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RESEARCH ARTICLE

Evaluation of Antitumor Activity of Ethanolic Extract of *Azadirachta indica* (Neem) Leaves against Uterine Cancer

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A B S T R A C T

This study evaluated the antitumor potential of the ethanolic extract of *Azadirachta indica* leaves in a murine model of uterine cancer. The study focuses on tumor volume reduction, tumor growth inhibition (%TGI), body weight changes, hematological responses, serum biomarkers, and final tumor weight following treatment with *A. indica* extract. Ethanolic extract of *A. indica* was prepared by the Soxhlet method, and high-performance liquid chromatography was performed to determine its bioactive compounds. The bioactive compounds include ferulic acid (32.83ppm), syringic acid (23.56ppm), chlorogenic acid (23.12ppm), quercetin (21.62ppm), vanillic acid (13.12ppm), cinnamic acid (8.47ppm), gallic acid (5.32ppm), p-coumaric acid (3.95ppm), and m-coumaric acid (2.85ppm). After tumor induction, animals were allocated into seven equal groups (n=12) with each group having 3 replicas. First five groups, G1, G2, G3, G4, and G5, were treated with 50, 100, 200, 400, and 800mg/kg of *A. indica* extract, respectively, for 30 days. G6 served as a positive control (tumor induced, non-treated), and G7 served as a negative control (non-tumor, non-treated). Tumor volume was recorded after every 10 days, and percentage tumor growth inhibition (%TGI) was also calculated to assess the dose-dependent activity. *A. indica-treated* groups demonstrated a marked reduction in tumor volume at higher concentrations (400 and 800mg/kg), that reflected by significantly elevated TGI% values with $P<0.05$. Body weight changes loss was observed in the positive control, whereas the treated groups showed dose-dependent improvement. Hematological analysis revealed that cancer progression led to anemia, leukocytosis, and reduced PCV, while *A. indica* extract restored RBCs and normalized WBC profiles at the highest concentration. Serum biochemistry revealed that the elevated levels of alanine transferase (ALT), aspartate aminotransferase (AST), creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP), and total proteins observed in cancer controls were significantly reduced in treated albino rats, suggesting both hepatoprotective and renoprotective effects. Moreover, the antioxidant activity of *A. indica* extract likely contributed to the improved hematological and biochemical profiles. Overall, the ethanolic extract of *A. indica* leaves exhibited potent dose-dependent anti-tumor activity and improved metabolism. These findings highlight the therapeutic potential of *A. indica*-based plant formulation as a safe, effective, and natural alternative for treating uterine tumors.

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INTRODUCTION

Uterine cancer or endometrial cancer is one of the most frequently diagnosed cancers present all over the world and contributes significantly to female morbidity and mortality (Crosbie *et al.*, 2022; Tang *et al.*, 2025). Endometrial cancers have been classified into two types, i.e., type 1 (estrogen-derived and low-grade) and type 2 cancers (old age) (Huvila *et al.*, 2021). Type 1 endometrial cancers, which develop due to estrogen stimulation, are usually

detected at an earlier age and are often confined to the uterus at the time of diagnosis. Type 2 endometrial cancers, on the other hand, tend to behave more aggressively, have a poorer prognosis, and are more likely to have spread beyond the uterus when diagnosed. (Setiawan *et al.*, 2013; Wang *et al.*, 2024). Type 2 endometrial cancers comprise serous carcinoma, clear cell carcinoma, carcinosarcoma, high-grade (grade 3) endometrioid carcinomas, and undifferentiated cancers (Masood and Singh, 2022; Raffone *et al.*, 2024). Uterine cancers are most frequently found in dogs, cats, and laboratory animals and are rarely seen in sheep, goats, and cattle. In dogs and cats, it includes adenocarcinoma, leiomyoma, and leiomyosarcoma (Hananeh *et al.*, 2019; Cruz-Gregorio *et al.*, 2022; Pinello *et al.*, 2022; Ercolin *et al.*, 2024). Among all neoplasms developed in the uterus, leiomyoma is most frequently observed in female dogs (Brodzki *et al.*, 2023). Endometrial cancer may occur in females of any age, though it is mostly diagnosed in older females. Uterine cancer occurs most frequently in North America and Northern Europe and least frequently in southern and Eastern Asia and Africa.

Serous carcinoma, clear cell carcinoma, carcinosarcoma, high-grade (grade 3) endometrioid carcinoma, and undifferentiated carcinoma together constitute type 2 endometrial cancers. In 2021, an estimated 0.5 million cases of uterine cancer were reported globally, with a 95% uncertainty interval (429916-513667) (Yang *et al.*, 2023; Webb and Jordon, 2024; Qiu *et al.*, 2025). Uterine cancer was ranked sixth in 2012 with 319600 estimated cases in humans and animals (Bray *et al.*, 2022; Tursunova *et al.*, 2022). Since 2007, the incidence and mortality rate of endometrial cancer have been growing, though at a slower pace; the mortality rate of endometrial cancer is growing at a rapid rate (Hazelton *et al.*, 2025).

Given the rising incidence and mortality due to uterine cancer in animals, conventional treatments, including surgery, chemotherapy, and radiotherapy, have been used over the years (van den Heerik *et al.*, 2021; Negadmonfared *et al.*, 2022). These treatments no doubt have significant importance, but often lead to significant side effects, including bleeding, infection, damage to surrounding tissues, fatigue, nausea, hair loss, and bone marrow suppression (Leung *et al.*, 2022). However, due to limitations and severe side effects, researchers are increasingly exploring alternative approaches such as plants and plant-derived products. Natural plant extracts have been used nowadays due to their antibacterial, antiviral, antifungal, and antitumor properties (Domingues *et al.*, 2022; Mueed *et al.*, 2023; Guo *et al.*, 2024; Kiełtyka-Dadasiewicz *et al.*, 2024). These potential effects of plants are due to the presence of phenolics, flavonoids, limonoids, and terpenoids present in them (Saini *et al.*, 2022).

