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Modulatory Effects of Some Selected Functional Foods on Physiological and Biochemical Indices of Testosterone-Dimethylbenzen(a)anthracene (DMBA)-Induced Prostate Cancer in Rats

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ABSTRACT

Prostate cancer remains a health concern globally, with emerging interest in functional foods as potential therapeutic interventions. Benzyl isothiocyanate, citrulline, and eugenol, found in Papaya, watermelon, and cloves, respectively, have demonstrated anticancer properties. This study investigated the modulatory effects of selected functional foods (papaya seeds, watermelon seeds, and clove) on physiological and biochemical parameters in testosterone-DMBA-induced prostate cancer in Wistar rats. Seventy male Wistar rats (8-10 weeks), were randomly divided into seven groups (n=10): normal control, induced control, combination diet containing 2% of the combined supplements, individual supplements (4% papaya seeds, 4% watermelon seeds, 2% clove), and flutamide treatment. Prostate cancer was induced with testosterone (3 mg/kg) and DMBA (65 mg/kg). Animals were fed supplemented diets, and various parameters were assessed. The combination diet group (Group 3) showed significantly higher feed intake (158.15±13.09 g vs. 88.36-111.48 g in the other induced groups) and demonstrated the lowest final body weight (146.1±10.67 g), with a 54.60% weight increase. It exhibited significantly elevated organ-to-body weight ratios, particularly in the liver ($6.38±0.22×10^{-3}$), kidney ($1.26±0.17×10^{-3}$), spleen ($1.39±0.07×10^{-3}$). Group 3 showed the lowest ALT levels (5.00±2.31 µ/L), however, with elevated urea (348.33±142.14 mg/dL) and the highest creatinine levels (1.30±0.20 meq/L). Watermelon supplementation resulted in significantly higher HDL (21.67±4.41 mg/dL). The findings suggest that dietary interventions using phytochemical-rich foods may be beneficial in managing prostate cancer. HDL improvement in the watermelon group aligns with antioxidant properties of flavonoids, which may counteract cancer-associated oxidative stress. Flutamide provided a baseline for efficacy but lacked the multi-targeted phytochemical benefits.

Keywords: Prostate cancer, functional foods, Papaya, watermelon, Clove, DMBA, phytochemicals, Flutamide.

Introduction

Prostate cancer (PC) represents a significant global health burden, ranking as the second most common cancer in men and fourth most prevalent overall.[1] In 2022, approximately 1.47 million new cases were diagnosed worldwide, accounting for 7.3% of all cancer cases, with 397,430 associated deaths.[2,3] Incidence rates vary considerably by region, with high rates in the United States (112 per 100,000 men) and France (82.3 per 100,000).[4,5] In Africa, PC poses a growing challenge with 93,173 new cases recorded in 2020, Nigeria showing one of the highest mortality rates at 27.9 per 100,000 men.[6,7] This elevated mortality in developing regions stems from late diagnosis, limited treatment access, and insufficient awareness of prostate health. [8, 9, 10] These disparities between developed and developing nations underscore the urgent need for context-specific screening and intervention strategies.

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Testosterone is crucial in the pathophysiology of prostate cancer via various interrelated processes. The enzyme 5α-reductase transforms testosterone, the main circulating androgen, into dihydrotestosterone (DHT) when it enters prostate cells. Compared to testosterone, DHT has around five times the same affinity for the androgen receptor (AR). Upon binding, DHT-AR complexes translocate to the nucleus, where they interact with androgen response elements (AREs) in DNA, recruiting coactivators and initiating the transcription of genes that regulate cell proliferation, survival, and differentiation.[11-16] Prostate epithelial cell proliferation is stimulated by this testosterone signalling system, which may also encourage neoplastic transformation in some circumstances. The AR signalling axis influences numerous cellular processes involved in carcinogenesis, including cell cycle progression through the regulation of cyclin-dependent kinases, the expression of anti-apoptotic proteins, and growth factor signalling pathways. Additionally, testosterone stimulation can induce chromosomal rearrangements, particularly TMPRSS2-ERG gene fusions, which are found in approximately 50% of prostate cancers and contribute to disease progression.[17-22] In established prostate tumours, persistent AR signalling drives cancer cell proliferation and survival, even in advanced disease states.[23-26] The cornerstone of treatment for advanced prostate cancer, androgen deprivation therapy (ADT), is based on this biological reliance. However, most tumours eventually develop resistance to ADT through various mechanisms, including AR amplification, AR mutations that allow activation by non-androgen ligands, and constitutively active AR splice variants that function without ligand binding.[23-30] The relationship between testosterone and prostate cancer is further complicated by observations that both very

low and high testosterone levels can be associated with aggressive disease, suggesting a non-linear relationship that challenges the traditional linear model of androgen action in prostate carcinogenesis.[31,32] The carcinogenic effects of DMBA further complicate this relationship; DMBA is known to induce DNA damage leading to mutations that promote tumorigenesis.[33,34] Given these complexities, interest is rising in exploring dietary interventions that may mitigate the effects of prostate cancer. The abundance of bioactive chemicals in natural products including papaya seeds, watermelon seeds, and clove buds has drawn attention to their possible health advantages. Papaya is recognised for its antioxidant properties and ability to boost immune function due to its high levels of vitamins C and E, carotenoids, and enzymes such as papain.[35] Watermelon contains lycopene, which has been associated with reduced oxidative stress and inflammation in various studies.[36,37] Clove is recognised for its eugenol content, which exhibits potent anti-inflammatory and analgesic properties.[38,39]

This study represents a comprehensive investigation into the combined effects of papaya seeds, watermelon seeds, and clove buds on physiological, haematological, and toxicological parameters in a testosterone-DMBA-induced prostate cancer model. While previous research has examined these natural products individually for various health conditions, our work uniquely explores their specific modulatory effects on prostate cancer-associated metabolic disturbances. This approach is particularly novel in addressing the growing burden of prostate cancer in resource-limited settings such as parts of Africa, where accessible dietary interventions could significantly impact patient management strategies by examining multiple physiological systems simultaneously, including liver function, kidney function, lipid metabolism, and haematological parameters. This research provides a holistic understanding of how these plant-based supplements interact with prostate cancer pathophysiology, filling a critical gap in the current literature on complementary approaches to prostate cancer management.

