RESEARCH PAPER

Exploring the Efficacy of Chebulinic Acid derived from *Terminalia chebula* and its Influence on Colonic Inflammation

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ABSTRACT
Chronic inflammatory disease has a major impact on patient. Therefore, in order to resolve the issue, this study aimed to explain the relief effect of Chebulinic acid (CA) from *Terminalia chebula* fruit on colitis. CA is the compound with the anti-inflammatory and anticancer movement which has been investigate through in vitro assays, categorised its composition by HPLC and in vivo experiments. The colitis mice model was designed after free drinking of 3% Dextran Sodium Sulphate (DSS) followed for six days with treatment low dose 25mg/kg and high dose 50mg/kg CA for seven days. The disease development measured by tracking changes the in-mouse weight and calculating disease activity index (DAI). The alterations in colon tissue were evaluated by determining the length of colon and conducting histopathological assessments. It is observed that CA notably reduced DAI scores and prevented the loss of weight with colonic shortening caused by DSS, significantly improving symptoms in affected mice, includes pathological injury to colonic tissue a physiologically significant reduction in disease activity index. This study verified the beneficial impact of the CA in reducing the Nitric Oxide (NO) secretion and also showed reduction in the expression of some cytokine like, IL-1β, IL-6, and TNF-α (Tumor necrosis factor) in Ulcerative Colitis (UC) mice. In conclusion, *T. chebula* offers new ideas to transform CA into a novel drug to treat ulcerative colitis and may be employed as an anti-inflammatory candidate drug in addition to the different chemical compounds currently in the medical markets.
Keywords: Chebulinic acid, Colonic inflammation, Inflammatory Bowel Disease, *Terminalia Chebula*
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INTRODUCTION

Terminalia chebula (also known as Hritaki in India) is considered a medicinal fruit, taken after ripening from of the plant, which belongs to the family of Combretaceae [1]. In previous scientific literatures, It had already been recorded as an extraordinarily beneficial ayurvedic medicine due to its detoxification ability for the human body [2]. Furthermore, its effectiveness has been recorded for removing toxins and repairing tissue on the gastrointestinal and respiratory systems for humans [3]. In Indian Ayurvedic literature, known as Chark Sahita also explains about a traditional Ayuvedic powder "Triphula" made up by the mixing the powders of 1. *Terminalia chebula*, (Haritaki. *Terminalia bellirica* (Bahera) and Phyllanthus emblica (Ambla), resolve various digestive issue and provide health benefits. This traditional ayurvedic powder is a good source of Chebulinic acid playing a role in clearing heat, detoxifying and nourishing the blood and improving diarrhoea. Thenceforth *T. chebula* is considered as dried ripe fruit from all of its varieties distributed in various places of South Asia, and its extract encompasses different compounds like tannins, flavonoids with various pharmacological purposes, such as antioxidant, antitumor, analgesic and so on [4].

Research has shown that, treating with the water extract of *T. chebula*, leads to an improved skin barrier, decreased immune cell infiltration, and reduced levels of inflammation-related mediators, demonstrating its effectiveness against atopic dermatitis in mice, indicating that *T. chebula* extract possess significant anti-inflammatory properties [5-6]. Additionally, it has been noted that the water extract of *T. chebula* can help to alleviate the symptoms of Dextran Sodium Sulphate (DSS) -induced ulcerative colitis in rats, by improved crypt structure and decrease myeloperoxidase in rat colon tissue [7]. The present study, we attempted to evaluate

the efficiency of the extract consisting of Chebulinic Acid (CA) biomarker of *T. chebula* fruit, wherein the anticancer, anti-inflammatory production potentials [8,9].

