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Research Article

Antitumor Activity of *Citrullus colocynthis* against Ehrlich Ascites Carcinoma Induced Solid Tumor Model in Mice

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ABSTRACT

Cancer has been a leading global health burden over the past two decades, and the primary mode of treatment has not shown a promising curative approach because toxicity and drug resistance associated with conventional chemotherapy highlight the need for safer, effective alternatives. *Citrullus colocynthis* (bitter apple) is a medicinal plant reported to possess antioxidant, anti-inflammatory, and cytotoxic activities. This study investigated the antitumor potential of *C. colocynthis* seed extract against Ehrlich ascites carcinoma (EAC)-induced solid tumors in mice**.** Solid tumors were established by s.c. injection of EAC cells (2×10^6 cells/mouse) in experimental animals. Animals were treated orally with ethanolic seed extract of *C. colocynthis* for 14 days. Tumor volume, body weight, hematological and biochemical parameters, antioxidant enzyme levels, and histopathological changes in tumor tissues were evaluated. Treatment with *C. colocynthis:* Substantial decrease in tumor weight and volume ($p < 0.001$). Antioxidant enzymes were restored toward normal levels, and altered hematological parameters were significantly improved. Histopathological examination revealed reduced mitotic activity and extensive tumor necrosis, confirming inhibition of tumor progression. The ethanolic seed extract of *C. colocynthis* could be used as an adjuvant therapy and can be considered along with the primary mode of treatment.

Introduction

Cancer is a major global health burden and a leading cause of morbidity and mortality. It is characterized by unregulated cellular proliferation, evasion of programmed cell death, angiogenesis, tissue invasion, and eventual metastasis to distant organs. Despite significant advancements in conventional therapeutic modalities, including chemotherapy, radiotherapy, and surgical resection, the clinical outcomes of these interventions are often compromised by severe systemic toxicity, undesirable side effects, and the emergence of multidrug-resistant cancer phenotypes. These limitations underscore the urgent need for innovative, safer, and efficacious anticancer strategies, particularly those derived from naturally occurring bioactive compounds with minimal adverse profiles. Medicinal plants have historically constituted a rich and versatile repository of pharmacologically active agents, offering a plethora of secondary metabolites capable of modulating diverse biological pathways. *Citrullus colocynthis* (L.) Schrad., colloquially known as bitter apple or desert gourd, is a member of the Cucurbitaceae family and has been extensively utilized in traditional medicine systems [1] for its wide spectrum of therapeutic properties, including antioxidant, anti-inflammatory, analgesic, antimicrobial, and cytotoxic activities.[2] The plant harbours a diverse array of bioactive constituents such as cucurbitacins, flavonoids, alkaloids, and glycosides, which collectively exhibit pronounced anti-proliferative, apoptotic, and chemopreventive effects in preclinical models. The most characteristic constituents of *C. colocynthis* are cucurbitacins, a group of highly oxygenated tetracyclic triterpenes with a cucurbitane skeleton. Compounds cucurbitacin E, cucurbitacin I, colocynthosides A and B

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have been isolated predominantly from the fruit pulp. [3,4] These compounds are intensely bitter and are largely responsible for both the therapeutic (antitumor, anti-inflammatory) and toxic (gastrointestinal irritant) effects of the plant. EAC is an aggressive, highly proliferative, transplantable murine tumour model originally derived from murine mammary adenocarcinoma.[5] It is extensively employed in experimental oncology research owing to its high reproducibility, rapid growth kinetics, and histopathological and biochemical resemblance to human malignancies. The EAC model serves as a robust and reliable platform for the systematic evaluation of novel antitumour agents and facilitates mechanistic insights into tumour suppression, oxidative stress modulation, and immunomodulatory responses.

Despite remarkable advances in oncology, ranging from molecularly targeted therapies and immuno-oncology to advanced surgical and radiotherapy techniques. Current cancer treatment paradigms remain fraught with significant limitations that hinder curative outcomes and contribute to disease recurrence and mortality. In light of these considerations, this study was designed to systematically evaluate the antitumour potential of the ethanolic seed extract of *C. colocynthis* against EAC-induced solid tumours in mice. The investigation encompasses comprehensive assessments of tumour growth inhibition, modulation of hematological and biochemical indices, augmentation of antioxidant defense mechanisms, and histopathological alterations within tumour tissues. By elucidating the mechanistic underpinnings of its anticancer activity, this study aims to substantiate the therapeutic potential of *C. colocynthis* as a potential lead compound for novel, plant-based oncological interventions.

