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Prostate Specific Antigen, Antioxidant and Hematological Parameters in Prostatic Rats Fed *Solanum macrocarpon* L. Leaves

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ABSTRACT

The effect of consumption of leaves of *Solanum macrocarpon* L. on the Prostate Specific Antigen (PSA) level, antioxidant status and hematological parameters in albino rats induced with Benign Prostate Hyperplasia (BPH) was studied. Twenty five animals divided into five experimental groups namely Normal Control group (NC-group), Benign Prostate Hyperplasia group (BPH-group), Finasteride-group, 5% *Solanum macrocarpon*-supplemented diet group (5% SMSD-group) and 10% SMSD-group were used in the study. The NC was not induced with BPH and fed a control diet (diet I). The BPH-group and Finasteride-group were induced with BPH but Finasteride-group was treated with finasteride and both were fed a control diet (diet I). Five percent SMSD-group and 10% SMSD-group were induced with BPH and fed with 5 and 10% *S. macrocarpon*-Supplemented Diet (SMSD), respectively. Benign prostate hyperplasia was induced in the animals by daily subcutaneous injections of Testosterone Propionate (TP) in olive oil for a period of 12 weeks and the animals were fed their respective diets throughout the duration. Parameters including Prostate Specific Antigen (PSA), hematological indices including hemoglobin and white blood cells *in vivo* antioxidant markers such as Superoxide Dismutase (SOD), Glutathione-S-Transferase (GST), glutathione (GSH) and catalase were determined. The histo-pathological changes of the prostate were also examined. The results showed that PSA levels decreased significantly ($p<0.05$) in groups fed with SMSD. Superoxide dismutase (SOD), Glutathione-S-Transferase (GST) and glutathione (GSH) levels increased significantly ($p<0.05$) while WBC were significantly decreased ($p<0.05$) in the groups fed SMSD. The histological studies showed a considerable improvement in the prostatic histo-architecture of the groups fed SMSD. These findings indicate that *S. macrocarpon*-supplemented diets may prevent or suppress the development of BPH and be useful in its treatment and management.

Key words: *Solanum macrocarpon*, benign prostate hyperplasia, prostate specific antigen, glutathione-S-transferase, superoxide dismutase

INTRODUCTION

Benign Prostate Hyperplasia (BPH) is a progressive pathologic condition associated with aging men and characterized by proliferation of prostatic tissues, prostate enlargement and lower urinary tract symptoms (Briganti *et al*., 2009). It is also associated with complex histological changes involving glandular and stromal hyperplasia, fibrosis and prostatitis (Chapple and Smith, 1994; Barnes, 2002). The prostate gland is a major secondary endocrine organ of males whose development and growth depends on androgen stimulation especially by dihydrotestosterone

