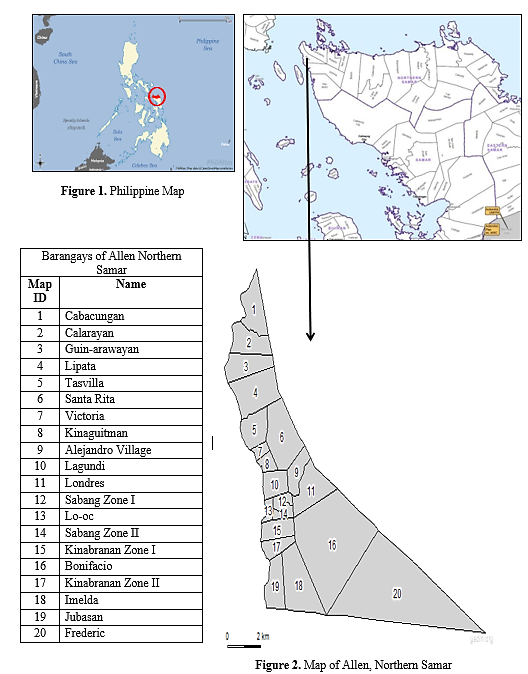
**TOXICITY EFFECTS OF AQUEOUS LEAF AND BARK EXTRACT OF *Cordia dichotoma* (ANONANG) IN MALE RATS**

**ABSTRACT**

**KEYWORDS:** *Cordia dichotoma, aqueous extract, histopathology, toxicity*

This study aimed to evaluate the toxicity effects of aqueous leaf and bark extracts of *Cordia dichotoma* (Anonang) in male rats. Thirty (30) young adult male Wistar rats, aged 8 to 10 weeks and weighing between 200-300 grams, were divided into three groups. Group I received a low concentration of the aqueous leaf and bark extract (3 mL), Group II received a moderate concentration (4 mL), and Group III received a high concentration (5 mL). The treatments were administered via intraperitoneal injection for 21 days. Twenty-four (24) hours after the final treatment, all rats were individually weighed and anesthetized with 95% ethanol before selected organs were dissected for histopathological analysis. Symptoms of toxicity and mortality were more pronounced in the groups treated with the aqueous leaf extract compared to those treated with the aqueous bark extract. However, there were no significant differences (p > 0.05) in physical observations, mortality rates, or body weights among the different extracts administered and concentrations over the 21 days. Histopathological examination of the liver and spleen revealed mild adverse effects on their structure and function, indicating the potential for selective toxicity of the extract or its components.

**INTRODUCTION**

According to the World Health Organization (WHO), between 70% and 90% of people worldwide, particularly in developing countries, rely on plant-derived medicines for their health needs (WHO, 2011). While medicinal plants are usually regarded as safe and effective compared to synthetic drugs, they are not completely devoid of side effects or toxicity. Studies indicate that plant-derived products may produce toxic effects due to secondary metabolites, leading to prolonged vascular resistance in rodent embryos and resulting in teratogenic effects (Ouedraogo et al., 2012). *Cordia dichotoma* G. Forst., locally known as Anonang*,* belonging to the family Boraginaceae,is a small to moderate-sized deciduous tree that grows widely in the Philippines (Ragasa, et al.,2015). Different parts of the plant have been documented to demonstrate properties such as anti-ulcer, contraceptive, anti-inflammatory, antihelmintic, analgesic, anticancer, antioxidant, antimicrobial, antifungal, hepatoprotective, and diuretic effects, and they are used for addressing issues related to the digestive system, respiratory conditions, urogenital health, cardiac problems, vascular concerns, and blood disorders (Prajapati, et al.,2017). Despite the reported therapeutic potential of Cordia dichotoma, there are only a limited number of comprehensive scientific studies that have confirmed or disproven its toxic effects in male rats. Therefore, this study was conducted to expand the current literature on the toxicity effects of the aqueous leaf and bark extracts of *Cordia dichotoma* in male Wistar rats.

