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*Research Article*

# Myricetin As A Chemopreventive Agent: Effects On Ki-67 Expression In NMU-Induced Prostate Cancer In Wistar Rats

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**Abstract**
Prostate cancer (PCa) ranks among the most prevalent malignancies affecting men globally, necessitating the search for effective chemopreventive agents. Myricetin, a flavonoid found in various fruits, vegetables, and herbs, has been characterized for its potential anticancer properties. This study investigated the effects of myricetin on Ki-67 expression, a marker of cellular proliferation, in N-Methyl-N-Nitrosourea (NMU)-induced prostate cancer in adult male Wistar rats. Forty-two rats were randomly assigned to seven groups. Group A served as normal control. Group B received 50mg NMU only. Group C received 50mg NMU treated with 50mg casodex. Group D received 100mg Myricetin only. Groups E, F, G received 50mg NMU treated with varying doses of myricetin (75mg, 150mg & 300mg myricetin), induction of NMU lasted for 28dys while treatment with myricetin lasted for 21days. Following 21 days of treatment, histopathological and immunohistochemical analyses were conducted to assess tissue changes and Ki-67 levels.
Results indicated that NMU-induced rats exhibited significant histopathological alterations, including glandular atrophy and heightened Ki-67 reactivity, indicative of increased cell proliferation. In contrast, rats treated with myricetin, particularly at doses of 100 mg and above, showed restoration of normal histo-architecture and reduced Ki-67 expression, suggesting ameliorative effect against malignant transformation.

These findings highlight the potential of myricetin as a chemopreventive agent in prostate cancer management. The study supports the consideration of natural compounds like myricetin in therapeutic strategies against prostate cancer, offering a promising avenue for safer and more effective cancer prevention.

**Keywords:** Prostate Cancer, Myricetin, Chemoprevention, Ki-67 Expression, N-Methyl-N-Nitrosourea (NMU)

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## 1. Background

Prostate cancer is one of the most frequently diagnosed malignancies and a leading cause of cancer-related deaths among men globally (**Error! Reference source not found.**; **Error! Reference source not found.**). Its pathogenesis is multifactorial, involving a combination of age, genetic factors, and exposure to environmental carcinogens. Experimental models have been instrumental in elucidating the molecular and histopathological features of prostate cancer. Among the most commonly used agents for inducing carcinogenesis in rodents is N-nitrosomethylurea (NMU)—a direct-acting alkylating compound that causes DNA damage and mutagenesis without metabolic activation (Error! Reference source not found.; Error! Reference source not found.).

In NMU-induced carcinogenesis, a hallmark event is uncontrolled cell proliferation, which can be tracked using molecular proliferation markers such as Ki-67. The Ki-67 protein is strictly expressed in active phases of the cell cycle (G1, S, G2, and M), but absent in quiescent cells (G0), making it a reliable and widely used biomarker for assessing tumor proliferation (**Error! Reference source not found.**; **Error! Reference source not found.**). Increased Ki-67 expression has been consistently observed in various pre-neoplastic and neoplastic tissues, including prostate carcinoma, and is frequently associated with poor prognosis and increased tumor aggressiveness (**Error! Reference source not found.**; **Error! Reference source not found.**).

Myricetin, a flavonoid found in fruits, vegetables, tea, and medicinal plants, has demonstrated promising anti-cancer, antioxidant, and anti-inflammatory activities (**Error! Reference source not found.**; Error! Reference source not found.). Myricetin exerts its anti-proliferative effects by modulating signaling pathways such as PI3K/Akt, MAPK, and NF-κB, leading to the suppression of oncogenic gene expression, cell cycle arrest, and induction of apoptosis (Error! Reference source not found.; Error! Reference source not found.).

Myricetin (MYR) has been shown to induce apoptosis in cancer cells through multiple mechanisms. It increases the release of cytochrome c and activates the caspase cascade by upregulating caspase-3, -8, and -9 expression, ultimately leading to programmed cell death in hepatocellular carcinoma in rats (**Error! Reference source not found.**). Additionally, when administered orally in a model of DMBA-induced breast cancer, myricetin was evaluated against vincristine and was found to elevate plasma erythrocyte lysate levels, increase breast superoxide dismutase activity, and inhibit plasma lipid peroxidation. These effects were comparable to, or even exceeded, those of vincristine (**Error! Reference source not found.**). Furthermore, in rats treated with both myricetin and 5-fluorouracil (5-FU), there was a significant reduction in inflammatory markers along with improvements in histological tissue architecture, indicating its protective and anti-inflammatory properties (**Error! Reference source not found.**).