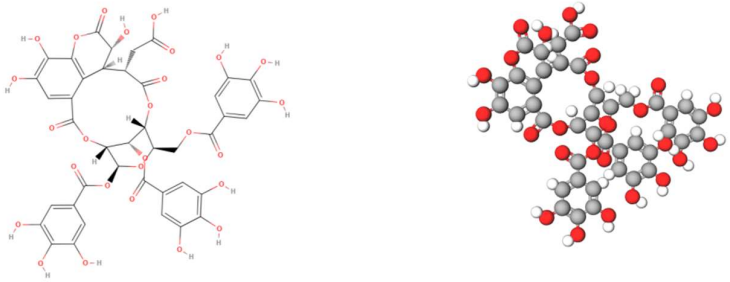

Figure 1: Chemical structure of Chebulinic Acid (CA)

Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD), characterized by tenacious inflammatory lesions in the mucosa and submucosa of the colon and rectum, resulting in recurrent attacks [10]. The main symptoms of UC are bloody diarrhoea, containing mucus, abdominal pain of different levels caused by rectal contraction, and even systemic toxicity in severe cases.

Chebulinic acid (CA) is known as a biomarker molecule in several medicinal plants, particularly 1. *Terminalia chebula*, (Haritaki) 2. *Terminalia bellirica* (Bahera) and *Phyllanthus emblica* (Ambla) showcase a wide array of pharmacological properties as given in Indian literature also and they have garnered significant attention due to its potential therapeutic advantages [11]. Chebulinic acid is well known for its potent antioxidant traits, and it plays an essential role for eliminating free radicals, safeguarding cells against oxidative harm [12].

Hence, this study used DSS-stimulated mice, inducing high level of inflammation, which was then treated with Chebulinic Acid (CA) extracted from *Terminalia chebula*, (Haritaki), taken as a therapeutic chemical against optimal inflammation on mice and simultaneously along with in-vitro anti-cancer properties. Importantly, it has been proven that CA inhibits the inflammation pathway by blocking of phosphorylation channels of TNF-α (Tumour Necrosis Factor), IL-1β (Interleukin) and IL-4 (Interleukin 4) to repair the tissue and is a well-established drug for clinical utilisation. Therefore, we aim to prove that CA can contrary UC based on animal model induced by DSS and an alternative treatment for mice colon that causes acute injury [13].

MATERIALS AND METHODS

Preparation and Evaluation of the *T. chebula* Extracts

T. chebula fruits were grinded and measured 200g powder subjected into water extract and concentrate it through rotary evaporation. After that, it was dried to yield into the extract powder and confirmed by liquid chromatography mass spectroscopy (LCMS) containing more amount of CA with other molecules [14].

HPLC analysis of the active ingredients of *T. chebula*

The Sample (1mg/mL) containing 10 µl injection volume was prepared by dissolving in methanol and filtered through 0.45 µm filter before injection. A gradient mobile phase of 0.1% formic acid in water (A) and acetonitrile (B) was set to a gradient elution initially with 0–5 min, 50% B; 5–8 min, 80% B; 8–10 min, 60% B; flow rate of 1.0 mL/min. Analysis carried on the YMC AQ-C-18 column (250 X 4.6 mm, 5µm) with 40°C column oven temperature, on Shimadzu-LC-20AD liquid chromatography equipped with an SPD-M20A Diode array detector, SIL 20 A HT auto injector, CBM-20A communication module (Japan) instrument. Absorbance observed at 254 nm [15].

Nitric oxide Content Determination

To determination of Nitric oxide, RAW264.7 was used to inoculate cells at a density of 5×105 in 96-well plates. The cells were split up into experimental groups for extract, LPS, and control. The supernatant was discarded after a typical 24-hour incubation period. Each group received drugs at doses ranging from 20 to 120µg/mL, whereas the control and LPS groups received culture solution. After an hour of incubation, the quantity of NO in the supernatant was ascertained by measuring the absorbance at 570 nm using a microplate reader [16].

Cell Viability Determination

To check the cytotoxicity of extract Chebulinic Acid on MCF 7 cell line, MTT 3-(4,5-dimethylthiazol-2-yl)-2,5-2,5-diphenyl tetrazolium bromide dye was used, which was further converted to purple coloured MTT-formazan by mitochondrial succinate dehydrogenase of live cells. 5000 cells were added per well of the 96-well plate. The cells were then treated with the provided for sample and kept for 48 and 72 hrs, respectively. After 48 and 72 hrs of treatment, the cells were incubated with 0.5 mg/ml MTT solution and incubated further for 4 hr. After discarding the media from each well, 200µl of DMSO was then added and incubated for the next 30 min. At last, colorimetric data were taken at 570 nm [17].

