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PSA And P53 As Diagnostic Markers in Prostate Pre-Malignancy: The Down-Regulating Ability of Uvaria Chamae Root Extract in Cadmium Chloride-Induced Pre-Malignancy

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Abstract

Background: This investigation was conducted to assess the potentials of ethanol root extract of *Uvaria chamae* in down-regulating and up-regulating PSA and p53 respectively as pre-malignant biomarkers in cadmium chloride-induced prostate pre-malignancy.

Material and methods: Prostate pre-malignancy was induced using 3mg/kg of $CDCl_2$ intraperitoneally once weekly for twenty-eight (28) days while anti-cancer activity of *Uvaria chamae* root extract was evaluated after pre-treatment of the experimental animals with $CDCl_2$ using the serum level of PSA and tissue expression of p53, which are important pre-malignant and malignant biomarkers.

Results: Results obtained from this investigation showed elevated serum level of PSA and high expression of p53 marker in $CDCl_2$-induced pre-malignant prostate tissue as well as increase number of positive cells after Image J analysis. Subsequently, post-treatment with ethanol root extract of *U. chamae* showed a significant and dose-dependent decrease in the serum level of PSA and poor expression of p53 marker especially in 2500mg/kg and 1500mg/kg of *U. chamae* administered groups, thus indicating the down-regulating ability of *U. chamae* root extract. These findings draw attention to the anti-cancer ability of *U. chamae* root on prostate pre-malignancy. Further studies should be employed to isolate the bio-active ingredients responsible for these great therapeutic effects.

Keywords: PSA; p53; uvaria chamae; prostate; pre-malignancy

Introduction

Prostate cancer is one of the leading causes of cancer deaths in men worldwide and is the most commonly diagnosed cancer in males [1,2]. The progress of prostate cancer is also influenced by exposure to various environmental agents [1]. Substances such as herbicides, insecticides and other organic compounds have been implicated in the development and progression of prostate cancer. These environmental toxins are continually produced or emitted through chemical processing and urban waste incineration and can enter the food chain via contamination of the soil [3]. p53 gene is a tumour suppressor gene in humans and animals that play an important role in DNA response damage, due to its capacity to coordinate multiple signaling pathways involved in DNA damage [4]. p53 genes have been classified as a guardian of the genome [4]. p53 genes are not only limited to those involved in the arrest of cell cycle and programmed cell death as revealed by gene expression microarrays, its activity can also affect other clusters of gene linked to diverse processes such as cell adhesion, transcription, cell mobility, DNA repair, membrane functions and metabolism [5]. p53 mutation is a common phenomenon in most cancers and usually associated with poor prognosis and progression of tumour [6]. Due to multiple splicing and alternative promoters, p53 family members express various forms of p53 proteins containing different isoforms. Many developments have been affected to comprehend the understanding of p53 biology [7]. p53 which is present in chromosome 17 is present in two forms namely, wild and mutant types. The wild type is usually unrecognized in tissues and has a half-life of about 30 minutes and is usually kept at a very low steady state [8, 9, 10]. However, the wild type is stabilized and accumulates in cells undergoing DNA damage or cells responding to stress. p53 activates the transcription of several genes by binding to a consensus binding site. The BAX genes involved in the regulation of apoptosis can also be activated by the p53 proteins. p53 genes are also important for G_1

