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# Acute and Subacute Toxicological Assessment of Coriander Triphala Tablets in Wistar Rats

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## ABSTRACT

This investigation was conducted to determine the safety profile of Coriander Triphala tablets (CTT) through acute and repeated-dose toxicity studies in Wistar rats. The herbal tablets were manufactured based on a previously established formulation protocol. Acute oral toxicity was evaluated by administering a single dose of 2000 mg/kg CTT to female rats, while a control group received distilled water. For the subacute assessment, sixty rats of both sexes were randomly allocated into six experimental groups. Animals were orally treated with CTT at doses of 200, 500, or 1000 mg/kg, while an additional satellite group received 1000 mg/kg; the control group was given distilled water for 28 consecutive days. Throughout the study period, changes in body mass, food intake, and water consumption were monitored. Clinical observations were recorded, followed by hematological testing, serum biochemical analysis, and microscopic examination of tissue samples. Administration of a single high dose of CTT did not result in mortality or observable adverse effects, indicating that the $LD_{50}$ value is greater than 2000 mg/kg. During the repeated-dose study, no meaningful alterations were detected in hematological indices across treatment groups. In contrast, biochemical analysis revealed dose-related increases in serum cholesterol, creatinine, and aspartate aminotransferase (AST) levels in male rats, whereas elevated alanine aminotransferase (ALT) and AST levels were observed in females receiving higher doses. Histological evaluation of hepatic tissue demonstrated evidence of sinusoidal congestion and hepatocellular swelling in both sexes. Renal tissue analysis showed mild to severe tubular epithelial degeneration and necrosis. The results indicate that prolonged administration of Coriander Triphala tablets may adversely affect hepatic and renal function at higher doses, underscoring the importance of careful dosing and clinical monitoring when using this traditional herbal formulation.

**Keywords:** Coriander Triphala, Acute toxicity, Subacute toxicity, Rat, Iranian traditional medicine

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## Introduction

Medicinal plants have served as therapeutic agents since antiquity and continue to play a significant role in modern drug development, accounting for more than one quarter of currently marketed pharmaceuticals [1, 2]. In parallel with this historical importance, the global reliance on herbal and naturally derived remedies has expanded substantially, with nearly four-fifths of the world's population incorporating such products into primary health care practices [3, 4]. This expanding utilization is often attributed to the ability of herbal preparations to manage certain disorders more affordably and with fewer adverse effects than synthetic medications, particularly in cases where conventional therapies show limited efficacy [5]. Consequently, contemporary health-care strategies are increasingly oriented toward multi-component herbal formulations capable of targeting several physiological pathways simultaneously [6].

Within this context, Iranian traditional medicine represents a comprehensive medical system that proposes numerous plant-based remedies for a wide range of disorders [7–10]. Coriander Triphala is one such formulation

traditionally prepared as an oral semisolid dosage form, consisting of the fruits of Terminalia chebula, Terminalia bellirica, Phyllanthus emblica, and Coriandrum sativum, combined with honey and almond oil. This formulation has long been prescribed for gastrointestinal complaints and for detoxifying purposes in traditional practice [11, 12].

The plant Terminalia chebula, a member of the Combretaceae family, yields fruits that are classified into three developmental stages: immature, mature, and fully mature [13]. In traditional medical systems, this plant has been used extensively for the management of digestive and hepatic disorders, diarrhea, dysentery, bleeding conditions, respiratory illnesses such as asthma and cough, infectious diseases, and dermatological conditions [14, 15]. Phytochemical investigations have demonstrated that T. chebula is particularly rich in tannin compounds, including gallic acid, ellagic acid, methyl gallate, ethyl gallate, chebulagic acid, corilagin, and hexahydroxydiphenic acid esters [16–18].

Phyllanthus emblica is another prominent medicinal plant traditionally employed for treating metabolic disorders such as diabetes and hyperlipidemia, as well as neurological and ocular diseases. This species is recognized as an abundant source of tannins, essential amino acids, and vitamins [19]. Similarly, Coriandrum sativum, widely known as coriander and commonly used as a culinary spice, has also been utilized in traditional medicine to relieve gastrointestinal disturbances, including flatulence, diarrhea, dysentery, indigestion, vomiting, fever, and memory impairment [20].

In earlier research, the traditional Coriander Triphala preparation was reformulated into a film-coated tablet, and its pharmaceutical quality attributes were systematically evaluated [21]. Despite its widespread traditional use, Coriander Triphala contains numerous biologically active compounds—particularly tannins—which have been associated with potential toxicity in vital organs such as the liver, kidneys, heart, and other tissues when consumed in high amounts or over prolonged periods. Accordingly, the present investigation was undertaken to systematically assess the acute and subacute toxicological effects of Coriander Triphala tablets (CTT) in Wistar rats in accordance with the guidelines issued by the Organization for Economic Co-operation and Development (OECD) [22, 23].

## Materials and Methods

### *Ethical approval*

The experimental protocol received ethical clearance from the Ethics Committee of Shahid Beheshti University of Medical Sciences (approval code: IR.SBMU.RETECH.REC.1400.1214). All animal procedures were performed in compliance with the National Institutes of Health (NIH) standards for the care and use of laboratory animals.

