CURCUMA LONGA EXTRACT IMPROVES SERUM ELECTROLYTES AND HORMONE PROFILE OF DIHYDROTESTOSTERONE - ESTRADIOL VALERATE INDUCED BENIGN PROSTATIC HYPERPLASIA MALE RATS

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ABSTRACT

The usefulness of methanol extract of Curcuma longa in management of benign prostatic hyperplasia (BPH) in rats was studied. Twenty male Wistar rats were divided into five groups of 4 rats each. BPH was induced by subcutaneous injection of dihydrotestosterone (DHT) and estradiol valerate (10:1) daily for 28 days. The normal control (NC) received subcutaneous olive oil (as vehicle) for the same duration. The disease control (HC) and drug control groups (DC) were given subcutaneous olive oil and oral finasteride (standard drug: 5 mg/kg bw) respectively after induction of BPH. Rats in the test groups (T_1 and T_2) were given 100 and 200 mg/kg.bw of C. longa methanol extracts orally for 28 days respectively, following disease induction. Phytochemical constituents of plant extracts, selected biomarkers of BPH, serum electrolyte and hormonal profile were determined using standard methods. Results revealed that C. longa have higher content of flavonoid (4.03 ± 0.01 mg/100 g) with lower concentration of terpene (0.40 ± 0.07 mg/100 g). There was significant decrease ($p<0.05$) in relative prostate weight and prostate specific antigen (PSA) in T_1 and T_2 compared to the HC group. Calcium and sodium showed significant ($p<0.05$) decreased following administration of plant extract while chlorine and bicarbonate recorded no ($p>0.05$) difference. There was a ($p<0.05$) decrease in serum total testosterone and increase in FSH level, but no difference ($p>0.05$) was seen in serum estradiol levels within all experimental groups. This study reveals that C. longa may be useful in the treatment and/or management of BPH and its complications.

Keywords: Benign prostatic hyperplasia, *Curcuma longa*, Induction, hormone profile, Prostate specific antigen, Serum electrolyte, Testosterone

INTRODUCTION

The use of complementary traditional medicine in the treatment of various diseases has expanded rapidly due to their affordability, accessibility and efficacy. Benign prostatic hyperplasia (BPH) is the most common disease of the prostate in aging men resulting from a progressive age-related non-cancerous enlargement of the epithelial cells and smooth muscle of the prostate gland (Paolone, 2010). Generally, BPH affects approximately one in four men in their 50s, one in three men in their 60s and one in two men in their 80s (Kramer *et al*.,

2007; Robert *et al*., 2009). In Nigeria, Ezeanyika *et al*. (2006) reported that one-in-four men older than 40 years have symptoms suggestive of BPH. The condition often affects individual's quality of life (Ojewola *et al*., 2017) and may progress into bladder dysfunction and eventually lead to acute urinary retention if not corrected (Roehrborn *et al*., 2008).

The etiology underlying the development of BPH is multifactorial and not well established. Although ageing represents the central mechanism implicated, recent findings have linked the development of BPH with hormonal alterations (Marker *et al*., 2003), metabolic syndrome (Rees and Kirby, 2014), nutritional factors (Bravi *et al*., 2006) and inflammation (Kok *et al*., 2009). However, none of these factors is completely understood and data on the hormonal profile and serum electrolytes in prostate pathologies are ambiguous. Dihydrotestosterone (DHT) a metabolite of testosterone that is formed by the breakdown of testosterone by an enzyme (5α-reductase) in the prostate cell-has been implicated as the main mediator of BPH development (Carson and Rittmaster, 2003).

Recent studies (Altaf *et al*., 2016; Manappallil *et al*., 2019) have suggested that certain treatment methods of BPH or acute urinary retention due to BPH can cause serum electrolyte disturbances in addition to any underlying chronic diseases such as kidney failure. Hydro-electrolytic disorders are very common in many clinical and surgical situations and may be fatal if not corrected. Recently, many developing countries worldwide are focusing on phytotherapy as an alternative medicine for the management of BPH. This approach is becoming popular due to the cost and unwanted side effects associated with the conventional medical treatment options (Traish *et al*., 2011) in addition to the fact that it is readily accessible, cheap and do not require medical prescription to be acquired.