Experimental animal

Male mice (6-8 weeks old, 25-30 g) C57BL/6 were divided into five groups, where each group had eight mice: Control group; DSS group; CA low-dose group (LD-25mg/kg); and CA high-dose group (HD-50 mg/kg). Mice were acclimatized in an atmosphere with constant temperature at 250 C and fed water for 6 days. All groups, without the control, treated with 3% DSS freely for the six days to build an acute UC model. The CA-treated group was administered the above doses once daily by orally while the same amount of water was given to the control and DSS groups. On the 7 days, DSS was replaced by drinking water, and CA were continued to be administered to the corresponding groups. On day 8, mice were sacrificed in the carbon dioxide chamber [18].

Disease Activity Index (DAI) assessment

Relevant indicators, such as body weight, food and water consumption, faecal characteristics, and blood in the stool, were recorded every day from day 1 to day 7. The following formula can be used to calculate the disease activity index (DAI) Figure. 5 DAI is equal to (weight change score + faecal trait score + blood in stool score)/3 [19].

Histopathological analysis of colon in mice

After the mice were sacrificed, large intestines were collected and measured for length. Colons lacking the cecum were kept in a tube for additional research after being cleaned of faeces using sterile saline. After cutting around 1 cm of the middle colon tissue, formalin was used to fix it. After being fixed, the colonic tissues were sectioned, embedded, and dehydrated. Morphological alterations were tracked using Haematoxylin-Eosin (HE). A light microscope (Olympus, Japan) was used to take pictures of the staining results. Several types of literature were consulted to determine the pathology score of the mouse colon tissue [20].

Measurement of Cytokine Levels in Mice

The cytokine contents of TNF-α and IL-4 and IL-1β in colonic tissues were assessed using an enzyme linked immunosorbent assay (ELISA). The cell culture supernatant (control and treatment) was spun down at 5000 rpm for 10 minutes and kept at -20°C until needed. The number of inflammatory components in the colonic tissue from each mouse group was measured in accordance with the guidelines for the IL-1β and IL-6 ELISA kits [21].

Statistical analysis

Data are shown as means ± SD (Standard Deviation) from triple replica of experiments using different mice. The analytical software known as SPSS (Chicago, IL, USA) was used for the experimental data. The least significant test was compared after one way analysis of variance (ANOVA) was used to examine statistical differences across several groups. Statistically significant differences were defined as p-values less than 0.05.

RESULTS

Chemical constituents of *T. chebula*

T. chebula powder was extracted in aqueous solvents fraction. It is found that there were comparatively few components in the aqueous phase by comparing the HPLC profiles. Nevertheless, compared to other fractions, the components were primarily grouped in the water fraction, as seen in (Figure.2). The chromatogram shows that the water fraction contains chebulic acid, gallic acid, corilagin, ellagic acid and Chebulinic acid. Gallic acid demonstrated a comparatively high abundance under a UV absorption wavelength of 275 nm. Nevertheless, compared to other fractions, the components were primarily grouped in the water fraction, as seen in (Figure. 2). We conducted a qualitative analysis using standard chemicals to determine the primary constituents of the ethyl acetate extract. The chromatogram of CA and its primary constituents, including gallic acid, Corilagin, ellagic acid, and Chebulinic acid, shows that the water fraction contains chebulic acid, gallic acid, Corilagin, ellagic acid, and Chebulinic acid. Gallic acid demonstrated a comparatively high abundance under a UV absorption wavelength of 275 nm.

