**CHAPTER ONE**

**INTRODUCTION**

* 1. **Background to the Study**

Benign prostatic hyperplasia (BPH) also known as benign prostatic hypertrophy have commonly been diagnosed among aged population with increasing prevalence (Chughatai ***et al,*** 2016). This disease causes lower urinary tract symptoms (LUTS) which may be categorized to be either obstructive or irritative symptoms. Obstructive symptoms such as prolonged micturition, feeling of incomplete bladder emptying, dribbling and irritative symptoms such as urgency, urge incontinence and nocturia (Herbert, 2005).So many studies have been carried out by researchers to mitigate the effect of this disease.

For example, Liqing ***et al,*** (2019) whose study was aimed at evaluating therapeutic effect against benign prostatic hyperplasia and the active constituents from  *Epilobium angustifolium L*, considered evaluating the in-vivo of anti-BPH by testosterone propionate (TP) induced BPH rats, after oral administration of n-butanol extract (BUE) of  *Epilobium angustifolium* at 100, 200 and 400 mg/kg body weight for 28 days. The prostate weight and index, plasma androgen level, histopathological alteration, oxidative and inflammatory related factors in prostate were assessed. They documented that BUE from *Epilobium angustifolium* showed a significant anti-BPH effect in vitro and further in vivo study demonstrated that BUE showed therapeutic effects against TP induced BPH in SD rats via down regulating of the androgen level, suppressing the expression of NF-KB and eventually alleviating the inflammatory responses and oxidative stress. They concluded that *Epilobium angustifolium* shows a therapeutic potential against BPH and its active compound may be used as candidate for BPH treatment.

Another Study which was aimed at investigating the effect of saw palmetto on benign prostate hyperplasia was carried out by Bent ***et al,*** (2006). They considered assigning 25 men over the age of 49 years who had moderate to severe symptoms of benign prostatic hyperplasia to one year of treatment with saw palmetto extract (160 mg twice a day) of placebo. Primary outcome measures were changes in the scores on the American Urological Association Symptom Index (AUASI) and the maximal urinary flow rate were assessed and Secondary outcome measures such as changes in prostate size, residual urinary volume after voiding, quality of life, laboratory values and rate of reported adverse effects were also assessed. It was documented that there was no significant difference between the saw palmetto and placebo groups in the change in AUASI score, prostate size, residual volume after voiding, quality of life, or serum prostate specific antigen levels during the one-year study. They concluded that saw palmetto did not improve symptoms of benign prostate hyperplasia.

Also,a study carried out by Zerafatjou ***et al,*** (2021) which was aimed at investigating the effect of Pumpkin seed oil (Cucurbita pepo) versus tamsulosin for benign prostatic hyperplasia symptom relief. They considered evaluating patients with BPH 50 years. In their method, Patients were also randomized into two groups. One group received 0.32 mg tamsulosin every night at bedtime and the other received 360 mg pumpkin seed oil twice a day. Patients age, height, weight and body mass index (BMI) were recorded. International prostate symptom score (IPSS) was filled out by the patients at baseline and then 1 month and 3 months after initiation of treatment. BPH associated quality of life (QoL), serum prostate specific antigen, prostate and post void residual volume, and maximum urine flow were also assessed at baseline and 3 months later. They documented that there was no significant decrease in IPSS and a significant improvement in QoL in both groups. They concluded that pumpkin seed oil relieved BPH symptoms with no side effects but was not as effective as tamsulosin.

Many of these scientists further recommends that more research should be carried out to find a better and more effective way of treating benign prostatic hyperplasia.

* 1. **Statement of the Problem**

Tony ***et al,*** (2016) in their study which was aimed at reviewing the Modern Minimally Invasive Surgical Treatments on benign prostatic hyperplasia (BPH), documented that BPH is a common problem among older men and is present in 8% of men aged 41 to 50, 40 to 50% of men aged 51 to 60, 70% of men aged 61 to 70, and more than 80% of men older than 80 years.

Anotherstudy which was aimed at reviewing the prevalence of benign prostatic hyperplasia and prostate cancer in Africans and Africans in the diaspora was carried out by Yeboah ***et al,*** (2016), Current literature was considered on the prevalence of benign prostatic hyperplasia, prostate cancer (PC) and benign prostatic hyperplasia co-existing with prostate cancer in Africans and other races and documented that BPH prevalence in Ghana is responsible for 60% acute retention of urine and 28.6% of haematuria. They also documented that worldwide prevalence of BPH varies from 20 – 62% in men over 50 years and this includes USA, UK, Japan and Ghana. Reports from South Africa indicate prevalence of over 50% in adult males of 60 years. BPH coexisting with prostate cancer reports from USA, UK, Japan and Ghana showed moderate association of BPH and prostate cancer. They concluded that recent evidence indicates a high prevalence of BPH and prostate cancer in Africans and men of African descent in diaspora, low prevalence of BPH and prostate cancer reported from some African countries is likely to be under reported and future prevalence studies both in the living and deceased are recommended to reveal the true prevalence of BPH and prostate cancer in Africans.

A documentationon the pathophysiology of BPH by McConnell, 1995 reported that thedevelopment of BPH requires the presence of testicular androgens during prostate development, aging and puberty. Another scientist stated that the levels of dihydrotestosterone (DHT) including androgen receptor remain high with aging, despite the fact that levels of testosterone are decreasing with age (Wilson ***et al,*** 1999). Andriole ***et al,*** (2004) reported that in the prostate, membrane bound enzymes steroid 5α-reductase converts testosterone into DHT and 90% of prostatic androgen is in the form of DHT.

Also the study by Tabe ***et al,*** (2019) which was aimed at investigating the phytochemistry, proximate analysis and GC – MS analysis of Essential Oils in Flower of Mistletoe Plant was carried out. Qualitative and quantitative analysis of the phytochemicals and nutritive value of the essential oils in mistletoe flower were investigated using standard methods and GC-MS. The qualitative results revealed that tannins, alkaloids, phenol and flavonoids were detected while terpenoid and saponin were not detected in the extract. The quantitative rats were tannin 0.84 ± 0.09 mg/100g, alkaloids 4.47 ± 0.24 mg/100g, phenol 8.46 ± 0.24 mg/100mg and flavonoid 1.71 ± 0.2 mg/100g. they concluded that the flowers have the potentials of promoting good health, reducing disease risk. It was documented by Trizah ***et al,*** (2013) that these chemical compositions of mistletoe exhibit antioxidative effects, which could be useful in the treatment of BPH.

**1.3Aim and Objectives of the Study**

**Aim**

The aim of this study was to examine the effects of hydromethanolic leaf extract of *Englerina gabonensis* on benign prostate hyperplasia in experimental animal models.

**Objectives**

The objectives of the study were:

1. To determine the effects of hydromethanolic leaf extract of *Englerina gabonensis* on body weights and prostate weights.
2. To determine the effects of hydromethanolic leaf extract of *Englerina gabonensis* on prostate specific antigen and testosterone.
3. To determine the effects of hydromethanolic leaf extract of *Englerina gabonensis* on oxidative stress parameters such as glutathione reductase (GSH), superoxide dismutase (SOD), catalase enzyme (CAT), malondialdehyde (MDA).
4. And to determine the effects of hydromethanolic leaf extract of *Englerina gabonensis* on prostate tissue histology.

**1.4 Significance of the Study**

Findings from the study will be beneficial to the society, considering the rise in the incidence of BPH from previous research. Greater demand is required from physicians or medical personnel for the discovery of more effective ways of controlling BPH. Thus, researchers that applied for newly recommended approach in the treatment of BPH will have a better insight from the result of this study. Health personnel’s will also be guided on the use of mistletoe extract in treatment of BPH. The investigation will uncover critical areas that many researchers could not explore. Thus, a new theory for the treatment of BPH will be established.

**1.5 Scope of the Study/Delimitation**

The scope of the study encompassed evaluation of Body weight and prostate weight, Testosterone and Prostate specific antigen, oxidative stress parameters such as Malondialdehyde, Catalase enzyme, Glutathione reductase, and Superoxide dismutase, Prostate tissue histology in benign prostatic hyperplasic induced rats, extract treated and normal rats.

**CHAPTER TWO**

**LITERATURE REVIEW**

**2.1 Theoretical/Conceptual Framework**

**2.1.1 *Englerina Gabonensis***

These are woody hemi-parasitic plant, commonly known as mistletoe, and can also be referred to as “Awuruse” in Aniocha North Local Government Area, Delta State Nigeria, which is where I hail from. This plant is made up of yellowish flowers, with white berries. They can be found growing on so many trees such as cocoa, pines, avocado, elms and oaks. They belong to plant family known as Loranthaceae (Burkill, 1985).

*Englerina gabonensis* are referred to as hemi-parasitic plants because of their dependence on their host plant for survival where they obtain their water and nutrients from. They can be connected to their host trees through a structure known hustorium.

In Nigeria, they can be found in so many crops such as citrus species, especially sweet orange (*Citrus sinensis*) and grape (*Citrus paradise*), and cocoa tree (*Theobroma cacao*) . All of these can be classified under the Loranthaceae family.

Often times, most of their host trees suffers poor growth, and productivity, which could eventually lead to death, especially during unfavorable weather conditions and if the host tree is small.

**2.1.2 Taxonomy classification**

Kingdom: Plantae-Plant

Division/Phylum: Magnoliophyta Flowering plant

Class: Dcot

Order. Santalales

Family. Loranthaceae

Genus. Englerina

Species. Englerina sp.

**2.1.3 Ethnopharmacological uses of *Englerina gabonensis***

The ethno pharmacology of *Englerina gabonensis* had for long been in the hands of herbal practitioners who claimed a general use to magical powers and counter sorcery, to treat mental conditions, sterility, and health problems associated with urino-genital system, rheumatism and pain. Teas made from this specie of mistletoe are believed to cure bone fracture and body pain (Kien’ichi ***et al,*** 2006).

**2.1.4 Pharmacological uses/Health benefits of *Englerina gabonensis***

**Cancer treatment**

The extract of *Englerina gabonensis* have been used for the cure of cancer. They contain triterpene acids or lectins which inhibits cell proliferation and also induced apoptosis. Research shows direct association of this extract with anti-cancer activity. It causes apoptosis in cancer cells (Catharines ***et al***, 2015).

**Cure for diabetes**

Study was conducted on rat model with diabetes induced with strepozotocin in order to evaluate effect of Mistletoe on an antioxidant system and lipid peroxidation. The research confirmed that mistletoe has the ability to reduce levels of blood glucose and stimulates production of insulin in pancreatic cells (Asuman ***et al,*** 2015).

**Relaxes muscles**

*Englerina gabonensis* has inhibitory effect on smooth muscles. The plant is effective in the management of cardiovascular disorders and hyperactive gut. Investigations shows a pharmacological base of smooth muscle relaxant effect of mistletoe in the gut and also vascular preparations. They have vasodilatory and antispasmodic effects. Current study shows the medicinal use of Mistletoe in diarrhea, colic and hypertension. Applying this herb as a poultice helps to provide relief from pain and also useful to aid painful and inflammatory health conditions such as gout and sciatica. It has good effect on muscles found in arteries, intestines and uterus. These properties help to calm muscles which assist in health conditions like dyspepsia (Taous ***et al,*** 2016).