Curcuma longa Linn. (turmeric) is a member of the ginger family (*Zingiberaceae*) and native to Southwest India. It is a rhizomatous herbaceous perennial plant and has a very long history of use in various forms of folk medicine because of its many health benefits. In Nigeria, the plant is traditionally used mainly for the relief of gastrointestinal disorders, arthritis, inflammation and gastritis and also as spices in food. *C. longa* has been reported to possess some potential therapeutic characteristics against several chronic diseases such as hyperglycemia (Garkuwa *et al.,* 2017), inflammation and oxidative stress (Konak and Şener, 2019). It has been shown to possess antimicrobial activity against food-borne pathogenic bacteria (Onwuegbuchu *et al*., 2021) and has been reported to have a hepatoprotective characteristic similar to Silymarin (Chattopadhyay *et al.,* 2004). These properties of *C. longa* in traditional medicine to treat diseases encouraged this research to evaluate its usefulness in the management of BPH and its potential effects on serum electrolytes level in male Wistar albino rats.

MATERIALS AND METHODS

Plant Collection and Preparation: Matured fresh *C. longa* (Tumeric) rhizomes were purchased from local daily market at Umudike, Abia State, Nigeria. The sample was identified (Onwuegbuchu *et al*., 2021) and authenticated by a plant taxonomist in the Department of Plant Science and Biotechnology, Michael Okpara University of Agriculture, Umudike. Voucher specimen number (MOUAU/PSB/BCH/077) was kept in the herbarium of the Department for referral. The samples were properly washed, cut into pieces, shade dried to a constant weight and processed into fine powder using a laboratory sized electric blender. The resulting powder was transferred into an airtight container and stored at room temperature until use. 100 g of the *C. longa powder* was macerated in a 250 mL of methanol for 48 hours and filtered with Whatman No. 1 filter paper. Then the filtrate was evaporated to dryness at 45 ^{o}C using water bath to obtain the crude extract.

Quantitative Phytochemical Screening: Flavonoid, saponin, tannins and alkaloids were evaluated according to the methods of Harborne (1998), while cardiac glycosides, phenol, anthocyanides, terpenes and steroids were

determined following the methods of Trease and Evans (1989). All chemicals and drugs used in the study were of analytical grade.

Experimental Animal: Fourty five (45) male albino rats of the Wistar strain weighing 90 – 130 grams were procured from the Animal Breeding Unit of College of Veterinary Medicine, Michael Okpara University of Agriculture, Umudike (MOUAU). The animals were housed in standard transparent cages with wheat husk bedding, renewed every 24 hours. They were kept under controlled room temperature (25 to 29 ^{0}C) and humidity (50 ± 20%) in a 12 hours light-dark cycle. Animals were acclimatized for two weeks to laboratory conditions before commencing the study. The animals were given standard rat feed (Vital Feed with 18% crude protein and 2800 kcal metabolizable energy) and had free access to water throughout the duration of the study. Ethical approval for the study (MOUAU/EC/21/081) was obtained from the MOUAU Committee on Animal Use and Care. All investigations were conducted in accordance with the accepted principles for laboratory animal use and care (NRC, 2011).

Acute Toxicity of *Curcuma longa:* The acute toxicity of the *C. longa* was determined in two phases using the methods of Lorke (1983), in which the outcome from each stage determines the next step. Fourteen mice were used for this study. Phase one is divided into three groups of two mice per group and were orally administered the extract at the doses of 100, 400 and 1000 mg/kg respectively. The animals were observed for at three hours intervals for 24 hours for behavioral sign of toxicity and mortality. Phase two was also made up of three groups of two mice per group which were orally administered the extract at the doses of 2000, 3000, and 5000 mg/kg respectively and also observed at three hours intervals for 24 hours for behavioral sign of toxicity and mortality. A confirmatory test was carried out by administering 5000 mg/kg to two animals and observed for mortality. LD_{50} was calculated from the formula; $LD_{50}= (M_0 + M_1)/2$, where M_0= highest dose that gave no mortality; M_1= highest dose that gave mortality.