phase arrest. Post DNA damage, mutations of the p53 genes are the most critical genetic alteration involved in carcinogenesis. P53 protein regulates its own function via MDM2 gene activation and the product encoded by MDM2 is a 90-kDa zinc finger protein (mdm2), which also contains a binding site for p53. In response to DNA damage, apoptotic cells undergo cell shrinkage and condensation of chromosomes. The p53 gene is otherwise called Tp53. In human cancers, it is one of the most mutated genes. It has several functions related to the proliferation of normal cell, apoptosis and repair of DNA [11, 12]. Several studies have been documented concerning p53 gene and prostate cancer and many studies have used immunohistochemistry to analyze the status of p53. In cancers, with the mutation of p53, the mutant gene does not normally metabolize and thus accumulates in the nucleus providing for its detection. The allelic loss of p53 gene on the chromosome 17 short arm is very common in many cancers. Prostate-specific antigen abbreviated as PSA is a protein produced by normal and malignant cells of the prostate gland. The PSA test measures the level of the protein in blood. To perform this test, blood sample is taken to the laboratory for analysis and the results are usually reported as nanograms of PSA per milliliter (ng/ml) of blood. The serum level of PSA is often increased in people with prostate cancer, and the PSA test was originally approved in 1986 by the FDA to monitor the progression of prostate cancer in males who had already been diagnosed with the disease. FDA in 1994, approved the PSA test to be employed in the detection of prostate cancer in men between 50 years and above. Until about 2008, many clinicians, scientists and professional organizations had encouraged PSA screening for prostate cancer beginning at age 50 yearly. Men who are at higher risk of prostate cancer have been recommended and encouraged to begin PSA screening at age 40 or 45. These include black men, men with germ line variants in *BRCA2* or *BRCA1* and men whose father or brother had prostate cancer [13]. Absolutely, there seems to be no specific normal or abnormal level of PSA in the blood. PSA levels of 4.0 ng/ml and lower can be considered normal. However, some individuals with serum levels of PSA below 4.0 ng/ml may be presented with prostate cancer and many with higher PSA levels between 4 and 10 ng/ml may not be presented with prostate cancer [13]. Additionally, several factors can cause fluctuation in the PSA level of an individual. For instance, the PSA level tends to increase with respect to age, size of the prostate gland as well as inflammation or even infection. A current prostate biopsy has the capacity to increase the serum level of PSA. Moreso, ejaculation or vigorous exercise such as cycling two days prior to testing can also elevate PSA serum level. Generally speaking, the higher the individual's PSA level, the more likely the possibility of occurrence of prostate cancer. The PSA screening is also used in monitoring men after surgical operation or after radiation therapy for prostate cancer to evaluate if cancer has recurred [14]. If the serum level of PSA of a patient seems to rise after undergoing prostate cancer treatment, it may show a sign of prostate cancer recurrence and such a biochemical relapse usually appears months or years before the recurrence causes symptoms. Investigations are currently ongoing to improve the PSA test for clinicians and other allied health professionals. These innovations actually have resulted to the following; free versus total PSA, pro-PSA, PSA density, PSA velocity and PSA doubling time, isoPSA, urinary biomarkers and 4kscore tests [14]. From time immemorial, medicinal plants have played a key role in the treatment and management of several categories of ailments [15]. Our plant of study, *U. chamae* is a small tree belonging to the family of Annonaceae [16, 17] The plant has been reported to be used in the treatment of a wide range of diseases including diarrhea, cerebral diseases, amenorrhea, piles, hematuria, hemolysis, miscarriage and for the relief of pains during child birth [18]. Consequently, Studies on the use of the plant on prostate pre-malignancy have not been reported, hence the novelty of this work.

Materials and Methods

Collection and identification of plant

The roots of *U. chamae* were excavated from a thick forest in Ikot Efre Itak, a small village located in Ikono Local Government Area of Akwa Ibom State, Nigeria and identified by Dr. Henry Akinnibosum of the Department of Plant Biology and Technology, University of Benin, Edo State, Nigeria. Eventually, Herbarium no UBH-U353 was issued and assigned to it.

Preparation of ethanol root extract of U. chamae

500g of *U. chamae* roots were chopped into small sizes, washed and air-dried for approximately one (1) week.

The roots were blended using an electric blender and subsequently soaked in 70% ethanol for three (3) days. The supernatant filtered from the solution was dried at about 45^{0}C in a water bath. The obtained dried plant extract was preserved in a refrigerator before the commencement of the experiment.

Experimental animals and set up

Thirty-six (36) adults male Wistar rats weighing 200-210g were used for this experiment. They were divided into 6 groups with 6 rats in each group. The rats were kept in clean wooden cages with beddings and given diet as well as clean drinking water at will. Prostate pre-malignancy was induced using 3mg/kg of cadmium chloride ($CdCl_2$) intraperitoneally, weekly for twenty-eight (28) days and post-treatment with *U. chamae* root extract was done orally and daily for twenty-eight (28) days according to the method described by [19]. The table below shows the experimental set up.