**Cardiovascular health**

It provides cardiovascular effects ad Nitric oxide pathway upregulation has been suggested to be underlying mechanism. Nitric oxide has vital role in pathophysiology of heart failure. *Englerina gabonensis* helps to lower blood pressure that prevents pressure on cardiovascular system which prevents the chances of shrinkage of arteries that induce atherosclerosis. It reduces the chances of lethal conditions such as coronary heart disease and stroke (Anato, 2016).

**Fig2.1 *Englerina Gabonensis* (Mistletoe)**

**Source: Burkill, 1995**

**2.2 Emperical Review**

**2.2.1 Effect of *Englerina gabonensis* on body weight and prostate weight**

A study which was aimed at investigating the chemical composition of mistletoe extract and its effect on protein, lipid metabolism and antioxidant status of alloxan induced diabetic rats was done by Onunogbo ***et al,*** (2012). They considered using twenty male rats for the experiment and alloxan was used to induce diabetes to the animals at dosage of 100mg/kg body weight respectively. The rats were divided into 5 groups: Group 1 received normal rat feeds. Group 2 received the feeds given to group 1. Group 3 received 20% aqueous extract of mistletoe, group 4 received 40%of the extract while group 5 diabetic rats received 60% of the extract. Experiment lasted for 4 weeks. and animals were treated with mistletoe extract. Blood glucose, cholesterol, triglycerides, Catalase and urea level were the parameters assessed. Result from their findings showed a significant decrease in the parameters apart from body weight compared to the diabetic group. 40 and 60% of the aqueous extract significantly ameliorated the altered protein status of the rats compared with the diabetic group while none of the concentrations of the extracts administered significantly ameliorated the altered weight of the rats compared with extract possessed antioxidant activity as seen from the total phenolic content. Reducing power test and the ameliorating effect on the catalase activity of the diabetic rats. They concluded that Mistletoe extract has the potentials of ameliorating hyperglycemia, altered protein, lipid metabolism and the antioxidant status of diabetic rats.

A research work by Kavya ***et al,*** (2021) was aimed at investigating the effect of mistletoe on the growth and proliferation of prostate cancer cells. In order to evaluate the effect of mistletoe on cell proliferation and survival, Androgen receptor (AR) positive (LNCaP, LAPC4 and VCaP) and AR negative (PC3 and DU-145) cell lines with *Helixor M* was treated. The data indicates that LNCaP and LAPC4 cells were most sensitive to *Helixor M* while PC3, DU-145, and VCaP cells were relatively resistant to treatment. While AR protein levels and NF-kappa B subunits remained unaffected by treatment, there was an induction of apoptosis along with a concomitant decrease in LC3B, an autophagy marker, in all the sensitive prostate cancer cell lines. In search of pathways that may synergize with growth inhibition by *Helixor M,* CRISPR knockouts of TBK1 was utilized, a kinase involved in autophagy induction, in LNCaP cells and tested whether TBK1 knockouts are synthetically lethal with *Helixor M*. It was concluded that *Helixor M* induced increased apoptosis in TBK1 knockouts as compared to parental LNCaPcells, which could lead to decrease in prostate weight.

The effect of chronic consumption of crude mistletoe extract on serum enzymes, weight and cytoarchitecture of the liver was studied in normal and high salt fed rats by Ofem ***et al,*** (2008). Twenty four albino rats of the Wistar strain were randomized into four groups of 6 rats each. Group 1 took normal rat chow + drinking water. Group 2 took same as group 1 + mistletoe extract (150mg/kg body weight) orally once daily. Group 3 took high salt (8% NaCl) diet + 1% NaCl drinking water and group 4 was fed same as group 3 + mistletoe extract (150mg/kg of body weight) orally once daily. The regimens lasted for six weeks. Their results evealed reduction in body weight and enlargement of the liver in salt fed (untreated) group relative to other groups. The mean ALP level (363.08 + 22.59 I.U/L) in group 2 animals was significantly reduced (P<0.01) compared with control (476.83 + 17.14 I.U/L). Group 3 had a significantly higher (P<0.05) ALP level (596.12 + 34.83 I.U/L) compared with control, while the reduction in ALP level observed in group 4 animals (536.33 + 37.33 I.U/L) was not significantly different from control or salt fed groups. The ALT and AST levels were significantly higher in salt fed rats (55.50 + 3.78; P<0.05 and 103.67 + 0.76; P<0.001 respectively vs control). The reductions in mean ALT (38 + 5.61) and AST (83.33 + 4.01) observed in group 2 were not significantly different from control values (45.83 + 0.04 and 88.67 + 1.28 respectively). The salt + extract fed rats had reduced ALT and AST levels compared to salt fed rats (P<0.01). Photomicrograph of a section of the liver in high salt fed group shows marked necrotic condition, pyknosis, karyorrhexis, numerous but deranged sinusoids, with many pockets of lipid deposits similar to that of alcoholic syndrome, signifying degeneration of the hepatocytes. They concluded that salt loading increases serum levels of ALT, ALP and AST and leads to reduction in body weight and increase in liver weight in rats; Chronic mistletoe consumption tends to ameliorate these anomalies.

**2.2.2 Effect of *Englerina gabonensis* testosterone and prostate specific antigen**

A research work which was aimed at investigating the effect of consumption of mistletoe leaf extracton the concentration of serum sex hormones (follicle stimulating hormone (FSH) luteinizing hormone (LH), testosterone and prolactin) was carried out by Ofem ***et al,*** 2014.24 female rats were divided into 4 groups, (n=6). Group 1 received normal rat chow + drinking water, Group 2 extract treated-1, group 3, extra treated-2 and group 4, extracts treated-3. Received 150mg/kg, 300mg/kg and 450mg/kg respectively of Viscum album extract once daily. Feeding lasted for 4 weeks. Some groups were administered different dose of extract. The result from their findings showed that the serum concentrations of FSH, LH, testosterone and prolactin in control group were 0.95±0.09 µlU/mL, 1.21±0.20 µlU/mL, 6.78±0.29ng/mL and 1.86±0.09 ng/mL respectively. FSH levels was significantly there was a significant increase in serum level of FSH, LH and testosterone and a significant decrease in prolactin compared to the control group. They concluded that moderate and controlled doses of mistletoe increases FSH, LH and testosterone but decrease prolactin concentration which could enhance reproductive function in normal person and those with loss of reproductive function.

Blessing and Asika, (2016) in their study on effects of methanolic leaf extract of African Mistletoe (*Loranthus* micranthus) on male sexual function in streptozotocin induced diabetic wistar rats documented that the leaves of African mistletoes (Loranthus micranthus) have been shown in traditional African setting to improve sexual function in diabetic males but data on scientific proofs of this therapeutic action of these leaves is scanty hence this study. In this study, the effect of methanolic extract prepared from the leaves of L. micranthus on serum testosterone levels, sperm count and motility in diabetic male wistar rats was studied. In their method, animals were randomly divided into four (4) groups made up of six (6) rats each and diabetes was induced in the rats by the administration of streptozotocin (100 mg/kg) for 7 days. Group A served as the control (untreated diabetes), groups B and C were treated with 150 mg/kg and 300 mg/kg respectively of the extract while group D received the 100 mg/kg of the standard antidiabetic drug (chlorpropamide). The duration of substance administration was fourteen days. On the fifteenth day, all the animals were lightly anaesthetized with ether and their blood collected for testosterone analysis. The rats were further dissected and the caudal epididymis of each incised and seminal fluid collected for sperm count and motility tests. Results showed diabetes to decrease male sexual functions (group A) when compared with standard reference value. Also, significant increase (p<0.05) in the level of serum testosterone, sperm count and sperm motility which was dose depended was showed with the extract administration (groups B and C) compared with control (group A). Chlorpropamide treated rats (group D) also showed a significantly increased male sexual function compared with the control, however, mistletoe was more potent.

They concluded From the findings of this study, that leaf extract of African mistletoes be studied in detail so as to know its therapeutic dose for it possible use as a therapeutic agent in the treatment of male infertility secondary to testosterone/sperm abnormalities.

Another study by Falilat ***et al,*** (2019) which was aimed at examining the effects of aqueous extract of Viscum album (Linn.) leaf on some biochemical parameters and ovarian morphology of oestradiol valerate-induced polycystic ovarian syndrome (PCOS) rats was carried out. Female rats were assigned into group A – G, (n=10) each. Group A (Control) were administered 0.5 ml of distilled eater. Groups B, C, D, F and G were PCOS-induced with single intramuscular injection of oestradiol valerate, each group received 0.5 ml of distilled water, 2.4 mg/kg body weight of metformin, 10, 50, 100 and 200 mg/kg body weight of the extract for 30 days. Vaginal smear cytology, serum follicle stimulating hormone, luteinizing hormone, testosterone, progesterone and polycystic ovarian morphology were assessed. The result showed that aqueous extract of Viscum album leaf significantly (p<0.05) reversed PCOS related increased serum concentrations of follicle stimulating hormone and testosterone and decreased concentration of luteinizing hormone towards the control values. And concluded that aqueous extract of Viscum album leaf ameliorated some clinical, biochemical and ovarian features of polycystic ovarian syndrome rats. No work has yet been done on the effect of mistletoe on Prostate specific antigen.

**2.2.3 Effect of *Englerina gabonensis* on oxidative stress biomarkers (MDA, SOD, CAT, GSH)**

Study on the effect of mistletoe on inhibition of peroxidation in liver and kidney of rats was carried out by Zheng ***et al,*** (2016). The study was aimed at exploring the antioxidant property of mistletoe alkali (MA). Animals were divided into 4 groups (n=8). CCl4 treated group (1mL/kg) body weight), MA treated group (90 mg/kg), CCl4 + MA treated group and normal control group. Oxidative stress was induced using carbon tetrachloride (CCl4) and after 4 weeks of treatment, Malondialdehyde (MDA), Lipid peroxidation product (LPO) was measured in serum and homogenates of liver and kidney.The level of glutathione (GSH), and activities of glutathione reductase (GR), glutathione peroxidase (GSPx), superoxide dismutase (SOD), and Glutathione-S-transferase (GST) in the liver and kidney were determined. The result showed a significant increase in CCl4-treated group, the level of MDA in serum of liver and kidney compared to controls. The levels of GSH and enzyme activities of SOD, GSPx and GR in liver and kidney were significantly decreased in comparison with controls. In CCl4+MA-treated group, the changes in the levels of LPO in serum of liver and kidney were not statistically significant compared to controls. The levels of SOD, GSPx and GR in the liver and kidney were significantly increased in comparison with controls. They concluded that MA has a protective effect against CCl4 toxicity by inhibiting the oxidative damage and stimulating GST activities.