Notably, myricetin has been shown to downregulate Ki-67 expression in various cancer models including colorectal, breast, and gastric cancers (**Error! Reference source not found.**; Error! Reference source not found.). However, limited data exists on its effects in NMU-induced prostate carcinogenesis, especially regarding cell proliferation markers such as Ki-67. Therefore, investigating the impact of myricetin on NMU-induced proliferative activity in the prostate may reveal its potential as a chemopreventive agent against prostate cancer.

Prostate cancer continues to pose a significant global health burden, being the most commonly diagnosed cancer in men in over 100 countries (**Error! Reference source not found.**; **Error! Reference source not found.**). Despite advancements in diagnostic techniques and therapeutic interventions, the disease's multifaceted nature and potential for progression to an aggressive form underscore the need for effective preventive strategies. Experimental rodent models utilizing N-nitrosomethylurea (NMU) have been widely used to study chemical carcinogenesis due to NMU's strong mutagenic and tumorigenic effects, particularly in hormone-sensitive organs like the prostate (Error! Reference source not found.; Error! Reference source not found.).

One of the defining features of tumorigenesis is hyperproliferation of epithelial cells, which can be monitored by the expression of Ki-67, a nuclear protein strongly correlated with cell cycle activity. Elevated Ki-67 labeling are considered predictive of tumor aggressiveness and unfavorable outcomindiceses in various cancers, including prostate carcinoma (**Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.**). In NMU-induced models, an increase in Ki-67 expression is indicative of active neoplastic transformation and proliferative stress within the affected tissues (**Error! Reference source not found.**).

Growing evidence supports the role of dietary flavonoids in modulating the pathogenesis of cancer by targeting oxidative stress, inflammation, and abnormal proliferation (Error! Reference source not found.; Error! Reference source not found.). Myricetin, in particular, has shown multiple anticancer effects, including antioxidant defense, suppression of pro-inflammatory cytokines, inhibition of tumor growth, and induction of apoptosis (**Error! Reference source not found.**; Error! Reference source not found.; Error! Reference source not found.). It also attenuates the expression of proliferative markers such as cyclin D1, PCNA, and Ki-67 in chemically and genetically induced cancer models (Error! Reference source not found.; Error! Reference source not found.).

Despite these promising outcomes, few studies have explored the specific relationship between myricetin administration, Ki-67 modulation, and NMU-induced proliferation in the prostate tissue. This study, therefore, aims to examine the effect of myricetin on Ki-67 expression in the prostate tissue of NMU-exposed Wistar rats, thereby evaluating its potential as a natural chemopreventive agent in prostate cancer models.

## 2. Methods

### 2.1 Chemicals Procurement

Myricetin was purchased from Source Natural, United State of America The compound was obtained with a purity of ≥ 95%, as verified by high-performance liquid chromatography (HPLC) and was stored according to the manufacturer's specifications to ensure stability and integrity, while N-methyl-n-nitrosourea was purchased from a reputable and licensed science laboratory store (Syncro systems) in Calabar, Cross River State. NMU was prepared in sterile distilled water at a concentration of 50 mg/mL immediately before use. The solution was protected from light and used within 24 hours to ensure its effectiveness in inducing carcinogenesis in the animal model. Phosphate-buffered saline (PBS) was prepared using analytical-grade sodium phosphate and sodium chloride, adjusted to a pH of 7.4 to maintain physiological conditions during experiments.

### 2.2. Animal procurement

Forty two (42) male Wistar rats between (100-180g) were used for this experiment; the animals were purchased from the Department of Veternary Medicine and brought to the animal house of the Department of Anatomy, University of Nigeria, Enugu campus. The rats were kept in the animal house of the Department of Anatomy for a period of 2 weeks under normal room temperature for acclimatization.