Induction of Benign Prostatic Hyperplasia: The animals were fasted for 12 to 14 hours with free access to water prior to the induction of BPH. BPH was induced in rats using a mixture of DHT and estradiol valerate (ratio 10:1) following the methods of Ejike and Ezeanyika (2011). Dose for induction of benign prostatic hyperplasia was formulated as 9 mg/kg body weight of DHT and 0.9 mg/kg body weight estradiol valerate given by subcutaneous injection every other day for 28 days. Stock was prepared by dissolving 1 g of DHT and 0.1 g estradiol valerate in 100 ml of olive oil. The induction of BPH was monitored by measuring the PSA levels from the blood drawn from the tail vein of the test group after 28 days of induction and compared with that of negative control rats before commencing the oral administration.

Experimental Design: A complete randomized experimental design comprising of five treatment groups replicated thrice with each replicate having three rats was used for the study. All administration after induction of BPH was done orally for duration of 28 days as follows: Group I: Normal; received distilled water orally and labeled NC. Group II: BPH disease control; received olive oil (1 ml/kg) and labeled HC. Group III: BPH; received finasteride (5 mg/kg; standard drug) and labeled DC. Group IV: BPH; received 100 mg/kg.bw of *C. longa* extract and labeled T_1 and Group V: BPH; received 200 mg/kg.bw of *C. longa* extract and labeled T_2. The sublethal dosage used for this study was obtain by dividing the LD_{50} (5000 mg/kg) by a factor (50) for the initial dose and subsequent dose was double. After 28 days, the rats starved overnight were anesthetized by a brief exposure to trichloromethane vapor. The blood was collected by cardiac puncture into a sterile plain tube and allowed to clot. Serum was separated within an hour of blood clotting by centrifugation at 1200 rpm for 5 minutes at room temperature to obtain the serum sample which was stored frozen at -20 ^{o}C until required for assay.

Relative Prostate Weight: Prostate, liver and kidney were excised, washed with normal buffered saline, weighed to obtain absolute organ weight. The relative organ weights were calculated for each rat as the ratio of absolute organ weight to final body weight multiplied by 100. The relative prostrate weight was expressed in g/1000 g, while other relative organ weights were expressed in g/100g.

Determination of Serum Electrolyte Levels: Serum sodium and potassium concentrations were determined using flame emission photometry method described by Margoshes and Vallee (1956). Serum chloride concentration was determined using the titration method of Schales and Schales (1941) which is based on the precipitation of chloride ions in serum using mercuric nitrate which reacts with diphenylcarbazone to produce a violet color. Titration method of Van Slyke and Neil (1924) was employed in determining the concentration of bicarbonate. The method is based on the release of carbon dioxide from bicarbonate ion in serum with dilute hydrochloric acid. The excess acid was then titrated with sodium hydroxide using phenyl red as indicator.

Assay of Hormone Profile and Serum Prostate Specific Antigen: Serum samples were assayed for estradiol, total testosterone (nmol/L) and follicle stimulating hormone (FSH) levels using radioimmunoassay (Diagnostic Products Corporation, USA) and the level of serum PSA was measured by enzyme-linked immunosorbant assay (ELISA) kit (BioCheck Inc., USA) strictly following manufacturer's instructions. The value was expressed in nano grams per ml (ηg/ml) of serum.

Statistical Analysis: Data obtained were statistically analyzed using one-way analysis of variance (ANOVA) with Turkey's multiple comparison post hoc tests to compare the level of significance between experimental means. Probability value of $p<0.05$ was considered as significant. The results were expressed as mean ± standard error of mean (SEM).