(DHT), an active metabolic product from the conversion of testosterone by steroid 5 "-reductase. It is documented that androgens and possibly estrogens constitute the primary factors responsible for prostate diseases (Shin *et al*., 2012a; De Nunzio and Tubaro, 2011; Farley, 2011). There is an increased accumulation of DHT in the prostate with aging which results in increased cell growth and hyperplasia (Carson and Rittmaster, 2003). Benign prostate hyperplasia also involves increased adrenergic tone in prostate smooth muscle mediated by "1-adrenoceptors (Michel *et al*., 1998). The drugs used in treatment of BPH include steroid 5 "-reductase inhibitors (finasteride) and "-adrenoceptor antagonists such as alfuzosin and terazosin (Gravas and Oelke, 2010). Prostate-Specific Antigen (PSA), a glycoprotein in humans encoded by the KLK3 gene and a member of the kallikrein-related peptidase family is secreted by the prostatic epithelial cells and performs various functions during copulation and fertilization (Menez *et al*., 2008). Serum PSA levels are often elevated in prostate disorders such as BPH and are used as a clinical marker for disease prognosis (Takizawa *et al*., 2010). Raised levels of serum PSA may also be suggestive of prostate cancer. BPH is not a known risk factor for prostate cancer but may increase the chance of its occurrence (Chang *et al*., 2012). The etiology of benign prostatic hyperplasia is complex and not completely elucidated but involves age-related hormonal alterations, metabolic syndrome and inflammation (Thompson and Yang, 2000). Also, several studies have shown that other processes such as chronic inflammation and increased oxidative stress may play important roles in the development of BPH (Sciarra *et al*., 2008; Matsumoto *et al*., 2010). Other possible risk factors include race, ethnicity and family history of occurrence of prostate cancer (Jemal *et al*., 2009). In addition, environment factors, especially dietary factors, may also play a role in prostate cancer incidence. The increase in prostate disorders due to dietary changes has been demonstrated in both human and animal studies (Rohrmann *et al*., 2007; Torricelli *et al*., 2013). Dietary fiber through the consumption of fruit and vegetables has been shown to be protective and associated with decreased incidence of BPH (Bisson *et al*., 2007; Babu *et al*., 2010). A positive association between consumption of vegetables and decreased incidence of diseases has been well documented. This is due to the antioxidant capacity and phytochemicals such as carotenoids, ascorbate, tocopherol, flavonoids and phenolics that are present in the vegetables (Liu, 2004; Hung *et al*., 2005). Free radicals generated under a number of conditions are involved in the onset of many diseases such as cancer, rheumatoid arthritis, cirrhosis and arteriosclerosis as well as in degenerative processes associated with ageing (Akinmoladun *et al*., 2007; Ziech *et al*., 2010). Humans are naturally protected against free radical damage by oxidative enzymes and proteins such as Superoxide Dismutase (SOD), Catalase (CAT) and glutathione as well as phytochemicals. Many plants have been identified as good sources of natural antioxidants which protect against degenerative diseases and cancer (Javanmardi *et al*., 2003; Arabshahi *et al*., 2007). *Solanum macrocarpon* L. is a widely consumed vegetable in Nigeria. *S. macrocarpon* otherwise known as the African eggplant and locally as "Igbagba" is a tropical perennial plant of the *Solanaceae* family (Bonsu *et al*., 2002). The vegetable which is usually eaten raw is used in the folkloric treatment of gout, rheumatism, angina, inflammatory tumours, cancerous tissues and Parkinson's disease (Oboh *et al*., 2005). Its anti inflammatory, anti-glaucoma, anti-asmathic, anti-allergic, anti-cancer and anti-viral properties are due to bioactive antioxidants such flavonoids and phenolic compounds (Cushnie and Lamb, 2005; Ruela de Sousa *et al*., 2007; Chinedu *et al*., 2011; Olajire and Azeez, 2011). It has also been reported to have protective effects against hepatotoxicity (Salawu and Akindahunsi, 2006; Olajire and Azeez, 2012). The high incidence of Benign Prostate Hyperplasia (BPH) and prostate cancer in humans and their influence on the quality of life of patients have made a search for their treatment a priority for public health (Napalkov *et al*., 1995). Prostate cancer ranks as the second

most common cancer and the sixth major cause of cancer death among men in the world (Ferlay *et al*., 2010; Jemal *et al*., 2010). The failure and unpleasant adverse effects associated with conventional anti-BPH drugs have revived interest in phytotherapeutic agents as safer and less toxic options (Bullock and Andriole Jr., 2006; Traish *et al*., 2011). Presently, phytotherapeutics has become popular in the treatment of BPH. Several plants, including *Sphaeranthus indicus*, *Echinacea purpurea* and *Roystonea regia* have been reported to possess anti-BPH potential (Skaudickas *et al*., 2009; Nahata and Dixit, 2011; Emeka and Obidoa, 2009). The employment of *S. macrocarpon* in ethnomedicine to manage inflammatory tumors motivated us to study its effects on BPH.