The methodology employed in this study aligns with its translational objectives by utilising a clinically relevant animal model that mirrors the complex pathophysiology of human prostate cancer. The testosterone-DMBA induction method accurately simulates the hormonal and carcinogenic factors involved in human prostate carcinogenesis, allowing for meaningful extrapolation to clinical scenarios. Our selection of physiological, hematological, and toxicological markers provides comprehensive insights into systemic responses to both cancer progression and dietary interventions, which are essential for understanding the holistic impact of these natural products. The percentage-based dietary supplementation approach (4% for papaya and watermelon seeds, 2% for Cloves) facilitates the practical translation of human nutritional recommendations, as these levels approximate achievable nutritional modifications. Additionally, our focus on commonly available natural products addresses the urgent need for accessible interventions in resource-limited settings, where conventional cancer treatments may be prohibitively expensive or unavailable. This makes our methodological approach particularly relevant to global health priorities in prostate cancer management.

This study aimed to investigate the modulatory role of these natural products on physiological, haematological, and toxicological markers in a rat model of testosterone-DMBA-induced prostate cancer. As prostate cancer continues to pose a significant health burden globally, especially in regions like Africa where resources are limited, there is an urgent need for innovative strategies that leverage dietary interventions to improve patient outcomes and quality of life. This research aims to contribute to this critical area by investigating the potential benefits of Papaya, watermelon, and Cloves in managing prostate cancer-related physiological changes.

Materials and Methods

Chemicals and reagents

All chemicals were of analytical grade and were obtained from trusted suppliers. Flutamide (CAS 13311-84-7, ≥99% purity), Carboxymethylcellulose (CAS 9004-32-4, analytical grade), Testosterone propionate (CAS 57-85-2, ≥98% purity), 7,12-dimethylbenz[a]anthracene (DMBA) (CAS 57-97-6, 95% purity), and Testosterone (CAS 58-22-0, ≥98% purity) were obtained from Beijing Solarbio Science & Technology Co., Ltd, Tongzhou Dist, Beijing, China. Chloroform (analytical grade, 99.8% purity) used for euthanasia was purchased from Sigma-Aldrich (St. Louis, MO, USA). All lipid analyses were performed on the Randox RX Daytona automated biochemistry analyser, with each sample analysed individually. The enzymatic colourimetric assay kits for ALT, AST, ALP, total protein, albumin, total bilirubin, conjugated bilirubin, creatinine, uric acid, and urea were obtained from Randox Laboratories Limited (Crumlin, UK). All biochemical and hematological analyses were performed in triplicate to ensure the reliability and reproducibility of the results. The mean values of these replicate measurements were used for statistical analysis and interpretation.

Equipment/Instrumentation

Blood collection was performed using BD Vacutainer® tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Centrifugation was conducted using a Denley BS400 centrifuge (Denley Instruments Ltd., UK) at 250 rpm for 10 minutes. Haematological parameters were assessed using a Sysmex XE-2100 automated haematology analyser (Sysmex Corporation, Kobe, Japan). Biochemical analyses were performed using a Randox RX Daytona automated biochemistry analyser (Randox Laboratories Limited, Crumlin, UK). Organ and body weights were measured using a calibrated Mettler Toledo PB3002 analytical balance (Mettler Toledo, Columbus, OH, USA) with a precision of 0.01 g. Feed ingredients were processed using a Waring commercial laboratory blender (Model 8010S, Waring Commercial, Torrington, CT, USA). Temperature and humidity were monitored using a ThermoPro TP50 digital hygrometer (iTronics Inc., USA).

Feed

Corn starch was extracted through a multi-step process. Initially, dried corn kernels were submerged in water for 48 hours to facilitate rehydration. The soaked kernels were then pulverised into a uniform consistency and passed through a 0.02 mm mesh cheesecloth, separating the solid residue from the starch-rich filtrate. The filtrate was allowed to settle for 2 hours, enabling phase separation. The supernatant liquid was carefully decanted, leaving behind a concentrated starch layer. This starch was dried thoroughly at ambient temperature and subsequently milled into a fine, uniform powder. The necessary feed components, including soya bean meal (SBM), pre-mix, salt mix, cellulose, palm oil, methionine, and bone meal, were acquired from a reputable local vendor in Kano, Nigeria.

Collection of Plant Material and Identification

Fresh specimens of Papaya, watermelon fruits including seeds, and clove buds were procured from a local market in Dutsin-Ma (12.4672° N, 7.4947° E), Katsina State, Nigeria, in July 2024. Subsequent taxonomic identification and authentication were conducted by a qualified botanist at the Plant Biology Department's Herbarium, Federal University, Dutsin-Ma, Katsina State. Voucher specimens were deposited with the following accession numbers: Papaya FUDMA/PSB/00004, Watermelon FUDMA/PSB/00118, and Clove FUDMA/PSB/00087. The collected papaya and watermelon fruits underwent initial processing, during which they were washed, dissected, and the seeds were carefully extracted. Seeds from Papaya, watermelon, and Clove were then subjected to separate cleaning and drying protocols. Seeds were dried for 72 hours in a well-ventilated area, stirring multiple times to ensure uniform drying. Following drying, the seeds were pulverised into fine powder using a laboratory-grade blender. The resulting powders were sieved to achieve uniform particle size and stored at room temperature for further analysis. This meticulous processing ensured the preparation of high-quality seed powders for subsequent experimentation.

Feed Formulation

A standardized rodent diet was formulated by combining the following components in specific proportions: corn starch (554.5 g/kg), SBM (320 g/kg), methionine (2.5 g/kg), vitamin and mineral pre-mix (2.5 g/kg), salt (2.5 g/kg), cellulose (45 g/kg), palm oil (60 g/kg), and bone meal

(12.5 g/kg). These ingredients were thoroughly mixed to create a nutritionally balanced and homogeneous diet that adheres to established rodent nutritional requirements.[40]

Diet supplementation
A supplemented diet was formulated by thoroughly mixing 98 g of standard rodent chow with 2 g of a proprietary blend consisting of papaya seed powder, watermelon seed powder, and clove powder in a ratio of 4:4:2, respectively. The 4:4:2 ratio balances therapeutic efficacy with safety considerations, providing optimal exposure to bioactive compounds while preventing eugenol-related toxicity associated with excessive clove consumption.

Experimental Animals
Seventy (70) male Wistar rats, aged 8-10 weeks, were procured from the Ebonyi State University's Department of Biological Sciences Animal House. Upon arrival, rats were housed in standard plastic cages and acclimatised to laboratory conditions (temperature: 25°C, humidity: 50%) for two weeks. During this period, they received standard rodent chow and water *ad libitum*, ensuring optimal health and well-being before experimentation. All animal handling and experimental procedures were conducted following and adhering to the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines. The samples were prepared in replicate. The study design and execution complied with international ethical standards for animal experimentation. Ethical approval was sought from the Animal Care and Use Research Ethics Committee (ACUREC) at Bayero University, Kano, where animal use protocol number (AUP): BUK/ACUREC/CAP/PG46 was assigned.