### 2.3 Study Design

This study adopted an experimental design to investigate the effects of myricetin on prostate cancer progression using an N-methyl-N-nitrosourea (NMU)-induced prostate cancer model in male Wistar rats. Forty two (42) adult male Wistar rats were used for this study; the rats were randomly divided into 7 groups (A, B, C, D, E, F, G). Group A was placed on feed and water ad libitum, group B was the negative control group induced with 50mg N-methyl-n-nitrosourea (MNU), group C was induced with MNU and treated with casodex, group D was treated with 100mg myricetin, group E was low dose induced with MNU and treated with 75mg myricetin, group F was medium dose induced with MNU and treated with 150mg myricetin, group G was the high dose induced with MNU and treated with 300mg of myricetin. The induction of prostate cancer was carried out using N-methyl-n-nitrosourea (NMU) following a well-established protocol. NMU was administered via weekly intraperitoneal injection to ensure proper absorption and systemic distribution. After the NMU solution was prepared, a 27-gauge needle was used to inject the desired volume into the peritoneal cavity of each animal. Each animal received a dose of 50 mg/kg body weight of NMU, calculated based on the average weight of the subjects. This dosage was selected based on previous studies demonstrating effective carcinogenesis (**Error! Reference source not found.**). NMU induction was performed once in a week and lasted for 28days. Post-treatment, animals were monitored closely for signs of distress, behavioral changes, or adverse reactions. Vital signs, including weight, activity levels, and grooming behaviors, were observed daily for the first weekly following NMU administration.

Throughout the treatment period, rats were monitored for tumor development, with key histopathological and biomarker analyses, particularly focusing on ki-67 levels, conducted at predetermined at the end of the experiment, Treatment groups received graded doses of 100mg of myricetin and 50mg of Casodex. Treatments with myricetin lasted for 21days after which rats were sacrificed and tissues preserved in 10% buffered formal Results were descriptively analyzed to assess the efficacy of myricetin in modifying tumor characteristics and proliferation rates.

The justification for using the NMU-induced prostate cancer model lies in its established relevance in cancer research, controlled tumor development, biological similarities to human disease, feasibility for therapeutic interventions, and reproducibility across studies.

### 2.4 Animal Sacrifice

The animal sacrifice procedure involved the use of ketamine as an anesthetic agent, sourced from Bex Pharmacy in Calabar. The dosage for administration was set at 100 mg/kg body weight and was administered via the intraperitoneal route. The animals were effectively anesthetized prior to sacrifice, facilitating humane treatment during the procedure.

**2.5 Assessment of Biomarkers**

Immunohistochemical staining ki-67 was used for the expression of prostate cancer cells proliferation index (**Error! Reference source not found.**).

**2.6 Histopathological Evaluation**

After a 21-day treatment period, rats are euthanized using an approved method, and prostates were harvested with sterile instruments. The harvested tissues were fixed in 10% neutral buffered formalin (NBF) to preserve their structure and cellular details, preventing further degradation. Following fixation, tissues were rinsed with phosphate-buffered saline (PBS) and trimmed to approximately 1 $cm^3$ to aid in subsequent processing.

The histological processing involves dehydrating the tissues through a graded series of ethanol solutions (70%, 80%, 90%, and absolute ethanol) to remove water. This was followed by clearing the tissues in xylene to make them transparent, and then infiltrating them with molten paraffin wax at 60°C. Once cooled, the paraffin-embedded tissues were sectioned into thin slices (5-7 micrometers) using a microtome and placed on glass slides.

For staining, the slides undergo deparaffinization in xylene and were rehydrated through decreasing ethanol concentrations. Sections were first stained with hematoxylin, which colors the cell nuclei blue, and then with eosin, which stains the cytoplasm and extracellular matrix pink. After staining, the slides were dehydrated, cleared in xylene, and mounted with a coverslip using a suitable mounting medium. This entire procedure allows for detailed histopathological examination of the prostate tissues.

**3. Results and Discussion**

**3.1 Histological Observations**

**Group A (Normal Control)**

The histological analysis of the prostate tissue from the normal control group (Group A) revealed well-preserved glandular architecture. The prostatic tissue exhibited clearly defined lumens, uniform epithelial cells, appropriate intraluminal secretions, an intact basement membrane, and a structured stroma composed of smooth muscle fibers (Fig. 1; Plate 1).