Table 1: Treatment regimen

Groups	Regimen	Duration
Control	given water and feed *ad libitum*	28 days
2	3mg/kg of $CdCl_2$ alone intraperitoneally	Once weekly for 28 days
3	3mg/kg of $CdCl_2$ intraperitoneally followed by oral administration of 150mg/kg of casodex	$CdCl_2$: once weekly for 28 days Casodex: once daily and orally for 28 days
4	3mg/kg of $CdCl_2$ intraperitoneally followed by 2500mg/kg of *Uvaria chamae* root extract	$CdCl_2$: once weekly for 28 days 2500mg/kg extract: once daily and orally for 28 days
5	3mg/kg of $CdCl_2$ intraperitoneally followed by 1500mg/kg of *Uvaria chamae* root extract orally	$CdCl_2$: once weekly for 28 days 1500mg/kg extract: once orally and daily for 28 days
6	3mg/kg of $CdCl_2$ intraperitoneally followed by 1000mg/kg of *Uvaria chamae* root extract orally	$CdCl_2$: once weekly for 28 days 1000mg/kg extract: once orally and daily for 28 days.

Evaluation of prostate specific antigen (PSA)

PSA assay was done using rat serum according to the method described by [20]. 100µl of sample was added to the wells and incubated for 90 minutes at about 37°C. The liquid was discarded and 100µl biotinylated detection (Ab) working solution was immediately added to each well and incubated for about 60 minutes at 37°C. The plate was washed and aspirated 3 times. 100µl HRP conjugate working solution was added and incubated for 30 minutes at 37°C. After which, the plate was aspirated and washed 5 times. 90µl substrate reagent was added and incubated for 15 minutes at 37°C. The plate was immediately read at 450nm and the results calculated.

Evaluation of p53

p53 was immunohistochemically evaluated using prostate tissues according to the method described by [21]. Sections were deparaffinized by passing through two changes of xylene for 10 minutes and were hydrated through graded series of alcohol (absolute, 95% and 70%) for 5 minutes. Sections were incubated for 60 minutes in 10M citrate buffer for antigen retrieval and submerged in 3% hydrogen peroxide/methanol solution for 15 minutes at room temperature. Sections were incubated in 10% normal goat serum to inhibit non- specific reaction against primary antibody for 30 minutes. Sections were incubated with p53 polyclonal primary antibody (Elabscience, Wuhan, China) at dilution of 1:200 for 90 minutes and covered with goat anti-rabbit IgG HRP conjugated secondary antibody for 40 minutes. Sections were rinsed in PBS for 5 minutes each. Antigen-antibody reaction was detected by reaction with diaminobenzidine (DAB). Sections were counterstained in Harry's hematoxylin for 1 minute and rinsed in distilled water, dehydrated in ascending grades of alcohol, cleared in xylene and mounted with DPX mountant.

Microscopy and counting of positive cells

Photomicrographs were obtained at 400x magnification after viewing with a light microscope (Primo star 415500-0057000) using the microscope's camera (PDV 010-82613119) attached to a personal computer (PC). Counting of positive cells for p53 was done and quantified using ImageJ software.

Results

PSA outcome

The result presented below shows a significant increase in the serum level of PSA in cadmium chloride alone treated group when compared to control and standard (casodex). There was a dose-

dependent and significant decrease in the serum levels of PSA of rats given various doses of *U. chamae* root extract (2500mg/kg, 1500mg/kg and 1000mg/kg) after the administration of cadmium chloride when compared to control, standard and cadmium chloride alone treated group (figure 1).

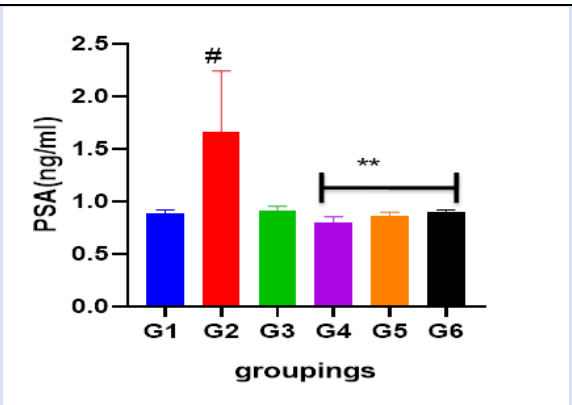

Figure 1: Serum PSA level following cadmium chloride-induced pre-malignancy.
#= significantly different from control and other treated groups
** =significantly different from from group 2 vs control vs standard