Materials And Methods

Plant Collection and Authentication

The seeds of *C. colocynthis* were procured from the local supplier and authenticated by Dr. Noorunnisa Begum, Research Officer (Botany), Central Ayurveda Research Institute. Bangalore, Yelahanka, India.

Preparation of Extract

The seeds of *C. colocynthis* were thoroughly cleaned with fresh water. The seeds were dried properly in the shade for 3 weeks. Dried seeds were coarsely powdered and utilized for the methanolic extract. The methanolic extraction was carried out by the soxhlet extractor technique. Coarsely powdered seeds were added to soxhlet with methanol for two cycles in 6 hours (Temperature -30°C). [6] The extract was filtered through the whatmen filter paper. The extract was weighed and stored in air-tight containers for further phytochemical and pharmacological studies.

Experimental Animals

Swiss albino mice of either sex (8–10 weeks old), weighing 25 to 30 g, were maintained as per the CPCSEA guidelines. The animals had free access to a standard pellet diet and water *ad libitum*. All experimental procedures were conducted in accordance with established guidelines for the care and use of laboratory animals, and the study protocol was duly approved by the Institutional Animal Ethics Committee (IAEC) of Karnataka College of Pharmacy, Bangalore. And protocol number: KCP-IAEC/14/23-24/06/28/03/24.

Ehrlich Ascites Carcinoma (EAC) Solid Tumor Model

For the establishment of the solid tumor model, EAC cells (1×10^6 cells per mouse) were administered via intramuscular injection into the right hind limb of each experimental animal. Following inoculation, the tumors were allowed to proliferate and establish for a period of 11 days. Therapeutic intervention with the designated treatment regimen commenced on the 12^{th} day post-tumor implantation and continued for a duration of 21 consecutive days.[6,7] This model provides a reproducible and reliable platform for evaluating the antitumor efficacy of experimental agents *in-vivo*, while facilitating detailed assessment of tumor growth kinetics, histopathological alterations, and associated physiological and biochemical parameters.

Group Selection

Animals were divided as followings, with n = 6/group

Group I: Normal control – Normal saline (2 mL/kg/b.w, *p.o.*).

Group II: EAC control: (Mice will be administration 1×10^6 cells/animal).

Group III: Test group: Received crude methanolic extract of *C. colocynthis* 50 mg/kg/Orally/21 days.

Group IV: Test group: Received crude methanolic extract of *Citrullus colocynthis* 100 mg/kg/orally/21 days.

Group V: Standard drug: Received 5-fluorouracil-20 mg/kg/*i.p.*/weekly twice.

Evaluation of Antitumor Activity in EAC-Bearing Mice[7]

Effect on body weight

Body weight was recorded at baseline and every 5 days to monitor tumor burden. Stabilization or reduction in treated groups indicates anti-proliferative and anti-ascitic effects.

Tumor size measurement

Tumor volume was measured every 5 days from day 11 using vernier calipers. Reduction in tumor size in treated groups reflects antitumor efficacy.

Effect on mean survival time (MST)

MST was calculated as the average of the day of the first and the last death. Prolongation of MST in treated groups compared to controls indicates therapeutic potential.

$$MST = \frac{(\text{Day of first death} + \text{Day of last death})}{2}$$

Percentage increase in life span (%ILS):

%ILS was determined to quantify improvement in host survival using: A higher % ILS reflects enhanced therapeutic efficacy in delaying tumor progression.

%ILS = (Mean survival of treated group/ Mean survival of control group)-1 × 100

Inflammatory cytokine (TNF-α) and antioxidant enzyme assessment

After sacrificing the animals, the tumor tissues were isolated and homogenized in ice-cold PBS, centrifuged, and the supernatant was used for TNF-α estimation via a sandwich ELISA kit. Cytokine levels indicate inflammatory and tumor-associated responses.[8,9] and antioxidant, reduced glutathione (GSH) was measured by Ellman's (DTNB) method; it reacts with DTNB to form a yellow-colored TNB, whose absorbance is measured at 412 nm and is directly proportional to the GSH concentration.[10]

Haematological Parameters

Blood was collected to assess haemoglobin, RBC, and WBC counts. Normalization of these values in treated groups indicates hematopoietic protection and systemic benefits.