Experimental Design
Following a two-week acclimation period, seventy male Wistar rats were randomly divided into seven groups (n = 10) with comparable average weights.

Grouping of Experimental Animals
Group 1: Normal control.
Group 2: Induced animals + standard rodent chow.
Group 3: Induced animals + supplemented diet + 2% of combined seeds (4% papaya seeds, 4% watermelon seeds, 2% clove).
Group 4: Induced animals + 4% of papaya seeds.
Group 5: Induced animals + 4% of watermelon seeds.
Group 6: Induced animals + 2% of clove bud.
Group 7: Induced animals + 10 mg of Flutamide.

The 4:4:2 ratios (Papaya: watermelon: clove) were selected based on bioactive compound concentrations, safety thresholds, and synergistic optimisation. Papaya and watermelon seeds were used in equal proportions, at 4% each, to provide sufficient bioactive compounds for anticancer activity while maintaining a therapeutic balance between apoptotic and vascular mechanisms. Clove was limited to 2% due to eugenol's high potency (9,000-15,000 mg/100 g) and potential toxicity, ensuring levels remain below the World Health Organisation (WHO) safety guidelines (2.5 mg/kg body weight), while still providing antioxidant and anti-inflammatory support. The total 2% supplementation maintains nutritional balance, feed palatability, and normal consumption patterns without overwhelming metabolic capacity, thereby creating an optimal formulation that maximises therapeutic benefits while minimising adverse effects through careful consideration of each component's bioactive profile and safety margins.

Induction Protocol
Initially, flutamide (25 mg/kg) was given daily via gavage for 2 weeks. Twenty-four hours after starting Flutamide, testosterone propionate (100 mg/kg) was injected subcutaneously. This was followed by an intraperitoneal injection of DMBA (65 mg/kg) 56 hours later. Finally, testosterone (3 mg/kg) was administered subcutaneously every 48 hours for 10 weeks, starting 1 week after DMBA induction.[41-42]

Measurement of Feed Intake, Water Intake, and Bodyweight
Daily feed and water consumption measurements were recorded to assess the feeding patterns of the Wistar rats. Uneaten feed and spillage were collected and weighed to calculate actual consumption. Water intake was monitored using calibrated bottles. Concurrently, body weight assessments were conducted weekly to monitor growth and development, ensuring comprehensive tracking of animal health and well-being throughout the experimental period.

Collection and Preparation of Sera Samples
Following the 16-week study period, rats were weighed and humanely euthanised via chloroform inhalation. Blood samples were collected via cardiac puncture and transferred to plastic red-top tubes for centrifugation. After clotting, serum was separated through centrifugation (Denley BS400, 250 rpm, 10 minutes). Subsequently, organs of interest (prostate, lungs, liver, kidney, heart, and spleen) were dissected, weighed, and organ-to-body weight ratios calculated. Comparing organ-to-body weight ratios between treatment groups and control groups provides insights into the effectiveness and safety of the intervention. Serum samples underwent various biochemical analyses to assess physiological changes. Haematological analysis provides a baseline assessment of the overall health status of the animals before and during treatment. This is crucial for identifying any pre-existing conditions or vulnerabilities that could influence treatment outcomes or be affected by the treatment itself. Serum lipid profile analysis was performed to assess the impact of these interventions on lipid metabolism and to determine whether they have beneficial or detrimental effects on cardiovascular risk. Serum liver enzymes analysis; prostate cancer and its treatments can influence metabolic processes, potentially affecting liver function. Analysing liver enzymes can provide insights into these metabolic changes and their impact on liver health. Serum kidney function, as indicated by serum creatinine, urea, and uric acid, is a key indicator of kidney function. Monitoring these parameters enables the detection of kidney damage or dysfunction, which can be caused by cancer itself or its treatments.

Assessment of Organ to Body Weight Ratio
The organ-to-body weight ratio for each group was calculated by dividing the weight of each dissected organ (prostate, lungs, liver, kidney, heart, and spleen) by the corresponding terminal body weight of the rat and then multiplying by 100 to obtain a percentage, as shown in equation (1).

$$\text{Organ to body weight ratio} = \frac{\text{Weight of organ (mg)}}{\text{Weight of rat}} X\ 100 \quad (1)$$

Haematological Analysis
An auto haematology analyser (XE-2100 by Sysmex Corporation) was used to determine the haemoglobin concentration (Hb), red blood cell count (RBC), total white blood cell count (WBC), lymphocytes, Monocytes, eosinophils, and Packed cell volume (PCV).[43]

Lipid Profile Analysis
Estimation of Serum Lipid
Spectrophotometric analysis was performed on serum lipid profiles using enzymatic colorimetric test kits (Randox RX Daytona).

Estimation of Serum Total Cholesterol (TC)
One thousand microlitres (1000 µL) of the reagent were given to each sample and standard. Following mixing, the mixture was incubated at 20–25°C for 10 minutes. After 30 minutes, the absorbance of the samples (A sample) and standards (A standard) was measured at a wavelength of 546 nm in comparison to the reagent blank. All determinations were performed in duplicate, and the mean values were calculated for each sample. The concentration of total cholesterol (TC) in the serum was expressed in mg/dL (equation 2).

$$\text{TC concentration} = \frac{\text{A sample}}{\text{A standard}} \; X \text{ concentration of standard (200mg/dL)} \quad (2)$$

Estimation of Serum Triacylglycerol (TAG)
All samples and standards were first treated with 1000 µL of the reagent. The mixture was combined and then incubated at 20–25°C for 10 minutes. After 30 minutes, the absorbance of the samples (A sample) and standards (A standard) at a wavelength of 546 nm was measured in comparison to the blank. All determinations were performed in duplicate, and the mean values were calculated for each sample. The concentration of triacylglycerol in the serum was measured in millimoles per litre (mmol/L) (equation 3).

$$\text{Triacylglycerol (mg/dL)} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \; X \text{ concentration of standard (200mg/dL)} \quad (3)$$