Another study by Kim ***et al,*** (2010) which was aimed at investigating the Protective effects of Korean mistletoe lectin (KML) on radical-induced oxidative stress was done. In the study, the radical scavenging effects and protective activities against oxidative stress of Korean mistletoe (Viscum album coloratum) lectin were investigated in vitro and with a cellular system using LLC-PK(1) renal epithelial cells. Oxidative stress was induced using sodium nitroprusside (SNP) and pyrogallol. The result under the LLC-PK cellular model, the cells showed declines in viability and increases in lipid peroxidation. He concluded that KML has protective activities against oxidative damage induced by free radicals.

Study aimed at investigating the effect of diertary supplementation of mistletoe extract (ME) on the growth performance, antioxidant and innate, immune responses of rainbow trout (Oncorhynchusmykiss) was carried out by Morteza ***et al,*** (2021). In the method used, Rainbow trout fingerlings were fed with diet supplemented with 0% (C), 0.5 (T1), 1.5 (T2), 2.5 (T3) and 4% (T4) mistletoe extract at different doses. At the end of the feeding trial, growth performance, serum antioxidant and innate immune responses and serum bactericidal activity against Aeromaonashydrophila were evaluated. Serum lysozyme, ACH50, total Ig, SOD, and bactericidal activity significantly increased in the ME fed fish with the highest value observed in the T3 treatment. The highest CAT and GPx values were recorded in T2 and T3 treatments. ME treatment significantly decreased serum MDA levels. Serum ALT activities were similar in the T2, T3 and T4 treatments and were significantly lower than those of T1 and control (C) treatments. Serum AST and ALP activities exhibited declines along with an increase in dietary ME levels in which the lowest activities were occurred in the T4 treatment. They concluded that dietary ME supplementation proved beneficial to rainbow trout as it stimulated its growth performance, innate immune and antioxidant systems, and promoted bactericidal activity.

A study carried out by Sakali ***et al,*** (2017) was aimed at investigating Protective Effect of Mistletoe Extract on Methotrexate – induced Nephrotoxicity in Rats. They considered using 32 female rats. The rats were divided into 4 groups: control group, HLX group (5mg/kg body weight, days 1-10, intraperitoneally (i.p)), MTX group (10mg/kg bw. Days 7,8 and 9, i.p. + 5mg/kg bw, days 1-10, i.p.). At the end of the experiment, glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), nitric oxide (NO), and myeloperoxidase (MPO) levels were measured and a histopathological analysis and comet assay were carried out. The result showed that MTX induced renal oxidative stress and nephrotoxicity in the rats. Pretreatment with HLX significantly improved the renal GSH-Px and SOD activities in the MTX + HLX was not significant. The histochemical evaluation revealed that HLX provided significant improvement in the MTX-induced renal degenerative changes, including tubule distension, interstitial inflammation, perirenal inflammation, glomerular congestion, glomerular degeneration and parenchymal hemorrhage, in the MTX + HLX group compared to the MTX- administered group. They concluded that HLX administration reduced the MTX-induced acute oxidative stress and nephrotoxicity in rats through its antioxidant and anti-inflammatory properties.

Shin ***et al,*** (2006) carried out a study to explore the antioxidant and free radical scavenger properties of mistletoe alkali (MA). The antioxidant effect of mistletoe alkali on the oxidative stress induced by carbon tetrachloride (CCl4) in rats was investigated. The rats were divided into four groups (n = 8): CCl4-treated group (1 mL/kg body weight), MA -treated group (90 mg/kg), CCl4+MA-treated group and normal control group. After 4 wk of treatment, the level of malondialdehyde (MDA), a lipid peroxidation product (LPO) was measured in serum and homogenates of liver and kidney. Also, the level of glutathione (GSH), and activities of glutathione reductase (GR), glutathione peroxidase (GSPx), superoxide dismutase (SOD), and glutathione-S-transferase (GST) in liver and kidney were determined. Scavenging effects on hydroxyl free radicals produced in vitro by Fenton reaction were studied by ESR methods using 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) as a spin trap reagent and H2O2/UV as the OH. Source. Urinary 8-hydroxydeoxyguanosine (8-OHdG) was determined by competitive ELISA.

The results showed that In CCl4-treated group, the level of LPO in serum of liver and kidney was significantly increased compared to controls. The levels of GSH and enzyme activities of SOD, GSPx and GR in liver and kidney were significantly decreased in comparison with controls. In CCl4+MA-treated group, the changes in the levels of LPO in serum of liver and kidney were not statistically significant compared to controls. The levels of SOD, GSPx and GR in liver and kidney were significantly increased in comparison with controls. There was a significant difference in urinary excretion of 8-OHdG between the CCl4-treated and MA-treated groups. They concluded that oxidative stress may be a major mechanism for the toxicity of CCl4. MA has a protective effect against CCl4 toxicity by inhibiting the oxidative damage and stimulating GST activities. And recommended that clinical application of MA should be considered in cases with carbon tetrachloride-induced injury

Afolabi ***et al,*** (2016) in their study on Antioxidant activity and protective effects of cocoa and kola nut mistletoe (Globimetula cupulata) against ischemia/reperfusion injury in Langendorff-perfused rat hearts documented that against cardiomyocyte damage following ischemia/reperfusion (I/R) injury is highly desirable in patients with ischemic heart disease. Hydromethanol extracts of Globimetula cupulata (mistletoe) growing on cocoa (CGCE) and kola nut (KGCE) trees were assessed for antioxidant content and cardioprotective potential against I/R. Graded concentrations (1–50 μg/mL) of CGCE or KGCE were tested on Langendorff-perfused rat hearts to evaluate the effects on the flow rate, heart rate, and force of cardiac contraction, while another set of hearts were subjected to biochemical analyses. Both extracts showed good antioxidant content and activity, but KGCE (EC50: 24.8±1.8 μg/mL) showed higher hydroxyl radical scavenging activity than CGCE (70.2±4.5 μg/mL). Both extracts at 3 μg/mL reversed (p < 0.001) membrane peroxidation and the significant decrease in nitrite level, coronary flow rate, and superoxide dismutase and catalase activity caused by the I/R cycle. They concluded that G. cupulata protects against ischemia–reperfusion injury in rat hearts via augmenting endogenous antioxidants and significant restoration of altered hemodynamic parameters.

**2.2.4 Effect of *Englerina gabonensis*on the histology of Prostate cells**

Study by Kavya ***et al,*** (2021) which was aimed at investigating the effect of mistletoe on the growth and proliferation of prostate cancer cells was done. In order to evaluate the effect of mistletoe on cell proliferation and survival, Androgen receptor (AR) positive (LNCaP, LAPC4 and VCaP) and AR negative (PC3 and DU-145) cell lines with *Helixor M* was treated. The data indicates that LNCaP and LAPC4 cells were most sensitive to *Helixor M* while PC3, DU-145, and VCaP cells were relatively resistant to treatment. While AR protein levels and NF-kappaB subunits remained unaffected by treatment, there was an induction of apoptosis along with a concomitant decrease in LC3B, an autophagy marker, in all the sensitive prostate cancer cell lines. In search of pathways that may synergize with growth inhibition by Helixor M, CRISPR knockouts of TBK1 was utilized, a kinase involved in autophagy induction, in LNCaP cells and tested whether TBK1 knockouts are synthetically lethal with *Helixor M*. It was concluded that *Helixor M* induced increased apoptosis in TBK1 knockouts as compared to parental LNCaP cells.

Catherina ***et al,*** (2015), in their study on A Natural Combination Extract of Viscum album L. Containing Both Triterpene Acids and Lectins Is Highly Effective against AML In Vivo documented that Viscum album L. extracts are widely used in complementary cancer medicine. Hydrophobic triterpene acids also possess anti-cancer properties, but due to their low solubility they do not occur in significant amounts in aqueous extracts. Using cyclodextrins they solubilised mistletoe triterpenes (mainly oleanolic acid) and investigated the effect of a mistletoe whole plant extract on human acute myeloid leukaemia cells in vitro, ex vivo and in vivo. Single Viscum album L. extracts containing only solubilised triterpene acids (TT) or lectins (viscum) inhibited cell proliferation and induced apoptosis in a dose-dependent manner in vitro and ex vivo. The combination of viscum and TT extracts (viscumTT) enhanced the induction of apoptosis synergistically. The experiments demonstrated that all three extracts are able to induce apoptosis via caspase-8 and -9 dependent pathways with down-regulation of members of the inhibitor of apoptosis and Bcl-2 families of proteins. Finally, the acute myeloid leukaemia mouse model experiment confirmed the therapeutic effectiveness of viscumTT-treatment resulting in significant tumour weight reduction, comparable to the effect in cytarabine-treated mice. They concluded that the combination viscumTT may have a potential therapeutic value for the treatment AML

**2.2.5 Effect of *Englerina gabonensis* on Biochemical Parameters (SOD, MDA, GSH, CAT) on the Pancreases, Liver, Kidney, Heart and Brain**

Study on the effect of *Phragmanthera Incana* (Schum). Harvested from Cocoa (*Theobroma Cacao*) and Kolanut (Cola Nitida) Trees on Fe2+ induced Lipid Oxidative Stress in Some Rat Tissues – In Vitro was carried out by Ogunmefun ***et al,*** (2015). The study was aimed at investigating the inhibitory effect of methanolic extract of *Phragmanthera incana* leaves, a mistletoe species harvested from Cocoa (Theobroma cacao) and Kolanut (Cola nitida) on FeSO4 induced lipid peroxidation in rat pancreas, liver, kidney, heart and brain in vitro. Extract was prepared with 90% methanol, subsequently, the antioxidant properties and inhibitory effect of the extract on Fe2+ induced lipid peroxidation in some rat tissues were determined invitro. Incubation of the different rat tissues homogenate in the presence of Fe caused a significant increase in the malondialdehyde (MDA) contents of the tissues. The methanolic extract of *Phragmanthera incana* leaves harvested from both Cocoa and Kolanut trees caused a significant decrease in MDA contents of all the tissues tested in a dose dependent manner. The extract of *Phragmanthera incana* leaves harvested from kolanut trees had a better inhibitory effect on Fe2+- induced lipid peroxidation in the rat tissues homogenates than that of *Phragmanthera incana* leaves harvested from cocoa trees. They documented that the higher inhibitory effect could be attributed to its significantly higher antioxidant properties as typified by their phenolic content. They concluded that oxidative stress associated with diabetes and its other complications could be potentially managed by harvesting *Phragmanthera incana* leaves as cheap neutraceuticals.

**2.2.6 Phytochemical compositions of *Englerina gabonensis***

A study carried out by Tabe ***et al,*** (2019) which was aimed at investigating the phytochemistry, proximate analysis and GC – MS analysis of Essential Oils in Flower of Mistletoe Plant, Quantitative analysis of the phytochemicals and nutritive value of the essential oils in mistletoe flower were investigated using standard methods and GC-MS. The qualitative results revealed that tannins, alkaloids, phenol and flavonoids were detected while terpenoid and saponin were not detected in the extract. The quantitative rats were tannin 0.84 ± 0.09 mg/100g, alkaloids 4.47 ± 0.24 mg/100g, phenol 8.46 ± 0.24 mg/100mg and flavonoid 1.71 ± 0.2 mg/100g. they concluded that the flowers have the potentials of promoting good health, reduce disease risk.