**METHODOLOGY**

***Locale of the Study***

The study was conducted at the University of Eastern Philippines Integrated Research Laboratory (UEP-IRL) from July to September 2023. The University of Eastern Philippines (UEP) is located at the western boundary of Catarman, Northern Samar (12° 29' 46" N, 124° 38' 19" E). The leaves and bark of *Cordia dichotoma* G. Forst., commonly known as Anonang, were collected in Allen, Northern Samar, Philippines (see Figures 1-2). The origin and historical distribution of the *Cordia* species remain unclear. Allen, located at 12° 29' 59.99" N, 124° 16' 60.00" E, is a fifth-class municipality in the northwestern part of Northern Samar, Philippines. It comprises 20 barangays and has a total population of 25,228, as reported by Phil Atlas in 2022. The majority of its continuously growing population depends on these natural resources for their livelihood on coconut production, farming, livestock-raising, and fishing (PSA, 2015).

***Experimental design and animals***

The study utilized an experimental method to investigate the toxicity effects of aqueous leaf and bark extracts of *Cordia dichotoma* in male rats. Both quantitative and qualitative analyses were conducted to explore the relationships between the variables. A total of 30 healthy, young adult male Wistar rats, aged between 8 to 10 weeks and weighing between 200-300g, were utilized. The animals were uniquely identified according to their body weights and were housed in screened cages under standard conditions of 22±3°C, with a relative humidity of 30-70%. They were maintained on a 12-hour light/dark cycle and provided with standard pellets and distilled water ad libitum, as per OECD guidelines (2001). The rats underwent a one-week acclimatization period in their cages to ensure normal growth and behavior before the commencement of the experiment.

***Procurement of Plants***

Fresh leaves and bark of *Cordia dichotoma* G. Forst. were collected from local areas in Allen, Northern Samar, Philippines. They were taken to the University of Eastern Philippines Integrated Research Laboratory (UEP-IRL) to prepare for extraction and their use as treatment variables in the experiment.

***Plant Extraction***

A sample of 100 grams of fresh leaves and bark from *Cordia dichotoma* was carefully washed under running tap water, followed by a final rinse with distilled water. The washed leaves and bark were then boiled in 1000 mL of distilled water at a ratio of 1:16 to prepare the extract. After boiling for 15 minutes, the solution was set aside to cool and was subsequently filtered using filter paper. The resulting aqueous extract of the leaves and bark of *Cordia dichotoma* was used to assess its toxicity effects in male Wistar rats, which included physical observations, and mortality rates, body weight measurement, and histopathological analysis.

***Test Substances Administration***

The animals were randomly assigned to three (3) groups, each consisting of five (5) animals, to conduct toxicity analysis. The treatment groups were designated as follows:

Group I received a low concentration of aqueous leaf and bark extract of *Cordia dichotoma* at a dose of 3 mL.

Group II received a moderate concentration of aqueous leaf and bark extract of *Cordia dichotoma* at a dose of 4 mL.

Group III received a high concentration of aqueous leaf and bark extract of *Cordia dichotoma* at a dose of 5 mL.

The experimental groups were given the plant extract via intraperitoneal administration at similar times each day (between 1:00 and 5:00 P.M.). In rare cases where a single concentration was not feasible, it could be divided into smaller fractions to be administered within 24 hours, following OECD Guidelines. After administration of the substance, food was withheld for an additional 3 to 4 hours.

***Toxicity Analysis***

The acute toxicity effects of the aqueous leaf and bark extract of *Cordia dichotoma* were evaluated in male rats. After the acclimatization period, the rats were randomly assigned to three (3) male groups (n=5). The initial body weight of the animals was recorded before the start of the treatments and then at least once a week until the treatments were completed. The rats were subjected to a fasting period overnight, during which they had *ad libitum* access to water. After this fasting period, the rats were weighed, and the test substance, *Cordia dichotoma* extract, was administered intraperitoneally at concentrations of 3 mL, 4 mL, and 5 mL for 21 days. After 24 hours following the last treatment, each rat was weighed individually, anesthetized with 95% ethanol, and then the selected organs were dissected for histopathological analysis. Behavioral observations of the animals were documented through both direct and indirect methods. Each rat was monitored individually for signs of toxicity at least once during the initial 30 minutes following dosing, at periodic intervals during the first 24 hours, particularly during the initial 4 hours, and then daily for a total of 14 days, following OECD guidelines (2001). In instances where no signs of toxicity or mortality were observed within the first 24 hours, testing proceeded with the next dose following the same protocol. This stepwise method persisted until the maximum concentration of 10 mL body weight was attained. If all subjects survived, they were subjected to daily monitoring for an additional 13 days (Halim, et al., 2011). The assessment of toxicological effects included alterations in general behavior, skin reactions, defecation patterns, hair loss, and other physiological activities, as well as any incidents of lethality or death occurring within 48 hours post-administration. All experimental protocols and procedures involving the animals were conducted following the ethical guidelines established by the Institutional Animal Care and Use Committee at the College of Veterinary Medicine, University of Eastern Philippines—Main Campus, University Town, Northern Samar.

