causing Oligozoospermia and Azoospermia in

males.

RECOMMENDATION

It is therefore clear that TNM possesses aphrodisiac properties to improve infertility in men. Men should be advised to take TNM.

DECLARATIONS

Consent for publication: All authors have read and agreed to the published version of the manuscript.

Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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