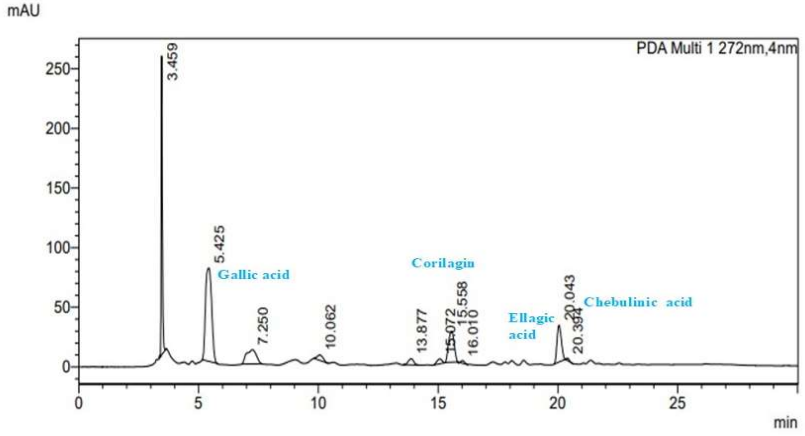

Figure 2: HPLC chromatogram of the *T. chebula* sample. 1: Gallic acid; 2: Corilagin; 3: Ellagic acid; and 4: Chebulinic Acid).

Nitric oxide anti-Inflammatory Activity assay

The cell lines were exposed to LPS, CA to study the impact on NO production. Cells treated with LPS stimulant exhibited a notable reduction in the NO production. The IC50 value for inhibition of NO production of CA was obtained as 36.39µg/ml. (Figure.3) showed that the reduction in NO production, adding an inflammation, was observed with CA group, indicating in vitro anti-inflammatory activity.

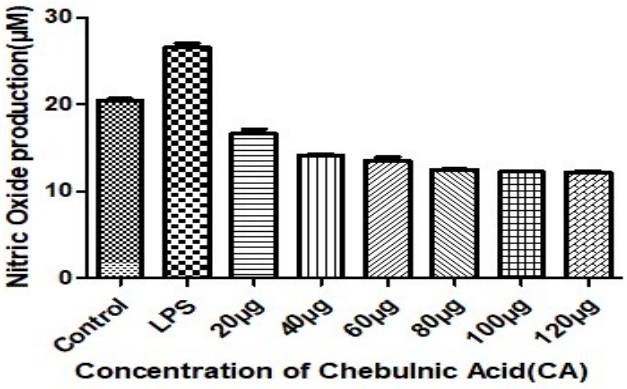

Figure 3: Measurement of NO production in Chebulinic Acid (CA).

Cell Viability Determination

Cell viability results of varying concentration of Chebulinic acid on cancer cell lines have been demonstrated. Abbreviations located next to the histogram are due to cell lines, while MCF-7 has been regarded a negative control. IC50 values for each were obtained, 13.97mg/ml of extracted chemical against MCF-7 cancer cell lines were reported respectively. The extracted chemical has no impact on viability against cancerous cell line and merely 20- 30 percent reduces the viability of cancer cell lines (Figure. 4).

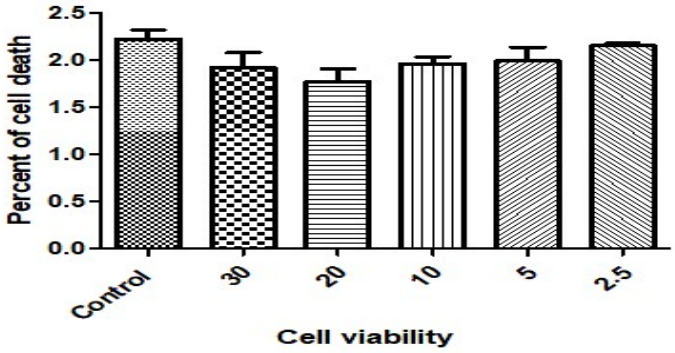

Figure 4: Effect of Chebulinic acid (CA) in cell viability.