p53 outcome

There was poor p53 expression in the tissue sections of animals in the control (figure 2). An increase in the percentage positive cells of 30% with a well-differentiated and intensed p53 expression was evident in the tissue sections treated with cadmium chloride alone (figure 3). A moderately differentiated p53 positivity and percentage positive cells of 7% was noted in the tissue sections treated with standard (casodex) after cadmium chloride induction (figure 4) and a poor p53 expression observed in the tissue sections of animals treated with 2500mg/kg of *Uvaria chamae* root extract after cadmium chloride induction with percentage positive cells of about 1% (figure 5). A reduction in percentage positive cells of about 6% coupled with poor p53 expression was evident in the tissue sections of animals treated with 1500mg/kg of *Uvaria chamae* root extract after cadmium chloride induction (figure 6). A moderately differentiated p53 expression with percentage positive cells of 10% was evident in the tissue sections of animals treated with 1000mg/kg of *Uvaria chamae* root extract after cadmium chloride induction (figure 7).

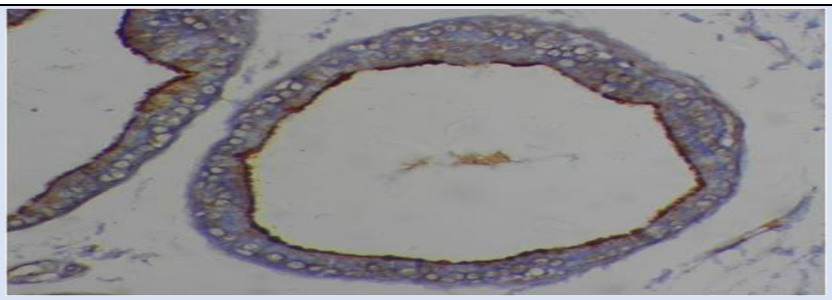

Figure 2: Photomicrograph of control rats given feed and water showing poor p53 expression (+). % of positive cells = 1%. p53,400x magnification.

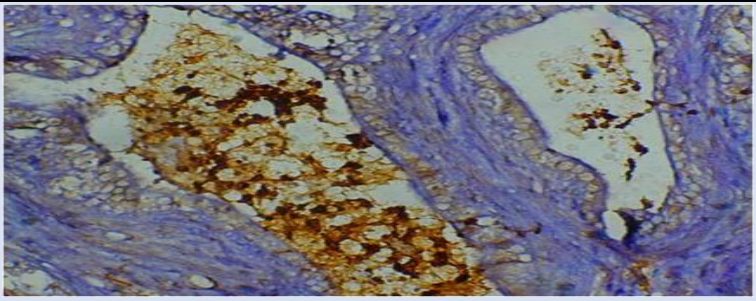

Figure 3: Photomicrograph of group 2 rats given 3mg/kg of $CDCl_2$ alone showing well- differentiated p53 positivity (+++). % of positive cells = 30%. p53, 400x magnification.

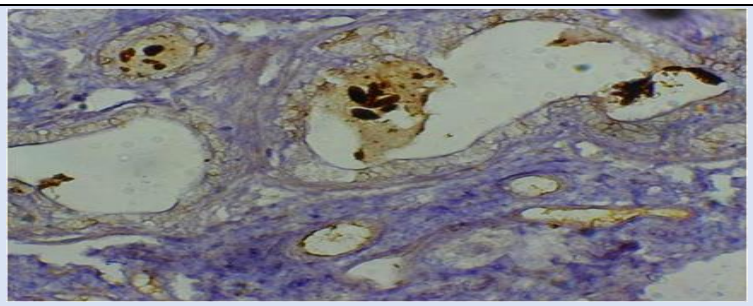

Figure 4: Photomicrograph of group 3 rats given 3mg/kg of $CDCl_2$ and 150mg/kg of casodex showing moderately differentiated p53 positivity (++). % of positive cells = 7%. p53, 400x magnification.