Azadirachta indica (neem) is a widely used medicinal plant famous for its antioxidant, antibacterial, and anticancer properties (Asghar *et al.*, 2022; Imran *et al.*, 2022; Wylie and Merrell, 2022). *A. indica* contains bioactive compounds such as nimbolid, quercetin, gedunin, and azadirachtin that have a significant anti-tumor effect as demonstrated in various in vitro and in vivo studies (Ibrahim *et al.*, 2023). The bioactive compounds not only prevent the tumor cells proliferation but also induce programmed cell death/apoptosis. They also interfere with several pathways, including NF-kB, P13K/Akt, and MAPK pathways, which are important for tumor cell survival, growth, and metastasis (Sarkar *et al.*, 2021; Svetikiene *et al.*, 2024). So, this study evaluates the phytochemical analysis and antitumor activity of the ethanolic extract of *A. indica* in a MNU-induced uterine cancer model and focuses on tumor volume, tumor growth inhibition, body weight changes, hematological balance, systemic biochemistry, and final tumor weight.

MATERIALS AND METHODS

Extraction of the ethanolic extract of *A. indica*: The botanical garden of the University of Agriculture Faisalabad was used to obtain fresh and healthy leaves of *A. indica* and identify them under the watch of a scientist at the Department of Botany, University of Agriculture Faisalabad. The dried leaves were washed and dried in shade during ten days in the Chemotherapy Lab, Department of Parasitology, University of Agriculture Faisalabad. The dried leaves were then ground into a coarse powder and extracted with 95% ethanol (UNI-CHEM®) in a Soxhlet apparatus between 8-12h. The extract was taken and filtered. The filtered extract was then concentrated via rotary evaporator (40°C) to get the required crude extract. This extract was then kept at 4°C in glass bottles with a capacity of 1000mL which were blue capped. The percentage yield (%) will be calculated as shown in the following formula.

$$\% \text{ yield} = \frac{\text{Weight of the dry extract}}{\text{Weight of dry leaves before extraction}} \times 100$$

Phytochemical determination via High-performance liquid chromatography (HPLC): HPLC was done at the Certified Central Hi-Tech Lab (ISO-9001: 2015), University of Agriculture Faisalabad, Pakistan. To conduct an HPLC analysis, 50mg of *A. indica* leaves extract was dissolved in 24mL of ethanol, and it was homogenized to give a uniform sample solution, followed by filtration and injection. The temperature of the mixture was held to 70°C for 2h, and the end solution was filtered with a nylon membrane filter (Biotech, Germany) of 0.45M size. The sample of extract of the *A. indica* leaves on gradient HPLC (LC-10A, SHIMADZU, JAPAN) was separated using the Shim-Pack CLC-ODS (C-18) 25cm × 4.6mm, 5µm column. Mobile phase gradient: chromatographic separation was performed with solvent-A (H2O: acetic acid-94:6, pH=2.27) and B (100% acetonitrile). Gradient at concentration of 15-16% solvent-B for 0-15minutes, and then at 45% solvent-B for 15-30minutes, and finally at 100% pure solvent-B for 30-45minutes were applied. The mobile phase rate was kept at 1mL/min and UV-visible detector was calibrated at a maximum wavelength of 280nm. The identification of phenolic compounds was done using the UV-visible spectra and the retention time against the standards. External calibration was used to calculate the concentration or the quantity of each component.

Animal preparation: Eighty-four female albino rats of the age of 6-8 weeks, weighing 340-345g, were bought and

acclimatized under ideal environmental conditions (temperature 22°C, humidity 50-55 and 12h light-dark cycle). Normal rodent food in pellet form was given using clean and fresh water. The treatment and care of animals were done as per the established guidelines and legislation adopted by the Animal Care and Use Committee of the University of Agriculture, Faisalabad, Pakistan, and reduced stress levels and improved handling of animals were attained through the research work.

Induction of uterine cancer: Purchasing of uterine smooth muscle cells (USMCs) was done from the Cell Bank of the Chinese Academy of Science (Shanghai, China), and uterine cancer was experimentally induced by using N-methyl-N-nitrosourea (MNU). A single dose of 2mg/rat was administered using a sterile microsyringe under light anesthesia. Mice were then monitored for various clinical signs and tumor development over the following days. Formation of palpable tumor nodules confirmed the successful induction before treatment initiation.

Experimental design: After confirmation of uterine cancer induction, female albino rats were randomly divided into seven experimental groups, with 12 animals in each group, and organized into 3 replicates per group to maintain statistical reliability. The first five groups, G1, G2, G3, G4, and G5, were treated with different concentrations as G1 at 50 mg/kg, G2 at 100 mg/kg, G3 at 200 mg/kg, G4 at 400 mg/kg, and G5 at 800mg/kg of the ethanolic extract of medicinal plant, respectively. G6 served as a positive control (tumor induced, non-treated), and G7 served as a negative control (non-tumor, non-treated), for monitoring of normal physiological parameters. Administration of all treatments was ensured once a day for 30 days through oral gavage. During the study, female albino rats were closely monitored for tumor volume, tumor growth inhibition, body weight changes, biochemical and serum analysis, and overall health. This experimental design allowed a comprehensive comparison between untreated animals, cancer-induced animals, and *A. indica* extract treated groups.

Tumor volume measurements: Tumor growth was monitored by measuring the length and width of palpable tumors at 7-day intervals. The tumor volume in mm^3 was calculated using the formula by Lee *et al.* (2007):

$$\text{Tumor volume } (mm^3) = \frac{L \times W2}{2}$$

Where L represents the length of the tumor, and W represents the width of the tumor.

This method indicates a reliable estimation of tumor progression during and after the treatment period.