Chebulinic acid improves physiological index DSS-induces mice model

After 7 days of the DSS group mice were listed and appeared to have visible symptoms including diarrhoea and bloody stools. At the same time DAI score reached at the peak. CA low-dose (CA-L, 25 mg/kg) and CA high-dose (CA-H, 50 mg/kg) were established. As seen in Figure 5, UC develops serious lesions in the colon, such as congestion, oedema and easy bleeding. The colon tissue of the DSS group showed some oedema and congestion, but not in the other groups, indicating that CA can stop colonic damage. The colon length of the DSS group was significantly shorter ($p < 0.001$), as seen in (Fig. 41). Administration of CA did not produce a statistically significant alteration in colon length compared with the DSS-treated group. Nevertheless, mice receiving the high-dose CA treatment (CA-H) exhibited a significant reduction in colon weight relative to the DSS group ($p < 0.05$ and $p < 0.01$), as illustrated in Figure 4C. In contrast, treatment with the low-dose CA (CA-L) did not result in a significant improvement in colon weight when compared with the high-dose treatment. A progressive decline in body weight was observed in the DSS-treated mice beginning on the fourth day of the experimental period. By the end of the study, animals in the CA-H group experienced the smallest reduction in body weight relative to the control group, indicating that high-dose CA treatment effectively attenuated DSS-induced weight loss.

