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Effect of *Celosia argentea* F. Cristata (L.) Schinz. on Prostate Specific Antigen, Antioxidant Status and Hematological Parameters in Rats Induced with Benign Prostate Hyperplasia

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ABSTRACT

The antioxidant status, Prostate Specific Antigen (PSA) level and hematological parameters in prostatic rats fed leaves of *Celosia argentea* L. were investigated in this study. A total of twenty five animals were divided into five experimental groups consisting of five animals each. The groups included a Control (C), Negative Control (NC), Positive Control (PC), test I and II. All the groups except C were induced with Benign Prostate Hyperplasia (BPH) by daily injections of testosterone propionate in olive oil. Positive Control (PC) was treated with finasteride. The C, NC and PC groups were fed a normal diet while test I and II were fed 5 and 10% *Celosia argentea*-Supplemented Diet (CASD), respectively. At the end of the experimental period of twelve weeks, the weights and Prostate Specific Antigen (PSA) of the animals were measured. Antioxidant markers including superoxide dismutase (SOD), glutathione-S-transferase (GST), reduced glutathione (GSH) and catalase (CAT) were determined. Hemoglobin and White Blood Cells (WBC) levels were also determined. A histo-pathological examination of the prostate of the animals in all the groups was carried out. The results obtained showed that PSA levels decreased significantly ($p<0.05$) in groups fed with CASD. The SOD, GST, CAT and GSH levels increased significantly ($p<0.05$) in the groups fed CASD. Hemoglobin and WBC levels were increased in the NC and PC groups. The animals in the groups fed with CASD had the highest increase in weight. The histological studies showed a considerable improvement in the prostate histology of the groups fed CASD. These findings indicate that consumption of *Celosia argentea*-supplemented diets may prevent or suppress the development of BPH in rats.

Key words: *Celosia argentea*, benign prostate hyperplasia, prostate specific antigen, superoxide dismutase, glutathione

INTRODUCTION

The Benign Prostate Hyperplasia (BHP) is a progressive hormonal age-related disease of men characterized by histological changes in the prostate. This illness is receiving growing attention due to the increase in its prevalence and contribution to a pattern of morbidity that is of public health concern (Wei *et al*., 2005). The proposed mechanisms underlying the pathogenesis of BPH are varied and include androgens, oxidative stress and inflammatory processes (Pace *et al*., 2010). The common therapeutic agents used in management of BPH are 5α-reductase inhibitors such as

finasteride which exhibit severe adverse effects due to its structural similarities to steroidal hormones (McConnell *et al*., 1998; Uygur *et al*., 1998; Vaughan *et al*., 2002; Foley and Kirby, 2003).

The use of plant-based therapies is as old as mankind and comparable to orthodox synthetic medications. Plants continue to provide a vibrant source for drug discovery and serve as potential leads for development of novel therapeutic compounds (Newman and Cragg, 2007; Geldenhuys *et al*., 2012; Nahida *et al*., 2012; Devi *et al*., 2013). The use of plant-based therapy in the management of prostatic diseases is not an exception (Skaudickas *et al*., 2009; Babu *et al*., 2010; Nahata and Dixit, 2011). *Celosia argentea* var. *cristata* L. is a member of the Amaranthaceae family. It is a tropical herbaceous plant with simple, alternate leaves and a dense, multiple flowered florescence (Iwu, 1993; Grubben, 2004; Koh *et al*., 2009). It is commonly grown and consumed as vegetable in Nigeria. The leaves have red pigments unlike the green variety. Plant products from *C. argentea* are traditionally employed as antipyretic, anti-inflammatory, antioxidant, antidiabetic, antidiarrheal and antimetastatic (Hayakawa *et al*., 1998; Vetrichelvan *et al*., 2002; Priya *et al*., 2004; Sharma *et al*., 2010; Malomo *et al*., 2011). They also have immune modulatory and hepatoprotective properties (Imaoka *et al*., 1994; Hase *et al*., 1996, 1997). Some of the chemical constituents of *C. argentea* include 2-descarboxy-betanidin, 3-methoxytyramine, 4-O-β-D-apifuranosyl-(1>2)-β-D-glucopyranosyl-2-hydroxy-6-methoxyacetophenone, amaranthin, betalimic acid, celogenamide A, celogentin, celosian, celosin, cristatain, dopamine, lyciumin, moroidin, nicotinic acid and (S)-tryptophan (Schliemann *et al*., 2001; Kobayashi *et al*., 2001; Morita *et al*., 2004; Shen *et al*., 2010; Wu *et al*., 2011). There is a growing need to develop novel preventive and therapeutic options for management of prostatic diseases as a result of their high incidence (Jemal *et al*., 2011). Epidemiological studies have shown an inverse association between intake of vegetables and risk of prostatic diseases (Liu *et al*., 2012). The several biological and pharmacological properties of *C. argentea* could be of benefit in the management of BPH and other prostatic diseases. The aim of this study was to investigate the effect of consumption of on BPH in rats.