Histopathological Investigations

The tumor tissue was collected and fixed in 10% formalin, processed, sectioned, and stained with H&E. Histological evaluation will assess necrosis, nuclear changes, inflammation, and tissue architecture, comparing treated and control groups to determine protective effects against tumor-induced damage.[11]

Statistical Analysis

Statistical data are presented as Mean ± S.E.M. (n = 6 per group). Differences among groups were evaluated using ANOVA followed by Tukey's post hoc test. Comparisons were made against the normal control group, and values of $p < 0.05$ were considered statistically significant.

RESULTS

The present study demonstrates that EAC tumor development is associated with profound physiological alterations, including rapid body weight gain (Table 1). Normal control animals showed only a slight body-weight increase (+6.6%), reflecting healthy growth, whereas untreated EAC controls exhibited a marked increase (+40.2%) due to ascites accumulation and tumor burden. Treatment with 5-FU resulted in a moderate weight gain (+25.4%), indicating partial tumor suppression but also suggesting drug-related toxicity. MeCC at 100 mg/kg produced only a minimal increase in body weight (+10.7%), due to ascites accumulation, significant tumor burden, high mortality (Table 1), increased systemic inflammation, and severe oxidative stress. While the standard drug 5-FU effectively suppressed tumor size and weight and reduced inflammatory marker levels, it was accompanied by considerable systemic toxicity, as reflected in poor survival outcomes. In contrast, treatment with MeCC revealed a clear dose-dependent effect. At the lower dose (MeCC 50), survival remained high, but tumor suppression was observed (Figs 1 and 2). Fig. 2 depicts the Kaplan–Meier survival curve showing survival probability as a function of time. The Y-axis represents the proportion of surviving animals, while the X-axis indicates days after treatment initiation. Each downward step in the curve corresponds to the death of an individual animal. The normal control, MS200, and MS400 groups maintained 100% survival throughout the study period. In contrast, the EAC control group showed a progressive decline in survival, reaching approximately 50% by the end of the experiment. The 5-FU–treated group exhibited the steepest reduction, with survival dropping to around 33%, likely due to systemic toxicity. Overall, the survival analysis confirms that MeCC at both doses preserved survival comparable to normal controls, whereas

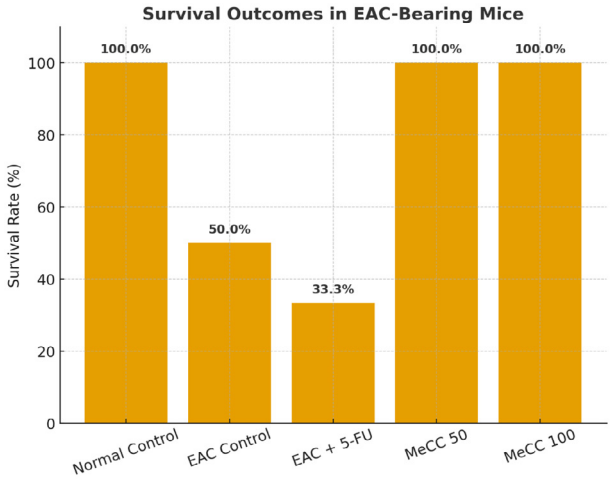


Fig. 1: Assessments of Survival outcome within the groups. Values are expressed as Mean +/- S.E.M., n =6

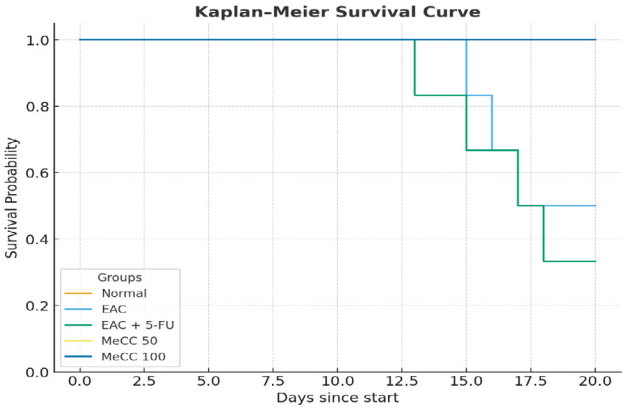


Fig. 2: Kaplan–Meier survival curve (survival probability vs time). Values are expressed as Mean +/- S.E.M., n =6