Tumor growth response: Tumor growth response was determined by calculating the tumor growth inhibition percentage (%TGI) by comparing the treated groups with the cancer control at different time intervals. The following formula was used by Bernard *et al.* (2012) for calculating % TGI

$$\%TGI = [1-\frac{Tt-Tt0}{Tc-Tc0}] \times 100$$

Where Tt = Final tumor volume of treated groups
Tt0 = Initial tumor volume of treated group
Tc = initial tumor volume of cancer control
Tc0 = initial tumor volume of cancer control

A high percentage of TGI indicates better antitumor activity of the *A. indica*

Body weight changes: The body weight of female albino rats was recorded after 10 days through the experimental period to monitor changes associated with tumor burden or treatment toxicity.

Hematological analysis: At the 30th day of the experiment, blood was collected through cardiac puncture under anesthesia. Hematological parameters, including hemoglobin, white blood cells, red blood cells, and packed cell volume, were analyzed using an automated Beckman Coulter AU480 chemistry analyzer (semi-automated). These measurements assessed the effect of *A. indica* extract on blood physiology and anaemia associated with cancer development.

Serological parameters: Serum was separated by centrifugation (Xian Yi centrifuge, Cence China) and analyzed for key biochemical markers. Liver function was assessed by using alanine aminotransferase (AST) levels. Similarly, renal function test was evaluated through blood urea nitrogen. Systemic inflammation was quantified using C-reactive proteins (CRP). These markers helped in determining the potential protective or toxic effects of *A. indica* extract in tumor-induced female albino rats.

Final tumor weight: On the 30th day, some of the female albino rats from each group were euthanized, and tumors were excised. After cleaning the connective tissues, the weighing of the tumor has been completed by using an analytical balance. Final tumor weight served as a direct indicator of treatment efficacy and correlated with tumor volume and % TGI.

Statistical analysis: The statistical analysis was done with two-way ANOVA to identify the effects of treatment on tumor volume, tumor growth inhibition, and body weight change at the end of the time in the case of the ethanolic extract of A. indica. One-way ANOVA and Tukey test were used to establish the difference between groups of hematological parameters, serum chemistry profiles, and final tumor weight. All the data were expressed as SEM to the right, and significance was determined at $P<0.05$.

RESULTS

Percentage yield of *A. indica* extract: Using the hydrodistillation process, a yield of 22.5% was determined for the ethanolic extract of *A. indica*.

Chemical composition of *A. indica* ethanolic crude extract: In the ethanolic crude extract of A. indica, 9 bioactive compounds were detected by the HPLC technique concentration of ferulic acid (32.83ppm) and syringic acid (23.56) were the highest among all components. These bioactive compounds are given in Table 1 with their chemical formula, molecular mass, retention time, and concentration in ppm. Similarly, the peaks of various concentrations are given in Fig.1.

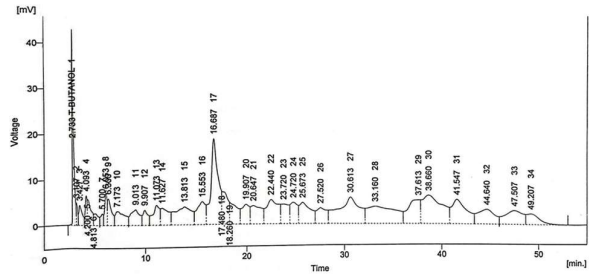

Fig.1: The high-performance liquid chromatography showed peaks against time.

Table 1: Phytochemical composition of ethanolic extract of *A. indica* leaves via high-performance liquid chromatography (HPLC)

Sr. No.	Chemical formula	Chemical component	Molecular mass (g/mol)	Retention time (RT)	Concentration (ppm)
1.	$C_{10}H_{10}O_4$	Ferulic acid	194.18	22.440	32.83
2.	$C_9H_{10}O_5$	Syringic acid	198.17	16.687	23.56
3.	$C_{16}H_{18}O_9$	Chlorogenic acid	354.31	15.553	23.12
4.	$C_{15}H_{10}O_7$	Quercetin	302.23	2.733	21.62
5.	$C_8H_8O_4$	Vanillic acid	168.148	13.813	13.12
6.	$C_9H_8O_2$	Cinnamic acid	148.16	24.720	8.47
7.	$C_7H_6O_5$	Gallic acid	170.12	4.200	5.32
8.	$C_9H_8O_3$	p-coumaric acid	164.16	17.480	3.95
9.	$C_9H_8O_3$	m-coumaric acid	164.16	19.907	2.85

Tumor volume measurement: Tumor volume (mm^3) is measured, and it is confirmed that the size of the tumor in the positive control group increases rapidly, reaching 1050.4 mm^3 on the 30th day. Ethanolic extract of *A. indica* produced a clear dose-dependent reduction in tumor growth at different time intervals. The highest dose, i.e., 800mg/kg, resulted in the lowest tumor volume with a diameter of 305.5 mm^3, demonstrating strong antitumor activity compared to the positive control ($P<0.05$). The tumor volume was determined at various concentrations of crude ethanolic extract of *A. indica* as shown in Table 2 and Fig. 2.

Table 2: Variations in tumor volume at various concentrations Effect of various concentrations ethanolic extract of *A. indica* on tumor volume

Treatment	Day 0 (mm^3)	Day 10 (mm^3)	Day 20 (mm^3)	Day 30 (mm^3)
G1	109.76 ± 0.91^{i}	358.60 ± 1.83^{g}	721.06 ± 1.55^{c}	1030.30 ± 3.96^{a}
G2	108.36 ± 0.89^{j}	353.23 ± 4.34^{g}	606.96 ± 4.29^{d}	860.26 ± 16.33^{b}
G3	105.43 ± 0.61^{j}	348.76 ± 2.48^{g}	457.10 ± 6.14^{e}	610.36 ± 5.76^{d}
G4	104.03 ± 1.18^{j}	300.4 ± 1.65^{h}	348.86 ± 15.17^{g}	406.16 ± 3.05^{f}
G5	101.86 ± 0.53^{j}	225.3 ± 4.01^{i}	233.86 ± 5.06^{h}	305.50 ± 3.79^{h}
G6	111.86 ± 0.59^{j}	376.76 ± 32.3^{fg}	748.30 ± 6.65^{c}	1050.4 ± 35.29^{a}
G7	0 ± 0^{k}	0 ± 0^{k}	0 ± 0^{k}	0 ± 0^{k}

G1: *A. indica* crude extract (50mg/kg); G2: *A. indica* crude extract (100mg/kg); G3: *A. indica* extract (200mg/kg); G4: *A. indica* extract (400mg/kg); G5: *A. indica* extract (800mg/kg); G6: Positive control; G7: Negative control. Values are presented as mean±SD. Statistically significant differences ($P<0.05$) are indicated by superscript letters, both across the groups (rows) for the same day and within groups (columns) over time.