MATERIALS AND METHODS

Plant material: The leaves of *S. macrocarpon* were purchased from a local market in Ota, Ogun State, Nigeria. The plant samples were identified and authenticated by a qualified plant taxonomist in the Department of Biological Sciences of Covenant University, Nigeria. The leaves were picked, air dried and ground to a powdered form prior to use.

Animals: A total of twenty five 16-week old male Wistar rats (*Rattus norvegicus*) weighing 200±30 g were purchased from the Animal breeding center of the Federal University of Agriculture, Abeokuta, Nigeria. The animals were housed in a room with temperature of 25±4°C and relative humidity of 65±5% with an alternating 12 h light and dark cycle. They were allowed access to food and water *ad libitum* prior and during the experimental period. All experimental procedures were carried out in compliance with Guidelines for the Care and Use of Laboratory Animals prescribed and approved by Covenant University Ethics committee.

Formulation of experimental diets: Three experimental diets namely diet I, diet II and diet III were formulated using maize, wheat offal, groundnut cake, fish meal, bone meal, oil, limestone, vitamin premix, salt and powdered leaves of *S. macrocarpon* according to the method adopted by Emeka and Obidoa (2009). Diet I was the control diet which did not contain powdered leaves of *S. macrocarpon*. Diet II (5% SMSD) and III (10% SMSD) were formulated by including 5 and 10% powdered leaves of *S. macrocarpon*, respectively (Table 1).

Table 1: Formulation of diets for different groups of rats (g/%)

	Diets		
Feedstuffs	I (Control)	II (SMSD 5%)	III (SMSD 10%)
Maize (flour)	50	50	50
Groundnut cake	9.6	9.6	9.6
Fish meal	6	6	6
Wheat offal	26	21	16
S. macrocarpon 5%	-	5	-
S. macrocarpon 10%	-	-	10
Bone meal	2.0	2.0	2.0
Oil	4.0	4.0	4.0
Lime stone	2.0	2.0	2.0
Salt	0.2	0.2	0.2
Premix (Vitamins)	0.2	0.2	0.2
Total (Approx)	100.00	100.00	100.00

Table 2: Animal grouping and treatment

Experimental group	Treatment	Feeding
I	Vehicle (olive oil)	Diet I
II	Testosterone propionate in olive oil (3 mg kg^{-1} b.wt.)	Diet I
III	Testosterone propionate in olive oil (3 mg kg^{-1} b.wt.)+Finasteride (5 mg kg^{-1})	Diet I
IV	Testosterone propionate in olive oil (3 mg kg^{-1} b.wt.)	Diet II
V	Testosterone propionate in olive oil (3 mg kg^{-1} b.wt.)	Diet III

Group I: Normal control-group, Group II: BPH group, Group III: Finasteride-treated group, Group IV: 5% SMSD-fed group (50 mg g^{-1}), Group V: 10% SMSD- fed group (100 mg g^{-1}). Diet I: Control, Diet II: 5% *Solanum macrocarpon*. Supplemented diet (5% SMSD), Diet III: 10% *Solanum macrocarpon*. Supplemented diet (5% SMSD)

Experimental design and animal treatment: The rats were acclimatized for two weeks before the experiment commenced and divided into five groups of five animals each (Table 2). BPH was induced by subcutaneous injection of Testosterone Propionate (TP) (Tokyo Chemical Ins. Co., Tokyo, Japan) while Finasteride, a 5 "-reductase inhibitor, purchased from Sigma-Aldrich, USA was used as standard anti-BPH drug (Arruzazabala *et al*., 2006). The normal control group (NC) was injected subcutaneously (s/c) with the vehicle (olive oil) only and fed diet I devoid of *S. macrocarpon*. The BPH-group was subcutaneously (s/c) injected TP in olive oil (3 mg kg^{-1} b.wt.) and fed diet I. The Finasteride-group was subcutaneously (s/c) injected TP in olive oil (3 mg kg^{-1} b.wt.), administered finasteride orally (5 mg kg^{-1}) and fed diet I. The 5% SMSD-group and 10% SMSD-group were subcutaneously (s/c) injected TP in olive oil (3 mg kg^{-1} b.wt.) and fed diet II (5% SMSD) and diet III (10% SMSD), respectively. Injection with TP and oral administration of finasteride were done daily. The animals had free access to feed and water *ad libitum* throughout the period of experiment that lasted for 12 weeks (Shin *et al*., 2012b).