RESULTS

Quantitative Phytochemical Constituents of Methanol Extract of *Curcuma longa:* The result of the quantitative phytochemical evaluation of methanol extract of *C. longa* is shown in Table 1. From the result, the extracts of *C. longa* have high content of flavonoid followed by alkaloid and tannin. Terpene and phenol had the lowest concentration.

Table 1: Quantitative phytochemical composition of methanol extract of *Curcuma longa*

Parameters	Concentration (mg/100 g)
Alkaloid	2.40 ± 0.07^{j}
Anthocyanin	1.61 ± 0.01^{e}
Cardiac glycoside	1.55 ± 0.04^{d}
Flavonoid	4.03 ± 0.04^{k}
Phenol	0.51 ± 0.02^{c}
Saponin	1.87 ± 0.14^{f}
Steroids	0.33 ± 0.02^{a}
Tannins	2.22 ± 0.04^{i}
Terpene	0.40 ± 0.07^{b}

Values are expressed as mean ± standard error of three determinations

Acute Toxicity of *Curcuma longa:* *C. longa* extract was not toxic because no mortality and behavioral sign of toxicity was recorded at the highest dose of 5000 mg/kg except for loss of appetite.

Effects of Extract on the Mean Body Weight of Animals: The results of mean body weight of animals treated with leaf extract of *C. longa* are showed in Table 2. The mean body weight of the animals treated with different doses of *C. longa* (T_1 and T_2) extract had less significant gain ($p<0.05$) in weight after 28 days of treatment compared with the NC.

Effect of *Curcuma longa* Extract Relative Organ Weight of Rats: The result for the effect of the extract on relative weight of prostate, liver and kidney is presented in Table 3. There was significant change ($p<0.05$) in relative liver, kidney and prostate weight in all the groups when compared with that of disease group (HC) after the 28-day experimental period.

Table 2: The body weight changes of benign prostatic hyperplasia male rats treated with methanol extract of *Curcuma longa*

Weight (g)	Group I (Normal control)	Group II (Disease control)	Group III (Drug control)	Group IV (100 mg/kg extract)	Group V (200 mg/kg extract)
Initial weight (g)	96.70 ± 1.06^{a}	104.00 ± 1.60^{b}	129.70 ± 3.70^{d}	117.00 ± 1.70^{c}	130.20 ± 1.90^{d}
Final weight (g)	142.10 ± 4.50^{b}	130.90 ± 5.90^{a}	149.40 ± 4.60^{d}	145.9 ± 3.01^{c}	144.70 ± 3.40^{c}
% body weight	43.40^{d}	26.00^{c}	19.70^{b}	19.80^{b}	10.00^{a}

Means on the same row with different letter superscripts are significantly different (p<0.05)

Table 3: Relative organ weights of benign prostatic hyperplasia male rats treated with methanol extract of *Curcuma longa*

Treatments	Absolute organ weight (g)			Relative organ weight (g)		
	Liver	Kidney	Prostate	Liver	Kidney	Prostate
NC	5.24 ± 0.17^{a}	1.27 ± 0.08^{a}	0.10 ± 0.05^{c}	3.69 ± 0.17^{b}	0.89 ± 0.08^{c}	0.07 ± 0.05^{c}
HC	5.28 ± 0.03^{c}	1.28 ± 0.02^{b}	0.20 ± 0.01^{d}	4.03 ± 0.03^{c}	0.97 ± 0.02^{c}	0.15 ± 0.01^{d}
DC	5.27 ± 0.03^{b}	1.28 ± 0.01^{b}	0.09 ± 0.02^{b}	3.53 ± 0.03^{a}	0.86 ± 0.01^{a}	0.06 ± 0.02^{b}
T1	5.28 ± 0.02^{c}	1.28 ± 0.01^{b}	0.09 ± 0.03^{b}	3.62 ± 0.02^{b}	0.88 ± 0.01^{b}	0.06 ± 0.03^{b}
T2	5.29 ± 0.02^{d}	1.29 ± 0.01^{c}	0.05 ± 0.06^{a}	3.66 ± 0.02^{b}	0.89 ± 0.01^{c}	0.03 ± 0.06^{a}