***Histopathological Analysis***

The liver and spleen were carefully dissected after an abdominal incision. These samples were subsequently isolated, weighed, and fixed in a 10% formalin solution at a 5:9 ratio for a minimum duration of 48 hours. After fixation, the samples were submitted to Vet Central Lab, Animal Diagnostic Laboratory Services in the Philippines, where they were processed for analysis. A thick section, measuring 5-6 μm, was prepared and stained with hematoxylin and eosin (H&E). The stained sections were then examined under a light microscope at a magnification of 40x to evaluate the histopathological changes occurring in the selected organs of the experimental animals.

***Statistical Analysis***

The data were analyzed using a two-way analysis of variance (ANOVA) with Statistical Package for the Social Sciences (SPSS) software, version 21. Following this analysis, post hoc Tukey's test was applied. The results are presented as the mean ± standard deviation (Mean ± SD). A significance level of p<0.05 was used to determine statistical significance.

**RESULTS AND DISCUSSION**

***Physical observations and mortality rates***

Administration of aqueous leaf extract of *Cordia dichotoma* over 21 days resulted in a 40% mortality rate, specifically observed in the following groups: rats were administered concentrations of 3mL on day 21, 4 mL on day 12, and 5 mL on day 22. The rats exhibited significant toxic symptoms, including alopecia (hair loss), reduced mobility, hunched posture, diarrhea, and porphyrin (red pigment) staining around the eyes, observed at the 3mL concentration. Notably, on day 7, one rat receiving the 3mL concentration developed lumps and pus-filled abscesses in the right forelimb, which erupted by day 9. The abscess began healing towards the end of the treatment period. On the other hand, administration of aqueous bark extract of *Cordia dichotoma* over 21 days resulted in a 0% mortality rate across all treatment groups. However, some minor adverse effects were noted, including slight reductions in mobility, hair loss, and soft stools. Notably, one male rat receiving a concentration of 4mL exhibited porphyrin staining, a red pigment, around the eyes. Additionally, lumps or pus-filled abscesses developed in the neck region on day 9, which subsequently ruptured on day 11, yet began to demonstrate signs of healing by the end of the treatment period. These findings indicate that the rat's mortality could be related to the accumulation of toxic effects from various phytoestrogens, which could vary based on the type of extract administered and concentration-dependent reactions. This result was consistent with the report by El-Newary, et al., (2022) that mortality began at a concentration of 8g/kg/day and continued up to 10g/kg/day. The concentration that resulted in a 50% mortality rate among animals within the first 48 hours was estimated to be 10g/kg/day. At higher doses, a consistent dose-dependent increase in mortality was observed. Additionally, a single dose of LCD extract resulted in reduced locomotion (hypoactivity) at doses equal to or lower than 3.5g/kg body weight. In contrast, higher doses led to a regular dose-dependent increase in mortality (Bhattacharya and Saha, 2013). Similar findings were reported by Al-Hamdani (2019), that doses of 1000, 2000, and 3000mg/kg of both aqueous and alcoholic extracts of *Cordia myxa* did not result in lethal effects, although some minor side effects were noted in mice. However, higher doses of 4000mg/kg and 5000mg/kg led to behavioral changes, including rapid breathing and an accelerated heartbeat, ultimately leading to death shortly after the oral administration of the extracts. Additionally, the methanolic extract of the bark was evaluated for acute toxicity at doses of 10, 100, and 1000mg/kg over 24 hours, and at doses of 2000, 3000, and 5000mg/kg over 48 hours. No toxicity, including mortality or behavioral changes, was observed within the 48 hours (Hussain, et al., 2020).