The body weights of the animals were measured weekly before and throughout the period of the experiment.

Collection of blood and prostate tissues: At the end of the experimental feeding period, the rats were fasted overnight and sacrificed under mild euthanasia with pentobarbital. Blood was collected by cardiac puncture into plain, heparinized and EDTA bottles, respectively for Prostate Specific Antigen (PSA) antioxidant and hematological determinations. The blood in the plain bottles was allowed to clot and the serum separated at 3500 rpm for 15 min was used for determination of Prostate Specific Antigen (PSA). Prostate tissues were rapidly excised and fixed in 10% formyl saline.

Determination of Serum Prostate specific antigen (PSA): The serum Prostate Specific Antigen (PSA) levels were determined with a PSA ELISA kit according to the manufacturer's instructions (Rapid Labs. Ltd, Colchester, Essex, UK) (Nilsson *et al*., 1997). The absorbance was measured at 450 nm using a microplate ELISA reader (Bio-Rad Laboratories, Inc.). The values were expressed as ng protein mL^{-1}.

Determination of antioxidant and hematological parameters: SOD was determined by the method of Zou *et al*. (1986). One unit of SOD activity was defined as the quantity of SOD required to inhibit 50% of reaction and expressed as units mg^{-1} protein. The activity of CAT was analyzed according to the method of Claiborne using H_2O_2 as substrate (Greenwald, 1985). The enzyme activity was measured following the disappearance of H_2O_2 at 570 nm and expressed as mol of H_2O_2

consumed min mg^{-1} protein. GSH level was determined by the procedure of Ellman (1959). The activity was expressed as mol NADPH consumed min mg^{-1} protein. GST activity was analyzed by the method of Habig *et al*. (1974). The activity was expressed as nmol CDNB-GSH conjugate min mg^{-1} protein. Hemoglobin and WBC were determined according to standard methods described by Dacie and Lewis (1991).

Histopathological examination: The prostate tissues were embedded in paraffin and cut into sections of three microns and stained with conventional hematoxylin and eosin solution according to standard methods described by Disbrey and Rack (1970). The tissue slices were viewed, photographed and interpreted by a consultant pathologist.

Statistical analysis: All the parameters studied were analyzed statistically by Tukey's multiple comparison tests using SPSS 13.1 software for Windows (SPSS Inc., Chicago, IL). Data were expressed as Mean±SEM of three replicates and differences were considered statistical significant at $p<0.05$.

RESULTS

Body weight, PSA and hematological parameters: The animals fed with diet II (5% SMSD) and III (10% SMSD) showed body weights that were significantly higher than the rats in the other groups fed with diet I (normal control). There were no significant differences in body weight changes among the other groups. The results in Table 3 indicate that rats in the Finasteride-group and 10% SMSD-group showed a significant reduction in serum PSA of 1.434±0.26 and 1.382±0.55 ng mL^{-1}, respectively compared to the BPH-group (2.079±0.33 ng mL^{-1}).

The WBC levels of the normal control and 10% SMSD-group significantly reduced to 7.173±0.97 and 9.30±0.49, respectively when compared to the BPH-group. No significant changes were seen in hemoglobin level in all the groups (Table 3).

Antioxidant and detoxifying markers: Significant increases in SOD, GSH and GST were seen only in the 10% SMSD-group (Table 4). No significant changes were seen in catalase activity in all the groups.