MATERIALS AND METHODS

Plant sample: The leaves of *C. argentea* were sourced locally from a market in Ota, Ogun State, Nigeria and duly identified by a plant taxonomist. The leaves were hand-picked, air dried and ground to a coarse powdered form.

Experimental animals: Twenty five male Wistar rats aged 8-10 weeks old and weighing between 200-250 g were purchased from the Federal University of Agriculture, Abeokuta, Nigeria. The rats were housed in metallic cages under humid tropical conditions and exposed to alternating 12 h light and dark cycle. They were allowed access to food and water *ad libitum* throughout the experimental period. All animal handling and 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.

Experimental diets: Three diets namely diet I, diet II and diet III shown in Table 1 were prepared according to the method adopted by Emeka and Obidoa (2009). Diet I was the control diet which did not contain leaves of *C. argentea*. Diet II and III were the test diets containing 5 and 10% powdered leaves of *C. argentea*, respectively.

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

	Diets		
Feedstuffs	I (Control diet)	II (5% CASD)	III (10% CASD)
Maize (flour)	50	50	50
Groundnut cake	9.6	9.6	9.6
Fish meal	6	6	6
Wheat offal	26	21	16
Celosia argentea 5%	-	5	-
Celosia argentea 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	Treatments	Feeding diet
C	Vehicle (olive oil)	I
NC	Testosterone propionate in olive oil (3 mg kg^{-1} body weight)	I
PC	Testosterone propionate in olive oil (3 mg kg^{-1} body weight)+Finastride (5 mg kg^{-1})	I
Test I	Testosterone propionate in olive oil (3 mg kg^{-1} body weight)	II
Test II	Testosterone propionate in olive oil (3 mg kg^{-1} body weight)	III

C: Control group, NC: Non-treated group, PC: Finasteride-treated group, Test I: CASD 5%, Test II: CASD 10%

Experimental procedure: 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 in the rats by subcutaneous injection of testosterone propionate in olive oil (3 mg kg^{-1} body weight) (Arruzazabala *et al.*, 2006). Finasteride (5 mg kg^{-1}) administered orally was used as standard BPH drug. The control group (C) was injected subcutaneously (s/c) with the vehicle (olive oil) only and fed control diet (diet I). The Negative Control group (NC) was induced with BPH and fed control diet (diet I) (BPH-group). The Positive Control group (PC) was induced with BPH, administered finasteride and fed diet I. The test group I and II were induced with BPH and fed diet II (5% CASD) and diet III (10% CASD), respectively. Induction with BPH by injection of TP and oral administration of finasteride were done daily and the animals had free access to feed and water during the experimental period of twelve weeks (Shin *et al.*, 2012a). The body weights of the animals were measured weekly.

Collection of blood and prostate tissues: The animals were fasted overnight and sacrificed under mild euthanasia with pentobarbital after twelve weeks of feeding and fresh blood was collected from them by cardiac puncture. The blood for determination of Prostate Specific Antigen (PSA) was allowed to clot and the serum separated at 3500 rpm for 15 min. The prostate tissues were also quickly removed and fixed in 10% formyl saline.