### *Reagents and chemicals*

Ketamine and xylazine used for anesthesia were obtained from Sigma (USA). Formaldehyde required for tissue fixation was supplied by Merck (Germany). Absolute ethanol was purchased from Razi Yeast and Alcohol Company (Iran). Hematoxylin and eosin staining reagents were sourced from Sigma (Germany). Commercial diagnostic kits for biochemical assays were provided by Pars Azmoon Company (Iran), while whole-blood hematology control materials were obtained from Man Company (Iran).

### *Preparation of coriander triphala tablets*

Coriander Triphala tablets (CTT) were produced following the formulation method described by Choopani *et al.* [21]. Each tablet contained 98 mg of each herbal component (T. chebula fruit, T. bellirica, Ph. emblica, and C. sativum), together with 14 mg of almond oil and 148 mg of honey. Tablet manufacture was carried out using the wet granulation technique. Standard pharmaceutical quality control tests—including weight uniformity, friability, hardness, disintegration, assay, and dissolution—were conducted. Quantification and standardization were based on total tannin content using the Folin–Ciocalteu method. Initially, total phenolic compounds were measured, after which tannins were selectively removed using hide powder, and the difference between these measurements was used to calculate total tannins [17].

### *Animals and housing conditions*

Fifty Wistar rats of both sexes were obtained from the Animal House of the Traditional Medicine and Materia Medica Research Center at Shahid Beheshti University of Medical Sciences, Tehran, Iran. Animals were housed under controlled laboratory conditions, including a 12-hour light/dark cycle, ambient temperature maintained between 23 and 25 °C, relative humidity of approximately 50%, and adequate ventilation. Standard laboratory chow and drinking water were provided ad libitum throughout the study period. All experimental procedures were conducted in accordance with internationally accepted guidelines for laboratory animal care and use.

*Acute oral toxicity evaluation*

Acute toxicity following oral administration of Coriander Triphala tablets (CTT) was investigated in accordance with OECD guideline 425 [22]. Ten female Wistar rats (8–12 weeks old; body weight 100–150 g) were selected and maintained under laboratory conditions for five days to allow acclimatization. Prior to dosing, food was withheld overnight while water remained available. Five animals were orally administered a single dose of CTT at 2000 mg/kg, prepared as an aqueous suspension, using a gavage technique. The remaining animals served as the control group and received distilled water at a dose volume equivalent to 1 mL/100 g body weight.

Animals were monitored continuously during the initial 24 hours following administration and subsequently examined once daily for a period of 14 days. Clinical assessments included evaluation of external appearance (skin and fur), ocular and mucosal conditions, motor activity, respiratory function, salivation, gastrointestinal disturbances, neurological manifestations (including tremors and convulsions), general behavior, and survival. Measurements of body weight, food intake, and water consumption were recorded throughout the observation period. At study termination, all animals were subjected to macroscopic examination to identify any gross pathological abnormalities.

*Subacute oral toxicity evaluation*

Repeated-dose toxicity was assessed using OECD guideline 407 with minor methodological adjustments [23]. A total of forty Wistar rats (100–120 g), comprising equal numbers of males and females, were randomly assigned to five experimental groups (n = 10 per group). Three groups received CTT orally at daily doses of 200, 500, or 1000 mg/kg for 28 consecutive days. A control group was administered distilled water at a volume of 1 mL/100 g body weight over the same duration.

To assess the reversibility or persistence of potential toxic effects, a satellite cohort of 20 rats (10 males and 10 females) was included. These animals were treated with either the highest dose of CTT (1000 mg/kg) or distilled water for 28 days, followed by a 14-day treatment-free recovery period prior to sample collection.

Throughout the experimental period, animals were inspected daily for clinical signs of toxicity, behavioral changes, and physical abnormalities. Body mass as well as food and water consumption were recorded regularly until the completion of the study. At the end of the treatment or recovery phase, animals were anesthetized using a ketamine–xylazine mixture (10:1), and blood samples were obtained by cardiac puncture for hematological and biochemical analyses. Animals were then euthanized, and the liver and kidneys were excised for further evaluation.

*Histopathological analysis*

Excised liver and kidney tissues were immediately fixed in 10% formalin. Following fixation, samples were dehydrated in graded ethanol, embedded in paraffin, and sectioned at a thickness of 5–7 μm using a microtome. Tissue sections were stained with hematoxylin and eosin and examined microscopically by a certified pathologist to identify histological alterations.

*Statistical procedures*

All numerical data were processed using GraphPad PRISM software (version 8). Statistical comparisons among groups were performed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test. Results are presented as mean ± standard deviation based on five independent measurements. Differences were considered statistically significant at $p < 0.05$.