Histopathology of prostate tissue: There were no changes in the histological configuration of prostate tissues of the rats in the NC-group (Fig. 1a). The tissues were regular in size with cuboidal

Table 3: Effects of *S. macrocarpon* on weight, PSA and hematological parameters

Experimental groups	Weight gain (%)	PSA (ng mL^{-1})	WBC (10^3 mm^3)	Hb (g dL^{-1})
I	38.2	1.382±0.55^a	7.173±0.97^a	15.914±0.26
II	34.5	2.079±0.33	11.50±0.47	23.010±1.30
III	34.1	1.914±0.80	13.76±0.17	22.250±0.53
IV	29.4	1.860±0.16	11.10±0.65	19.699±1.03
V	55.9^a	1.434±0.26^a	9.30±0.49^a	20.717±0.38

Data were presented as Means±SEM of five rats. Group I: Normal control-group, Group II: BPH group, Group III: Finasteride-treated group, Group IV: 5% SMSD-fed group (50 mg g^{-1}), Group V: 10% SMSD-fed group (100 mg g^{-1}), A: Significant ($p<0.05$) compared to BPH group (Group II), PSA: Prostate-specific antigen, WBC: White blood cells, Hb: Hemoglobin, SMSD: *Solanum macrocarpon* supplemented diet

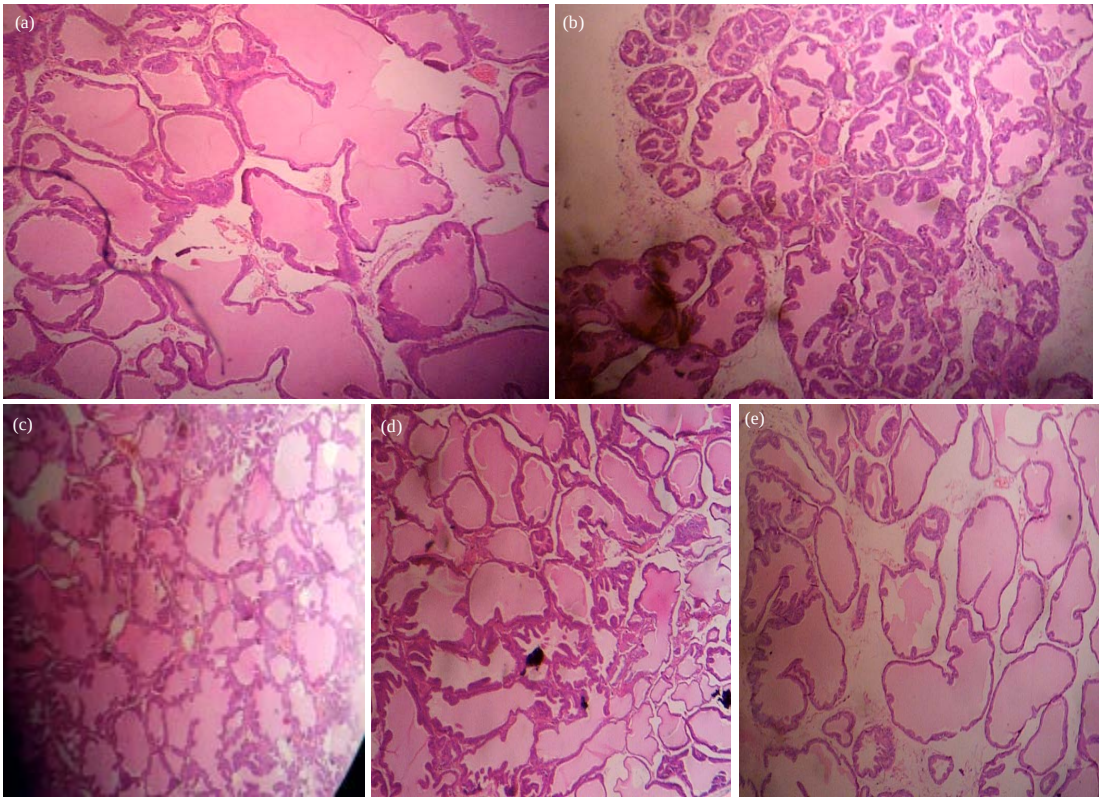

Fig. 1(a-e): Histopathological observations on prostate sections from the experimental groups at (×40). (a) Normal control group, (b) BPH-group (3 mg kg^{-1} s.c. TP), (c) Finasteride-group (d), 5% SMSD-group and (e) 10% SMSD-group