***Tannins***

A study aimed at reviewing applications and possibilities of tannins extraction processes by Atanu ***et al,*** (2020) was carried out. In his report, It was documented that tannins are found in most of the species throughout the plant kingdom. He also documented that their function is to protect the plant against predation and might help in regulating the plant growth. Also he stated that there are two major groups of tannins which are hydrolysable and condensed tannins. Also it was reported that tannins are being used as important effective chemicals for the tanning of animal hides in the leather processing industry since the beginning of the industry. Tannins have been used as mineral absorption and protein precipitation purposes since 1960s. they are also used for iron gall ink production, adhesive production in wood based industry, anti-corrosive chemical production, uranium recovering chemical form seawater and removal if mercury and methylmercury from solution. They documented that tannins are considered as bioactive compound in nutrition science. It was also documented that the application of tannins as medicine is another new dimension in medical science.

Another study which was aimed at reviewing the effect of Tannins in Human Health by King-Thom Chung ***et al,*** (1998) was done. It was documented that tannins are water soluble polyphenols that are present in many plant foods. It was reported that they are responsible for decrease in food intake, growth rate, feed efficiency, net metabolizable energy, and protein digestibility in experimental animals. Foods rich in tannins have been considered to have low nutritional value. They documented that incidence of certain cancers like esophageal cancer have been found to be related to tannins-rich food consumption such as betel nuts and herbal teas, which suggests that tannins might be carcinogenic. Other reports indicated that the carcinogenic activity of tannins might be related to components associated with tannins rather than tannins themselves. Many reports indicated negative association between tea consumption and incidences of cancers. Tea polyphenols and many tannin components were suggested to be anticarcinogenic. Many tannin molecules have been shown to reduce the mutagenic activity of a number of mutagens. They reported that the anti-carcinogenic and anti-mutagenic potentials of tannins may be relating to their anti-oxidative property which is important in protecting cellular oxidative damage including lipid peroxidation. Their antimicrobial properties are associated with the hydrolysis of ester linkage between gallic acid and polyols hydrolyzed after ripening of many edible fruits. Tannins in these fruits serves as natural defense mechanism against microbial infections. They documented that the antimicrobial property of tannic acid can be used in food processing to increase the shelf life of certain foods such as catfish fillets. Tannins have also been reported to exert other physiological effects such as accelerate blood clotting, reduce blood pressure, decrease the serum lipid level, produce liver necrosis and modulate immunoresponses.

***Alkaloids***

A study aimed at reviewing the therapeutic effect of alkaloids by Roy  ***et al,*** (2017)was done. It was documented that alkaloids are the important secondary metabolites that are known to possess therapeutic properties. The compound on the basis of their biosynthetic precursor and heterocyclic ring system, have been classified into various categories which are indole, piperidine, purine, tropane, pyrrolizidine, imidazole, quinolozidine, isoquinoline and pyrrolidine alkaloids. They documented that alkaloids are able to prevent the onset of various degenerative diseases by free radical scavenging or binding with the oxidative reaction catalyst.

Another study by Badri ***et al,*** (2019) was aimed at reviewing the pharmacological activities of alkaloids. They reported that these chemicals and biomolecules are very complex. They documented that alkaloids are compounds of a very diverse class of secondary plant metabolites, alkaloids such as anticholinergics, antitumor, diuretic, antiviral, antihypertensive, antiulcer, analgesic and anti-inflammatory have been linked to the extensive list of biological activities.

***Phenols***

A study by Oluwaseun ***et al,*** (2021) aimed at reviewing extraction of phenolic compounds reported that phenolic compounds are parts of secondary metabolites mostly found in plant species with enormous structural diversities. They can exist as glycosides or aglycones; matrix or free-bound compounds and comprising mostly polymerized or monomer structures.

Study aimed at reviewing the Chemopreventive Properties of Fruit Phenolic Compounds and Their Possible Mode of Actions by Vasantha ***et al,*** (2014) was done. It was documented that Fruit phenolics such as flavonoids, chalcones, stilbenoids, lignans, and phenolic acids possess antioxidative and antiproliferative effects which contribute to their chemopreventive or chemoprotective activity. This review reported that theAntioxidant properties of fruit phenolics regulate oxidation reactions by their abilities to counteract, reduce, and repair cellular damage resulting from oxidative stress within the body. They also documented that phenols exert antiproliferative effects such as regulation of various transcription and growth factors, subcellular signaling pathways of cancer cell proliferation, xenobiotic metabolizing enzymes, apoptosis, and tumor angiogenesis.

***Flavonoid***

Panche ***et al,*** (2016) study which was aimed at reviewing the potentials of Flavonoids, documented thatFlavonoids are group of natural substances with variable phenolic structures, are found in fruits, vegetables, grains, bark, roots, stems, flowers, tea and wine. They reported that Flavonoids are considered as an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal and cosmetic applications which can be attributed to their anti-oxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties coupled with their capacity to modulate key cellular enzyme function. Also stated that research on flavonoids received an added impulse with the discovery of the low cardiovascular mortality rate and also prevention of CHD.

**2.2.7 Lethal dose of *Englerina gabonensis***

Research carried out by Eno ***et al,*** (2000) was aimed at investigating the effect of a Nigerian specie of Viscumalbum leaf extract on blood pressure of normotensive and Doca-induced hypertensive rats. Acute toxicity studies showed that the crude extract had an LD50 value of 417.5 mg/kg. In their method, Male white albino mice (20-25g) were randomly assigned to 7 groups of 10 Animals per group. Each group was injected Intraperitoneally with one of the following Doses: 50, 100, 200, 400, 800 or 1600mg/kg of The crude extract. The control group was Injected with isotonic saline. The maximum Volume given to all groups was 0.5ml. The Groups were returned to their home cages, and Provided with food and water ad libitum. After 24 hr., the mortality in each cage was assessed. The percentages mortalities were converted to Probit units (probability unit) using a standard Probit table (13,14) and plotted against the Log10 of the dose of the extract. Regression Lines were fitted by the least squares method and confidence limits for the LD50 values were calculated by the method of Litchfield and Wilcoxon (1949).

**2.2.8 Benign Prostatic Hyperplasia**

A study by Chughatai ***et al,*** (2016) aimed at reviewing Benign prostate hyperplasia, documented that benign prostatic hyperplasia (BPH), causes lower urinary tract symptoms (LUTS). The disease is a common diagnosis among the ageing male population with increasing prevalence. Many risks factors, both modifiable and non-modifiable, can increase the risk of development and progression of BPH and LUTS. The symptoms can be obstructive (resulting in urinary hesitancy, weak stream, straining or prolonged voiding) or irritative (resulting in increased urinary frequency and urgency, nocturia, urge incontinence and reduced voiding volumes), or can affect the patient after micturition (for example, postvoid dribble or incomplete emptying). They reported that BPH occurs when both stromal and epithelial cells of the prostate in the transitional zone proliferate by processes that are thought to be influenced by inflammation and sex hormones, causing prostate enlargement.

**2.2.9 Risk factors of Benign Prostatic Hyperplasia**

Study by Kellogg ***et al,*** (2007) aimed at reviewing Modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptom was carried out. They reported that Benign prostatic hyperplasia is generally not regarded as a preventable disease. Accumulating evidence suggests that modifiable factors may influence the risk of benign prostatic hyperplasia and lower urinary tract symptoms. A structured, comprehensive literature review was done to identify modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptoms among observational studies of older men.

In their result, outcome measures used to define benign prostatic hyperplasia in clinical studies include histological analysis of prostate tissue, radio-graphically determined prostate enlargement, acute urinary retention, decreased urinary flow rate, pressure flow studies consistent with bladder outlet obstruction, history of benign prostatic hyperplasia surgery, physician diagnosed benign prostatic hyperplasia and American Urological Association symptom score or International Prostate Symptom Score. They documented that factors that potentially increase the risk of benign prostatic hyperplasia and lower urinary tract symptoms include obesity and diabetes. Factors that potentially decrease the risk include increased physical activity and moderate alcohol consumption. Other candidate factors for which clear risk patterns have not yet emerged are dyslipidemia, hypertension, smoking, diet and environment.

They concluded that diabetes, physical activity and alcohol intake may substantially influence the risk of benign prostatic hyperplasia and lower urinary tract symptoms in older men.

**2.3.0 Pathophysiology of Benign Prostatic Hyperplasia**

A study which was aimed at reviewing the pathology of benign prostatic hyperplasia by Roehrborn ***et al,*** (2008) was carried out. It was reported from that study thatthe development of BPH, androgenic hormones testosterones and dihydrotestosterone play at least a permissive and important role. Growth factors and other hormones including estrogens may also play a role.

It was documented that BPH is characterized by an increased number of epithelial and stromal cells in the periurethral area of the prostate. It was suggested that the observed increase in cell number may be because of epithelial and stromal proliferation or to impaired programmed cell death or apoptosis leading to cellular accumulation.

In the prostate, the nuclear membrane bound enzyme steroid 5α-reductase converts testosterone hormone into dihydrotestosterone (DHT). 90% of total prostatic androgen is in the form of DHT. Inside the cell, both testosterone and DHT bind to the same high affinity androgen receptor protein. The hormone receptor then binds to specific DNA binding sites in the nucleus, which results in increased transcription of androgen dependent genes and ultimately stimulation of the protein synthesis. In addition to these direct effects many growth factors and their receptors are regulated by androgens. Thus, the action of testosterone and DHT in the prostate is mediated indirectly through autocrine and paracrine pathways. Interaction between growth factors and steroid hormones may alter the balance of cell proliferation versus cell death to produce BPH.

**2.3.1 Medical and plant extract therapy for Benign Prostatic Hyperplasia**

***Medical therapy***

A research work carried out by Brandon ***et al,*** (2015) which was aimed at reviewing the highlights on the current state of the art with respect to medical therapy for lower urinary tract symptoms secondary to benign prostatic hyperplasia. It was documented that alpha blockers are considered first line when treating BPH-LUTS in men with small prostates and 5-alpha reductase inhibitors are recommended in men with large symptomatic prostates. While phosphodiesterase-5 inhibitors are the mainstay of erectile dysfunction therapy, they also play a role in treating BPH-LUTS. They documented that combination therapies can be used to provide short term symptom relief with long term disease management. They concluded that medical therapy remains the main treatment option for men with BPH-LUTS.

***Plant extracts therapy***

Liqing ***et al,*** (2019) whose study was aimed at evaluating therapeutic effect against benign prostatic hyperplasia and the active constituents from *Epilobium angustifolium L,* considered evaluating the in-vivo of anti-BPH by testosterone propionate (TP) induced BPH rats, after oral administration of n-butanol extract (BUE) of *Epilobium angustifolium* at 100, 200 and 400 mg/kg body weight for 28 days. The prostate weight and index, plasma androgen level, histopathological alteration, oxidative and inflammatory related factors in prostate were assessed. They documented that BUE from *Epilobium angustifolium* showed a significant anti-BPH effect in vitro and further in vivo study demonstrated that BUE showed therapeutic effects against TP induced BPH in SD rats via down regulating of the androgen level, suppressing the expression of NF-KB and eventually alleviating the inflammatory responses and oxidative stress. They concluded that *epilobium angustifolium* shows a therapeutic potential against BPH and its active compound may be used as candidate for BPH treatment.