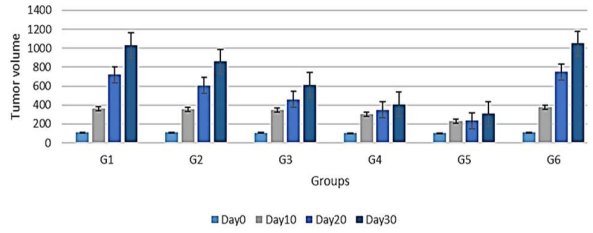

Fig. 2: Variations in tumor volume by various concentrations of *A. indica* extract, where G1: *A. indica* extract (50mg/kg); G2: *A. indica* extract (100mg/kg); G3: *A. indica* extract (200mg/kg) G4: *A. indica* extract (400mg/kg); G5: *A. indica* extract (800 mg/kg); G6: Positive control; G7: Negative control.

Tumor growth response: Tumor growth inhibition analysis showed a clear dose-dependent antitumor effect of *Azadirachta indica* extract. The positive cancer control exhibited no inhibition, while all treated groups demonstrated reduced tumor progression. Lower doses of ethanolic extract of *A. indica* produced moderate inhibition, whereas higher doses (400 and 800mg/kg) showed strong suppression of tumor growth. The maximum inhibition (78.31%) was observed at 800mg/kg, indicating significant therapeutic potential. Overall, the extract effectively limited tumor expansion across treatment groups as described in Table 3.

Table 3: Tumor growth measurements at various concentrations of the ethanolic extract of *A. indica* on tumor growth inhibition

Treatment groups	Initial volume (mm^3)	Final volume (mm^3)	Final-initial volume (mm^3)	TGI (%)
G1	109.76	1030.3	920.53	1.92^{d}
G2	108.36	860.26	751.90	19.93^{c}
G3	105.43	610.36	504.93	46.20^{b}
G4	104.03	406.16	302.13	67.82^{b}
G5	101.86	305.50	203.63	78.31^{a}
G6	111.86	1050.40	938.53	0.00^{d}
G7	0.00	0.00	0.00	0.00^{d}

G1: *A. indica* crude extract (50mg/kg); G2: *A. indica* crude extract (100mg/kg); G3: *A. indica* extract (200mg/kg); G4: *A. indica* extract (400mg/kg); G5: *A. indica* extract (800mg/kg); G6: Positive control; G7: Negative control. Statistically significant differences ($P<0.05$) are indicated by superscript letters among the experimental groups (rows).

Body weight changes: The body weight (g) of female albino rats having experimentally induced uterine tumors differed significantly among treatment groups over the 30-day study period. Progressive increase in body weight was observed from day 0 to day 30, with G5 (800mg/kg) showing the highest body weight gain, followed by G4 (400mg/kg) and G3 (200mg/kg). This indicates a protective or growth-promoting effect of the treatments. On the other hand, G6 (positive control) showed a continuous reduction in body weight and reached the lowest value (207.1±7.86) by day 30 (Table 4 and Fig. 3). This reflects the adverse effects of tumor progression. The negative control group showed a mild weight increase when compared with the low-dose treatment groups, i.e., G1 and G2. Statistical analysis confirmed the significant difference among groups and over time ($P<0.05$). Overall, the treatments were effective in gaining body weight and supported normal growth in treated animals.

Table 4: Body weight of experimental albino rats following treatment with various concentrations of *A. indica* extract

Treatment	Day 0 (g)	Day 10 (g)	Day 20 (g)	Day 30 (g)
G1	324.8 ± 3.15^{ghi}	335.2 ± 2.53^{efg}	364.2 ± 1.63^{abcde}	367.33 ± 0.82^{abcde}
G2	325.53 ± 3.39^{ghi}	342.7 ± 2^{defg}	366.43 ± 1.56^{abcde}	372.53 ± 2.86^{abcd}
G3	295.6 ± 41.93^{i}	345.76 ± 1.54^{cdefg}	370.4 ± 1.55^{abcd}	376.93 ± 1.67^{abc}
G4	330.9 ± 5.82^{fgh}	347.53 ± 1.69^{bcdefg}	373.66 ± 1.04^{abcd}	380.9 ± 2.53^{a}
G5	337.26 ± 2.09^{efg}	352.66 ± 1.42^{abcdefg}	380 ± 1.48^{ab}	384.33 ± 1.63^{a}
G6	323.1 ± 2.64^{ghi}	298.86 ± 2.05^{hi}	218.9 ± 1.2^{j}	207.1 ± 7.86^{j}
G7	320.13 ± 0.65^{ghi}	341.36 ± 1.02^{defg}	359.46 ± 2.47^{abcdef}	366.33 ± 1.71^{abcde}

G1: *A. indica* crude extract (50mg/kg); G2: *A. indica* crude extract (100mg/kg); G3: *A. indica* extract (200mg/kg); G4: *A. indica* extract (400mg/kg); G5: *A. indica* extract (800mg/kg); G6: Positive control; G7: Negative control. Statistically significant differences ($P<0.05$) are indicated by superscript letters among the experimental groups (rows).

Hematological analysis: Hematological analysis was performed at 30th day and revealed significant differences among the treatment groups. Hb (14.23g/dL), RBC count ($8.63 \times 10^6/\mu L$), and PCV (43.33%) were highest at

800mg/kg concentration. This indicates improved erythropoiesis, while the positive control group showed the lowest values, reflecting anemia caused by tumor progression. The highest WBC count in the positive control suggests an inflammatory response, while the treatment groups maintained lower and normal WBC levels (Table 5 and Fig. 4). Statistical analysis confirmed significant differences among groups (P<0.05).