**Results and Discussion**

Analysis of tablet composition revealed a total tannin content equivalent to 64.19 mg of pyrogallol per tablet. During the acute toxicity limit test, none of the animals receiving a single oral dose of 2000 mg/kg CTT exhibited mortality. Furthermore, no acute toxic manifestations—including hypersalivation, neurological disturbances, gastrointestinal symptoms, lethargy, or convulsions—were observed during the first 24 hours post-administration. Throughout the observation period, treated animals displayed no abnormal changes in physical appearance, respiratory function, feeding behavior, water intake, body weight progression, or thermoregulation. In accordance with the criteria outlined in OECD guideline 425, CTT was classified as non-toxic at the tested dose level, and the median lethal dose ($LD_{50}$) was estimated to be greater than 2000 mg/kg. Consequently, further confirmatory acute toxicity testing was not required. Data related to body weight changes and food and water consumption during the limit test are summarized in **Tables 1 and 2.**

**Table 1.** Body weight measurements of rats after acute limit-dose exposure to Coriander Triphala tablet

| Group | Baseline (Week 0) | Week 1 | Week 2 |
|---|---|---|---|
| Control | 156.60 ± 8.50 | 160.00 ± 7.34 | 164.40 ± 7.63 |
| Treatment (2000 mg/kg CTT) | 161.44 ± 8.00 | 166.60 ± 6.94 | 173.60 ± 7.50 |

CTT: Coriander Triphala tablet

**Table 2.** Effects of Coriander Triphala tablets on food and water consumption following the limit test

| Group | Water Consumption (ml/day) | Food Consumption (g/day) |
|---|---|---|
| Treatment (2000 mg/kg CTT) | 38.91 ± 7.60 | 18.85 ± 2.80 |
| Control | 43.50 ± 8.50 | 15.96 ± 3.39 |

CTT: Coriander Triphala tablet

The potential subacute toxic effects of Coriander Triphala tablets (CTT) were investigated by administering the formulation orally to rats at daily doses of 200, 500, and 1000 mg/kg body weight over a 28-day period. Animals in the control group received distilled water at a volume of 1 mL/100 g body weight. At the conclusion of the treatment period, comprehensive evaluations were conducted, including hematological profiling, serum biochemical analysis, and histopathological examination of target organs. In parallel, animals were monitored throughout the study for general clinical manifestations and behavioral abnormalities. During the entire 28-day exposure period, no overt signs of toxicity—such as excessive salivation, reduced activity, diarrhea, tremors, seizures, or death—were observed in any treatment group.

As summarized in **Table 3**, repeated oral administration of aqueous CTT did not result in statistically significant alterations in body weight at any time point during or after the treatment period when compared with control animals ($p<0.05$). These findings indicate that daily gavage of CTT at doses of 200, 500, and 1000 mg/kg for 28 consecutive days did not adversely affect normal growth patterns in the experimental rats.

The influence of prolonged CTT administration on food and water intake in both male and female rats is presented in **Table 4**. Analysis of the data demonstrated that consumption of food and water remained stable throughout the experimental period, with no significant differences detected between treated animals and controls before, during, or after CTT exposure ($p<0.05$), despite daily oral dosing for 28 days.

Hematological findings following subacute exposure to CTT are detailed in **Table 5**. Evaluation of all measured blood parameters—including white and red blood cell counts, hemoglobin concentration, hematocrit, erythrocyte indices (MCV, MCH, MCHC), platelet count, red cell distribution width (RDW%), reticulocyte percentage, coagulation indices (PT and PTT), and differential leukocyte counts (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)—revealed no statistically significant deviations from control values across all treatment groups ($p<0.05$).

Biochemical analysis of serum samples from male rats, as shown in **Table 6**, indicated that oral administration of CTT at doses of 200, 500, and 1000 mg/kg did not significantly affect glucose, urea, alanine aminotransferase (ALT), total protein, albumin, sodium, potassium, or total bile acid levels compared with controls. In contrast, significant elevations in serum cholesterol and creatinine concentrations were detected in males receiving 500 and 1000 mg/kg of CTT ($p<0.01$ and $p<0.05$, respectively). Additionally, a significant increase in aspartate aminotransferase (AST) activity was observed at the highest dose level (1000 mg/kg; $p<0.05$).

In female rats, treatment with CTT at doses of 200, 500, and 1000 mg/kg did not produce statistically significant changes in serum glucose, urea, cholesterol, creatinine, total protein, albumin, sodium, potassium, or total bile acid concentrations when compared with the control group.