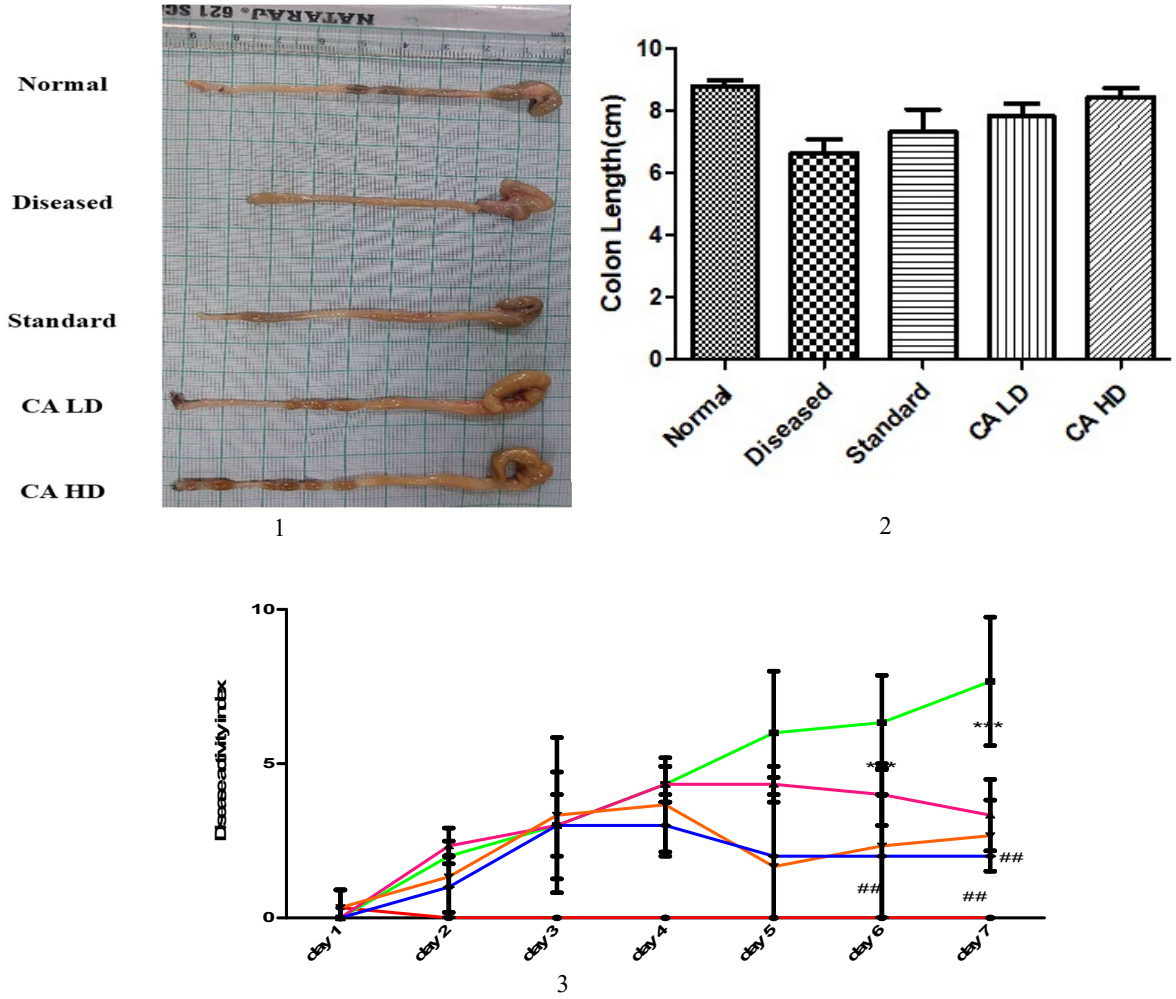

Figure 5: Physiological changes in experimental mice in groups. 1) Macroscopic pictures of colons. 2) Colon length 3). Changes in DAI.

Colonic injury in UC mice

The colon is severely damaged by colitis, as evidenced by the control group mice's intact colonic mucosal, submucosal, and muscular layers, regular crypt surface, neatly ordered crypt, and many goblet cells. On the other hand, mice in the DSS group showed severe damage to the mucosal layer of colonic tissue, clear gland and crypt destruction, loss of goblet cell, and inflammatory cell infiltration. The colon histopathological score (Figure. 6.1B) revealed that the DSS group's score was over ten times higher than the control groups, exhibiting a clear upward trend, while the positive drug groups and the CA treatment group's scores somewhat declined, with the CA-LD group's decline being more pronounced. Goblet cell mucus is essential for intestinal defence. The colon of the control group was rich in goblet cells in addition to being full of mucus, according to the HE staining data. Goblet cells and mucus discharge were both markedly decreased following DSS induction. The colon damage brought on by DSS was lessened by the CA intervention, and there was a notable increase in goblet cells along with a partial recovery of mucus secretion.