Estimation of Serum High-Density Lipoprotein Cholesterol (HDL-C)
After letting the mixture settle for ten minutes at room temperature, it was centrifuged for ten minutes at 4000 rpm. HDL-C percentage was detected in the supernatant. The HDL fraction's cholesterol content, which was kept in the supernatant, was measured. All determinations were performed in duplicate, and the mean values were calculated for each sample. Equation (4)

$$\text{HDL} - \text{C (mg/dL)} = \frac{\text{Absorbance of sample } X \text{ concentration of standard (50mg/dL)}}{\text{Absorbance of standard}} \; X \; 2 \quad (4)$$

Estimation of Serum Low-Density Lipoprotein Cholesterol (LDL-C)
The serum level of LDL-C was measured according to protocol.[44] And calculated as in (equation 5)

$$\text{LDL (mg/dL)} = \text{Total Cholesterol} - \text{HDL} - \frac{\text{Triglycerides}}{5} \quad (5)$$

Liver Function Analysis
Utilising enzymatic colorimetric assay kits from Randox Laboratories Limited (Crumlin, UK), serum enzymes Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and Alkaline Phosphatase (ALP) were measured spectrophotometrically while following the manufacturer's laboratory protocols.

Estimation of Aspartate Aminotransferase (AST)
After adding 1.0 mL of a reagent—which includes enzyme, coenzyme, and L-oxoglutarate to a test tube, 0.1 mL of the sample was added in order to measure the concentration of Aspartate Amino Transferase (AST). The solution was well mixed, and the absorbance was measured at 340 nm. The absorbance readings were taken at 1-minute intervals for 3 minutes. The change in absorbance per minute (ΔA/min) was calculated by subtracting the final absorbance from the initial absorbance and dividing by the time interval. Equation (6) All determinations were performed in duplicate, and the mean values were calculated for each sample.

$$\text{AST activity (U/L)} = \Delta\text{A/min} \times 1746 \quad (6)$$

Estimation of Alanine Aminotransferase (ALT)
ALT activity was measured by pipetting 1.0 mL of working reagent (TRIS buffer, lactate dehydrogenase, L-alanine, NADH, and 2-oxoglutarate) into a 37°C cuvette, gently mixing, and timing with a stopwatch. The first absorbance reading was recorded after 1 minute, and differences between absorbance readings at 1, 2, and 3 minutes were recorded. Absorbance change per minute (ΔA/min) was calculated from the mean result (equation 7). All determinations were performed in duplicate, and the mean values were calculated for each sample.

$$\text{ALT activity (U/L)} = \Delta\text{A/min} \times 3333 \quad (7)$$

Estimation of Alkaline Phosphatase (ALP)
Three millilitres of the substrate solution were pre-incubated for fifteen minutes at 37°C. 9.5 mL of 0.085 N NaOH in the substrate solution combined with 0.5 mL of the sample served as the blank (zero-time assay). The mixture of substrate and sample was further incubated for 15 minutes at 37°C. Following incubation, the mixture was measured at 405 nm against the reference blank after 0.5 mL was added to 9.5 mL of 0.085 N NaOH. The moles of p-nitrophenol produced by ALP indicated its activity (equation 8). All determinations were performed in duplicate, and the mean values were calculated for each sample.

$$\text{ALP activity (U/L)} = \Delta\text{A/min} \times 2757 \quad (8)$$

Estimation of Total Protein (TP)
Three test tubes—the blank, the standard, and the sample—were pipetted with 1 mL of the biuret reagent. Test tubes were filled with 0.020 mL of distilled water, 0.02 mL of standard, and 0.02 mL of test sample. After combining the contents, they were incubated at 25°C. Equation 8 was used to compare the absorbances of the sample (Asample) and standard (Astandard) to the reagent blank. Equation (9). All determinations were performed in duplicate, and the mean values were calculated for each sample.

$$\text{Total Protein (g/dL)} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \; X \text{ concentration of standard 6g/dL)} \quad (9)$$

Estimation of Serum Albumin
Three millilitres (3 mL) of BCG reagent were placed in three test tubes designated blank, standard, and sample. The test sample, reference reagent, and 0.01 mL of distilled water were then pipetted into the tubes. For five minutes, the mixtures were incubated at 25°C. Following incubation, the absorbance of the sample (Asample) and the standard (Astandard) at 630 nm was measured using spectrophotometers in comparison to the reagent blank (equation 10). All determinations were performed in duplicate, and the mean values were calculated for each sample.

$$\text{Albumin (g/dL)} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \; X \text{ concentration of standard (4 g/dL)} \quad (10)$$

Estimation of Total Bilirubin
Albumin-bound bilirubin is released when diazotised sulphuric acid and coffee are used to measure total bilirubin levels. Serum. First, reagents and equipment were used to estimate total bilirubin. Serum sample (0.2 mL) was pipetted into blank, standard, and sample test tubes. Next, we filled each test tube with 2.5 mL of diazo reagent and allowed them to sit at room temperature for 10 minutes. Following incubation, the absorbance of the sample (Asample) and standard (Astandard) was measured at 546 nm in relation to the reagent blank (equation 11). All determinations were performed in duplicate, and the mean values were calculated for each sample.

$$\text{Total Bilirubin (mg/dL)} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \; X \text{ concentration of standard (5mg/dL)} \quad (11)$$

Kidney Function Analysis
A Randox Laboratories Limited (Crumlin, UK) automated biochemistry analyser was used to measure the levels of serum creatinine, uric acid, and urea in accordance with the manufacturer's laboratory protocols.

Estimation of Creatinine
To extract the serum from the blood cells, it was centrifuged. 1.0 mL of alkaline picrate solution was added to 0.1 mL of serum that had been pipetted into a test tube. To enable the reaction, the mixture was incubated for five minutes at room temperature. A spectrophotometer was used to test the sample's absorbance at 520 nm. A blank sample of alkaline picrate solution was also evaluated in order to account for background absorption (equation 12 and 13). All determinations were performed in duplicate, and the mean values were calculated for each sample.

Creatinine (mg/dL) =

$$\frac{\Delta A \text{ of sample}}{\Delta A \text{ of standard}} \; X \; \text{Concentration of standard (2 mg/dL)} \quad (12)$$

$$\text{Creatinine (mEq/L)} = \frac{\text{Creatinine (mg/dL)}}{113.12 \times 1} \; X \; 10 \quad (13)$$

Estimation of Urea

To extract the serum from the blood cells, it was centrifuged. 1.0 mL of urease enzyme solution was added to a test tube containing 0.1 mL of serum that had been pipetted there. At 37°C, the mixture was incubated for ten minutes. After that, 1.0 mL of phenol and hypochlorite solutions were added to the test tube. After thorough mixing, the mixture was incubated for ten minutes. The test tube was then filled with 1.0 mL of sodium hydroxide solution and carefully swirled. The absorbance of the blue solution at 578 nm was measured using a spectrophotometer (equation 14). All determinations were performed in duplicate, and the mean values were calculated for each sample.