**Table 3.** Effects of Coriander Triphala tablets on body weight changes following the subacute toxicity study

| Sex | Group | Week 0 | Week 1 | Week 2 | Week 3 | Week 4 |
|---|---|---|---|---|---|---|
| **Female** | Control | 151.42 ± 6.00 | 165.60 ± 5.94 | 178.60 ± 7.20 | 183.20 ± 6.50 | 193.60 ± 5.50 |
| | CTT (200 mg/kg) | 161.30 ± 5.00 | 167.60 ± 5.94 | 175.60 ± 7.50 | 189.60 ± 8.50 | 199.60 ± 5.50 |
| | CTT (500 mg/kg) | 161.40 ± 8.00 | 168.60 ± 5.94 | 179.60 ± 7.50 | 189.60 ± 8.50 | 198.60 ± 5.50 |
| | CTT (1000 mg/kg) | 160.35 ± 5.00 | 168.60 ± 6.90 | 178.60 ± 7.50 | 182.50 ± 4.50 | 193.50 ± 5.50 |
| **Male** | Control | 149.20 ± 5.50 | 155.20 ± 6.22 | 168.40 ± 5.60 | 179.60 ± 5.62 | 194.40 ± 7.50 |
| | CTT (200 mg/kg) | 156.20 ± 6.50 | 168.50 ± 4.34 | 174.40 ± 7.63 | 184.40 ± 7.63 | 196.20 ± 6.62 |
| | CTT (500 mg/kg) | 146.60 ± 8.30 | 157.35 ± 6.30 | 167.40 ± 3.40 | 177.20 ± 6.50 | 192.30 ± 7.20 |
| | CTT (1000 mg/kg) | 152.60 ± 5.50 | 168.65 ± 5.34 | 172.40 ± 5.60* | 184.40 ± 7.62 | 190.60 ± 8.60 |

CTT: Coriander Triphala tablet; No significant differences were found ($p>0.05$).

**Table 4.** Influence of repeated oral administration of Coriander Triphala tablets on food consumption and water intake during the subacute toxicity study

| Group | Female Water (ml/day) | Female Food (g/day) | Male Water (ml/day) | Male Food (g/day) |
|---|---|---|---|---|
| Control | 42.50 ± 7.50 | 14.60 ± 2.40 | 44.20 ± 2.30 | 15.50 ± 2.45 |
| CTT (200 mg/kg) | 39.91 ± 5.60 | 16.85 ± 2.80 | 40.90 ± 6.40 | 16.80 ± 2.50 |
| CTT (500 mg/kg) | 40.50 ± 8.50 | 16.96 ± 2.30 | 43.50 ± 6.50 | 17.70 ± 2.40 |
| CTT (1000 mg/kg) | 42.90 ± 6.60 | 17.20 ± 2.35 | 39.90 ± 5.60 | 18.25 ± 2.80 |

CTT: Coriander Triphala tablet; No significant differences were found ($p>0.05$).

**Table 5.** Hematological profile of rats following subacute exposure to Coriander Triphala tablets

| Parameter | Unit | Female Control | Female CTT (200 mg/kg) | Female CTT (500 mg/kg) | Female CTT (1000 mg/kg) | Male Control | Male CTT (200 mg/kg) | Male CTT (500 mg/kg) | Male CTT (1000 mg/kg) |
|---|---|---|---|---|---|---|---|---|---|
| Hb | g/dL | 14.87 ± 1.62 | 14.84 ± 0.32 | 15.86 ± 0.81 | 15.82 ± 0.82 | 15.78 ± 0.74 | 15.78 ± 0.46 | 15.52 ± 1.67 | 16.32 ± 0.64 |
| Hct | % | 40.60 ± 1.30 | 38.52 ± 1.14 | 40.80 ± 2.30 | 40.70 ± 2.47 | 40.90 ± 1.95 | 42.34 ± 1.87 | 40.46 ± 4.78 | 42.50 ± 2.16 |
| WBC | $\times 10^3/\mu L$ | 8.57 ± 2.47 | 6.32 ± 1.07 | 8.36 ± 0.63 | 6.38 ± 1.66 | 10.96 ± 3.76 | 8.08 ± 0.93 | 7.44 ± 2.33 | 8.18 ± 1.13 |
| RBC | $\times 10^6/\mu L$ | 7.48 ± 0.57 | 7.13 ± 0.44 | 7.42 ± 0.51 | 7.35 ± 0.36 | 7.36 ± 0.64 | 7.88 ± 0.30 | 7.79 ± 0.93 | 8.21 ± 0.36 |
| Platelet | $\times 10^3/\mu L$ | 569.33 ± 46.19 | 624.20 ± 83.86 | 594.00 ± 36.05 | 549.75 ± 30.34 | 536.40 ± 67.18 | 553.60 ± 58.28 | 586.00 ± 66.66 | 575.00 ± 74.43 |
| MCV | fL | 55.87 ± 0.82 | 53.90 ± 2.31 | 54.70 ± 1.80 | 55.10 ± 1.76 | 53.94 ± 1.03 | 52.90 ± 1.21 | 53.00 ± 0.90 | 53.18 ± 1.25 |
| MCH | pg | 22.07 ± 0.63 | 20.80 ± 0.91 | 21.26 ± 0.68 | 21.42 ± 0.62 | 20.80 ± 0.48 | 20.22 ± 0.69 | 20.32 ± 0.34 | 20.42 ± 0.63 |
| MCHC | g/dL | 39.52 ± 1.23 | 38.54 ± 0.89 | 38.86 ± 0.25 | 38.88 ± 0.21 | 38.58 ± 0.37 | 37.50 ± 0.76 | 38.34 ± 0.64 | 38.40 ± 0.64 |
| PT | s | 15.25 ± 0.85 | 16.12 ± 0.25 | 14.72 ± 1.21 | 15.65 ± 1.23 | 16.72 ± 0.90 | 15.22 ± 1.63 | 14.56 ± 1.36 | 15.82 ± 1.45 |
| PTT | s | 14.85 ± 0.55 | 14.50 ± 0.23 | 13.80 ± 0.75 | 14.25 ± 0.50 | 14.42 ± 1.03 | 13.25 ± 0.86 | 13.56 ± 1.14 | 15.72 ± 0.75 |
| Reticulocytes | % | 2.53 ± 1.72 | 2.04 ± 0.92 | 2.70 ± 0.45 | 2.72 ± 0.86 | 2.70 ± 0.28 | 2.00 ± 0.67 | 1.75 ± 0.77 | 2.36 ± 1.08 |
| RDW | % | 12.15 ± 0.26 | 12.28 ± 0.38 | 12.63 ± 0.15 | 12.28 ± 0.28 | 12.82 ± 1.03 | 12.06 ± 0.60 | 12.66 ± 1.96 | 12.34 ± 0.37 |
| Neutrophils | % | 70 | 69 | 75 | 70 | 69 | 68 | 70 | 74 |
| Lymphocytes | % | 30 | 31 | 25 | 30 | 31 | 32 | 30 | 26 |
| Basophils | % | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Monocytes | % | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Eosinophils | % | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