Measurement of Prostate Specific Antigen (PSA): The serum Prostate Specific Antigen (PSA) levels were determined with a PSA ELISA kit according to the manufacturer's instructions. The absorbance was measured at 450 nm in a microplate ELISA reader. The values were expressed as ng protein mL^{-1} (Nilsson *et al.*, 1997).

Determination of antioxidant status: The 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 U mg^{-1} protein. The activity of CAT was analyzed according to the method of Greenwald (1985) using H_2O_2 as substrate. The enzyme activity was measured following the disappearance of H_2O_2 at 570 nm and expressed as mole of H_2O_2 consumed/min/mg protein. GSH level was determined by the procedure of Ellman (1959). The activity was expressed as mole NADPH consumed/min/mg protein. GST activity was analyzed by the method of Habig *et al.* (1974). The activity was expressed as nmol CDNB-GSH conjugate/min/mg protein. Hemoglobin and WBC were determined according to standard methods described by Dacie and Lewis (1991).

Examination of prostate histopathology: The prostate tissues were processed according to standard procedure described by Disbrey and Rack (1974). The tissues were embedded in paraffin and cut into sections of three microns and stained with conventional hematoxylin and eosin solution. The tissue slices were viewed, photographed and interpreted by a consultant pathologist.

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

RESULTS

Body weight, PSA and antioxidant levels: The animals fed with diet II (5% CASD) and III (10% CASD) showed body weights that were significantly higher than the rats in the other groups fed with diet I (control diet). The results in Table 3 indicate that rats in the PC (finasteride-treated), test I (5% CASD) and test II (10% CASD) groups showed significant decreases in serum PSA of 1.9144±0.80, 1.828±0.16 and 1.8354±0.13 ng mL^{-1}, respectively compared to 2.079±0.33 ng mL^{-1} of the NC (non-treated) group.

The WBC levels of the test I (5% CASD) and test II (10% CASD) groups significantly reduced to 7.56±1.71 and 6.333±1.35, respectively when compared to the NC (non-treated) group. Hemoglobin level was significantly increased in the NC (non-treated) group and PC (finasteride-treated) group (Table 3).

Antioxidant status: There were significant increases in SOD, CAT and GSH in the C (control), test I (5% CASD) and test II (10% CASD) groups (Table 4). The GST was increased only in the test II (10% CASD) group.

Table 3: Effects of *Celosia argentea* on weight, PSA and hematological parameters

Experimental groups	Weight gain (%)	PSA (ng mL^{-1})	WBC (10^3 mm^3)	Hb (g dL^{-1})
C	38.2	0.382±0.55	7.173±0.97	15.914±0.46[a]
NC	34.5	2.079±0.33	11.50±0.47	23.010±1.30
PC	34.1	1.9144±0.80	13.76±0.17	22.250±0.53
Test I	45.5[a]	1.828±0.16[a]	7.56±1.71[a]	16.774±0.77[a]
Test II	43.2[a]	1.8354±0.13[a]	6.333±1.35[a]	16.129±0.37[a]

Data were presented as Means±SEM of five rats. C: Control-group, NC: Non-treated group, PC: Finasteride-treated group, Test I: 5% CASD-fed group (50 mg g^{-1}), Test II: 10% CASD-fed group (100 mg g^{-1}). a: Significant ($p<0.05$) compared to NC: Non-treated group, PSA: Prostate-specific antigen, WBC: White blood cells, Hb: Hemoglobin, CASD: *Celosia argentea* -supplemented diet