Urea (mg/dL) =

$$\frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \; X \; \text{concentration of standard (80 mg/dL)} \quad (14)$$

Estimation of Uric Acid

To extract the serum from the blood cells, it was centrifuged. 1.0 mL of uricase enzyme solution was put to a test tube containing 0.1 mL of serum that had been pipetted there. At 37°C, the mixture was incubated for five minutes. A spectrophotometer was used to test the sample's absorbance at 293 nm. Subtract the sample's absorbance upon incubation from its absorbance prior to incubation (equation 15) to measure the absorbance decrease. All determinations were performed in duplicate, and the mean values were calculated for each sample.

Uric Acid (mg/dL) =

$$\frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \; X \; \text{concentration of standard (mg/dL)} \quad (15)$$

Data Analysis

SPSS software (Statistical Package for Social Sciences, version 21; SPSS Inc., Chicago, IL, USA) was used to analyse the data. SEM, or standard error of mean, is used to present the results. The study utilised Duncan's multiple comparison test to identify significant variations in group means. A significance level of $p < 0.05$ was established.

Results and Discussion

The feed intake data revealed distinct patterns across the seven experimental groups (Table 1). The most notable finding is the maintenance of feed intake in Group 3 (supplemented with combined Papaya, watermelon, and cloves), which was statistically equivalent to that of normal controls and significantly higher than in all other treatment groups. This effect suggests that the bioactive compounds present in these supplements have complementary mechanisms of action.

A study demonstrated that phytochemical combinations demonstrate enhanced bioavailability and improved modulation of inflammatory cytokines compared to individual compounds.[45,46] The results align with findings that demonstrated improvement in nutritional parameters when using polyphenol-carotenoid combinations in cancer intervention studies.[47] Group 7, treated with the anti-androgen medication flutamide, showed feed intake levels that were not statistically different from the cancer control group. The present findings suggest that the standard flutamide dose may not adequately address the systemic effects of prostate cancer that impact feed intake, highlighting a potential advantage of the combined phytochemical approach employed in Group 3. The superior performance of the combined supplement can be explained through multiple mechanisms.

Table 1: Effect of Testosterone-DMBA-Induced Prostate Cancer in Wistar rats on Feed Intake

Group	Feed intake (g)
1	151.76±3.99[a]
2	104.48±7.69[b]
3	158.15±13.09[a]
4	88.36±5.79[b]
5	94.25±8.79[b]
6	99.77±6.35[b]
7	111.48±7.90[b]

Values represent mean ± SEM. Values with identical superscripts do not exhibit significant differences (P<0.05), while values with different superscripts exhibit significant differences.

Lycopene from watermelon has demonstrated anti-inflammatory effects through the inhibition of the NF-κB pathway,[48] while Papaya's enzymatic compounds improve protein digestion and nutrient absorption.[49] Eugenol in cloves provides antioxidant protection and modulates taste perception.[50,51] Together, these compounds appear to create a comprehensive approach to improving feed intake through complementary pathways.

Table 2: Effect of Testosterone-DMBA-Induced Prostate Cancer in Wistar rats on Water Intake

Group	Water intake (ml)
1	174.70±5.58[a]
2	161.23±9.67[a]
3	130.45±10.82[b]
4	108.33±6.84[b]
5	113.49±10.95[b]
6	127.07±8.99[b]
7	128.39±10.54[b]

Values represent mean ± SEM. Values with identical superscripts do not exhibit significant differences (P<0.05), while values with different superscripts exhibit significant differences.

The findings for water intake suggest that while feed intake was significantly affected by cancer induction, water intake remained relatively stable, indicating differential effects on feeding and drinking behaviours (Table 2). All intervention groups, including Group 3 with the highest feed intake, exhibited significantly lower water intake compared to both control groups. Some studies have proposed that certain phytochemicals improve metabolic efficiency and reduce oxidative stress.[52] This, in turn, could enhance cellular water retention, thereby reducing the physiological drive for water consumption. The similarity in water intake between Flutamide and phytochemical interventions suggests potentially overlapping mechanisms affecting water homeostasis, despite their distinct pharmacological properties. Both pharmaceutical and phytochemical interventions may improve kidney function, reducing compensatory water consumption. Specifically, papaya extracts, rich in antioxidants and bioactive compounds, have been shown to mitigate oxidative stress and reduce histopathological damage in renal tissue, suggesting their potential protective effects against toxin-induced kidney inflammation,[53] potentially normalizing kidney function. Lycopene, a bioactive compound found in watermelon, reduces oxidative damage in renal tubules by inhibiting NF-κB pathway activation, as demonstrated in models of toxin-induced nephropathy.[54,55,56] This protection may improve water reabsorption efficiency, resulting in reduced water requirements. Similarly, Clove's eugenol component has demonstrated significant antioxidant activity in renal tissue through activation of Nrf2 pathways.[57] It has been documented in a study that specific polyphenols like eugenol exhibit potent antioxidant and anti-inflammatory

properties, contributing to the protection of tissues and modulation of molecular pathways involved in oxidative stress and inflammation,[58] potentially improving water conservation at the renal level. Flutamide, antagonizing androgen receptors, may indirectly alter vasopressin-related pathways in contexts where testosterone's AR-dependent signalling modulates AVP activity, such as social memory.[59] The ability of both phytochemical combinations and Flutamide to normalize water consumption may represent an essential aspect of comprehensive cancer management. Remarkably, the comparable effects of natural interventions and pharmaceutical treatment suggest potential complementary approaches for symptom management. The combined Papaya, watermelon, and clove supplementation (Group 3) resulted in the lowest weight gain among all groups, significantly lower than even the cancer control group (Table 3). This finding appears paradoxical, especially considering the previously discussed improvement in feed intake observed in this group.