NC = Normal control, HC = Disease control, DC = Drug control, T1= 100 mg/kg bw, T2= 200 mg/kg bw, means on the same row with different letter superscripts are significantly different (p<0.05)

Table 4: Serum electrolytes concentrations of benign prostatic hyperplasia male rats treated with methanol extract of *Curcuma longa*

Treatments	Sodium (Na)	Bicarbonate	Chlorine (CL)	Calcium (Ca2+)
NC	127.23 ± 2.31^{a}	26.85 ± 1.29	96.75 ± 1.50^{c}	9.18 ± 0.36^{c}
HC	169.10 ± 2.15^{c}	27.25 ± 1.26	96.25 ± 1.50^{c}	13.01 ± 0.21^{d}
DC	197.30 ± 17.83^{d}	27.00 ± 1.15	95.25 ± 1.50^{b}	8.36 ± 0.15^{b}
T1	157.88 ± 2.54^{b}	27.13 ± 0.48	94.50 ± 1.50^{a}	6.93 ± 0.60^{a}
T2	162.67 ± 1.77^{c}	27.50 ± 0.58	94.00 ± 1.41^{a}	8.71 ± 0.13^{b}

NC = Normal control, HC = Disease control, DC = Drug control, T1= 100 mg/kg bw, T2= 200 mg/kg bw, means on the same row with different letter superscripts are significantly different (p<0.05)

Following the oral administration of methanol extract of *C. longa*, there was significant decrease (p<0.05) in relative prostate weights in the experimental group (T_1andT_2) compared to the HC. Similar trend was seen in the relative weight of liver and kidney.

Effect of Methanol Extract of *Curcuma longa* on Serum Electrolytes: Table 4 showed the effect of extract administration on serum electrolytes of DHT-estradiol valerate induced BPH Wistar albino rats. There was no significant differences (p>0.05) in bicarbonate and chloride levels in all the variables evaluated when compared with the disease control group (HC). The result of serum sodium and calcium concentration revealed a significant decrease (p<0.05) in all experimental groups when compared with the disease control groups (HC).

Effect of Methanol Extract of *Curcuma longa* on Serum PSA and Hormone Profile: There was significant decrease (p<0.05) in the serum PSA levels (Figure 1) and total serum testosterone levels (Figure 2) but significant increase (p<0.05) in FSH levels (Figure 3) in the experimental groups ($T_1$and T_2) when compared with that of the HC. But no significant effect (p>0.05) was seen with estradiol levels (Figure 4) in all experimental groups.

DISCUSSION

Phytotherapy is increasing becoming important in the treatment of numerous diseases due to many side effects of surgery, synthetic drugs and long latency of benign prostatic hyperplasia (BPH) thus phytotherapy based on product derived naturally from plant has emerged as an alternative treatment for BPH (Allkanjari and Vitalone, 2015).

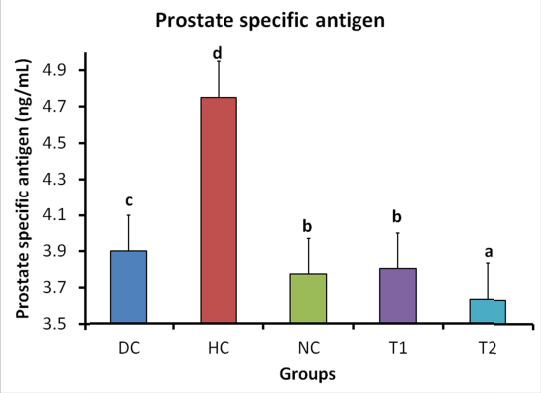

Figure 1: Prostate specific antigen levels in benign prostatic hyperplasia male rats treated with methanol extract of *Curcuma longa*