**Group B (Nitrosourea)**

In contrast, the prostate tissue from the nitrosourea-treated group (Group B) demonstrated significant histological alterations. The tissue exhibited atrophy, hyperplastic epithelial cells, degenerating acini, and a marked infiltration of inflammatory cells within the stroma. These changes suggest the presence of benign prostatic hyperplasia (Fig. 1; Plate 2).

**Group C (Nitrosourea + Casodex)**

The examination of the prostate tissue in Group C, which received casodex treatment alongside nitrosourea, indicated further histological deterioration. This group displayed atrophy of the prostatic glands, hyperplastic changes in the epithelial cells, inflammatory modifications within the acini, and signs of fibrosis affecting the smooth muscle fibers and blood vessels (Fig. 1; Plate 3).

**Group D (100 mg Myricetin)**

Conversely, the histological assessments for Group D, treated with 100 mg of myricetin, revealed a return to near-normal histo-architecture. The prostatic tissue displayed well-defined acini, healthy epithelial cells, visible intraluminal secretions, an intact basal cell layer, and organized smooth muscle within the stroma (Fig. 1; Plate 4).

**Group E (N-methyl-N-nitrosourea + 75 mg Myricetin)**

The prostate tissue treated with 75 mg of myricetin in Group E exhibited some protective effects; however, histological examination revealed atrophy of the prostatic glands, hyperplastic changes in glandular epithelial cells, and evidence of fibrosis within the smooth muscle and blood vessels of the prostatic stroma (Fig. 1; Plate 5).

**Group F (N-methyl-N-nitrosourea + 150 mg Myricetin)**

The histological evaluation for Group F, which received 150 mg of myricetin, indicated a well-preserved histo-architecture. The tissue displayed a normal glandular structure, healthy epithelial and basal cell layers, clear intraluminal secretions, and well-organized smooth muscle in the stroma (Fig. 1; Plate 6).

**Group G (N-methyl-N-nitrosourea + 300 mg Myricetin)**

Finally, the immunohistochemical evaluation of prostatic tissue treated with 300 mg of myricetin revealed a similarly favorable profile. The tissue exhibited a well-preserved histo-architecture and negative Ki-67 reactivity (Fig. 2; Plate 7), indicating a strong protective effect against cellular proliferation and potential malignancy.

**Figure 2:** Photomicrographs showing the immunohistochemical expression of Ki-67 within different experimental groups of prostate gland tissues.

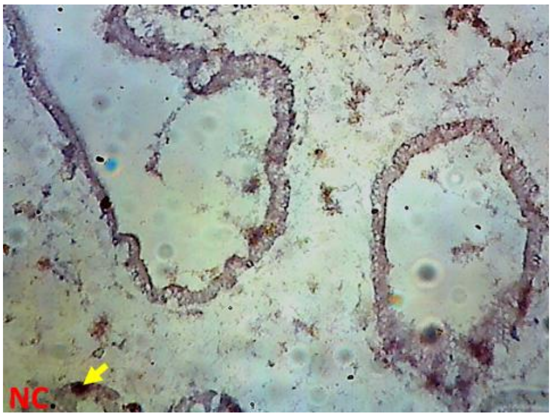


Plate 1: Photomicrograph of a transverse section of a normal control prostate tissue illustrating Ki-67 positive reactivity (Ki-67 stain x400).