Table 3: Changes on Body Weight of Testosterone-DMBA-Induced Prostate Cancer in Wistar Rats

	Initial body weight(g)	Final body weight(g)	Body weight diff (g)	Increase in weight (%)
1	92.5±5.70^{a}	296±10.27^{c}	203.50	220.00
2	100.5±3.66^{a}	196±10.20^{a}	95.50	95.02
3	94.5±7.68^{a}	146.1±10.67^{b}	51.60	54.60
4	99.2±6.88^{a}	169.7±18.42^{ab}	70.50	71.07
5	97.7±3.31^{a}	171.6±9.26^{ab}	73.90	75.64
6	85.9±3.86^{a}	162.1±13.79^{ab}	76.20	88.71
7	84.6±4.30^{a}	159.3±10.66^{ab}	74.70	88.30

Values represent mean ± SEM. Values with identical superscripts do not exhibit significant differences (P<0.05), while values with different superscripts exhibit significant differences.

A study has shown that certain phytochemical combinations have demonstrated improvements in health parameters, such as tumour suppression and immune modulation, in cancer models. However, their effects on weight regulation remain unexplored.[60] However, this phenomenon might be due to high thermogenesis associated with the cancer condition.[61] Groups receiving individual supplements (Groups 4-6) exhibited intermediate weight gain, statistically indistinguishable from both the cancer control (Group 2) and each other (Table 4). These results differ from findings reporting that watermelon supplementation led to significant improvements in weight regulation and metabolic health in animal models, including reductions in body weight and BMI, as evidenced by studies on its antioxidant and anti-inflammatory properties.[62] The lack of significant differences among individual supplement groups suggests that none of these supplements alone provided a substantial advantage in terms of body weight maintenance. Interestingly, the clove supplementation group (Group 6) showed the highest percentage increase among individual supplement groups, approaching the cancer control level, potentially indicating a marginal beneficial effect consistent with findings on eugenol's metabolic effects.[63] The flutamide treatment group (Group 7) showed weight gain comparable to individual supplement groups and statistically indistinguishable from the cancer control. The similarity between pharmaceutical and phytochemical interventions suggests that while both approaches may address specific cancer parameters, they do not fully restore normal growth patterns, possibly due to persistent metabolic alterations associated with the cancer state. The body weight data presents a complex picture wherein normal controls exhibit expected robust growth, cancer induction significantly impairs weight gain, and interventions, particularly the combined supplement, result in even further reduced weight gain despite improving other parameters. These findings challenge simplistic interpretations of weight gain as a uniformly positive outcome in cancer models and suggest that metabolic reprogramming induced by phytochemical combinations may represent a mechanistically distinct approach to cancer management compared to traditional pharmaceutical interventions. The combined supplement group (Group 3) consistently exhibited the highest organ-to-body weight ratios across multiple systems, while the normal control group (Group 1) generally showed the lowest ratios

Table 4: Changes of Organ to Body Weight Ratio of Testosterone-DMBA-Induced Prostate Cancer in Wistar Rats

Group	LBW ($\times10^{-3}$)	KBW ($\times10^{-3}$)	SBW ($\times10^{-3}$)	HBW ($\times10^{-3}$)	LUBW ($\times10^{-3}$)	PRBW ($\times10^{-3}$)
1	3.16±0.13^{c}	0.57±0.04^{b}	0.36±0.04^{d}	0.32±0.02^{b}	0.66±0.19^{c}	0.35±0.14
2	4.21±0.13^{bc}	0.74±0.04^{b}	0.43±0.06^{cd}	0.40±0.03^{ab}	1.33±0.14^{b}	0.66±0.24
3	6.38±0.22^{a}	1.26±0.17^{a}	1.39±0.07^{a}	0.53±0.09^{a}	1.89±0.23^{a}	0.74±0.07
4	3.64±0.25^{bc}	0.65±0.07^{b}	0.47±0.02^{cd}	0.36±0.02^{ab}	1.06±0.08^{bc}	0.32±0.03
5	3.64±0.11^{bc}	0.68±0.02^{b}	0.53±0.02^{bcd}	0.36±0.08^{ab}	0.85±0.05^{bc}	0.44±0.07
6	4.67±0.76^{b}	0.96±0.22^{ab}	0.62±0.10^{bc}	0.43±0.05^{ab}	1.35±0.28^{b}	0.56±0.18
7	4.17±0.26^{bc}	0.87±0.13^{b}	0.71±0.07^{b}	0.42±0.05^{ab}	0.93±0.07^{bc}	0.70±0.14

Values represent mean ± SEM. Values with identical superscripts do not exhibit significant differences (P<0.05), while values with different superscripts exhibit significant differences. Key: LBW: Liver to body weight ratio, KBW: Kidney to body weight ratio, SBW: Spleen to body weight ratio, HBW: Heart to body weight ratio, LUBW: Lung to body weight ratio, PRBW: Prostate to body weight ratio.

Notably, while statistical significance was observed in most organ systems, prostate to body weight ratios did not show statistically significant differences despite numerical variations. The consistently elevated organ ratios in the combined supplement group likely reflect increased metabolic demands for processing multiple bioactive compounds. This aligns with a study demonstrating that certain phytochemicals, such as hyperforin, may upregulate hepatic and renal cytochrome P450 systems via nuclear receptor activation, though others inhibit these enzymes, resulting in variable drug metabolism outcomes.[64] Potentially, resulting in organomegaly through cellular hypertrophy and hyperplasia.

The dramatic splenic enlargement in Group 3 suggests significant immunological activation. In a study on "Bioactive components saffron and their pharmacological properties.", it was documented that bioactive components, including polyphenols and carotenoids, exhibit immunomodulatory properties by influencing pathways such as NF-κB, which may contribute to enhanced immune cell activity.[65] This immunostimulatory effect may contribute to anticancer activity through enhanced tumour immunosurveillance. The elevated organ-to-body weight ratios may partially reflect the reduced overall body weight rather than absolute organ enlargement. These changes likely reflect adaptive metabolic and immunological responses rather than pathological effects, given the improved feed intake previously observed in this group. The lack of significant differences in prostate ratio despite the prostate cancer model suggests complex mechanisms beyond simple prostate size modulation.

Despite the established cancer model and various interventions, all groups maintained statistically similar hematological parameters. The absence of significant hematological alterations in intervention groups compared to the cancer control suggests that the potential therapeutic effects of these interventions likely operate through mechanisms independent of systemic hematopoietic modulation. As shown in some studies., phytochemical interventions may primarily affect cancer microenvironment, cellular signaling pathways, and metabolism rather than systemic hematological parameters.[66,67] The hematological stability observed in this study presents an interesting contrast to the significant organ weight changes, particularly the pronounced splenic enlargement in the combined supplement group (Table 5). Despite the significantly enlarged spleen, no corresponding changes in circulating leukocyte or platelet counts were observed. This dissociation suggests that the splenic changes likely reflect altered tissue architecture, resident cell populations, or metabolic activity rather than increased hematopoietic function.