Table 1: Evaluating the effects of a test drug on morphological parameters in EAC (Ehrlich Ascites Carcinoma) induced solid tumors, comparing untreated vs treated groups

Group	*Body weight (g) before RX*	*Body weight (g) after RX*	*% Change in B.w.*	*Tumor size (mm)*	*Tumor weight (g)*	*Mortality (%)*	*Overall effect*
Normal control	28.7 ± 2.5	30.6 ± 2.78	+ 6.6	0	0	0	Normal physiology
EAC control (Untreated)	26.98 ± 1.3	37.82 ± 1.6	+ 40.2	19.5 ± 2.0	5.5 ± 2.3	50.0	Rapid tumor progression
EAC + Standard (5-FU)	27.95 ± 2.6	35.04 ± 3.3	+ 25.4	16.5 ± 1.0	1.5 ± 0.8	66.7	Strong tumor suppression, but systemic toxicity
MeCC 50	24.76 ± 1.97	34.67 ± 2.78	+40.0%	17.33 ± 3.45	6.60 ± 1.58	0	Halt tumor progression
MeCC 100	26.78 ± 2.15	29.65 ± 3.78	+10.7%	14.66 ± 1.75	2.90 ± 1.23	0	Mild tumor suppression without mortality

Values are expressed as Mean+/- S.E.M., n =6

significant mortality was observed in the EAC and 5-FU groups and biochemical improvements were minimal. EAC induction caused a marked reduction in haemoglobin, RBC count, total leukocyte count, neutrophils, lymphocytes, and platelets compared with normal controls, indicating severe haematological impairment. Treatment with the standard drug 5-FU partially restored these parameters. MeCC treatment produced a dose-dependent improvement in all haematological indices, with the 100 mg/kg dose showing values closer to those observed with the standard drug, suggesting better protection against EAC-induced hematological toxicity (Tables 2 and 3). TNF-α levels (Fig. 3) even exceeded those of the disease control, and only a modest recovery of GSH (Fig. 4). EAC induction markedly increased the pro-inflammatory cytokine TNF-α and caused severe depletion of GSH, indicating pronounced inflammation and oxidative stress. Treatment with the standard drug 5-FU significantly reduced TNF-α levels and partially restored GSH, reflecting its antitumor and moderate antioxidant effects. MeCC at 50 mg/kg was ineffective, showing even higher TNF-α levels than the disease control with minimal GSH recovery, suggesting a pro-inflammatory response at the lower dose. In contrast, MeCC at 100 mg/kg strongly suppressed TNF-α, nearly

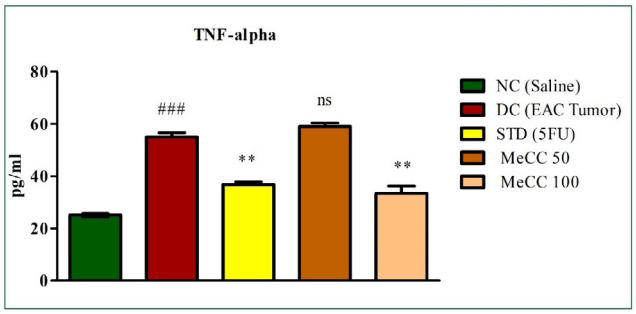
Table 2: The effects of test drug on hematological parameters in the EAC model

Group	*Hb (g/dL)*	*RBC count (×10^6/μL)*	*TLC (×10^3/μL)*	*Neutrophils (%)*	*Lymphocytes (%)*	*Platelet count (×10^3/μL)*
NC (Normal Control)	13.6 ± 1.74	6.86 ± 1.21	4.8 ± 0.84	15.8 ± 1.24	80.8 ± 10.43	899 ± 24.46
DC (EAC tumor, untreated)	8.16 ± 2.13	4.11 ± 1.6	2.88 ± 0.51	9.48 ± 2.12	48.48 ± 8.54	539.4 ± 43.22
STD (5-FU)	10.68 ± 3.5	5.35 ± 1.8	3.744 ± 0.44	12.34 ± 3.2	63.04 ± 2.4	701.22 ± 74.1
MeCC 50	8.40 ± 1.4	4.24 ± 0.1	2.97 ± 0.98	9.76 ± 1.22	49.92 ± 3.75	555.37 ± 87.12
MeCC 100	9.24 ± 0.3	4.66 ± 0.09	3.26 ± 0.22	10.74 ± 1.98	54.91 ± 6.90	610.9 ± 18.30