CTT: Coriander Triphala tablet; WBC: white blood cells; RBC: red blood cells; Hb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; Retic: reticulocyte; PT: prothrombin time; PTT: partial thromboplastin time. No statistically significant differences were observed ($p>0.05$).

**Table 6.** Serum biochemical alterations observed after subacute oral treatment with Coriander Triphala tablets

| Parameter | Unit | Female Control | Female CTT (200 mg/kg) | Female CTT (500 mg/kg) | Female CTT (1000 mg/kg) | Male Control | Male CTT (200 mg/kg) | Male CTT (500 mg/kg) | Male CTT (1000 mg/kg) |
|---|---|---|---|---|---|---|---|---|---|
| Cholesterol | mg/dL | 42.87 ± 5.97 | 52.12 ± 6.88 | 50.37 ± 7.63 | 44.00 ± 5.96 | 33.25 ± 4.48 | 44.30 ± 11.57 | 57.80 ± 17.19** | 57.62 ± 9.39** |
| Creatinine | mg/dL | 0.67 ± 0.02 | 0.72 ± 0.16 | 0.74 ± 0.17 | 0.66 ± 0.10 | 0.49 ± 0.06 | 0.61 ± 0.28 | 0.74 ± 0.11* | 0.74 ± 0.05* |
| Glucose | mg/dL | 172.00 ± 18.35 | 168.80 ± 17.85 | 172.24 ± 15.41 | 182.20 ± 28.59 | 175.00 ± 22.38 | 186.00 ± 25.45 | 168.60 ± 18.33 | 174.20 ± 24.23 |
| Urea | mg/dL | 52.50 ± 5.01 | 49.80 ± 5.98 | 44.80 ± 4.00 | 42.30 ± 4.67 | 48.80 ± 6.21 | 54.40 ± 12.50 | 49.90 ± 9.46 | 42.50 ± 1.54 |
| ALT | U/L | 52.00 ± 4.58 | 53.75 ± 6.92 | 55.00 ± 5.56 | 84.66 ± 10.06* | 32.33 ± 3.37 | 32.26 ± 5.85 | 31.50 ± 6.53 | 45.66 ± 11.25 |
| AST | U/L | 202.00 ± 13.07 | 202.25 ± 9.67 | 243.33 ± 27.02 | 253.00 ± 23.66* | 185.25 ± 17.72 | 189.50 ± 11.50 | 232.00 ± 27.92 | 232.25 ± 20.90* |
| Albumin | g/L | 3.26 ± 0.58 | 3.43 ± 0.55 | 2.78 ± 0.62 | 3.01 ± 0.23 | 3.13 ± 0.49 | 3.40 ± 0.46 | 3.29 ± 0.85 | 3.45 ± 0.77 |
| Total Protein | g/L | 6.40 ± 0.46 | 6.68 ± 0.56 | 6.97 ± 0.80 | 6.78 ± 0.56 | 6.66 ± 0.59 | 6.58 ± 0.69 | 6.44 ± 0.98 | 6.54 ± 0.56 |
| Potassium | mEq/L | 4.68 ± 0.29 | 4.62 ± 0.64 | 4.88 ± 0.49 | 4.68 ± 0.53 | 4.81 ± 0.56 | 5.15 ± 0.67 | 5.04 ± 0.66 | 4.86 ± 0.61 |
| Total Bile Acids | µmol/L | 18.25 ± 1.85 | 19.12 ± 1.25 | 19.72 ± 1.21 | 20.65 ± 1.23 | 14.80 ± 1.61 | 17.20 ± 1.16 | 16.60 ± 1.68 | 17.82 ± 1.65 |
| Sodium | mEq/L | 141.50 ± 4.50 | 140.40 ± 1.14 | 142.20 ± 3.83 | 142.00 ± 3.67 | 141.60 ± 2.70 | 141.00 ± 1.58 | 142.80 ± 4.65 | 145.60 ± 3.13 |

AST: aspartate aminotransferase; CTT: Coriander Triphala tablet; ALT: alanine aminotransferase; *p<0.05,**p<0.0

The serum levels of AST and ALT were markedly elevated after oral dosing with 1000 mg/kg CTT suspension relative to controls ($p<0.05$). Liver histopathology from male and female rats is shown in **Figure 1**. Tissue architecture remained unremarkable in controls and the 200 mg/kg CTT group. However, doses of 500 and 1000 mg/kg CTT induced mild-to-moderate hepatocyte congestion and hydropic degeneration, as illustrated.