Table 5: Effect of Testosterone-DMBA-Induced Prostate Cancer in Wistar Rats on Haematological Parameters

Group	WBC (10^3/µL)	LYMPH (10^3/µL)	GRANU (10^3/µL)	RBC (10^6/µL)	HGB (g/dL)	MCV (fL)	MCH (pg)	PLT (10^3/µL)
1	3.50±0.35^a	6.13±0.38^a	2.67±0.19^a	5.67±0.28^a	14.00±0.55^a	88.13±5.23^a	34.47±2.85^a	168.00±10.69^a
2	4.40±0.66^a	6.23±0.23^a	2.63±0.15^a	5.63±0.27^a	12.00±0.44^a	85.00±3.27^a	32.97±2.82^a	171.00±9.87^a
3	4.73±0.17^a	6.40±0.06^a	2.73±0.33^a	5.87±0.28^a	13.00±0.52^a	84.63±2.77^a	32.23±3.24^a	187.33±0.33^a
4	4.40±0.25^a	6.57±0.27^a	2.47±0.07^a	5.87±0.07^a	12.00±0.83^a	88.90±1.50^a	30.17±0.03^a	166.33±11.33^a
5	5.03±1.46^a	6.03±0.52^a	2.70±0.38^a	5.37±0.54^a	11.00±0.73^a	84.93±3.33^a	28.67±1.48^a	161.00±26.91^a
6	5.13±0.39^a	6.37±0.03^a	2.83±0.37^a	6.10±0.00^a	13.00±0.67^a	87.40±0.00^a	28.70±0.70^a	200.33±3.33^a
7	4.97±0.52^a	6.07±0.50^a	2.83±0.15^a	6.17±0.17^a	11.00±1.50^a	90.03±3.63^a	32.00±1.90^a	188.33±14.62^a

Values represent mean ± SEM, n=3. Values with identical superscripts do not exhibit significant differences (P<0.05), while values with different superscripts exhibit significant differences. Key: WBC: White blood cell, LYMPH: Lymphocytes, GRANU: Granulocytes, RBC: Red blood cell, HGB: Hemoglobin, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, and PLT: Platelets.

While total cholesterol and triglyceride levels showed no statistically significant differences among groups despite substantial numerical variations, significant differences were observed in HDL and LDL cholesterol levels, indicating specific impacts on lipoprotein metabolism (Table 6). The relatively high cholesterol levels observed in the flutamide group align with clinical observations documenting that anti-androgen therapy can increase serum cholesterol through alterations in hepatic lipid metabolism and reduced peripheral utilization.[68] The elevated HDL levels in the watermelon group are particularly noteworthy and align with findings reporting significant improvement in HDL functionality with lycopene supplementation by modulating the activity of HDL-associated enzymes such as paraoxonase-1 (PON-1), lecithin cholesterol acyltransferase (LCAT), and cholesterol ester transfer protein (CETP).[69]

Table 6: Effect of Testosterone-DMBA-Induced Prostate Cancer in Wistar Rats on Serum Lipid Profile

Group	CHOL (mg/dL)	TRIG (mg/dL)	HDL (mg/dL)	LDL (mg/dL)
1	44.77±11.24^a	54.87±17.09^a	15.00±2.89^{ab}	18.77±8.08^b
2	45.07±18.61^a	83.53±13.03^a	10.67±4.33^{ab}	17.70±13.28^b
3	70.30±31.50^a	94.10±17.97^a	6.00±2.08^b	45.37±28.61^{ab}
4	41.33±16.08^a	77.07±15.08^a	13.33±4.41^{ab}	12.60±10.02^b
5	67.13±14.38^a	101.93±25.71^a	21.67±4.41^a	25.10±20.62^b
6	93.83±43.44^a	74.47±7.83^a	8.33±1.67^b	37.23±17.88^{ab}
7	115.80±27.83^a	86.23±17.09^a	9.17±3.63^b	89.37±21.88^a

Values represent mean ± SEM, n=3. Values with identical superscripts do not exhibit significant differences (P<0.05), while values with different superscripts exhibit significant differences. Key: CHOL: Cholesterol, TRIG: Triglycerides, HDL: High Density Lipoproteins, LDL: Low Density Lipoproteins.

The lycopene-rich composition of watermelon likely contributes to these beneficial effects on HDL metabolism. Conversely, the significantly lower HDL levels in the combined supplement, Clove, and flutamide groups raise important questions about potential antagonistic interactions or dose-dependent effects. A study demonstrated that certain phytochemical combinations can exhibit complex effects on HDL metabolism, potentially through competitive interactions that regulate lipoprotein metabolism.[70] The markedly elevated LDL in the Flutamide could be attributed to reduced hepatic LDL receptor expression following androgen suppression, as androgens normally upregulate LDL receptor expression through sterol regulatory element-binding protein 2 (SREBP-2) activation.[71] The intermediate LDL levels in the combined supplement and clove groups suggest partial anti-androgenic effects of these interventions, consistent with

their known phytoestrogenic and aromatase-modulating properties.[72,73] The findings highlight the necessity of incorporating metabolic effects into cancer interventions and indicate that targeted phytochemical strategies may provide more favourable metabolic outcomes than traditional therapies. The elevated ALT in the watermelon group contrasts with findings that reported hepatoprotective effects of lycopene in various experimental models.[74] This unexpected finding might reflect specific interactions between lycopene and the testosterone-DMBA model (Table 7).

Table 7: Effect of Testosterone-DMBA-Induced Prostate Cancer in Wistar Rats on Serum Liver Function Enzymes

Group	ALT(U/L)	AST(U/L)	ALP(U/L)	TP(g/dL)	ALB(g/dL)	TB(mg/dL)
1	13.67±2.40^{b}	42.33±15.76^{a}	27.00±6.85^{ab}	16.53±2.67^{a}	2.73±0.03^{a}	104.00±31.38^{a}
2	16.00±3.61^{ab}	22.33±6.57^{a}	21.00±1.23^{bc}	15.73±0.89^{a}	2.73±0.58^{a}	96.00±13.67^{a}
3	5.00±2.31^{b}	11.67±6.12^{a}	24.00±3.35^{abc}	5.80±1.01^{b}	1.30±0.35^{a}	94.00±20.04^{a}
4	8.67±4.10^{b}	25.67±8.69^{a}	26.00±3.51^{ab}	12.63±4.13^{ab}	2.73±0.81^{a}	53.00±22.76^{a}
5	32.33±12.98^{a}	28.67±9.39^{a}	35.00±5.04^{a}	14.37±4.36^{ab}	2.10±0.36^{a}	112.00±40.09^{a}
6	17.67±2.40^{ab}	30.33±5.46^{a}	18.00±1.79^{bc}	13.07±0.85^{ab}	2.10±0.25^{a}	166.00±63.99^{a}
7	14.00±1.00^{b}	15.67±7.69^{a}	13.00±1.23^{c}	11.27±2.14^{ab}	2.57±0.45^{a}	57.00±9.65^{a}