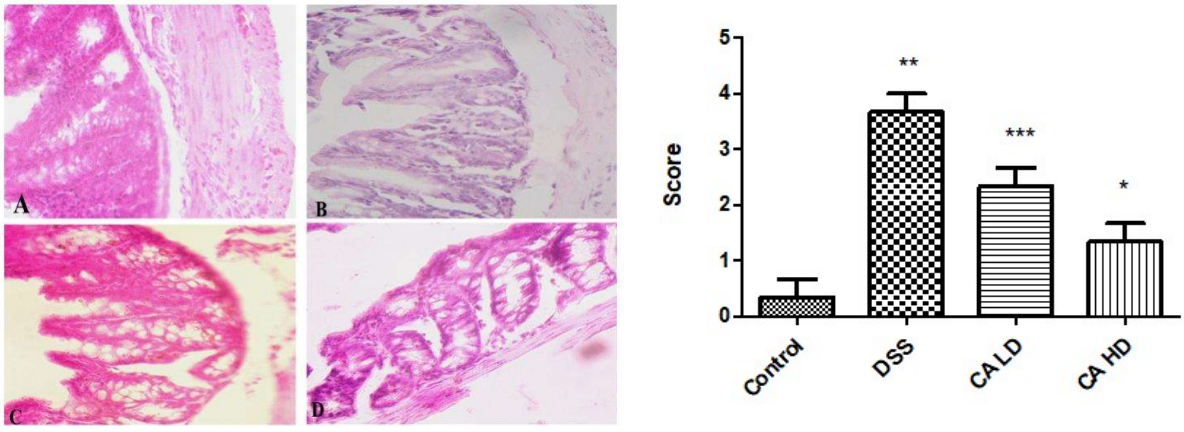

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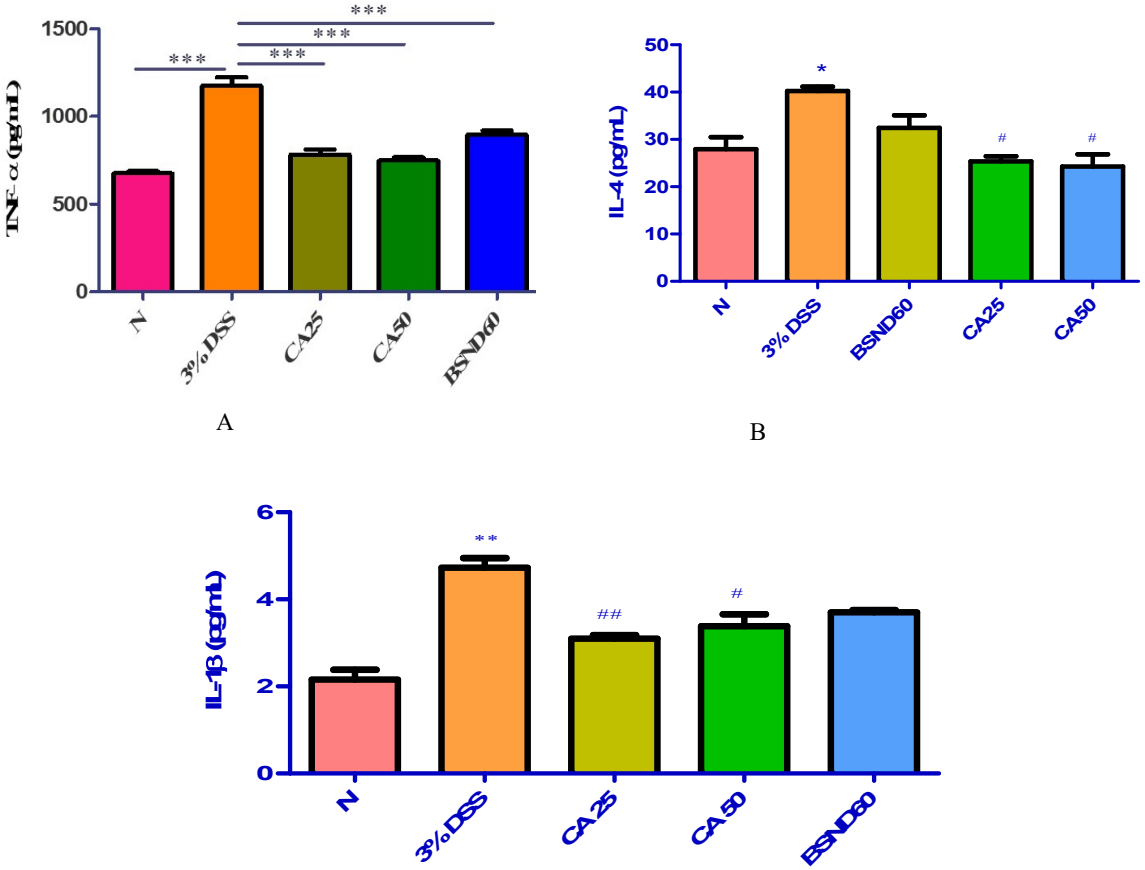
Figure 6: Impact of CA in colon histopathological damage. (1) Haematoxylin-Eosin staining of colons. HE staining results for the (A) control group, (B) Diseased group; (C) CA-LD group; and (D) CA-HD group. (2) Histopathological score of colon tissues.

Effect of cytokine levels

Pro-inflammatory cytokine concentrations in the intestinal tissues of mice. TNF-α, IL-4, and IL-1β expressions were significantly higher in the colonic tissues of UC animals in the DSS group than in the control group. While the IL-1β level in the CA-25 group dropped by more than half when compared to the DSS group, the IL-4 content in the CA-50 group was lower compare to the standard (BSND) group (Figure. 7).



A B

Figure 7: Pro-inflammatory cytokine content measurement: (A) TNFα content, (B) IL-1β content, (C) IL-4 content.