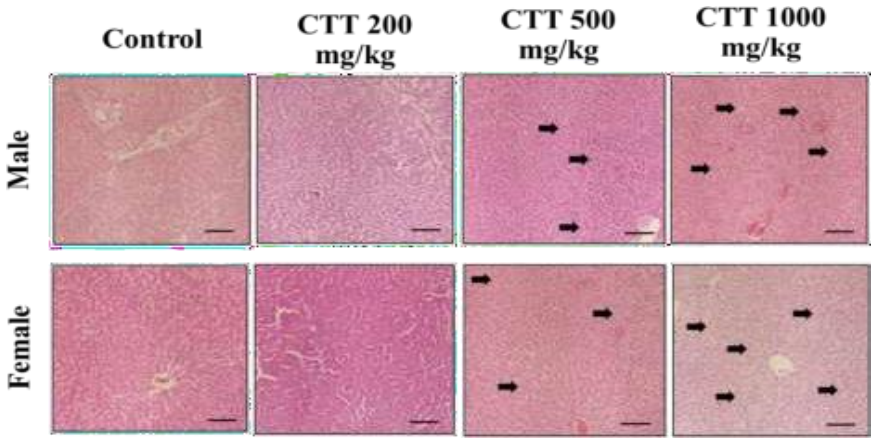


**Figure 1.** Representative liver histology across treatment groups; black arrows mark hydropic degeneration in hepatocytes; H&E stain. CTT: Coriander Triphala tablet; Scale bar = 100 µm.

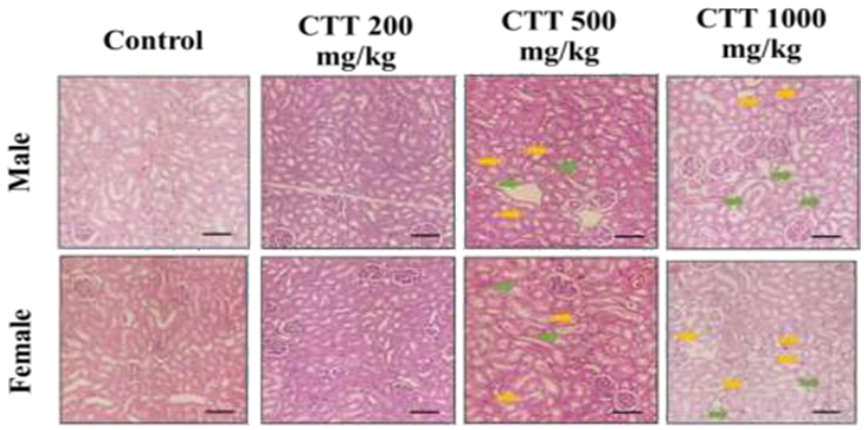


**Figure 2.** Representative kidney histology from treatment groups; yellow arrows indicate renal tubules with necrotic debris and incomplete epithelial lining; green arrows highlight individual necrotic cells showing eosinophilic cytoplasm and karyorrhexis; H&E stain. CTT: Coriander Triphala tablet; Scale bar = 100 µm.

In rats dosed with 500 or 1000 mg/kg CTT, kidney sections revealed varying severity of tubular necrosis, including widespread epithelial sloughing and degenerative changes. No obvious clinical signs of toxicity or behavioral alterations were noted in the satellite recovery group. Hematological values in this group were unaffected by 1000 mg/kg CTT **(Table 7).** In contrast, several biochemical markers differed significantly from controls. As presented in **Table 8**, 1000 mg/kg CTT in the satellite group caused notable rises in serum cholesterol ($p<0.01$) and creatinine ($p<0.05$) in both sexes, along with higher ALT activity ($p<0.05$). Remaining biochemical indices showed no treatment-related changes. Patterns of hematological and biochemical alterations in the satellite cohort closely mirrored those observed in the main 1000 mg/kg group.

Coriander Triphala is a traditional Iranian herbal preparation combining fruits of Terminalia chebula, Terminalia bellirica, Phyllanthus emblica, and Coriandrum sativum in a semisolid oral form traditionally indicated for gastrointestinal disorders and related conditions [11, 12]. A film-coated tablet version was previously developed and quality-tested by Choopani *et al*. [21]. These plant constituents are rich in bioactive compounds, notably tannins, which can exert organ-specific toxicity [24]. The common perception of superior safety for botanicals over conventional pharmaceuticals often promotes casual use without awareness of possible risks [25, 26]. Accordingly, the current investigation examined acute and subacute toxicity profiles of CTT in Wistar rats per OECD recommendations.