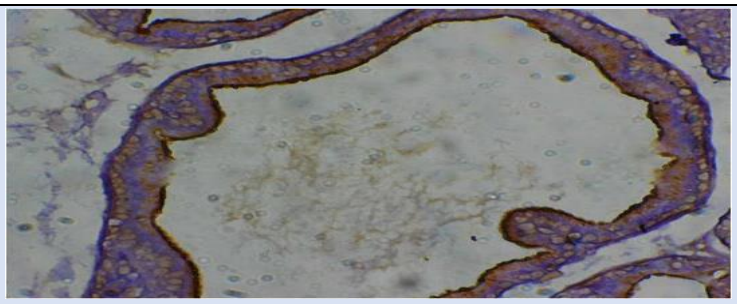

Figure 5: Photomicrograph of group 4 rats given 3mg/kg of $CDCl_2$ and 2500mg/kg of *Uvaria chamae* root extract showing poor expression of p53 (+). % of positive cells = 1%. p53, 400x magnification.

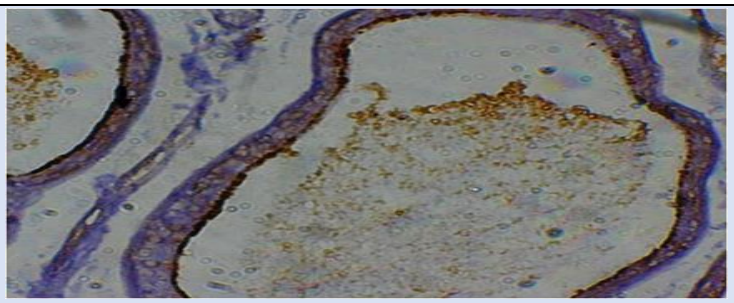

Figure 6: Photomicrograph of group 5 rats given 3mg/kg of $CDCl_2$ and 1500mg/kg of *Uvaria chamae* root extract poor expression of p53 (+). % of positive cells = 6%. p53, 400x magnification.

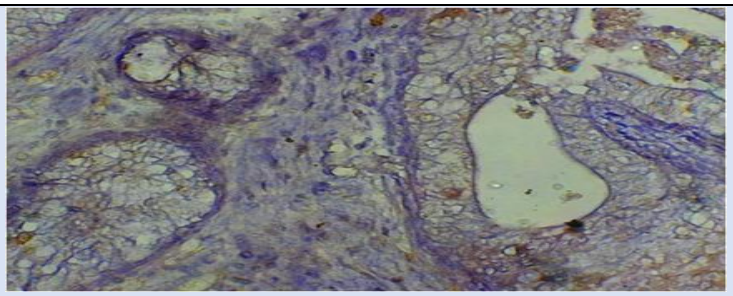

Figure 7: Photomicrograph of group 6 rats given 3mg/kg of $CDCl_2$ and 1000mg/kg of *Uvaria chamae* root extract showing moderately differentiated p53 (++). % of positive cells = 10%. p53 400x magnification.

Discussion

From our findings, prostate specific antigen (PSA) was seen to be elevated in the cadmium chloride treated group but significantly and dose-dependently suppressed in *Uvaria chamae* treated groups when compared to the standard and control. Prostate specific antigen belongs to the kalikrein family of proteases and has been documented to be derived from epithelial cells in the ducts of the prostate [22]. Since PSA levels have been reported to be directly correlated with prostate size and cancer, serum levels of PSA have been used as a biomarker for cancer of the prostate [23]. In rats, the kalikreins are encoded by a multigene family and is androgen dependent [24]. Clinical investigations have reported that, serum levels of PSA are directly proportional to prostate tumour volume and stage [25]. PSA has been extensively studied as a tissue-specific tumour marker and its discovery has elevated the hope for early detection of cancer of the prostate especially at a very