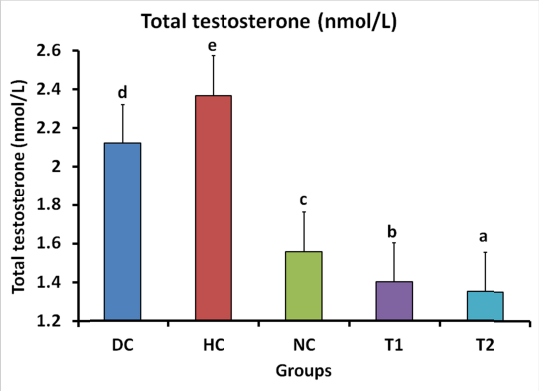

Figure 2: Total serum testosterone levels in benign prostatic hyperplasia male rats treated with methanol extract of *Curcuma longa*

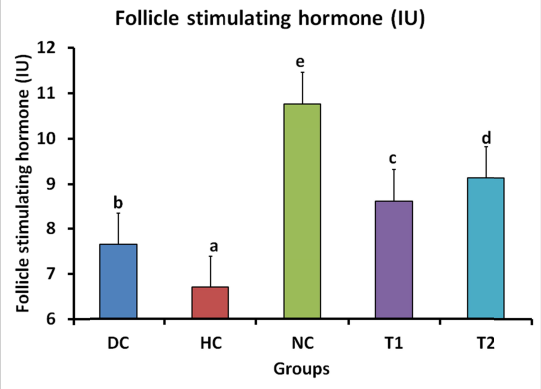

Figure 3: Follicle stimulating hormone levels in benign prostatic hyperplasia male rats treated with methanol extract of *Curcuma longa*

The results of the preliminary phytochemical evaluation of the methanol extracts of *C. longa* showed high concentration of flavonoids, alkaloids, tannins and saponins.

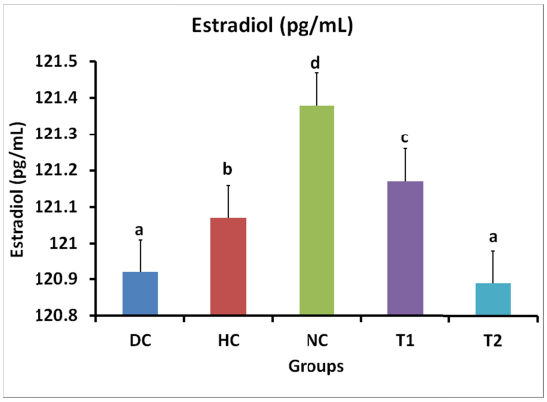

Figure 4: Serum estradiol levels in benign prostatic hyperplasia male rats treated with methanol extract of *Curcuma longa*

The result of this study is in agreement with Pawar *et al*. (2015) and Onwuegbuchu *et al*. (2021) who also reported high content of flavonoid and alkaloid in *C. longa* extracts. Flavonoids, phenol and tannin have been reported to exert multiple biological activities including antimicrobial, cytotoxicity, anti-inflammatory as well as antitumor, but the best described property of these biological compounds is their capacity to act as powerful antioxidants (Kumar and Pandey, 2013) thus protecting the body from free radicals and reactive oxygen species actions. The observed effects of *C. longa* extracts in this study could be attributable to the large number of bioactive compounds present in the plant.

The result of the percentage body weight gain showed a reduction in percentage body weight gain in disease control rats when compared with the NC rats. This result agrees with Shin *et al*. (2012) who reported a reduction in body weight in the presence of BPH. The low percentage gain in body weight seen in disease group may be attributable to loss of appetite as a result of discomfort caused by BPH induction. The result also revealed that administration of plant extract caused significant reduction in the percentage body weight gain of the animals when compared with disease control group (HC). The body weight changes serve as a sensitive indicator of the general health status of animals. This shows that the extract has an effect on the overall weight of the animals thus suggesting that *C. longa* extract is effective in

regulation of body weight gain and obesity (Kim *et al*., 2016).