Values are expressed as Mean+/- S.E.M., n =6

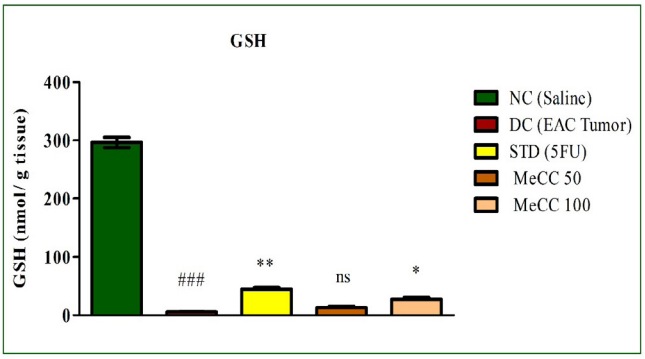
Table 3: Statistical analysis of haematological parameters

Parameter	*DC vs NC*	*STD vs DC*	*MeCC 50 vs DC*	*MeCC 100 vs DC*	*Overall Trend*
Hb (g/dL)	↓↓↓ $p < 0.001$	↑↑ $p < 0.01$	ns	↑ $p < 0.05$	DC caused anemia; STD & MeCC100 improved Hb
RBC count (×10^6/μL)	↓↓↓ $p < 0.001$	↑↑ $p < 0.01$	ns	↑ $p < 0.05$	DC reduced RBCs; recovery with STD & MeCC100
TLC (×10^3/μL)	↓↓↓ $p < 0.001$	↑ $p < 0.05$	ns	↑ $p < 0.05$	DC induced leukopenia; partial recovery with STD & MeCC100
Neutrophils (%)	↓↓ $p < 0.01$	↑ (ns to $p < 0.05$)	ns	ns	Mild neutropenia in DC, slight recovery
Lymphocytes (%)	↓↓↓ $p < 0.001$	↑↑ $p < 0.01$	ns	↑ $p < 0.05$	Strong lymphopenia in DC, reversed by STD & MeCC100
Platelet count (×10^3/μL)	↓↓↓ $p < 0.001$	↑↑ $p < 0.01$	ns	↑ $p < 0.05$	Thrombocytopenia in DC, improved by STD & MeCC100



Values are expressed as Mean+/- S.E.M., n =3, ###p<0.001 compared to normal control, **$p < 0.01$ and ns $p > 0.05$ compared to disease control, EAC Tumor

Fig. 3: Assessments of TNF alpha in tissue homogenate.



Values are expressed as Mean+/- S.E.M., n =3, ###$p < 0.001$ compared to normal control, **$p < 0.01$, *$p < 0.05$, and ns $p > 0.05$ compared to disease control, EAC Tumor

Fig. 4: Assessments of GSH in tissue homogenate

comparable to 5-FU, and significantly improved GSH levels, demonstrating dose-dependent anti-inflammatory and antioxidant protection. Overall, EAC progression is associated with elevated inflammation and oxidative stress, while higher-dose MeCC exhibits clear protective efficacy. However, the higher dose (MeCC 100) showed a marked reduction in tumor size and weight, normalization of body weight changes, and strong survival benefits, alongside significant suppression of TNF-α and partial restoration of GSH, indicative of anti-inflammatory and antioxidant activity (Fig. 5A). The tissue displays normal skeletal muscle architecture with long, cylindrical multinucleated fibers showing clear striations (A- and I-bands) and peripheral nuclei. The muscle fibers are arranged in parallel bundles without branching, and the section shows uniform architecture with no cellular atypia, abnormal mitoses, or invasive features (Fig. 5B). The tumor section reveals densely packed round to polygonal cells with large hyperchromatic nuclei and scant cytoplasm. There is a complete loss of normal tissue architecture with high cellular density, prominent nuclear pleomorphism, and irregular nuclear contours. Angiogenic vascular channels

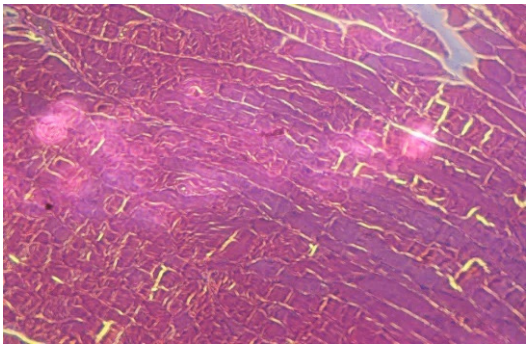


Fig. 5A): Normal subcutaneous tissue. H&E,10X. Long, cylindrical, multinucleated cells with peripheral nuclei. Striations: Clear alternating light and dark bands (A-bands and I-bands). Arrangement: Parallel bundles without branching.