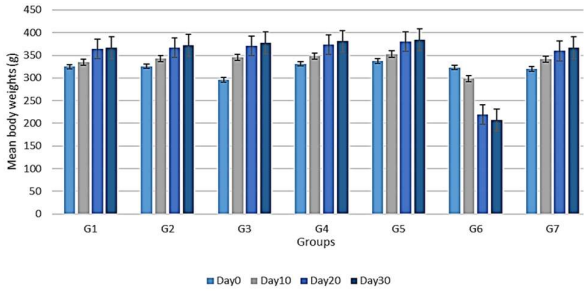

Fig. 3: Body weight measured at various concentrations of *A. indica* extract, G1 received *A. indica* crude extract (50mg/kg); G2 received *A. indica* crude extract (100mg/kg); G3 received *A. indica* extract (200mg/kg); G4 received *A. indica* extract (400mg/kg); G5 received *A. indica* extract (800mg/kg); G6 was Positive control; G7 served as Negative control.

Serum analysis: Similar to hematological parameters, serum analysis was also done on the 30th day, which showed a significant variation among the groups. Liver enzymes, including ALT and AST, were markedly elevated in the positive control group, which indicates liver damage due to tumor progression. Kidney function markers, including BUN and creatinine, were also highest in the positive control group, reflecting renal impairment. Similarly, CRP, which is a marker of systemic inflammation, was significantly elevated in the tumor-induced, non-treated group. On the other hand, treatment groups from G1 to G5 maintained lower levels, indicating reduced inflammatory response. Total protein levels were lowest in G6 and significantly higher in treatment groups, particularly in G5 when the concentration of *A. indica* extract was 800mg/kg (Table 6 and Fig. 5). This suggests the better preservation of protein metabolism.

Table 5: Hematological parameters measured at various doses of *A. indica* crude ethanolic extract

Treatments	Hemoglobin (g/dL)	Red blood cells (10^6/µL)	White blood cells (10^3/µL)	Packed cell volume (%)
G1	10.2±0.16^{e}	6.3±0.16^{d}	10.56±0.28^{b}	32.33±0.47^{c}
G2	11.43±0.2^{d}	6.76±0.12^{cd}	9.4±0.16^{c}	35±0.81^{b}
G3	12.6±0.16^{c}	7.26±0.12^{cd}	8.4±0.16^{d}	37±0.81^{b}
G4	13.4±0.16^{b}	8.4±0.16^{b}	7.8±0.08^{de}	42±0.81^{a}
G5	14.23±0.28^{a}	8.63±0.12^{b}	7.46±0.12^{e}	43.33±0.94^{a}
G6	9.26±0.12^{f}	5.4±0.16^{e}	12.7±0.21^{a}	28.33±0.47^{d}
G6	14.06±0.3^{ab}	13.46±0.24^{a}	7.66±0.12^{e}	43±0.81^{a}

G1 received *A. indica* crude extract (50mg/kg); G2 received *A. indica* crude extract (100mg/kg); G3 received *A. indica* extract (200mg/kg); G4 received *A. indica* extract (400mg/kg); G5 received *A. indica* extract (800mg/kg); G6 was Positive control; G7 served as Negative control. Values are presented as mean±SD. Different superscript letters within the same columns represent significant differences (P<0.05) among groups.