Study aimed at investigating the effect of saw palmetto on benign prostate hyperplasia was carried out by Bent ***et al,*** (2006). They considered assigning 25 men over the age of 49 years who had moderate to severe symptoms of benign prostatic hyperplasia to one year of treatment with saw palmetto extract (160 mg twice a day) of placebo. Primary outcome measures were changes in the scores on the American Urological Association Symptom Index (AUASI) and the maximal urinary flow rate were assessed and Secondary outcome measures such as changes in prostate size, residual urinary volume after voiding, quality of life, laboratory values and rate of reported adverse effects were also assessed. It was documented that there was no significant difference between the saw palmetto and placebo groups in the change in AUASI score, prostate size, residual volume after voiding, quality of life, or serum prostate specific antigen levels during the one-year study. They concluded that saw palmetto did not improve symptoms of benign prostate hyperplasia.

Zerafatjou ***et al,*** (2021) in their study which was aimed at investigating the effect of Pumpkin seed oil (Cucurbita pepo) versus tamsulosin for benign prostatic hyperplasia symptom relief: a single blind randomized clinical trial, considered evaluating patients with BPH 50 years. In their method, Patients were also randomized into two groups. One group received 0.32 mg tamsulosin every night at bedtime and the other received 360 mg pumpkin seed oil twice a day. Patients age, height, weight and body mass index (BMI) were recorded. International prostate symptom score (IPSS) was filled out by the patients at baseline and then 1 month and 3 months after initiation of treatment. BPH associated quality of life (QoL), serum prostate specific antigen, prostate and post void residual volume, and maximum urine flow were also assessed at baseline and 3 months later. They documented that there was no significant decrease in IPSS and a significant improvement in QoL in both groups. They concluded that pumpkin seed oil relieved BPH symptoms with no side effects but was not as effective as tamsulosin.

Study aimed at investigating the effect of Pygeumafricanum on benign prostatic hyperplasia was done by Timothy ***et al,*** (1998). They considered using men with symptomatic BPH. Comparison of preparations of *Pygeum africanum* with placebo with a treatment duration of at least 30 days was done. Urologic symptom scores (Boyarsky, American Urologic Association Score, International Prostate Symptom Score:IPSS), mean urine flow (MUF), residual urine volume; changes in prostate size, urinary frequency, nocturia, quality of life score (QoL) and overall physician/patient health was assessed. They documented that of the 13 trials of *Pygeum africanum* versus placebo identified, 12 reported a beneficial effect on at least one measure of effectiveness; overall symptoms, nocturia, peak urine flow or residual volume. None of the trials showed an effect of *Pygeum africanum* worse than placebo or active control. They concluded that *Pygeum africanum* is effective in men with symptomatic benign prostatic hyperplasia.

**CHAPTER THREE**

**MATERIALS AND METHODS**

**3.0 COLLECTION OF PLANT MATERIALS**

The 150kg of fresh Leaves of *England Gabonensis* was obtained from Khana Local Government in Port Harcourt, River State Nigeria and authenticated with hebarium number UPH/P/278 in the department of Plant Science and Biotechnology, Faculty of Science, University of Port Harcourt, Nigeria.

**3.1 PREPARATION OF PLANT MATERIAL AND EXTRACTION**

Leaves were washed to remove dirt, and dried using ultraviolent light. The plant was later grinded into powder form using a machine.

**METHOD OF EXTRACTION OF PLANT MATERIALS**

This was done using Maceration Method. Active ingredients using Hydromethanolic solvent (30:70) ratio (H20: Methanol). The crushed plant samples (150kg) were stocked in aspirator jar. Solvent mixture was prepared by diluting 70ml of methanol with 30ml of water. Above 9liters of the mixture was poured into the aspirator jar and the mixture shaken for 30 minutes and was left stand for 24hours. Extra was running off through the aspirator jar tap attached at the bottom. The concentration of the Extract was obtained by diluting the solvent through simple distillation process. Residents were concentrated by vaporizing in an oven at 100°C to remove traces of methadone and water.

The extra finally weighed 56g.

**PREPARATION OF DRUGS**

**Goup3**

240.29g = 300mg/kg *Englerina Gabonensis*

1g of rat = 300/1000 = 0.3mg

240.29g = 240.29 x 0.3 = 72.09mg of *Englerina Gabonensis* per ml

8rats x 10x 72.09mg =5,766mg/ml

5.8g per 80ml

4ml of D.M.S.O and 76ml of distilled water (80ml)

**Group4**

253.29g = 150mg/kg *England Gabonensis*

1g of rat = 150/1000 = 0.25mg

253.29g = 253.29 x 0.25 = 37.99mg of *Englerina Gabonensis* per ml

8rats x 10 x37.99mg = 3,039mg/mL

3.0g per 80ml

2.5ml D.M.S.O and 77.5ml of distilled water (80ml)

**Group5**

262.71g = 300mg/kg *England Gabonensis*

1g of rat = 300/1000 = 0.3mg

262.71g = 262.71x 0.3 = 78.81mg of *Englerina Gabonensis* per mL

8rats x 10 x 78.81mg = 6,305mg/mL

6.3g per 80ml

3ml D.M.S.O and 77ml of distilled water (80ml)

**Group6**

**Finasteride**

272.17g = 5mg

70kg man = 70,000g

1g of rat = 5/70,000 = 0.000071mg

272.17g = 272.17 x 0.000071 = 0.019mg of Finasterideper ml

**Group2**

**Testosterone**

205g = 25mgTestosterone

70kg man = 70,000g

1g of rat = 25/70,000 = 0.00036mg

205g = 205x 0.00036 = 0.074mg of Testosterone per ml

If 200g = 0.32mL (Mbaka ***et al,*** 2017)

205g = X

X = 205 x 0.32/200 = 0.32mL

Rats of 205g received 0.32mL of Testosterone

**Estradiol**

205g = 10mg Estradiol

70kg man = 70,000g

1g of rat = 10/70,000 = 0.00014mg

205g = 205 x 0.00014 = 0.029g of Estradiol per ml

If 200g = 0.2mL (Mbaka ***et al,*** 2017)

205g = X

X = 205 x 0.2/200 = 0.2mL

Rats of 205g received 0.2mL of Estradiol

**Group4**

**Testosterone**

193.14g = 25mg Testosterone

70kg man = 70,000g

1g of rat = 25/70,000 = 0.00036mg

193.14g = 193.14g x 0.00036 = 0.070mg of Testosterone per ml

If 200g = 0.32mL (Mbaka ***et al,*** 2017)

193.14g = X

X = 193.14 x 0.32/200 = 0.32mL

Rats of 193.14g received 0.32mL of Testosterone

**Estradiol**

193.14g = 10mg Estradiol

70kg man = 70,000g

1g of rat = 10/70,000 = 0.00014mg

193.14g = 193.14g x 0.00014 = 0.027g of Estradiol per ml

If 200g = 0.2mL (Mbaka ***et al,*** 2017)

193.14 = X

X = 193.14 x 0.2/200 = 0.2mL

Rats of 193.14g received 0.2mL of Testosterone

**Group5**

**Testosterone**

205.43 = 25mg Testosterone

70kg man = 70,000g

1g of rat = 25/70,000 = 0.00036mg

205.43g = 205.43g x 0.00036 = 0.074mg of Testosterone per ml

If 200g = 0.32mL (Mbaka ***et al,*** 2017)

205.43 = X

X = 205.43 x 0.32/200 = 0.32mL

Rats of 205.43g received 0.32mL of Testosterone

**Estradiol**

205.43g = 10mg Estradiol

70kg man = 70,000g

1g of rat = 10/70,000 = 0.00014mg

205.43 = 205.43g x 0.00014 = 0.029g of Estradiol per ml

If 200g = 0.2mL (Mbaka ***et al,*** 2017)

205.43g = X

X = 205.43 x 0.2/200 = 0.2mL

Rats of 205.43g received 0.2mL of Estradiol

**Group6**

**Testosterone**

228.17g = 25mg Testosterone

70kg man = 70,000g

1g of rat = 25/70,000 = 0.00036mg

228.17g = 228.17g x 0.00036 = 0.22mg of Testosterone per ml

If 200g = 0.32mL (Mbaka ***et al,*** 2017)

228.17g = X

X = 228.17 x 0.32/200 = 0.32mL

Rats of 228.17g received 0.32mL of Testosterone

**Estradiol**

228.17g = 10mg Estradiol

70kg man = 70,000g

1g of rat = 10/70,000 = 0.00014mg

228.17g = 228.17g x 0.00014 = 0.032g of Estradiol per ml

If 200g = 0.2mL (Mbaka ***et al,*** 2017)

228.17g = X

X = 228.17 x 0.2/200 = 0.2mL

Rats of 228.17g received 0.2mL of Estradiol

**3.2 STUDY DESIGN**

A total of forty six adult male *wistar* rats weighing from 160-205g were used. The animal was obtained from animal house in the Department of Physiology Faculty of basically Medical Sciences, College of Health Science, University of Port Harcourt, Nigeria.

The 46 *wistar* rats were grouped into 6, with 7 rats in group1 and 6, and 8 rats in group2 to group5.

Study1 : One animal each from the induced group (2,4,5,6) were used to determine prostate weight and all the animals in the group were used to determine body weight after induction of Benign prostatic hyperplasia.

Study2: Six animals each from group1 and group6, and seven animals each from group2 to group5 were used in determination of body weight and prostate weight, oxidative stress biomarkers (SOD, MDA, GSH, CAT), testosterone and Prostate Specific Antigen and Histology after treatment with extract.

**3.2.1 TESTOSTERONE AND ESTRADIOL ADMINISTRATION AND PREPARATION**

Rats were induced with benign prostatic hyperplasia by subcutaneous injection of testosterone and estradiol in staggered doses (three times a week respectively) for three weeks (Mbaka ***et al,*** 2017). The steroid hormones were diluted with corn oil which served as the solvent. 19mL of Corn oil was added to 1mL (25 mg) of testosterone to form 20 mL stock solution while 24 mL of corn oil was added to 1 mL (10 mg) of estradiol to give a stock solution of 25 mL. From the stock solution, 200g of rats were injected with 0.32 mL of testosterone and 0.2mL of estradiol respectively according to their body weights.

The table below shows the groups that received testosterone and estradiol

**Table3.2.1a**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Induced Groups** | **Group Name** | **Number of rats** | **Administration** | **Dose/day** |
| 2 | BPH induced | 8 | Testosterone and Estradiol | 0.32ml and 0.2ml thrice weekly |
| 4 | BPH + | 8 | Testosterone and Estradiol | 0.32ml and 0.2ml thrice weekly |
| 5 | BPH + | 8 | Testosterone and Estradiol | 0.32ml and 0.2ml thrice weekly |
| 6 | BPH + | 7 | Testosterone and Estradiol | 0.32ml and 0.2ml thrice weekly |

**3.2.2 STUDY 1: DETERMINATION OF BODY WEIGHT AND PROSTATE WEIGHT OF THE ANIMALS AFTER INDUCTION OF BENIGN PROSTATIC HYPERPLASIA**

The body weight and prostate weight of animals were determined on the final day (Day 21) of benign prostatic hyperplasic induction between 10:00a.m to 12:00pm.