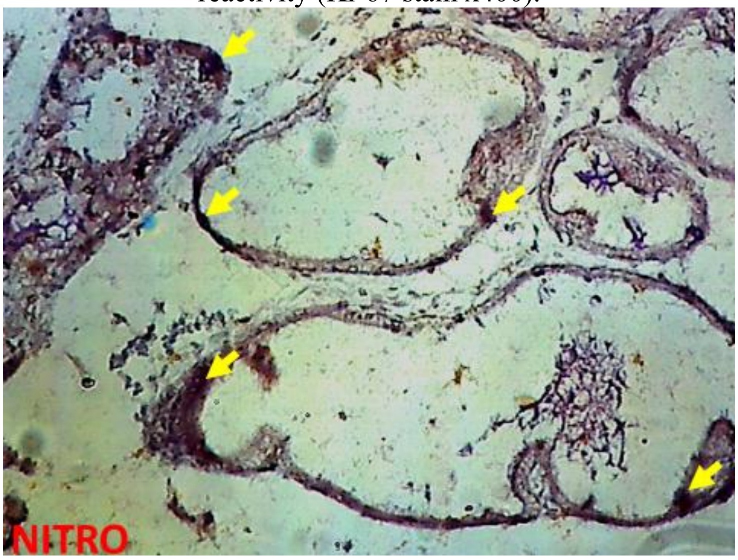


Plate 2: Photomicrograph of a transverse section of nitrosourea-treated prostate tissue exhibiting Ki-67 positive reactivity (yellow arrow) (Ki-67 stain x400).


Plate 3: Photomicrograph of a transverse section of a nitrosourea-treated prostate tissue showing Ki-67 positive reactivity (yellow arrow) (Ki-67 stain x400).

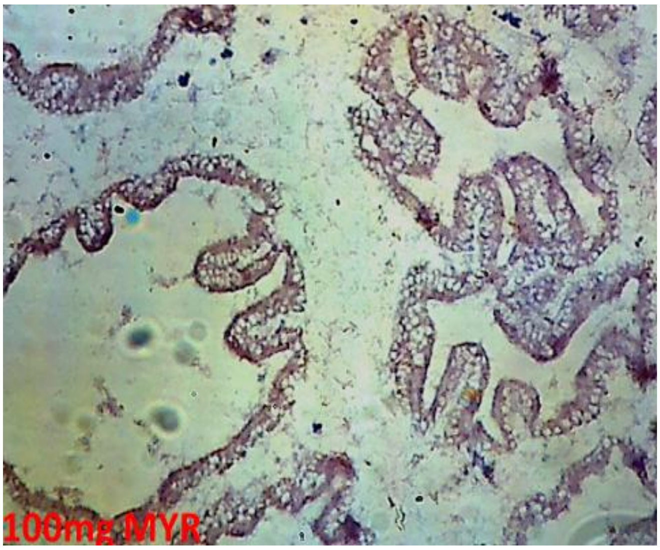


Plate 4: Photomicrograph of a transverse section of a 100 mg Myricetin-treated prostate tissue indicating Ki-67 negative reactivity (Ki-67 stain x400).

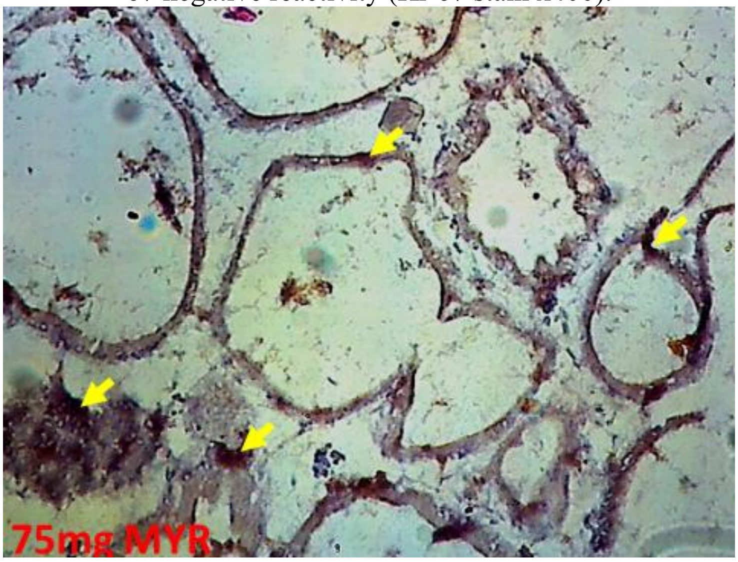


Plate 5: Photomicrograph of a transverse section of a 75 mg Myricetin-treated prostate tissue demonstrating Ki-67 positive reactivity (yellow arrow) (Ki-67 stain x400).