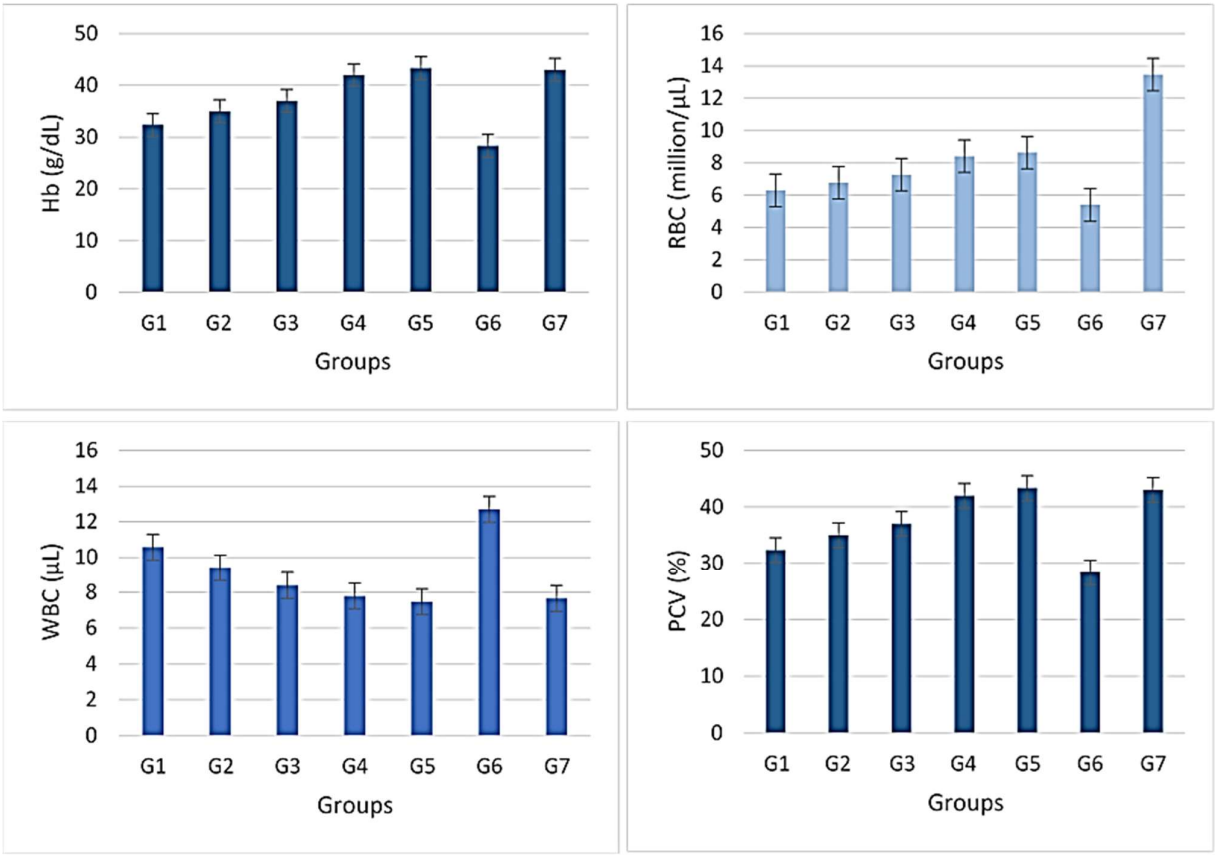

Fig. 4: Hematological parameters measured at various doses of *A. indica* crude ethanolic extract. G1 received *A. indica* crude extract (50mg/kg); G2 received *A. indica* crude extract (100 mg/kg); G3 received *A. indica* extract (200 mg/kg); G4 received *A. indica* extract (400 mg/kg); G5 received *A. indica* extract (800 mg/kg); G6 was Positive control; G7 served as Negative control.

Table 6: Serum biochemistry measurements at various concentrations of the ethanolic extract of *A. indica*

Treatments	ALT (U/L)	AST (U/L)	BUN (mg/dL)	Creatine (mg/dL)	C-reactive proteins (mg/L)	Total proteins (g/dL)
G1	82±1.63^{b}	182±1.63^{b}	33±0.81^{b}	0.76±0.01^{b}	9.43±0.12^{b}	5.3±0.08^{d}
G2	68±1.63^{c}	175.33±2.49^{b}	27±0.81^{c}	0.62±0.01^{c}	7.3±0.08^{c}	5.73±0.09^{c}
G3	54.66±0.94^{d}	109±5.09^{c}	23±0.81^{d}	0.54±0.01^{d}	5.3±0.16^{d}	6.26±0.12^{b}
G4	44±1.63^{e}	95.33±0.47^{d}	19±0.81^{e}	0.47±0^{e}	3.4±0.08^{e}	6.9±0.08^{a}
G5	41±0.81^{e}	80.33±0.47^{e}	17.66±0.47^{e}	0.45±0^{e}	2.9±0.08^{f}	7±0.08^{a}
G6	98.66±0.94^{a}	223.66±2.62^{a}	39±0.81^{a}	0.9±0.01^{a}	11.36±0.04^{a}	4.4±0.16^{e}
G6	41.33±0.94^{e}	77.66±2.05^{e}	17.66±0.47^{e}	0.45±0^{e}	2.7±0.08^{f}	7±0.08^{a}

G1 received *A. indica* crude extract (50mg/kg); G2 received *A. indica* crude extract (100mg/kg); G3 received *A. indica* extract (200mg/kg); G4 received *A. indica* extract (400mg/kg); G5 received *A. indica* extract (800mg/kg); G6 was Positive control; G7 served as Negative control. Values are presented as mean±SD. Different superscript letters within the same columns represent significant differences (P<0.05) among groups.