Table 4: Effects of *S. macrocarpon* on antioxidant markers

Experimental groups	SOD (Units mg^{-1} protein)	CAT (Units mg^{-1} protein)	GSH (μM)	GST (Units mg^{-1} protein)
I	11.695±1.66	3.840±0.42	4.030±0.65	1.214±0.08
II	4.225±1.95	2.702±0.05	2.832±0.30	1.284±0.06
III	6.032±1.30	2.690±0.33	2.832±0.30	1.394±0.10
IV	5.131±1.58	3.190±0.19	2.398±0.41	1.228±0.17
V	9.620±1.33[a]	3.455±1.220	4.719±0.52[a]	1.876±0.07[a]

Data were presented as Means±SEM of five rats. Group I: Control group, Group II: BPH-group, Group III: Finasteride-group, Group IV: 5% SMSD-group (50 mg g^{-1}), Group V: 10% SMSD- group (100 mg g^{-1}). A: Significant ($p<0.05$) compared to BPH-group (Group II), SOD: Superoxide dismutase, CAT: Catalase, GSH: Glutathione, GST: Glutathione -S-transferase, SMSD, *Solanum macrocarpon* supplemented diet

epithelial cells. The BPH-group showed enlarged gland with hyperplastic cells characterized by papillary epithelial cells with multi-vacuolated cytoplasm projecting into the glandular lumen and decreased glandular luminal area (Fig. 1b). The Finasteride-group showed reduced hyperplasia (Fig. 1c). The effects of SMSD on the prostate histology are shown in Fig. 1d and 1e. The rats fed 5% SMSD showed reduced hyperplasia while those fed 10% SMSD showed almost normal prostate cells when compared to the normal control group.