curable stage. Therefore, measurements of serum levels of PSA are one of the most specific and suitable indicators to evaluate and monitor response to prostate cancer treatment and to provide a signal concerning residual and recurrent disease [26]. Studies have shown that PSA levels are dependent on testosterone [27]. However, changes in the serum levels of PSA associated with ADT may spring from androgen-dependent prostatic cell death with subsequent decrease in the cell volume of the prostatic cells. Investigation of the regulation of the pharmacokinetic parameters and PSA secretion in *in vivo* studies have been poorly documented [28]. It has been demonstrated that the PSA value of patients at 60 years predicted not only a lifetime risk of clinically detected prostate cancer but also metastases and death from the disease [29]. Administration of *Uvaria chamae* root extract depicted the actions of ADT by inducing a reduction in the androgen-regulated production of PSA. The decrease in PSA levels after administration of varying doses of *Uvaria chamae* root extract is most likely due to tumour cell death and/or decreased expression of androgen receptor-stimulated PSA in the tumour cells resulting in androgen-independent induction of PSA gene expression which is regulated by androgen receptor dependent pathway [30, 31, 32]. Our results are in tandem with the works of [30] who documented a decrease in PSA after primary or standard ADT in prostate cancer patients.

Furthermore, p53 expression was up-regulated significantly in the cadmium chloride alone treated animals when compared to control and standard. p53 is a tumour suppressor protein which plays a critical role in DNA damage [4]. Its occurrence is very common in many cancers and is associated with cancer progression and poor prognosis [6]. Our findings revealed a high p53 expression of about 30% and this result corresponds to other reported studies which indicated a positivity rate of about 10 to 22 percent. Our findings corroborate that of [33] who reported a positive staining rate of 51% of p53 in patients with cancer. Similarly, p53 reactivity has been reported in high grade prostatic intraepithelial neoplasia cells in some tumours [34]. Expression of p53 was also reported in a certain study to be present in about 58% and 39% of high grade and low-grade tumours respectively. It is worthy to note that, the percentage of p53 positivity tends to be higher in a higher tumour grade. The proportion of this positive stain could be associated with the application of antigen retrieval method in the laboratory. Studies on higher expression of p53 in prostate cancer have also been reported by [35] who employed a similar antigen-retrieval method in the laboratory. Scientific evidence demonstrates that, functional inactivation as well as mutation of p53 protein is a universal and acceptable feature of most cancers [36], thus the role of Tp53 as a prognostic marker as well as a good predictor therapy response cannot be overemphasized. Administration of cadmium chloride elicited activation of oncogenes, DNA damage and activation of Tp53 which upon activation, p53 directly causes the regulation of gene transcription to cause diverse cellular processes [37]. Due to these diverse stress stimuli, p53 level rose substantially due to the activation of several signaling pathways [37]. p53 caused the induction of apoptosis in non-transformed cells by directly initiating transcriptional activation of pro-apoptotic proteins such as PUMA and NOXA proteins [38]. Expression of p53 was down-regulated in all the *Uvaria chamae* treated animals and this resulted in the reduction of positive stained cells across groups when compared to control and standard. A down-regulation of 1%, 6% and 10% of positive cells were dose-dependently observed when compared to control and standard. This down-regulation can be linked to the association between p53 and the bioactivities of *Uvaria chamae*. The root extract is believed to act as an androgen deprivation therapy to initiate apoptosis of the mutant cells thereby down-regulating p53 expression. Several studies have demonstrated low expression of p53 after androgen ablation therapy. [39] demonstrated a decrease in p53 expression in the prostate of patients treated with ADT when compared to untreated ones. Similarly, [40] demonstrated hormonal therapy advantage due to a decrease in p53 positivity in tumour cells after hormonal therapy. Therefore, the loss of p53 effectors of apoptosis such as PUMA and NOXA proteins as well as cell cycle arrest hinders the development of tumour. Administration of varying doses of *Uvaria chamae* is believed to cause induction of apoptosis through the loss of PUMA and NOXA which is a potential mechanism of action through which many anti-cancer drugs kill malignant cells [38]. It is noteworthy to say that p53 is an important prognostic and predictive indicator for cancer and can assist in the development of a novel anti-cancer therapy.

Conclusion

Results obtained from this study showed that ethanol root extract of *U. chamae* down-regulated the serum level of PSA and p53 expression in cadmium chloride-induced prostate pre-malignancy. Furthermore, our study is novel and showed that *U. chamae* root possesses strong anti-cancer property in prostate pre-malignancy.

Declarations

Ethical Approval

Ethical approval was obtained from Research Ethics Committee of College of Medical Sciences, University of Benin, Benin City for approval. Approval number CMS/REC/2022/275 was given.

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Competing Interests

Authors have declared that no competing interests exist.

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