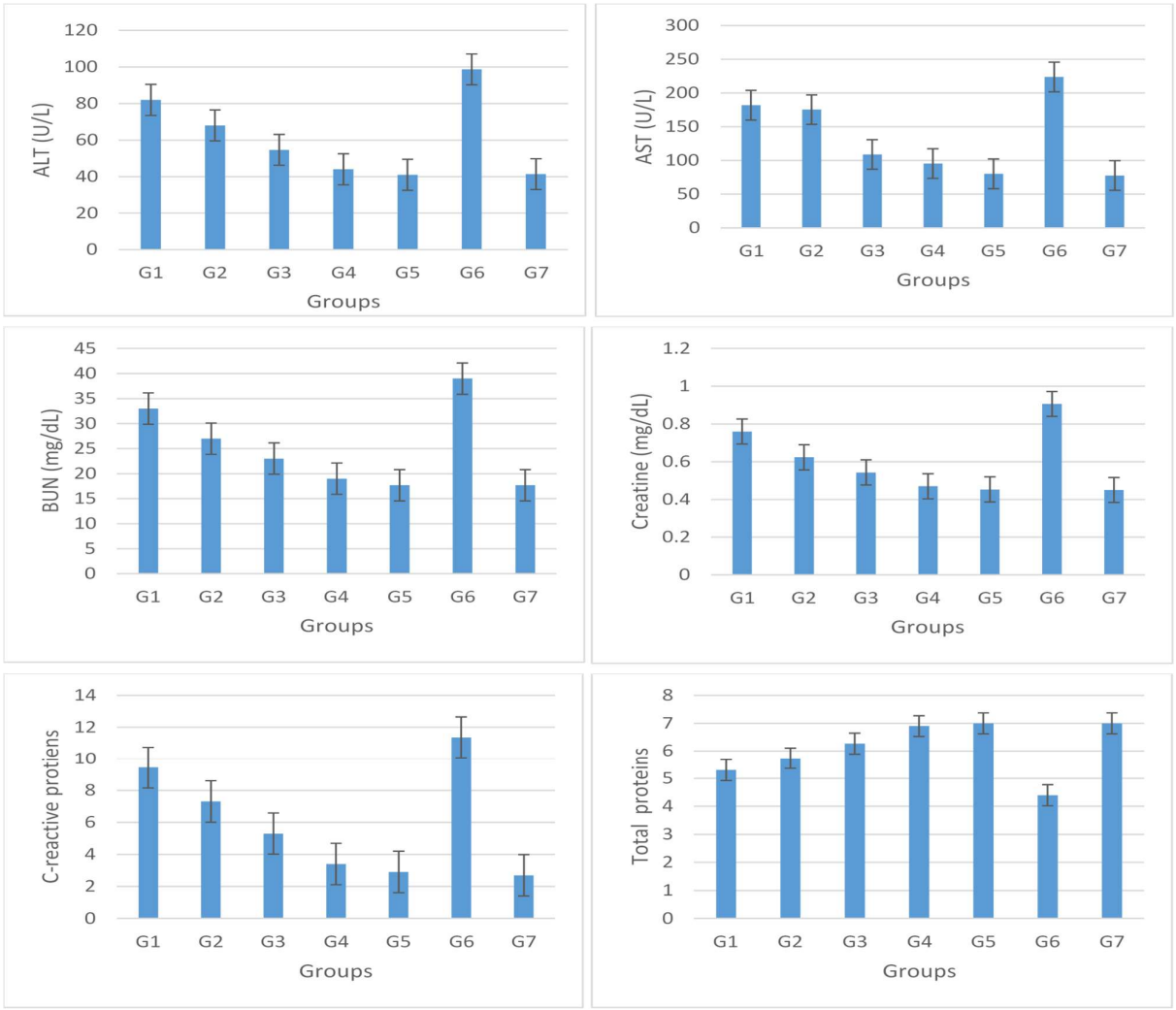

Fig. 5: Effect of various concentrations of the crude ethanolic extract of *A. indica* at the serum chemistry. G1 received *A. indica* crude extract (50mg/kg); G2 received *A. indica* crude extract (100mg/kg); G3 received *A. indica* extract (200mg/kg); G4 received *A. indica* extract (400mg/kg); G5 received *A. indica* extract (800mg/kg); G6 was Positive control; G7 served as Negative control.

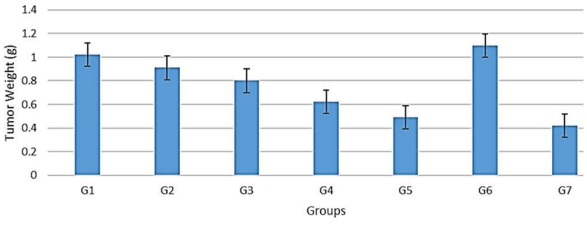

Fig. 6: Effect of various concentrations of *A. indica* extract on final tumor weight, whereas G1 received *A. indica* crude extract (50mg/kg); G2 received *A. indica* crude extract (100mg/kg); G3 received *A. indica* extract (200mg/kg); G4 received *A. indica* extract (400mg/kg); G5 received *A. indica* extract (800mg/kg); G6 was Positive control; G7 was Negative control.

Final tumor weight: Final tumor weight was determined at 30th day, and a significant difference among treatment groups. Albino rats present in the positive control group exhibited the highest tumor weight, while in the treated groups, there was a marked reduction in tumor weight, but G5 demonstrated the greatest inhibition. The results from G1 to G5 were dose-dependent. Statistical analysis confirmed significant differences among groups (P<0.05) as shown in Fig. 6. Overall, these results suggest that the administration of the highest concentrations of *A. indica* extract reduces tumor volume, tumor growth, and tumor weight.

DISCUSSION

Medicinal plants have long been recognized as a rich source of bioactive compounds with antioxidant (Pammi *et al.*, 2023), antimicrobial (El-Saadony *et al.*, 2025), and anticancer potential (Albahri *et al.*, 2024; Shinohara *et al.*, 2025). Medicinal plants have a natural origin, are less toxic, and have broader pharmacological actions that make them attractive alternatives to synthetic chemotherapeutic agents (Güneş *et al.*, 2022; Abd El-Hack *et al.*, 2023; Ramsridhar *et al.*, 2025). Among these, *A. indica* is widely used as one of the most potent medicinal plants due to its phytochemical profile, including azadirachtin, nimbolid, quercetin, and various other limonoids (Nagini *et al.*, 2024). In the present research study, when HPLC of ethanolic extract of *A. indica* was performed, different bioactive compounds including ferulic acid (32.83ppm), syringic acid (23.56ppm), chlorogenic acid (23.12ppm), quercetin (21.62ppm), vanillic acid (13.12ppm), cinnamic acid (8.47ppm), gallic acid (5.32ppm), p-coumaric acid (3.95ppm), and m-coumaric acid (2.85ppm) have been detected. These results are in line with the previous study by Singh *et al.* (2005), who reported various concentrations of gallic acid, quercetin, and ferulic acid in *A. indica* extract when HPLC was performed. In another study similar type of composition was determined by Sarkar *et al.* (2023), who confirmed the presence of quercetin, gallic acid, vanillic acid, p-coumeric acid, and ferulic acid in *A. indica* extract. By keeping this in mind, the bioactive compounds, the recent study determined the therapeutic effect of the ethanolic extract of *A. indica* leaves against experimentally induced uterine cancer in female albino rats. The study was focused on tumor volume, tumor growth inhibition, body weight changes, hematological alterations, serum biomarkers, and final tumor weight. Overall, the study demonstrates a remarkable dose-dependent anti-tumor effect, with the higher concentrations (400mg/kg and 800mg/kg) providing the greatest therapeutic effects.