DISCUSSION

This study investigated the influence of consumption of leaves of *S. macrocarpon* on testosterone-induced BPH. BPH is an age-related disease associated with hormonal changes, increased proliferation and suppression of apoptosis of prostatic cells (Novara *et al*., 2006; Liu *et al*., 2007). The results obtained indicate that this plant food has protective effects against the development of BPH as seen in the reduction in PSA levels, improved prostate histological patterns and increased antioxidant capacity. PSA is usually elevated in prostate disorders and is a reliable marker for BPH and prostate cancer. A decrease in PSA is associated with reduced prostate hyperplasia as a direct consequence of 5"-reductase inhibition or anti-inflammatory actions (Sing *et al*., 1991). BPH is caused by dihydrotestosterone, a metabolite obtained from the conversion of testosterone by 5"-reductase (McConnell *et al*., 1992). Consequently, inhibitors of 5"-reductase which block production of DHT ultimately slow down the development of BPH. Common inhibitors of 5"-reductase are pharmacological agents such as finasteride. However, there is strong evidence that phytochemical agents are also effective inhibitors of 5"-reductase and contributes to significant reduction in DHT concentrations (Geavlete *et al*., 2011). This study showed that consumption of *S. macrocarpon* reduced the level of PSA in a concentration dependent manner with the 100 mg g^{-1} showing the best effect. Several factors including lifestyle affect the level of PSA (Woo *et al*., 2012). It is suggested that *S. macrocarpon* may have 5"-reductase inhibitory activity similar to the results obtained for other plant foods and hence prevent the development of BPH (Akinsola *et al*., 2012). However the actual mechanism of action will need to be further investigated. Several phytochemicals have been demonstrated to reduce prostatic disorders and prostate cancer (Adlercreutz *et al*., 1993; Kolonel *et al*., 2000). *S. macrocarpon* is rich in some of these phytochemicals and sterols which may provide an explanation for the reduction in PSA level (Sanchez-Mata *et al*., 2010; Halinski *et al*., 2012). The histological findings showed recovery in the prostatic histoarchitecture especially of the epithelial cells of rats fed *S. macrocarpon*. This observation further supports the protective effects of *S. macrocarpon* against BPH. Similar histological effects have been observed for other plants (Shin *et al*., 2012a). The development of BPH is associated with cellular damage induced by oxidative stress (Aydin *et al*., 2006; Mchedlidze and Shioshvili, 2006). Several studies have reported the anti-BPH properties of plant foods (Skaudickas *et al*., 2009; Nahata and Dixit, 2011). In addition, phytotherapeutic options such as extracts from *Pygeum affricanum* bark and saw palmetto fruits have been widely used to manage BPH (Nickel *et al*., 2008; Abe *et al*., 2009). Supplementation of diet with vegetables may increase consumption of antioxidants phytochemicals such as carotenoids, tocopherol and phenolic compounds which have been found to inhibit cellular damage induced by oxidative stress (Palozza *et al*., 1997). Several plants have been found to reduce oxidative stress in testosterone-induced BPH in rats (Prasad *et al*., 2008; Lopez *et al*., 2009) Saw palmetto extract, which is commonly used to treat BPH, has shown antioxidant effects (Belostotskaia *et al*., 2006). Therefore, antioxidants can be considered good candidates to suppress the development of BPH. *S. macrocarpon* has been reported to have potent antioxidant properties due to its polyphenolic composition (Olajire and Azeez, 2011). The increase in the oxidative capacity seen as increased activities of SOD and GST and increased level of GSH of the rats fed *S. macrocarpon* could provide a possible alternative mechanism for the protective effects of the plant against BPH (Zhang *et al*., 1998). The antioxidant polyphenolic compounds in *S. macrocarpon* might underlie its protective effects against BPH, however, the available data do not clearly confirm this hypothesis (Odukoya *et al*., 2007; Sodipo *et al*., 2008). Therefore, more studies are needed on the relationship

between the antioxidant effects of *S. macrocarpon*, its constituents and the development of BPH. Hematological parameters showed no significant difference in hemoglobin and reduced level of WBC in the control and group fed *S. macrocarpon*. Testosterone administration has been found to stimulate erythropoiesis and when administered over a long period of time increased erythrocyte activity and cause polycythemia. An increased number of WBC can occur abnormally as a result of an infection, cancer, or toxic chemical (Mansour *et al*., 2007). Reduced WBC showed that the immune system was not compromised in animals fed *S. macrocarpon* which may be due to its content of immune-boosting phytochemicals (Romieu *et al*., 2008; Bub *et al*., 2003). This result agrees with previous study that *S. macrocarpon* may help preserve the body's adaptive response to stress such as BPH (Olajire and Azeez, 2012). The weights of the animals in all the groups were found to have increased. However, the groups fed with 10% *S. macrocarpon* diet supplement had the highest increase in weight as shown in Table 3. The increase in weight could be as a result of high energy releasing nutrients such as Carbohydrate, protein and lipid found in the plant (Dougnon *et al*., 2012; Oboh *et al*., 2005). The increase in weight could also be attributed to more consumption of the plant-supplemented diets by the animals due to their palatability. Leaves of *S. macrocarpon* are usually consumed raw without processing by humans.

Further studies are necessitated to confirm the effect of the plant food on BPH as well as prostate cancer in humans. In conclusion, consumption of *S. macrocarpon* leaves appear to be protective against prostate hyperplasia and are a promising candidate for further laboratory and clinical research on prostate related diseases including prostate cancer.

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