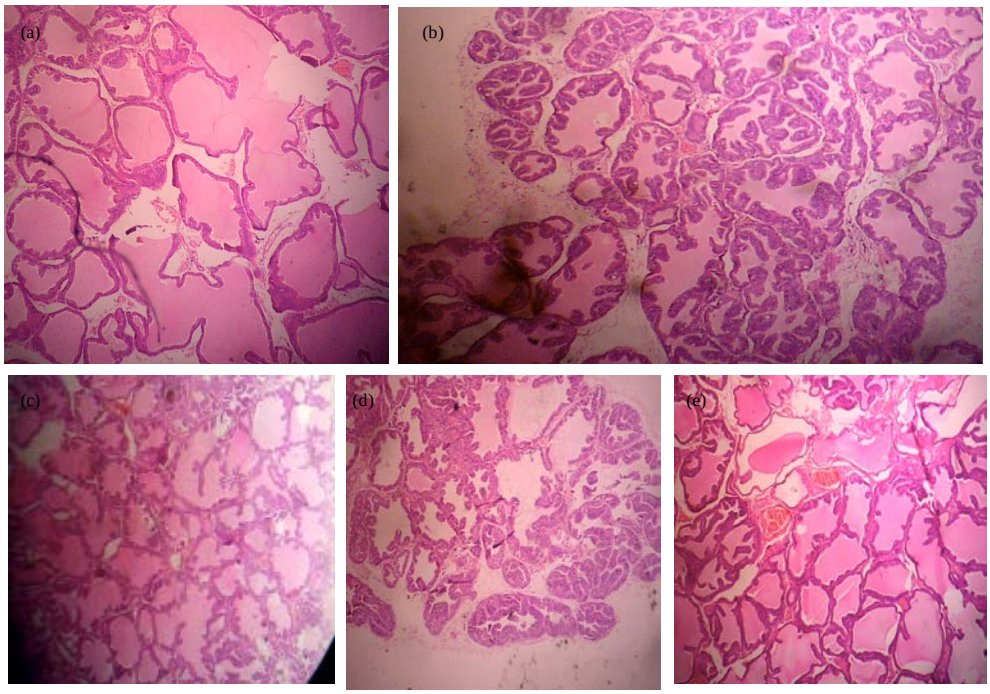

Fig. 1(a-e): Histopathological observations on prostate sections from the experimental groups at ×40. (a) C: Control group, (b) NC: Non-treated group, (c) PC: Finasteride-treated group, (d) Test I: CASD 5% group and (e) Test II: CASD 10% group

Table 4: Effects of *Celosia argentea* on antioxidant markers

Experimental groups	SOD (U mg^{-1} protein)	CAT (U mg^{-1} protein)	GSH (µM)	GST (U mg^{-1} protein)
C	11.695±1.66[b]	3.84±0.42[b]	5.030±0.65[b]	1.214±0.08
NC	4.225±1.95	2.702±0.05	2.832±0.30	1.284±0.06
PC	5.032±1.30	2.69±0.33	2.832±0.30	1.394±0.10
Test I	6.832±1.44[b]	3.346±0.54[b]	3.631±0.48[b]	1.096±0.03
Test II	8.586±1.42[b]	4.491±0.78[b]	4.345±1.51[b]	2.045±0.09[b]

Data were presented as Means±SEM of five rats. C: Control-group, NC: Non-treated group, PC: Finasteride-treated group, Test I: 5% CASD-fed group (50 mg g^{-1}), Test II: 10% CASD-fed group (100 mg g^{-1}). b: Significant ($p<0.05$) compared to NC: Non-treated group. SOD: Superoxide dismutase, CAT: Catalase, GSH: Glutathione, GST: Glutathione-S-transferase, CASD: *Celosia argentea*-supplemented diet

Prostate histopathology: The prostate epithelial cells of the animals in the C (control) group showed normal histological features characterized by regular size and cuboidal shape (Fig. 1a). The prostate tissues of animals in the NC (non-treated) group showed abnormal histological features seen as enlarged gland characterized by hyperplastic epithelial cells (Fig. 1b). The histological characteristics of prostate tissues of animals in the PC (finasteride-treated), test I (5% CASD) and test II (10% CASD) groups showed reduced hyperplasia (Fig. 1c-e).