Animals were placed on a weighing balance and their weights were recorded. Animals were anaesthetized with chloroform and then dissected with surgical blade. The prostate gland was excised and weighed and values were recorded.

1. Phytochemical Screening. Analysis of the major phytochemical constituents was carried out qualitatively using standard procedures by Akefe ***et al,*** (2017).
2. Test for alkaloids: One gram of extract was dissolved in 5mL of water and Dragendoffs reagent was added. The presence of orange red precipitate indicates the presence of alkaloids.
3. Test for ardenolides: One gram of extract was dissolved in 2ml of glacial acetic acid containers one drop of FeCl3 solution. The mixture was then poured into a test tube containing 1ml of concentrated H2SO4. A browning at the inter phase indicates the presence of s deoxy sugar, characteristic of cardenolides.
4. Test for anthraquinone: To test for anthraquinone, 0.5g of the extract was mixed with 5ml of ferric chloride and 5ml dilute hydrochloric acid in s test tube. It was then boiled on a water bath for 5 minutes. It was cooled and silently ammonia about half of it volume was added and shaken. The absence of colouration indicates the absence of anthraquinones.
5. Test for saponins: Extact 0.5g of the extract was dissolved in distilled water in a test tube. The absence if persistent from a thing on warming was taken as preliminary evidence for the absence of saponins.
6. Test for tannins: Five drops of ferric chloride was added to 1g of extract contained in a test tube and mixed. A blue black color indicates the presence of tannins.
7. Test for flavonoids: Exactly 5ml of dilute ammonis solution was added to a portion of the extract followed by the addition of connections H2SO4. A yellow colouration was observed which indicates the presence of flavonoids.
8. Test for carotenoids: Two drops of saturated SbCl3 in CHCl3 was added to 1g of the extract in test tube. A blue green color eventually changing to red indicates the presence of carotenoids.

**3.2.3 EXTRACT ADMINISTRATION AND PREPARATION**

Extract was administered once daily for 24days by oral route according to the method of Ofem ***et al,*** (2007). Stock preparation was obtained by dissolving the extract with distilled water and dimethyl sulfoxide (D.M.S.O). Group specific dose of extract was then administered in 1mL of the prepared solution using syringe feeding method.

The table below shows the groups that received extract and finasteride.

**Table 3.2.3b**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Treatment Groups** | **Group Name** | **Number of rats** | **Administration** | **Dose/day** |
| 3 | Extract Only | 7 | *Englerina Gabonensis* | 300mg/kg daily |
| 4 | + Extact | 7 | *Englerina Gabonensis* | 150mg/kg daily |
| 5 | + Extract | 7 | *Englerina Gabonensis* | 300mg/kg daily |
| 6 | + Finasteride | 6 | Finasteride | 5mg/kg daily |

The table below shows all the groups.

**Table 3.2.3c**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Treatment Groups** | **Group Name** | **Number of rats** | **Administration** | **Dose/day** |
| 1 | Control | 6 | Distilled water | 1ml daily |
| 2 | BPH induced | 7 | Testosterone and Estradiol | 0.32ml and 0.2ml |
| 3 | Extract Only | 7 | *EnglerinaGabonensis* | 300mg/kg daily |
| 4 | BPH + Extact | 7 | Testosterone and Estradiol + *Englerina Gabonensis* | 0.32ml and 0.2ml + 150mg/kg daily |
| 5 | BPH + Extract | 7 | Testosterone and Estradiol + *Englerina Gabonensis* | 0.32ml and 0.2ml + 300mg/kg daily |
| 6 | BPH + Finasteride | 6 | Testosterone and Estradiol +Finasteride | 0.32ml and 0.2ml + 5mg/kg daily |

**3.3 SACRIFICING OF THE ANIMALS AND SAMPLE COLLECTIONS**

Rats were sacrificed after 24 days of extract administration after anaesthesia with chloroform.

**Organ Collection:** The prostate gland was excised, weighed and stored in a plane bottle containing 10mls of formaline.

**Blood Collection:** The blood samples were collected through cardiac puncture and were put into plane bottle immediately. The prostate gland was homogenized using phosphate buffet with PH of 7.4 (0.2M). The homogenate was then centrifuged at 5000 revolution for 15 minutes, and supernatural was obtained while pellets were at the bottom. About 1ml of normal saline was added, centrifuged at 4000rpm within 10 minutes, the serum, the prostate pellets and supernatural was preserved in freezer for analysis.

**3.3.1 STUDY 2: DETERMINATION OF TESTOSTERONE AND PROSTATE SPECIFIC ANTIGEN, OXIDATIVE STRESS PARAMETERS (MALONDIALDEHYDE, SUPEROXIDE DISMUTASE, CATALASE ENZYME, GLUTHATHIONE REDUCTASE), PROSTATE TISSUE HISTOLOGY.**

**DETERMINATION OF TESTOSTERONE AND PROSTATE SPECIFIC ANTIGEN**

Enzyme linked immunoassay technique was used for the quantitative determination of testosterone concentration and PSA evaluation.

**TESTOSTERONE**

**Principle**

The principle of Testosterone ELISA Kit was based on the binding of antigen to antibody, after binding the interaction was coupled with an enzyme and read with an ELISA micro plate reader.

**Procedure**

1. Kits and sample was allowed to equilibrate to room temperature
2. 10microlitre (µL) of sample was added to each well
3. 50 µL of Testosterone enzyme reagent was added and mixed followed by the addition of 50 µL of Testosterone biotin reagent.
4. This was left to incubate at room temperature for 1 hour.
5. After the incubation, wells were washed and then 100 µL of substrate solution was added and incubated in the dark for 20 minutes.
6. Finally, 50 µL of stop solution was used to stop the reaction and read using a microplate reader at 450nm.

**PROSTATE SPECIFIC ANTIGEN**

**Principle**

The principle of PSA ELISA Kit was based on specific binding of antigen to antibody, binding produces an interaction which can be read with an ELISA micro plate reader, to quantify the amount of PSA.

**Procedure**

1. To formatted PSA wells, 25µl of sample was pipette; this was followed by the addition of 100 µl of PSA enzyme reagent.
2. The plate was mixed and incubated for thirty minutes at room temperature.
3. The plate was washed and four times by adding and decanting 350 µl of wash buffer
4. After which 100 µl of working substrate solution was added and incubated away from light for 15 minutes.
5. The reaction was stopped after 15 minutes using the stop solution provided by manufacturer And wells read at 450 nm

**EVALUATION OF BIOCHEMICAL ANALYSIS**

**DETERMINATION OF MALONDIALDEHYDE (MDA)**

Lipid peroxidation was determined by measuring formation is ofthiobarbituric acid reactive substrate (TBARS) as reported by Ohkawa and Ohishi (1979).

**Principle:** This was based on acidic condition, where the MDA formed due to peroxidation of fatty acid which reacts with reagents, 2-thiobarbituric acid (TBA), to give a pink colour complex with absorbance of 532nm. The chromophore is extractable into organic solvents using butanol.

Reagents: Distilled water, Thiobarbituric acid (TBA), Tris-kcl buffer of PH 7.4 with 4% sulphosalicyclic acid.

**Procedure**

1. 20 labelled test tubes was arranged while 500ul was pipetted into these test tubes.
2. 500ul of 4% sulphosalicyclic acid was placed into the test tubes centrifuged at 1000, revolution pet minute at 4°C using 10minutes
3. The supernatants were decanted using 1ml of Thiobabituric acid (TBA) was placed into 1.5ml of the tris-kel buffer.
4. The mixture was boiled within 1 hour and a pink chromogen was obtained.
5. The test tubes was left to cool and absorbance was read using spectrophotometer at a wavelength of 532nm.
6. An empty test tube was prepared that contains 1ml of TBA, 1.5ml of the tris-kel buffer and 1ml if distilled water was put first to zero the machine before reading the absorbance.

**DETERMINATION OF SUPEROXIDE DISMUTASE (SOD)**

The superoxide dismutase level of the sample was evaluated using the description by Kakkar ***et al,*** (1984) and the values were expressed in U units/1ml.

**Principle:** This was based on inhibition bof NADH-Phenzinemethodulphatemittoblue tetrazolium formazon.Colour formed towards end of reaction was extracted into butanol and measured at 560nm.

Reagent: Sodium hydroxide ( NSDH, 780um) ,Pyrophosphate buffer PH 7.8 ( 0.052M) glacial acetic acid and Phenazinemethodulphate (186).

**Procedure**

1. 20 labelled test tube was arranged while 500ul was pipetted into these tubes.
2. 500ul of 4% sulphosalicyclic acid was placed into the test tube centrifuged at 1000 revolution pet minute at 4°C using 10 minutes.
3. The supernatants were decanted using 1ml of Thiobabituric acid (TBA) was placed into 1.5ml of the tris-kel buffer.
4. The mixture was boiled within 1 hour and a pink chromogen was obtained.
5. The test tube was left to cool and absorbance was read using spectrophotometer at wavelength of 532nm.
6. An empty test tube was prepared that contains 1ml of TBA, 1.5ml of the tris-kel buffer and 1ml of distilled water which was put first to zero the machine before reading the absorbance.

**DETERMINATION OF CATALASE**

**Principle:** Catalase activity was performed with spectrophotometric determination of hydrogen peroxide (H2O2) this forms a stable complex with Ammonium molybdate at an absorbance of 505nm ( Goth, 1991). The principle of assay includes the incubation of 50ul serum with 1.0ml substrate ( 65umol pet 1ml H2SO2 in 60mmol/ 1 phosphate buffer, PH 7.4) at 37°C using 60 seconds. In using this procedure, the serum catalse activities linear up to 100 Ku/l. The enzymatic reaction is stopped with 2.0ml of 32.4nmol/ 1 ammonium molybdate (NH4)6 Mo7O24, 4H2O). The yellow complex of hydrogen peroxide and molybdate was measured using 405nm. One unit CAT decomposes 1 umol of hydrogen peroxide / 1 minute using assay conditions.

Reagents: (0.065M) hydrogen peroxide (H202), 60mmol/ 1 Sodium- Potassium phosphate buffer. PH 7.4 32.4mmol/1, Ammonium molybdate. (NH4)6 Mo7O24, 4H20)

**Preparation of standards at different concentrations**

**Table 3.3.1a**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Reagents | Sample (ul) | Blank (ul) | Blank 2 (ul) | Blank 3 (ul) |
| Ammonium molybdate | 1000 | - | - |  |

**Procedures**

1. The samples and reagents were brought to 37°C. Samples, blank 1, blank 2, blank 3, test tubes were prepared pipetted into the test tubes.
2. The tubes was incubated for 60 seconds at 37°C.
3. The reading of absorbance was gotten at 450nm against blank 3.