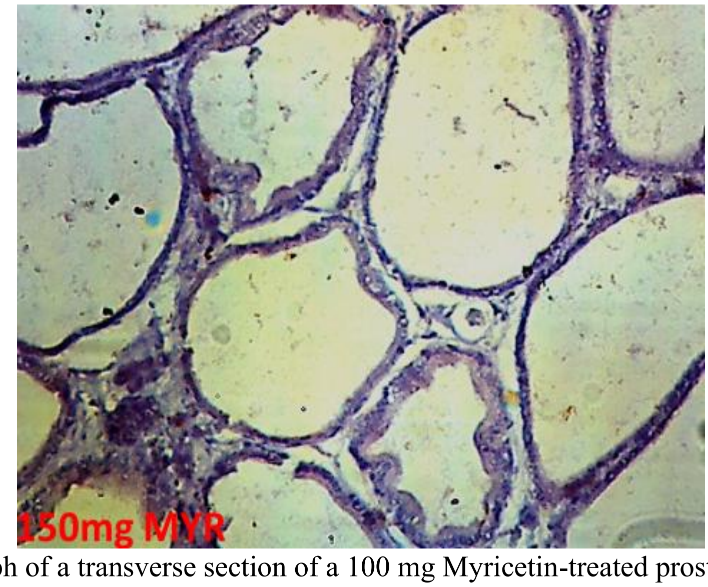


Plate 6: Photomicrograph of a transverse section of a 100 mg Myricetin-treated prostate tissue showing Ki-67 negative reactivity (Ki-67 stain x400).

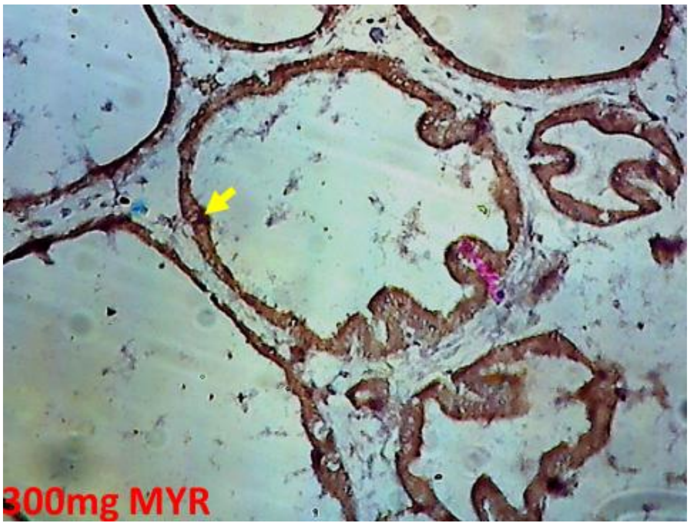


Plate 7: Photomicrograph of a transverse section of a 300 mg Myricetin-treated prostate tissue indicating Ki-67 negative reactivity (Ki-67 stain x400).

**4. Discussion**

The present study explored the effects of myricetin on Ki-67 expression and histopathological characteristics in N-Methyl-N-Nitrosourea (NMU)-induced prostate cancer in adult male Wistar rats. The findings demonstrate that myricetin exerts a notable protective effect against the proliferative and histological changes associated with prostate cancer progression, emphasizing its potential as a chemopreventive agent.

Histological analyses revealed significant differences between the NMU-induced prostate tissues and those treated with myricetin. Group B, which received NMU without any treatment, exhibited substantial histopathological alterations characterized by glandular atrophy, hyperplastic changes, and inflammatory infiltrates. This aligns with previous studies indicating that NMU exposure leads to morphological changes typical of prostate cancer, such as the development of benign prostatic hyperplasia (BPH) and tumorigenesis (**Error! Reference source not found.**). The structural abnormalities observed in Group B underscore the debilitating effects of NMU, highlighting the need for effective countermeasures.

In contrast, Group D, which received 100 mg of myricetin, demonstrated a remarkable recovery in histoarchitecture with a near-normal appearance of the prostate glands. The presence of well-defined acini, healthy epithelial cells, and intact stroma suggests that myricetin effectively reverses NMU-induced damage. Such restorative effects of myricetin on prostate tissues may be attributed to its known bioactive properties, including antioxidant and anti-inflammatory effects, which have been previously reported to contribute to its anticancer activities (**Error! Reference source not found.**; **Error! Reference source not found.**). The ability of myricetin to modulate cellular proliferation and promote apoptosis stands out as a critical factor in its protective role (**Error! Reference source not found.**).