Acute toxicity testing involved a single 2000 mg/kg oral dose of aqueous CTT suspension. No evidence of acute adverse effects emerged, including salivation, lethargy, loose stools, tremors, seizures, or mortality within 24 hours. Additionally, no meaningful deviations occurred in appearance, behavior, respiration, feed/water intake, weight gain, or body temperature throughout monitoring. Comparable absence of acute and subchronic toxicity for another polyherbal product in rats was described by Sholikhah *et al*. [27]

**Table 7.** Effect of Coriander Triphala tablet on hematological parameters in satellite group

| Parameter | Male Control | Male CTT (1000 mg/kg) | Female Control | Female CTT (1000 mg/kg) |
|---|---|---|---|---|
| WBC ($\times10^3/\mu L$) | 9.56 ± 6.52 | 8.02 ± 3.83 | 8.02 ± 1.12 | 7.88 ± 4.01 |
| RBC ($\times10^6/\mu L$) | 8.45 ± 0.63 | 7.95 ± 0.39 | 7.85 ± 0.67 | 7.65 ± 0.66 |
| Hb (g/dL) | 16.88 ± 0.72 | 15.35 ± 0.43 | 15.07 ± 0.28 | 15.80 ± 0.36 |
| Hct (%) | 42.60 ± 0.92 | 41.65 ± 1.18 | 40.50 ± 0.30 | 39.80 ± 1.87 |
| MCV (fL) | 54.84 ± 0.83 | 53.08 ± 2.02 | 54.65 ± 0.25 | 54.00 ± 0.06 |
| MCH (pg) | 22.62 ± 1.36 | 22.32 ± 0.54 | 21.12 ± 0.65 | 20.32 ± 0.42 |
| MCHC (g/dL) | 39.65 ± 0.27 | 38.43 ± 0.60 | 38.35 ± 0.26 | 38.36 ± 0.13 |
| Platelet ($\times10^3/\mu L$) | 564.65 ± 74.20 | 580.10 ± 72.32 | 580.21 ± 35.32 | 555.05 ± 25.32 |
| Reticulocytes (%) | 2.00 ± 0.28 | 2.02 ± 1.01 | 2.36 ± 1.12 | 2.35 ± 0.84 |
| RDW (%) | 12.20 ± 0.25 | 12.22 ± 0.32 | 12.25 ± 0.36 | 12.63 ± 0.41 |
| PTT (s) | 15.66 ± 0.22 | 15.25 ± 0.65 | 14.64 ± 0.55 | 14.65 ± 0.33 |
| PT (s) | 17.65 ± 0.36 | 15.36 ± 1.14 | 16.32 ± 0.65 | 15.23 ± 1.65 |
| Lymphocytes (%) | 28 | 30 | 32 | 26 |

| | | | | |
|---|---|---|---|---|
| Neutrophils (%) | 70 | 72 | 73 | 68 |
| Eosinophils (%) | 0 | 0 | 0 | 0 |
| Monocytes (%) | 0 | 0 | 0 | 0 |
| Basophils (%) | 0 | 0 | 0 | 0 |

Hb: hemoglobin; Hct: hematocrit; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; PT: prothrombin time; PTT: partial thromboplastin time; RBC: red blood cells; RDW: red cell distribution width; Retic: reticulocyte; WBC: white blood cells; CTT: Coriander Triphala tablet. No significant differences were found ($p>0.05$).

**Table 8.** Influence of Coriander Triphala tablet on biochemical indices in the satellite group

| Parameter | Unit | Male Control | Male CTT (1000 mg/kg) | Female Control | Female CTT (1000 mg/kg) |
|---|---|---|---|---|---|
| Glucose | mg/dL | 169.00 ± 20.33 | 173.35 ± 19.31 | 174.12 ± 22.45 | 178.44 ± 33.00 |
| Urea | mg/dL | 45.55 ± 8.00 | 44.89 ± 3.66 | 50.22 ± 4.50 | 47.44 ± 5.05 |
| Cholesterol | mg/dL | 40.00 ± 2.87 | 62.11 ± 3.21** | 36.23 ± 4.05 | 56.80 ± 7.00** |
| Creatinine | mg/dL | 0.45 ± 0.12 | 0.78 ± 0.04* | 0.60 ± 0.05 | 0.74 ± 0.28* |
| AST | U/L | 180.22 ± 12.00 | 210.31 ± 18.00 | 208.23 ± 10.00 | 230.00 ± 12.02 |
| ALT | U/L | 32.02 ± 1.50 | 58.65 ± 9.80* | 48.90 ± 5.00 | 80.56 ± 10.25* |
| Albumin | g/L | 3.40 ± 0.24 | 3.50 ± 0.32 | 3.80 ± 0.22 | 3.74 ± 0.69 |
| Total Protein | g/L | 5.49 ± 0.65 | 5.44 ± 0.75 | 5.80 ± 0.74 | 5.20 ± 0.55 |
| Potassium | mEq/L | 4.32 ± 0.45 | 4.65 ± 0.35 | 4.41 ± 0.96 | 4.84 ± 0.65 |
| Sodium | mEq/L | 142.00 ± 1.02 | 144.05 ± 2.03 | 145.00 ± 1.80 | 140.30 ± 1.87 |
| Total Bile Acids | µmol/L | 15.65 ± 1.02 | 16.65 ± 1.43 | 16.66 ± 1.31 | 17.85 ± 1.55 |