**Preparation of reagents for Catalase activity**

**Table 3.3.1b**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Reagents | Samples (ul) | Blank (ul) | Blank 2 (ul) | Blank 3 (ul) |
| Samples | 50 | - | - | - |
| Substrate (H2O2) | 1000 | 1000 | 1000 | - |
| Phosphate buffer | - | - | 50 | 1050 |
| Ammonium molybdate | - | 1000 | 1000 | 1000 |
| Serum | - | 100 | - | - |

**DETERMINATION OF GLUTHATHIONE**

Reduced glutathione (GSH) was determined by the method of Ellman, (1959)

**Principle**

Glutathione reductase catalyses the reduction of (GSSG) in the presence of NADPH, which is oxidized to NADPH+ . The decrease in absorbance at 412nm is measured.

**Table 3.3.1c**

|  |  |  |  |
| --- | --- | --- | --- |
| Reagent | Sample | Blank | Blank |
| Buffer | 400 | 400 | 500 |
| GSH | 200 | 200 | 200 |
| Sodium azide | 100 | 100 | 100 |
| H2O2 | 100 | 100 | 100 |
| Sample | 100 | 100 | - |

**Procedure**

1. 10% TCA was added to homogenate and centrifuged.
2. 1.0ml of supernatants was treated with 0.5ml of Ellmans reagent (19.8 mg of 5, 5’-dithiobisnitro benzoic acid (DTNB) in 100 ml of 0.2% sodium nitrate and 3.0 ml of phosphate buffer (0.2M, pH 8.0).
3. The absorbance was read at 412 nm.

**TISSUE HISTOLOGY AND PREPARATION**

The prostate tissue harvested from each group was fixed in a bottle containing 10mls of formalin. Before embedding in paraffin wax, the prostate gland was removed and dehydrated in increasing concentrations of alcohol; 70%, 80%, 90% and absolutely alcohol (100%). The organ was treated with acetone and then cleared in xylene for 30 min to engage the tissue transparency followed by impregnating and embedding in paraffin wax. The embedded tissue was sectioned at 5 micrometer, mounted on a slide and stained with Hematoxylin and Rosin (H&E) stains. Each section was examined under light microscope for structural changes and photomicrographs were taken (Mbaka ***et al,*** 2014).

**3.4 MEASUREMENT OF BODY/ORGAN WEIGHTS OF THE ANIMALS**

Initial body weights of the animals were measured at the beginning of the research, and final body weight before sacrifice. The weight of the prostate gland was measured after sacrifice. The weights were measured with weighing balance, and carried out by placing the animals and organs on the weighing balance and the values were recorded.

**3.5 TIME FRAME**

This research work was done in the animal house Department of Human physiology from November 2020 to February 2021

**3.6 ETHICAL AND ENVIRONMENTAL CONSIDERATION**

Ethical approval was done by the University of Port Harcourt Research Ethics Committee at its 78th meeting held on Thursday, 15th July, 2021. UPH/CEREMAD/REC/MM78/035.

**3.7 CONFLICT OF INTEREST**

The author declared that no conflict interests existed.

**3.8 STATISTICAL ANALYSIS**

Statistical analysis was carried out using statistical package for social science software (SPSS version 20.0) Difference between groups was evaluated using ANOVA test (analysis of variance) with mean and standard error of mean (M±S.E.M). P value < 0.05 statistically is significant.

**CHAPTER FOUR**

**RESULTS AND DISCUSSION**

**Table4.1 The Effects of *Englerina gabonensis* on Body weight and Prostate weight in BPH induced male *wistar* rats.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Treatment Groups** | **Group name** | **Body weight (Day0) (g)** | **Body weight (Day1) (g)** | **Body weight**  **(Day 25) (g)** | **Prostate weight (Day1) (g)** | **Prostate weight (Day25) (g)** |
| Group 1 | Control | 200.27±3.12 | 237.50±5.58 | 191.14±9.10 | 0.4 | 0.4±0.03 |
| Group 2 | BPH induced | 205.00±11.18 | 211.29±3.38a | 222.38±18.07 | 0.8 | 0.74±0.05a |
| Group 3 | Extract (300mg/kg) | 222.43±5.42 | 240.29±6.55 | 203.13±6.77 | 0.3 | 0.27±0.03b |
| Group 4 | BPH+Extract (150mg/kg) | 193.14±10.28 | 253.29±3.04 | 195.38±8.78 | 0.6 | 0.321±0.03b |
| Group 5 | BPH+Extract (300mg/kg) | 205.43±11.09 | 262.71±9.35a | 191.88±14.43a | 0.5 | 0.29±0.03b |
| Group 6 | BPH+Finasteride | 228.17±18.98 | 272.17±2.14a | 211.00±23.36 | 0.7 | 0.25±0.02a,b |

Values are Mean ± SEM, n=6 and n=7,a= Significant difference compared to control at p<0.05, BPH = Benign prostate hyperplasia,b=Significant difference compared to BPH group at p<0.05.

**Table4.1.2 The Effects of *Englerina gabonensis* on Prostate specific antigen and Testosterone in BPH induced male *wistar* rats.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Treatment Groups** | **Group name** | **Testosterone (Day25) ng/ml** | **Prostate specific antigen**  **(Day 25) ng/ml** |
| Group 1 | Control | 4.78±1.40 | 0.79±0.03 |
| Group 2 | BPH induced | 0.324±0.07 | 1.81±0.23a |
| Group 3 | Extract (300mg/kg) | 5.27±0.34 | 1.26±0.06a,b |
| Group 4 | BPH+Extract (150mg/kg) | 7.10±0.53b | 1.15±0.04a,b |
| Group 5 | BPH+Extract (300mg/kg) | 15.98±3.41a,b | 1.19±0.05a,b |
| Group 6 | BPH+Finasteride | 19.11±3.50a,b | 0.90±0.06b |

Values are Mean ± SEM, n=6 and n=7, a= Significant difference compared to control, BPH = Benign prostate hyperplasia, b=Significant difference compared to BPH group at p<0.05

**Table4.1.3 The Effects of *Englerina gabonensis* on Oxidative stress markers in BPH induced male *wistar* rats.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Treatment Groups** | **Group name** | **MDA**  **(Day25) /ml** | **CAT**  **(Day 25) U/ml** | **GSH**  **(Day25) red(nmol/L)** | **SOD**  **(Day 25) U/ml** |
| Group 1 | Control | 4.30±0.29 | 52.28±17.25 | 108.99±6.25 | 80.00±3.36 |
| Group 2 | BPH induced | 11.67±0.07a | 13.01±1.47a | 40.64±4.08a | 68.49±5.52 |
| Group 3 | Extract (300mg/kg) | 9.41±0.86a | 51.29±4.57b | 91.90±3.05a,b | 71.19±5.52 |
| Group 4 | BPH+Extract (150mg/kg) | 6.05±0.60b | 32.24±10.36 | 94.45±4.08b | 84.24±4.17 |
| Group 5 | BPH+Extract (300mg/kg) | 6.25±0.61b | 26.24±7.53 | 89.11±1.60a,b | 90.00±2.52b |
| Group 6 | BPH+Finasteride | 7.29±0.58a,b | 51.46±14.36a | 90.56±2.89a,b | 90.56±2.81b |

Values are Mean ± SEM, n=6, n=7,a= Significant difference compared to control, BPH = Benign prostate hyperplasia, b=Significant difference compared to BPH group at p<0.05, CAT=Catalase enzyme, MDA= Malondialdehyde, SOD=Superoxide dismutase, GSH=Glutathione reductase.

**4.2 Analysis of data**

**4.2.1 The Effects of *Englerina gabonensis* on Body weight and Prostate weight in BPH induced male *wistar* rats.**

The results of the effect of *Englerina gabonensis* on body weight of male *wistar* rats (Table 4.1.1)showed on significant increase (P > 0.05) in test group3, 4 and 6 compared to control group and non significant decrease ( p < 0.05) in test group 3, 4 and 6 compared to induced group. However, there was a significant increase (P <0.05) in test Group2 and Group5 compared to the control group. While the results for the effect of *Englerina gabonensis* on prostate weight showed significant decrease (p < 0.05) in the test group 3, 4, 5 and 6 compared to the induced group. There was a significant decrease (p < 0.05) in test group2 and 6 compared to control group. Non significant decrease (p > 0.05) in test group3 and 5 compared to control group and non significant increase (p > 0.05) in test group4 compared to control group

**4.2.3 The Effects of *Englerina gabonensis*on Prostate specific antigen and Testosterone in BPH induced male *wistar* rats.**

The results for the effect of *Englerina gabonensis* on Testosterone (Table 4.1.2) showed significant increase (p < 0.05) in test group4, 5 and 6 compared to the induced group and control group. There was no significant increase (p > 0.05) in test group 3 compared to the control group and induced group. There was no significant increase (p > 0.05) in test group4 compared to control group and non significant decrease (p > 0.05) in test Group2 compared to control group.

The result for the effect of *Englerina gabonensis* on prostate specific antigen showed significant decrease (p < 0.05) in the test group 3, 4, 5compared to the induced group and control group. There was no significant increase (p > 0.05) in test group 6 compared to control group.

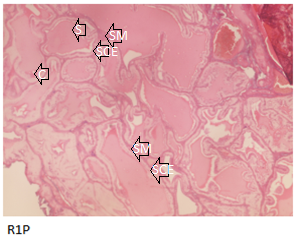
**4.2.4 The Effects of *Englerina gabonensis*on Oxidative stress markers in BPH induced male *wistar* rats.**

The results for the effect of *Englerina gabonensis* on Malondialdehyde (Table 4.1.3) showed a significant decrease (p < 0.05) in the test group 4, 5 and 6and non significant decrease in test group3 (p > 0.05) compare to the induced group. There was a significant increase (p < 0.05) in test Group2, 3 and 6 compared to control group and non significant increase (p > 0.05) in test group 4 and 5 compared to control group.

The results for the effect of *Englerina gabonensis* on Catalase enzyme (Table 4.1.3) showed no significant increase in test group 4, 5 and 6 (p > 0.05) compare to the induced group and non significant decrease in group4 and 5 compared to the control group. There was a significant increase (p < 0.05) in test Group2, 3 and 6 compared to control group and non significant increase (p > 0.05) in test group 4 and 5 compared to control group. There was a significant decrease (p < 0.05) in Group2 and Group6 compared to control group

The results for the effect of *Englerina gabonensis* on Glutathione reductase (Table 4.1.3) showed significant increase (p < 0.05) in test group 3, 4, 5 and 6 compared to induced group and non significant decrease (p > 0.05)in test group4 compared to the control group. There was a significant decrease (p < 0.05) in test Group2,3,5 and 6 compared to control group.

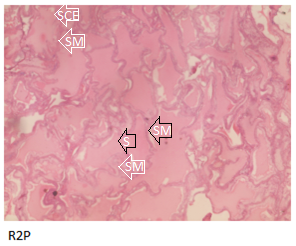
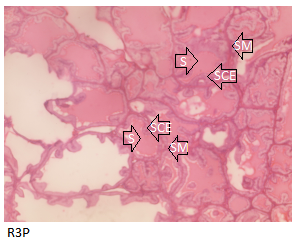
The results for the effect of *Englerina gabonensis* on Superoxide dismutase (Table 4.1.3) showed no significant increase (p < 0.05) in test group 3 and 4 compared to induced group and a significant increase (p < 0.05) in test group 5 and 6 compared to induced group and control group. There was no significant decrease in test Group2 and 3 compared to control group.