Tumor volume study revealed a continuous decline in tumor size in all the *A. indica*-treated groups compared with the positive cancer control. The untreated positive control group showed rapid and continuous tumor enlargement, which reflects the aggressive nature of MNU-induced uterine carcinogenesis. In contrast the albino rats treated with 800mg/kg showed a substantial decrease in tumor size. These values are almost non-significant compared to the values from the negative control. These findings align with the previous study conducted by Lin *et al.* (2020), who demonstrated that extract from *Prunella vulgaris* significantly reduces the uterine carcinoma as compared to the control group in albino rats. Similarly, another study by Al Qaisi *et al.* (2024) demonstrated the cytotoxic and antiproliferative activity of extracts obtained from *Ruta graveolens, Peganum harmala,* and *Citrullus colocynthis* and their phytochemicals such as polyphenols and flavonoids. These phytochemicals are known to inhibit angiogenesis, cell division, and tumor survival pathways. In another study conducted by Ogbole *et al.* (2017) demonstrated that the extract of *Eluesine indica* plant has a cytotoxic effect against rhabdomyosarcoma cancer cell lines. The high percentage of TGI is observed in high dose groups, which further supports the therapeutic potential of the extract to manage tumor progression. These results are aligned with the study conducted by Rabelo *et al.* (2021), who demonstrated that crude, methanolic, and ethyl acetate fractions of *Calotropis procera* showed strong antiproliferative and anti-progression properties, thus reducing tumor viability, inducing cell cycle arrest, and promoting apoptosis without affecting normal cells in canines. This inhibition of tumor growth is also achieved through various mechanisms, including oxidative stress modulation and suppression of inflammatory mediators associated with cancer progression. The results of the present research study were also aligned with the study conducted by Oh *et al.* (2023), who demonstrated that IMMUNIES (primarily contains *Dendropanax morbiferus*), a traditional herbal product, has safety evaluations and anticancer activity against mammary and liver tumors in dogs. In another study conducted by Dumitraş *et al.* (2022) demonstrated that rhodoxanthin extracted from *Taxus baccata* and its chemical compounds, including retro-cartonoides, flavonoids, and phenolics, have antioxidant activity and possess potential cytotoxic effect against B16F10 murine malignant melanoma.

Changes in body weight are a sensitive indicator of systemic toxicity and cancer-associated metabolic disorders. In the present study, the positive control group showed significant body weight loss due to consistent metabolic alterations. Treatment with the ethanolic extract of *A. indica* improved weight gain in a dose-dependent manner, with the highest dose preserving near normal body weight. These results of the study are aligned with a study of Mendoza-Martínez *et al.* (2022), in which the activity of a polyherbal product containing *Achyrantes aspera*, *Trachyspermum ammi*, *Citrullus colocynthis*, *Andographis paniculata*, and *Azadirachta indica* was evaluated and confirmed improvement in body weight, thickening of subcutaneous fat, alterations in blood metabolites, and modified gene expression. Our research findings are also aligned with the study conducted by Ugwu *et al.* (2023), who demonstrated the significant and dominant effect of ethanolic extract of *Sphenocentrum jollyanum* on the body weights of rodents. These studies suggest that *A. indica* extract not only limits tumor burden but also improves cancer-related metabolic distress. Better appetite, decreased inflammation and safety of essential organs could be referred to as the reason that the body weight got better. The hematological investigation showed notable red blood cell and white blood cell counts depression in the control group which is an indication of anemia of chronic disease and inflammatory response in tumors. At high concentrations, ethanolic extract of *A. indica* had a significant restoring effect on HB, RBC, PCV, and WBC. The findings are in line with the results of the research by Azadeh *et al*. (2022) who demonstrated that *E. coli* ethanolic extract of licorice root had various effects on hematological indices in dogs with benign hyperplasia of the prostate. The 30-day daily oral treatment was tolerated and BUN, creatinine, ALT, ALP, and CRP serum markers improved without any changes to the normal RBC or HCT count. This recovery of the hematological parameters improved the general health condition and physiological resistance to malignancies. On the same note, serological biomarkers also confirmed the therapeutic effect of the *A. indica* extract. The high increase in alanine transferase (ALT), aspartate aminotransferase (AST), blood urea

nitrogen (BUN), creatinine, and C-reactive proteins (CRP) occurred due to the induction of the uterine tumor (Suliman *et al*., 2023). These parameters are evidence of hepatic injury, renal dysfunction, and systemic inflammation which are typical effects of tumor expansion and development of the chemical carcinogenesis (Hamdi *et al*., 2021). These serum markers have been significantly improved in case of treatment of uterine cancers induced by MNU in female albino rats on treatment with ethanolic extract of *A. indica*. Such normalization of the serum biomarkers demonstrated the protection against hepato-renal damage, and it is because antioxidant, anti-inflammatory, and detoxifying effects of *A. indica* extract stabilize cell membranes, reduce oxidative stress, and enhance organ functions (Kumar *et al*., 2024). The significant decrease in the levels of CRP in the high-dose groups demonstrates that the growth of the tumor, its metastasis and inflammation at the systemic level were inhibited to a great extent. Lastly, tumor weight values were also in line with tumor volume and findings of TGI that had a significant decrease when subjected to the increased doses of *A. ind*ica extract. The lowest tumor weights were revealed into the 800mg/kg concentration and emphasize the cytotoxic and antiproliferative effect of the *A. indica* extract on uterine tumor tissues. The findings are not surprising since the findings of Metwally *et al*. (2014) have validated that the peak concentration of *A. indica* extract lowered the tumor weight of Ehrlich ascites carcinoma in female Swiss albino mice. The biochemical and hematological improvements also have a strong correlation with these tumor weight reductions, indicating that there is a strong therapeutic response caused by the bioactive compounds found in *A. indica* extract. Altogether, the current research proves that the ethanolic extract of *A. indica* has powerful anticancer and antitumor effects on the MNU-initiated uterine carcinoma, and their effectiveness depends on the dose in a dose-dependent manner.

Conclusions: This study demonstrates that the ethanolic extract of *A. indica* leaves provides significant protection against uterine tumors in female albino rats. The extract reduced tumor volume, increased tumor growth inhibition, and prevented cancer-related cachexia in a dose-dependent manner. Improvements in body weight, hematological balance, and serum biochemical markers further indicate strong systemic and organ-protective effects. Overall, the ethanolic extract of *A. indica* shows potent antitumor, antioxidant, and immune modulatory properties, which support its potential as a safe, natural therapeutic option for managing uterine tumors in veterinary settings.

Authors contribution: RW and HX were involved in all stages of this study, from conceptualization to writing and editing. YY conceived and designed the project/study, investigation, methodology, validation, and visualization.SZ was responsible for conducting the experiment. RW, YY and SZ performed histopathological analysis and interpreted results. HX performed the immunohistochemical analysis. RW, YY and, and HX were involved in the investigation and visualization. All authors have approved the final manuscript.

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