DISCUSSION

There is an established positive association between consumption of vegetables and decreased incidence of diseases. This is usually attributed to the natural antioxidants and phytochemicals

such as carotenoids, flavonoids and phenolics that are commonly present in vegetables (Liu, 2004; Hung *et al*., 2005; Arabshahi *et al*., 2007). Free radicals are involved in the onset of many diseases such as cancer 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 intake of phytochemicals (Lobo *et al*., 2010). This study investigated the effect of consumption of *Celosia argentea* leaves on Benign Prostate Hyperplasia (BPH) in rats. BPH is an age-related disease associated with hormonal changes and hyperplasia of prostatic cells (Briganti *et al*., 2009). The reduction in PSA levels, improved prostate histopathology and increased antioxidant capacity of rats fed with *C. argentea* indicate that consumption of this vegetable could offer protection against BPH. Several factors including nutritional lifestyle affect the level of PSA (Woo *et al*., 2012). Elevated levels of PSA are usually associated with prostate disorders such as BPH. A decrease in PSA is linked to a reduction in prostate hyperplasia due to inhibition of prostatic 5α-reductase. The 5α-reductase is the enzyme that converts testosterone to dihydrotestosterone (DHT) which is implicated in development of BPH (McConnell *et al*., 1992). Several plant foods have been reported to have 5α-reductase inhibitory activity and hence prevent the development of BPH (Abe *et al*., 2009; Nahata and Dixit, 2011; Akinsola *et al*., 2012). *Celosia argentea* is rich in phytochemicals that can inhibit 5α-reductase and reduce PSA levels (Shen *et al*., 2010; Wu *et al*., 2011; Halinski *et al*., 2012). There is strong evidence that phytochemical agents are effective inhibitors of 5α-reductase that consequently leads to reduction in DHT concentrations and slows down BPH (Geavlete *et al*., 2011).

Diets supplemented with Nigerian vegetables may increase the intake of natural antioxidants such as flavonoids and other phenolic compounds (Salawu *et al*., 2011; Azeez *et al*., 2012). These phytochemicals are known to prevent diseases by inhibiting cellular damage induced by reactive oxygen species (Palozza *et al*., 1997; Liu, 2004; Hung *et al*., 2005). Oxidative stress and inflammatory processes are implicated in the development of BPH (Aydin *et al*., 2006; Pace *et al*., 2010). Several plants such as saw palmetto have been reported to reduce oxidative stress in BPH (Prasad *et al*., 2008; Hevesi *et al*., 2009; Lopez *et al*., 2009; Belostotskaia *et al*., 2006). In this study, rats fed CASD showed a high antioxidant capacity as reflected in the increase in SOD, CAT and GST activities as well as GSH levels. The increased antioxidant capacity of this vegetable could provide a possible alternative mechanism for its protective effects against development of BPH. Similarly, *C. argentea* has been reported to have potent antioxidant properties due to its content of flavonoids and phenolic compounds (Malomo *et al*., 2011). The relationship between the antioxidant effects of *C. argentea*, its constituents and the development of BPH needs to be investigated further as the current available data is not sufficient.

Hemoglobin and WBC were increased in the rats induced with BPH. Testosterone administration is associated with stimulation of erythropoiesis (Bachman *et al*., 2014). An increased number of WBC is usually a result of pathological conditions such as infection, cancer, or toxic chemical (Mansour *et al*., 2007). The reduction in WBC in the animals fed CASD showed the modulation of the immune system by constituents of *C. argentea*. This result is similar to the immune-modulatory activity of celosin reported by Hase *et al*. (1997). It can be inferred that *C. argentea* may protect against development of BPH via modulation of the body's immune response to it.

The development of BPH is associated with cellular damage. The histological findings in this study showed stabilization of the prostate histology especially in the prostatic epithelial cells of rats

fed 10% CASD. A similar histological observation has been reported for other plants (Shin *et al.*, 2012b). This observation further reinforces the protective effects of *C. argentea* against the development of BPH.

The animals in the groups fed with CASD had the highest increase in weight as shown in Table 3. An increase in weight could be as a result of high energy releasing nutrients such as carbohydrate, protein and lipid found in the plant foods (Oboh *et al.*, 2005; Dougnon *et al.*, 2012). 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 *C. argentea* are commonly used in the preparation of soups and stews in Nigeria.

In conclusion, consumption of *C. argentea* leaves appear to be protective against benign prostate hyperplasia and are a promising candidate for further laboratory and clinical research on prostate related diseases including prostate cancer.

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