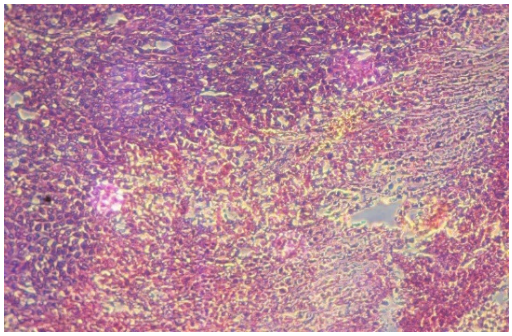


Fig. 5B): Disease solid tumor tissue (EAC Control): H&E,10X. Large hyperchromatic nuclei and scant cytoplasm. No organized muscle fibers, connective tissue. Prominent pleomorphism, dense chromatin, and irregular nuclear contours.

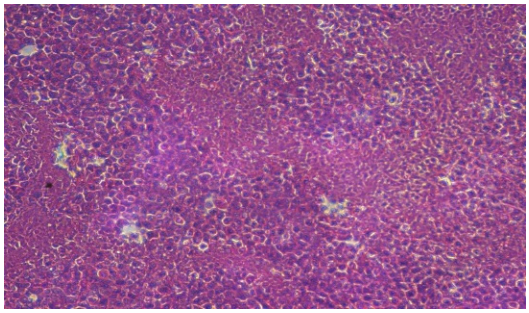


Fig. 5C): Standard control: (5-fu). H&E,10X. Reduced cellular density; tumor cells appear more scattered, Darkly stained nuclei with a high nuclear-to-cytoplasmic ratio. Nuclei appear less pleomorphic, some evidence of nuclear shrinkage, Partial restoration of organization; some clearance in intercellular spaces.

are evident, indicating rapid tumor growth and aggressive morphology (Fig. 5C). Compared to the EAC control, the 5-FU group shows reduced cellular density with scattered tumor cells, decreased nuclear pleomorphism, and partial restoration of tissue organization. Increased necrotic and apoptotic areas are observed, indicating effective antitumor activity and reduced tumor burden (Fig. 5D). The MeCC 50 group shows diffuse and disorganized tissue architecture with dense tumor cell clusters. Numerous vacuolated spaces and cytoplasmic condensation are

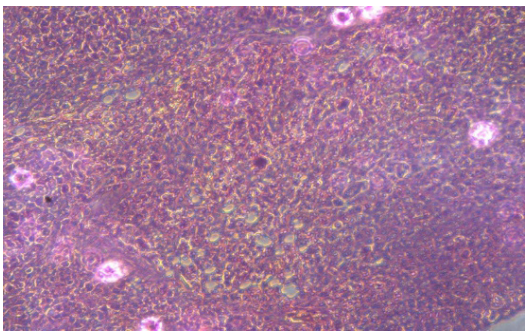


Fig. 5D): MeCC 50, H&E,10X. Cells appear densely packed, with round nuclei and loss of normal tissue pattern.
The pink–purple stained regions indicate cytoplasmic condensation and nuclear crowding, typical of tumor cell clusters.