**Plate 4..2.5 The Effects of *Englerina gabonensis* on Prostate tissue histology in BPH induced *wistar* rats.**

Control (Group1)

BPH induced (Group2)

Extract Only (300mg/kg) Group3

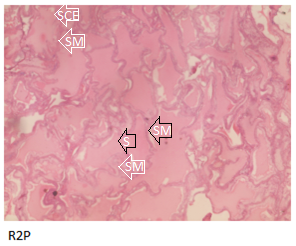
 

Photomicrograph of cross section of normal prostate gland indicating interglandular smooth muscle fibers (SM), interglandular simple columnar epithelium (SE) and glandular stroma (S). (H&E stain). Mag x100.

Photomicrograph of cross section of prostate gland of test Group2 indicating a thin strip of interglandular smooth muscle fibers (SM), extensive glandular hyperplasia (S) and a thin simple columnar epithelia lining (SCE)(H&E stain). Mag x100 compared to the control group. While test Group3 indicating reduced glandular hyperplasia (S), thick interglandular simple columnar epithelial (SCE) and thick interglandular smooth muscle fibers (SM)(H&E stain). Mag x100 compared to control group.

**Plate 4.2.6 Effects of *Englerina Gabonensis in* on Prostate tissue histology in BPH induced *wistar* rats.**

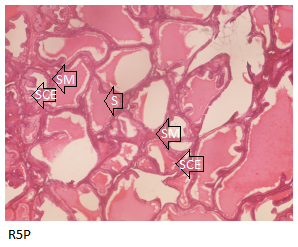
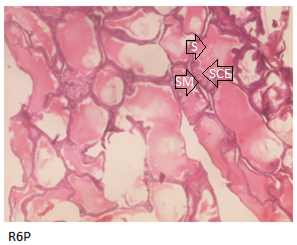
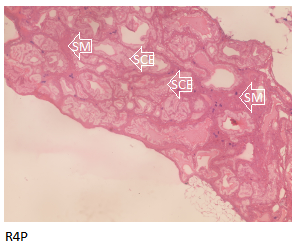
BPH induced (Group2)



BPH + Finasteride (Group6)

BPH + Extract (300mg/kg) Group5

BPH + Extract (150mg/kg) Group4



Photomicrograph of cross section of prostate gland of test Group2 indicating a thin strip of interglandular smooth muscle fibers (SM), extensive glandular hyperplasia (S) and a thin simple columnar epithelia lining (SCE). (H&E stain). Mag x100.

Photomicrograph of cross section of prostate gland of test Group4 indicating reduced glandular hyperplasia (S), large interglandular simple columnar epithelial (SCE) and thick interglandular smooth muscle fibers (SM) (H&E stain). Mag x100. compared to induced Group2. Test Group5 indicating reduced glandular stroma (S), thick interglandular simple columnar epithelial (SCE) and thick interglandular smooth muscle fibers (SM) (H&E stain). Mag x100 compared to induced Group2. test Group6 indicating reduced glandular stroma (S), largeinterglandular simple columnar epithelial (SCE) and thick interglandular smooth muscle fibers (SM) (H&E stain). Mag x100 compared to induced Group2.

**4.3 Discussion of Findings**

**4.3.1 Effects of *Englerina gabonensis* on Body weights and Prostate weight in BPH induced *wistar* rats.**

**Body weight**

Body weight is a very vital factor which can be useful in monitoring the improvement of drug administration therapy in experimental animal studies.

From the result of this study, the extract *Englerina gabonensis,* showed no significant decrease (p > 0.05) in the body weights of the induced animals which agrees with the study of Onunogbo ***et al,*** (2012). This may be due to the Phytochemical constituent (polyphenols) of the extract. The suggested mechanism of action is narrowed to the ability of polyphenols in promoting lipid metabolism by activating AMP activating protein kinase to attenuate lipogenesis and enhance lipolysis, and decreasing lipid accumulation by inhibiting the differentiation and proliferation of pre-adipcytes (Haibo ***et al,*** 2016).

**Prostate weight**

Prostate weight in benign prostatic hyperplasia is very important to note as Benign prostatic hyperplasic conditions have been characterized with prostate hypertrophy. The result from this study showed that the extract *Englerina gabonensis* caused a significant decrease (p < 0.05) in prostate weight which agrees with the study of Kavya, ***et al,*** (2021). The decrease may be associated with the Phytochemical constituent (Polyphenols) of the extract. The mechanism of action may be due to the preventive ability of Polyphenols against prostate inflammation. Clinical study of 5α-reductase inhibitors reported that patients with inflammatory findings on prostate biopsy specimens had higher prostate volumes. Cytokines derived from inflammatory cells also induce growth factors. Among them, interleukin (IL)-1α induces fibroblast growth factor (FGF)-7, and the IL-1α-related system is involved in proliferation (Kensuke ***et al,*** 2021). Polyphenols inhibits prostate inflammation which may result to a decrease in prostate volume, leading to a decrease in prostate weight.

**4.3.2 Effects of *Englerina gabonensis* on Testosterone and Prostate specific antigen in BPH induced *wistar* rats**

**Testosterone**

Testosterone is an important steroid hormone required in the development of benign prostatic hyperplasia. In benign prostatic hyperplasic conditions, testosterone has been documented to be low as more of it has been converted to dehydrotestosterone (DHT). From the result of this study, the extract *Englerina gabonensis* caused a significant increase (p < 0.05) in testosterone which agrees with the study of Ofem ***et al,* (**2014). This result can be associated to their Phytochemical (Polyphenols) constituent as Polyphenols have been documented to increase the level of testosterone (Beigip ***et al,*** 2017). The mechanism of action can be linked to Polyphenols having the ability to inhibit steroidogenic enzymes. In the case of benign prostatic hyperplasia, they inhibit 5alpha reductase enzyme, which is an enzyme that catalyzes the conversion of testosterone to dehydrotestosterone (DHT). DHT accumulation in the prostate gland leads to hyperplasic or hypertrophic conditions. Therefore Polyphenols act by increasing testosterone level and decreasing dehydrotestosterone level.

**Prostate specific antigen**

Prostate specific antigen test have been used as an important biomarker for prostate cancer. In benign prostatic hyperplasic conditions, prostate specific antigen also plays an important role as more PSA are produced in this case. The result from this study showed that the extract *Englerina gabonensis* caused a significant decrease (p < 0.05) in Prostate specific antigen which is a new finding from this study. This result may not directly be associated with the Phytochemical constituent (Polyphenols) of the extract as other studies have documented that Polyphenols increases the level of PSA in men (Clin ***et al,*** 2013). Therefore, there may be other factors which could lead to the result obtained, which is open for further investigations. The mechanism of action that led to the result may be explained by any factors that have the potential of inhibiting the production of extra proteins within the prostate gland during benign prostatic hyperplasic conditions. In Benign prostatic hyperplasia, extra proteins such as killekreins are produced in the prostate gland which may be leaked into the blood resulting into hyperplasic or hypertrophic condition of the prostate.

**4.3.3 Effects of *Englerina gabonensis*on Oxidative stress markers (MDA, CAT, GSH, SOD) in BPH induced *wistar* rats.**

Oxidative stress markers such as malondialdehyde (MDA), catalase enzyme (CAT), glutathione reductase (GSH) and Superoxide dismutase (SOD) are important biomarkers in the development of benign prostatic hyperplasia. An increase in oxidative stress which results to an increase in MDA and decrease in CAT, GSH and SOD could result to benign prostatic hyperplasic condition. The result from this study showed that the extract *Englerina gabonensis* caused a decrease in oxidative stress as shown by the significant decrease in MDA (p<0.05) and significant increase (p<0.05) in CAT, GSH and SOD. This result agrees with the findings of Zheng  ***et al,*** (2016).The result may be due to the Phytochemical constituent (Polyphenols) of the extract, as Polyphenols have been documented by Ring  ***et al,* (**2010) to exhibit antioxidative properties. The mechanism of action can be narrowed to the ability of Polyphenols in suppressing the generation of free radicals, thus reducing the rate of oxidation by inhibiting the formation of or deactivating the active species and precursors of free radicals. More frequently, they act as direct radical scavengers of the lipid peroxidation chain reactions (chain breakers). Chain-breakers donate an electron to the free radical, neutralizing the radicals and themselves becoming stable (less reactive) radicals, thus stopping the chain reactions.

**Effects of *Englerina gabonensis* on Prostate tissue histology in BPH induced *wistar* rats.**

The histology of the prostate gland is very important to note in benign prostatic hyperplasic conditions as benign prostatic hyperplasia have been characterized as an hypertrophy and hyperplasia of the stroma and epithelial cells of the prostate gland. The result from this study showed that the extract *Englerina gabonensis* caused a decrease in the hyperplasia of the glandular stroma of the prostate gland. This also may be due to the Phytochemical constituent (Polyphenols) of the extract, as Polyphenols have been documented by Perera ***et al,* (**2016) to have antiproliferative properties. The mechanism of action can be associated to the inhibitory ability of polyphenols in increasing the number of nodules in the prostate cell thereby preventing hyperplasia of the cells.

**CHAPTER FIVE**

**SUMMARY, CONCLUSION AND RECOMMENDATIONS**

**5.1 Summary of Findings**

From the research no significant decrease (p > 0.05) in body weights of the induced animals occurred due to extract administration. This agrees with the findings of Onunogbo ***et al,*** (2012).

This research showed that there was a significant decrease (p < 0.05) in prostate weight of the induced animals caused by extract administration. This agrees with the findings of Kavya ***et al,*** (2021).

From the research a significant increase (p < 0.05) in testosterone occurred in the induced animals due to extract administration. This agrees with the findings of Beigip ***et al,*** (2017)

This research showed a significant decrease (p < 0.05) in prostate specific antigen in the induced animals caused by extract administration.

From the research a significant increase in CAT, SOD, GSH and significant decrease (p<0.05) in malondialdehyde occurred in the induced animals due to extract administration This agrees with the findings of Zheng ***et al,***(2016).

This research showed a decrease in the glandular stroma of the prostate gland in the induced animals due to extract administration. This is in agreement with the findings of Perera ***et al,*** (2016).

**5.2 Conclusion**

From this research, hydromethanolic leaf extract of *Englerina gabonensis* showed therapeutic potential against benign prostatic hyperplasia (BPH), by decreasing oxidative stress and prostate specific antigen and increasing the level of testosterone in benign prostatic hyperplasic induced rats. And its active chemical component may be used for BPH treatment.

**5.4 Recommendations**

Further studies should be carried out to confirm if the decrease in prostate specific antigen showed by the extract was as a result of their phytochemical composition or not.

* 1. **Contribution to Knowledge**

This study was able to show a significant decrease in Prostate specific antigen on benign prostatic hyperplasic induced rats after treatment with hydromethanolic leaf extract of *Englerina gabonensis.*

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