The immunohistochemical analyses of Ki-67 expression further corroborate these findings, as Ki-67 is recognized as a cellular proliferation marker that reflects tumor aggressiveness (Mohamed). The increased Ki-67 reactivity observed in Group B emphasizes the heightened proliferative activity associated with NMU-induced carcinogenesis. In stark contrast, myricetin-treated groups (specifically Groups D, F, and G) exhibited diminished Ki-67 reactivity, indicating reduced cellular proliferation in treated tissues. The absence of significant Ki-67 expression in Group D, treated with 100 mg myricetin, illustrates its potential in curbing proliferation and suggests a favorable chemopreventive effect.

Interestingly, the lower doses of myricetin (75 mg) in Group E also resulted in positive Ki-67 reactivity, indicating that while there may be protective effects at lower doses, the efficacy of myricetin appears to be dose-dependent, with higher doses yielding superior outcomes concerning both histopathology and Ki-67 expression. This observation aligns with the notion that dosage optimization is crucial in therapeutic approaches using natural compounds (**Error! Reference source not found.**).

Overall, the findings of this study contribute to a more profound understanding of myricetin's role as a potential chemopreventive agent in prostate cancer. Given the rising incidence of prostate cancer and the limitations of current treatment options (**Error! Reference source not found.**), the identification of natural compounds such as myricetin provides an exciting avenue for research and therapeutic intervention. Furthermore, the study's implications extend beyond histopathological impact; with the ability to modulate biomarkers like Ki-67, myricetin presents a dual benefit of potentially reducing tumor burden while offering a relatively safe dietary adjunct with minimal side effects compared to conventional chemotherapy agents.

## Conclusion

In summary, this investigation demonstrates that myricetin substantially mitigates the effects of NMU-induced NMU-induced prostate cancer, possibly through inhibiting cell proliferation as indicated by decreased Ki-67 levels. These results advocate for further preclinical and clinical exploration into the potential of myricetin as a chemopreventive strategy against prostate cancer, which may lead to efficacious

## DECLARATIONS

### Abbreviations

1. PCa - Prostate Cancer
2. NMU - N-Methyl-N-Nitrosourea
3. b.w - Body Weight
4. HPLC - High-Performance Liquid Chromatography
5. PBS - Phosphate-Buffered Saline
6. FAREC-FBMS - Faculty of Animal Research Ethical Committee, Faculty of Basic Medical Sciences
7. NBF - Neutral Buffered Formalin
8. H&E - Hematoxylin and Eosin (staining technique)
9. BPH - Benign Prostatic Hyperplasia

**Ethics declarations**

**Ethics approval and consent to participate**

Ethical approval was obtained from the Faculty of Animal Research Ethical Committee (FAREC-FBMS) at the Faculty of Basic Medical Sciences, University of Calabar, Calabar, with protocol number 338ANA1024.

**Consent for publication**

All the authors read and approved the final manuscript.

**Competing interests**

The authors declare no conflict of interest.

**Availability of data and materials**

Not applicable.

**Funding**

This research received no external funding.

**Authors' contributions**

Author Contributions Statement

N.M.U. contributed to the conceptualization and design of the study, performed the experiments, and drafted the manuscript. A.U.A. provided critical input in the study design, supervised the experimental procedures, and contributed to the manuscript writing and revision. M.E.O. conducted data analysis and interpretation and supported the manuscript's drafting and revision process. T.E.I. assisted with the histopathological analysis and contributed to the interpretation of results. C.E.F. contributed to the study design, data interpretation, and provided revisions to the manuscript. F.C.O. assisted in the experimental design and provided feedback on the manuscript. A.A.N. contributed to the methodology and assisted in data collection. U.C.K. provided support in the histological analysis and manuscript revision. O.E.I. aided in data collection and analysis and contributed to the manuscript preparation. A.U.K. provided expertise in the research methodology and contributed to the manuscript editing.

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