Values represent mean ± SEM, n=3. Values with identical superscripts do not exhibit significant differences (P<0.05), while values with different superscripts exhibit significant differences. Key: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, TP: Total protein, ALB: Albumin, TB: Total bilirubin

A study demonstrated that some dietary phytochemicals can induce phase I hepatic enzymes through activation of pregnane X receptor (PXR),[75] potentially explaining the observed ALT elevation. The significantly lower ALT in the combined supplement group compared to the watermelon group suggests potential antagonistic interactions among the phytochemicals that might mitigate the ALT-elevating effect observed with watermelon alone. The absence of significant AST alterations despite significant ALT changes might reflect enzyme induction rather than hepatocellular damage, consistent with the significantly enlarged liver observed in the combined supplement group. ALP levels showed significant differences among groups. The elevated ALP in the watermelon group parallels the ALT findings, suggesting consistent hepatic effects of this intervention. The profoundly reduced total protein in the combined supplement group is particularly noteworthy and contrasts with the relatively normal protein levels in groups receiving individual supplements. The reduced protein levels in the combined supplement group could be interpreted in the context of the previously observed enlarged liver and normalized feed intake in this group. Studies showed that phytochemicals can modulate multiple metabolic pathways, potentially influencing cellular metabolism and signalling. These compounds have been shown to target various pathways involved in energy metabolism, inflammation, and oxidative stress, which could indirectly affect protein synthesis by altering the cellular metabolic environment,[76,77] potentially explaining these seemingly contradictory findings. Despite the significant differences in total protein, albumin levels showed no statistically significant differences among groups. This dissociation between total protein and albumin changes suggests selective alterations in non-albumin protein fractions, including globulins and other hepatic secretory proteins, which indicates that certain phytochemicals selectively modulate specific protein synthesis pathways while preserving others, particularly those essential for homeostatic functions like albumin production. Total bilirubin levels showed substantial numerical variations. However, these variations did not reach statistical significance, likely due to high individual variability as reflected in the large standard errors. The absence of significant bilirubin elevation in any group suggests preserved hepatic excretory function despite the other biochemical alterations observed.

Serum urea in the combined supplement group (Group 3) was elevated and statistically significant compared to all groups. The magnitude of elevation compared to normal controls suggests significant renal functional impairment or altered nitrogen metabolism with this specific intervention (Table 8). A study documented that certain phytochemical combinations can induce profound metabolic alterations through synergistic effects on multiple pathways.[77] Interestingly, none of the individual supplements (Groups 4-6) produced comparable urea elevations, suggesting unique interactive effects specific to the combination.

Table 8: Effect of Testosterone-DMBA-Induced Prostate Cancer in Wistar rats on Serum Kidney Function Parameters

Group	UREA (mg/dL)	CREA (mEq/L)	URIC (mg/dL)
1	38.33±19.22^{b}	0.90±0.12^{ab}	3.47±0.35^{a}
2	70.00±5.00^{b}	0.90±0.15^{ab}	3.97±1.45^{a}
3	348.33±142.14^{a}	1.30±0.20^{a}	3.33±0.13^{a}
4	83.33±13.64^{b}	0.93±0.07^{ab}	3.10±0.38^{a}
5	110.67±40.32^{b}	0.80±0.15^{b}	3.37±0.35^{a}
6	59.00±14.29^{b}	0.83±0.12^{ab}	2.80±0.46^{a}
7	123.33±28.92^{b}	1.00±0.17^{ab}	3.17±0.86^{a}

Values represent mean ± SEM, n=3. Values with identical superscripts do not exhibit significant differences (P<0.05), while values with different superscripts exhibit significant differences. Key: Crea: Creatinine.

This observation aligns with findings demonstrating that certain phytochemicals exhibit dramatically different effects when administered in combination versus individually, attributed to altered bioavailability, metabolic interactions, or receptor competition.[78,79,80,81] The elevated creatinine in the combined supplement group, while less dramatic than the urea changes, further supports potential renal functional impairment with this intervention. According to another study, even modest creatinine elevations can indicate significant glomerular filtration impairment.[82] This pattern aligns with the previously observed enlarged kidneys in this group, suggesting structural and functional renal alterations. The relatively lower creatinine in the watermelon group is noteworthy and aligns with findings that documented renoprotective effects of lycopene.[83,84] This effect could be attributed, among others, to lycopene's potent

antioxidant properties and specific effects on renal hemodynamics through nitric oxide pathway enhancement.[85] Uric acid levels showed no statistically significant differences among groups. This stability in uric acid levels despite significant alterations in other renal parameters is noteworthy and suggests selective impairment of specific renal functions rather than global dysfunction. Some studies proposed that uric acid handling involves distinct renal transporters and pathways that may be differentially affected by disease processes and interventions.[86,87,88,89]

Conclusion

This study examined the impact of Papaya, watermelon, and clove supplementation on testosterone-DMBA-induced prostate cancer in Wistar rats, uncovering intricate physiological relationships with considerable implications for cancer management. The combined supplementation normalized feed intake to levels comparable with healthy controls through complementary anti-inflammatory, digestive, and taste perception mechanisms, yet paradoxically resulted in the lowest weight gain among all groups, suggesting beneficial metabolic reprogramming. While the combined supplement group exhibited pronounced organomegaly and potential nephrotoxicity indicated by elevated serum urea and creatinine levels, watermelon supplementation alone demonstrated the most favorable lipid profile with increased HDL levels and normal liver and kidney function. In contrast, conventional flutamide treatment resulted in elevated LDL levels, indicating potential metabolic disadvantages compared to phytochemical approaches. The absence of significant hematological changes across all groups emphasizes the tissue-specific rather than systemic effects of both the cancer model and interventions, showing the need for comprehensive assessment in evaluating disease progression and therapeutic efficacy. Future research should focus on mechanistic investigations, toxicological assessments, optimized formulations, long-term efficacy studies, translational research, bioavailability evaluations, and tumor microenvironment effects.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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