AST: aspartate aminotransferase; CTT: Coriander Triphala tablet; ALT: alanine aminotransferase; *$p<0.05$, **$p<0.01$

Previous investigations reported the absence of toxic manifestations following administration of a polyherbal formulation at an oral dose of 2000 mg/kg, concluding that its median lethal dose ($LD_{50}$) exceeded this level [27]. Similarly, Jayesh *et al*. assessed the acute oral toxicity of an aqueous acetone extract derived from Terminalia bellirica fruits in Wistar rats and found that a single 2000 mg/kg dose produced no observable acute adverse effects in female animals, indicating an $LD_{50}$ greater than 2000 mg/kg [28]. In line with these findings, the current investigation estimated the $LD_{50}$ of Coriander Triphala tablet (CTT) to be above 2000 mg/kg based on OECD guideline 425 [22]. These observations imply that short-term oral exposure to CTT at doses up to 2000 mg/kg does not induce clinically relevant acute toxicity. Nevertheless, it should be emphasized that these results were derived exclusively from experiments conducted in female rats and therefore cannot be directly extrapolated to humans, highlighting the necessity for clinical evaluation. Consequently, on the basis of the acute toxicity outcomes, a subacute toxicity assessment was undertaken to explore the potential effects of repeated CTT administration.

For the subacute toxicity evaluation, male and female rats received oral doses of CTT at 200, 500, or 1000 mg/kg daily for 28 consecutive days. Throughout the experimental period, animals exhibited no apparent signs of toxicity, including excessive salivation, lethargy, diarrhea, tremors, convulsions, or mortality.

Body weight is widely regarded as a sensitive marker of general physiological status in experimental animals [29], while adequate food and water consumption are essential determinants of animal health and well-being [30, 31]. Accordingly, changes in body mass as well as food and water intake were monitored during the study. The findings demonstrated that neither body weight nor dietary and fluid intake differed significantly between CTT-treated rats and the control group, irrespective of sex.

Hematological and biochemical indices are commonly employed by clinicians and researchers to assess systemic health in both humans and laboratory animals [32]. Therefore, these parameters were comprehensively analyzed in male and female rats following subacute exposure to CTT. The results revealed no statistically significant alterations in hematological variables compared with controls. In contrast, biochemical analyses showed that male rats receiving 500 and 1000 mg/kg of CTT exhibited elevated serum cholesterol and creatinine concentrations, along with a significant increase in aspartate aminotransferase (AST) activity at the highest dose. In female rats, administration of 1000 mg/kg CTT resulted in increased serum AST and alanine aminotransferase (ALT) levels relative to controls.

Histopathological examination of hepatic tissues from both sexes indicated that exposure to CTT at doses of 500 and 1000 mg/kg induced vascular congestion and mild to moderate hydropic degeneration of hepatocytes. Likewise, renal tissue analysis revealed varying degrees of tubular epithelial necrosis and degenerative changes

in male and female rats treated with these higher doses, whereas animals receiving 200 mg/kg displayed normal liver and kidney histology.

The liver and kidneys are among the most critical organs responsible for metabolism and elimination of xenobiotics [33, 34]. Consequently, structural damage to these tissues may impair their physiological functions and contribute to systemic health risks. Hepatic injury is typically associated with hepatocellular damage accompanied by increased serum ALT and AST activities [35]. In the present study, the observed elevation of these enzymes correlated well with histological evidence of hepatocyte degeneration in rats exposed to CTT doses exceeding 500 mg/kg, suggesting the onset of liver parenchymal injury. Similarly, serum creatinine serves as a key indicator of renal function, reflecting the kidneys' ability to clear metabolic waste products from circulation [36]. Elevated creatinine levels, as detected in this study, are consistent with renal tubular necrosis and degeneration, a hallmark of kidney injury [37].

Animals in the satellite group did not exhibit changes in behavioral patterns, hematological parameters, or overt toxicity-related signs compared with controls. However, significant increases in serum cholesterol, creatinine, and ALT levels were detected. Other biochemical indices remained unchanged. These findings indicate that withdrawal of CTT did not result in substantial recovery from the subacute toxic effects, nor did it reveal delayed-onset toxicity, suggesting persistence of certain biochemical disturbances.

## Conclusion

The findings of the present study demonstrate that CTT does not induce significant acute toxicity in rats at an oral dose of 2000 mg/kg. Repeated administration at 200 mg/kg during the subacute toxicity study did not adversely affect biochemical, hematological, histological, behavioral, or general health parameters. In contrast, administration of higher doses (500 and 1000 mg/kg) resulted in increased serum levels of cholesterol, creatinine, AST, and ALT, accompanied by histopathological alterations in hepatic and renal tissues. Collectively, these results suggest that prolonged intake of CTT at elevated doses may compromise liver and kidney function. Therefore, careful medical supervision and precautionary measures are recommended when considering long-term therapeutic use of this formulation.

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