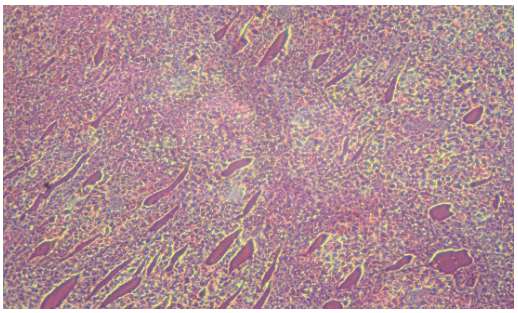


Fig. 5E): MeCC 100, H&E,10X. there is still a high population of round tumor-like cells, but distribution looks less compact in some areas. Muscle bundles are still visible but appear thinner, fragmented, and separated by infiltrating tumor cells. This suggests partial protection, but not complete.

noted, indicating degenerative changes. The section lacks normal structural integrity, suggesting limited therapeutic effect at this dose (Fig. 5E). MeCC 100 shows partial improvement compared to the EAC control, with less compact tumor cell distribution and visible but fragmented muscle bundles infiltrated by tumor cells. The tissue still lacks regular alignment, although lighter patchy areas suggest necrosis or early host response, indicating moderate protective effects. These findings suggest that MeCC exerts its protective effect primarily at higher doses, where it can modulate tumor growth and biochemical disturbances without the toxicity associated with standard chemotherapy, highlighting its potential as a safer alternative therapeutic approach.

Discussion

The present study evaluated the antitumour activity of the methanolic extract of *C. colocynthis (*MeCC) against EAC-induced solid tumours in Swiss albino mice. Treatment with MeCC produced a dose- dependent reduction in tumour weight and volume, a significant prolongation of MST, and an increase in %ILS, particularly at the higher dose, compared with the untreated EAC control group. These findings indicate that *C. colocynthis* possesses measurable antineoplastic activity, aligning with earlier reports describing its cucurbitacin-rich extracts as cytotoxic and pro-apoptotic in cancer models.[12,13] Histopathological examination supported these results. Tumour tissues from untreated EAC-bearing mice showed dense cellularity, pleomorphic nuclei, and extensive angiogenesis, features consistent with aggressive tumor biology. In contrast, MeCC-treated groups demonstrated partial restoration of tissue architecture, evidence of necrosis, and apoptotic bodies, especially at higher doses, suggesting that the extract inhibits proliferation and promotes programmed cell death.[12,13] These effects resemble those produced by cucurbitacins and related triterpenoids isolated from *C. colocynthis,* which have been shown to disrupt STAT3 and MAPK signaling pathways and induce apoptosis in resistant cancer cell lines.[13] The haematological and biochemical profiles of treated animals further support a protective effect. The higher dose of MeCC normalized body weight and improved antioxidant status (e.g., glutathione recovery), while suppressing pro-inflammatory mediators such as TNF-α.[12] This dual antioxidant–anti-inflammatory action is consistent with the phytoconstituents of *C. colocynthis,* including flavonoids and phenolic acids, which have previously demonstrated free radical scavenging and cytotoxic effects *in-vitro.* When compared with the standard drug 5-fluorouracil (5-FU), MeCC achieved appreciable tumour suppression with minimal systemic toxicity. Although 5-FU markedly reduced tumour burden, it was associated with notable systemic adverse effects, as reflected by reduced survival despite strong tumour inhibition. Similar observations have been reported in other plant-based studies against EAC, where extracts of *Prosopis cineraria* and *Bauhinia variegata* showed protective efficacy with less toxicity than conventional agents.[14,15] The findings also align with reports on other natural compounds such as ursolic acid and theaflavins, which suppress tumour angiogenesis and modulate redox balance in EAC models.[14,3] Together, these data highlight the potential of *C. colocynthis* as a source of bioactive molecules for anticancer therapy. Nevertheless, variability in response between low and high doses suggests that therapeutic efficacy depends on optimal dosing and phytochemical concentration, warranting further standardization. Despite promising results, certain limitations merit consideration. The precise molecular targets of MeCC were not explored in this study. Future research should characterise its active constituents, particularly cucurbitacins and glycosides, and elucidate their mechanisms of action using proteomic and genomic tools. Additionally, long-term toxicity studies are needed, as excessive ingestion of colocynth preparations has been associated with gastrointestinal irritation and hepatotoxicity in humans.[12]

Conclusion

The study shows that the methanolic extract of *C. colocynthis* (MeCC) has significant antitumour activity

against EAC-induced solid tumours in mice. MeCC reduced tumor size, prolonged survival, and improved biochemical and histological profiles, supporting its cytotoxic, antioxidant, and anti-inflammatory properties. Compared with 5-fluorouracil (5-FU), MeCC produced notable tumor suppression, indicating a favourable safety profile. These findings suggest that *C. colocynthis* is a promising adjuvant therapy along with the primary mode of treatment, but it has to work on active constituents, and standardization and safety are essential before clinical use.

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