DISCUSSION

It had been previously characterized the major compounds in *T.chebula* by HPLC technique where these compounds were examined successfully against inflammation. Similarly main component of *T. chebula* is Chebulinic acid was also proved including Gallic acid, Corilagin, Chebulagic acid, Ellagic acid. Chebulinic acid is active ingredient in *T.chebula* extract (TCE) previously examined excellent pro-inflammatory effect, against arthritis mice model [22-23]. Since, we speculate that Chebulinc acid of *T.chebula* may contribute to pro-inflammatory activity in inducing mice colitis model. Henes, it could be considerable for humans also.

Nitric Oxide serve as a multifunctional paracrine and autocrine signalling molecule which involves in many physiological and pathological process, such as blood pressure regulation and neurotransmission [24]. In this study, the Chebulinic acid derived from *T. chebula* extract demonstrated a significant reduction in NO production in dose dependent manner. Most research indicates that, plant extract effectively lower NO production are useful of pro-inflammatory agent [25]. But in the present study it is shown that, Chebulinc acid has the ability for decreasing the NO production.

DSS-induced UC is a perfect model for researching the pathophysiology of UC and assessing medication efficacy since its symptoms and histological alterations are strikingly comparable to those of human UC [26]. DSS can promote inflammation, damage the intestinal mucosal barrier, impede the growth of epithelial cells, and result in colitis [27]. In order to assess the impact of TCE on DSS-induced acute UC in mice, we created a mouse model of acute UC using 3% DSS. Significant weight loss, diarrhoea, stool blood, and severe colon shortening will occur in mice that consume DSS continuously. According to our findings, TCE intervention alleviated diarrhoea and blood in the stool, decreased the DAI index, and prevented colon shortening brought on by DSS in the model group of mice. According to pathological findings, DSS modelling may harm colon tissue's crypt structure, which could result in inflammatory cell infiltration [28]. The main roles of goblet cells are to synthesise and secrete protective mucus, sense changes in the surrounding environment, contribute to intestinal immunity, and play a crucial role in controlling intestinal health [29]. In colon tissue slices from the DSS group of mice, goblet cell loss and a reduction in mucus output were also noted. TCE treatment can stop oxidative stress in mice and repair these DSS-induced alterations. Variations in the body's level of oxidative stress also have an impact on the development of UC. The water fraction of plant extract has been shown to influence the oxidative stress level in UC mice, which may contribute to the effects of UC [30]. Additionally, our findings demonstrated that TCE primarily impacted oxidative stress levels by altering oxidative product, antioxidant, and antioxidant enzyme levels.

In patient of colitis, the body harbors both cytokines pro inflammatory and anti- inflammatory, which are essential maintaining the homeostasis and regulating immune cell activation as well as tissue integrity [31]. Pro-inflammatory cytokines like IL-4 and IL-1β are significant contributors to the progression of colitis with higher levels in individual suffering from this condition. TNF-α is a characteristic of DSS induced colitis and has the ability to enhance the expression of IL-4 and IL-1β. Based on our experimental results, CA is capable for alleviate colitis by reducing the inflammatory response like mentioned above [32-33].

CONCLUSION

It concluded based on present investigation which demonstrated the protective efficacy of CA against dextran sodium sulfate (DSS)-induced colitis in a murine model. Phytochemical characterization revealed that *Terminalia chebula* is predominantly composed of bioactive constituents, including gallic acid, corilagin, ellagic acid, and chebulinic acid. The experimental findings indicate that CA exerts significant anti-colitic activity by alleviating clinical manifestations, preserving the histological integrity of colonic tissues, and mitigating oxidative stress associated with intestinal inflammation. Furthermore, CA-mediated modulation of the gut microbial community appears to play a pivotal role in suppressing inflammatory responses and restoring intestinal homeostasis in DSS-treated mice. Collectively, these findings highlight the therapeutic potential of CA as a promising natural bioactive compound for the prevention and management of inflammatory bowel disease and support its further investigation as a potential candidate for the development of novel anti-colitis therapeutics.

CONFLICT OF INTEREST

There is no conflict of interest between authors.

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