In this study the prostate weight significantly increased in the disease group compared with the NC and the extract treated groups. This could be due to growth in the quantity of cellular components of the prostate tissue (Akbari *et al.,* 2021). When sufficiently large, the prostate constricts the urethral canal and cause partial or complete obstruction of the urethra (Parsons and Kashefi, 2008). The result is also in agreement with Veeresh Babu *et al*. (2010) who reported increase in prostate weight as one of the important biomarkers in the development of BPH. Thus many studies have tested the inhibitory effects of various substances on the development of BPH by measuring relative prostate weight. Therefore the reduction of prostate weight by methanol extract of *C. longa* may be the reason for its use in the management of BPH.

From the results, variations in different electrolyte concentrations were observed among the groups. Clinically electrolyte such as sodium, chloride and bicarbonate ions are among the parameters that are useful in the determination of kidney function (Ahmad *et al*., 2013). A significant increase in serum sodium ion was observed in HC when compared to the NC. This could be attributable to the inability of the kidneys to excrete adequate sodium from the tubular fluid due to BPH, which led to the excess sodium ion levels in the diseased animals. The plant extracts reduced sodium concentration in treated rats though the effect was not significant when compared with the untreated group.

A total calcium levels is often measured as part of routine health screening and abnormal result is an indicator of an underlying problem often associated with kidney disease (Kim *et al*., 2011). The calcium concentration of the diseased animal in this study increased significantly ($p<0.05$) when compared with that of the NC. However, administration of the plant extracts showed a dose-dependent reduction in calcium concentration in treated groups. Bicarbonate buffer system is the most important amongst blood buffers when the pH of the blood is considered (Kendrick *et al*., 2017) thus any reduction in serum bicarbonates implies a reduction in blood pH. However the result showed no significant alteration of bicarbonate concentration in all groups indicating that the induction of BPH did not alter the pH haemostasis. The low serum chloride concentration observed in the treated groups may be associated with metabolic alkalosis which could be due to volume loss from gastric content as gastric fluid is rich in chloride (CL^-). The result of this study is in line with previous study reported by Garkuwa *et al.* (2021).

Prostate specific antigen (PSA) is produced in the prostate and it is normally present in small quantities in the serum (Lilja, 2003). However, its level is elevated under the condition of BPH and prostate cancer. Thus a decrease in PSA is associated with reduction in BPH due to inhibition of 5-alpha reductase, the enzyme that catalyze the conversion of endogenous testosterone to hydrotestosterone which is one of the underlying cause of BPH (Iweala and Ogidigo, 2015). From the result, the PSA level in disease control was found to be significantly higher than that of the NC. This is in agreement with report of Wilt and N'Dow (2008) who reported an increase in PSA due to BPH. Several medicinal plants and products have been reported to possess 5-alpha reductase inhibitory activity and attenuate the development of BPH. In this study, the methanolic extract of *C. longa* caused great reduction in the PSA level indicating that it has a positive effect in the management of BPH.

From the result, there was a significant increase in testosterone in disease group when compared to the NC group and the extract treated groups. The increase in testosterone level in BPH rats seen in this study agrees with the reports of Stege and Carlstrom (1992), however, the result of this study is not in agreement with Weisser and Krieg (1997) that observed reduction serum testosterone levels in BPH animals, while Suzuki *et al*. (1995) revealed no relationship between testosterone levels and the prostate dimensions. Therefore the reduction in testosterone level in the groups treated with the extracts at the concentrations used in this study is an indicator of the potential effect of *C. longa* in the management of BPH

which could be attributed to the presence of wide array of phytochemicals present in the plant.

Conclusion: *C. longa* methanolic extract has shown a great potential in reducing the relative weight of prostate, PSA level and improved serum electrolyte level that was altered due to BPH induction. The study showed that methanol extract of *C. longa* could be useful in the management of BPH and the results will contribute significantly to the search for locally available medicinal plants for the management and/or treatment of BPH. Thus it is not unreasonable to attribute this effect observed in the study the presence of active bioactive constituents present in *C. longa*

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