***Effects of leaf extract on body weight***

Figure 3 shows the effects of aqueous leaf extract of *Cordia dichotoma* on the body weight of male Wistar rats, administered at different levels of concentration at 21 days. At the start of the study, the initial body weight of male rats receiving concentrations of 4 mL (267g) and 5 mL (267g) was significantly higher than that of the 3 mL group (217g). By day 7, the body weight of rats in the 3mL treatment group exhibited a significant increase of 10g, resulting in a total weight of 227g, while the 4 mL group experienced a decline of 54g, reducing their weight to 213g. The 5 mL group maintained a body weight of 267g. On day 14, the body weight in the 3mL group increased significantly by 40g, while the 4mL group achieved a gain of 27g. In contrast, the average weight of the 5 mL group remained at 267g. After 21 days, the 3mL group achieved a significant weight increase of 300g, with a weight gain of 33g. The 4 mL group reached a total weight of 340g, reflecting an increase of 100g, and the 5 mL group recorded a notable weight of 420g, a substantial gain of 153g. On the final day of the study, the average body weight of the 3 mL group was significantly elevated to 320g, with a gain of 20g, similar to the 4 mL group, which also experienced a gain of 20g. Conversely, the 5 mL group encountered a slight reduction, concluding at 320 g, which represented a loss of 100 g. The average body weight gain for male rats over the 21 days was 103g for the 3mL group, 93g for the 4 mL group, and 53g for the 5 mL group. The results indicate that the varying concentrations of aqueous leaf extract from *Cordia dichotoma* did not cause harm to the average body weight of the rats, even after prolonged administration. Furthermore, the average body weight gains measured every seventh day revealed no statistically significant correlation (p<0.05) between the administration of the aqueous leaf extract and the different levels of concentration. Herbal extracts can contribute to the suppression of an animal’s appetite, which leads to a reduction in the body weight of animals. A decrease in body weight could be associated with normal physiological adaptation responses of the body toward plant extracts or compounds, which lead to low appetite and, hence, lower caloric intake by the animal. High doses of plant extracts or compounds might also induce stress in the animals, thereby reducing their food intake, which may lead to reductions in their body weights (Olayode, et al.,2020). Additionally, long-term administration of *Cordia dichotoma* fruit methanol extract, when administered to alloxan-induced diabetic rats, reversed the weight loss, and the animals returned to near normal when compared to the disease control group (Mishra and Garg, 2011).

***Effects of bark extract on body weight***

Figure 4 shows the effects of aqueous bark extract from *Cordia dichotoma* on the body weight of male Wistar rats at 21 days. The initial body weight of male rats receiving a concentration of 5 mL (270g) was significantly higher compared to those receiving 3 mL (267g) and 4 mL (267g). On day 7, the body weight of the rats treated with 3 mL showed a significant decrease of 14g, reducing to 253g, while the 5 mL group experienced a slight decrease of 3g. The body weight of the 4 mL group remained stable throughout this period. By day 14, the rats in the 3 mL group (267g) showed a significant weight increase of 14g compared to those in the 4 mL (280g) and 5 mL (280g) groups, which both increased by 13g. After 21 days, the 5 mL group continued to gain weight, reaching 287g, an increase of 7g compared to the 3mL group, which decreased to 253g (a decrease of 14g), and the 4 mL group, which decreased to 253g (a decrease of 27g). On the final day, the rats receiving a concentration of 5 mL achieved the highest body weight of 333g, with an increase of 46g. This was followed by the 4 mL group at 307g (an increase of 54g) and the 3 mL group at 280g (an increase of 27g). The total average weight gain was 13g for the 3 mL group, 40g for the 4 mL group, and 63g for the 5 mL group. The results indicate that administering aqueous bark extract of *Cordia dichotoma* to male rats at various concentration levels (3 mL, 4 mL, and 5 mL) did not negatively affect their average weight gain over an extended period. This lack of impact may be due to typical physiological adaptations to the plant extracts or their bioactive compounds. Additionally, administration of the aqueous bark extract at different concentration levels over 21 days did not result in significant changes (p<0.05) in the body weight of male Wistar rats, as the computed values were not statistically significant at the 0.05 level.

**Figure 3.** Body weight (g) of male Wistar rats treated with aqueous leaf extract of *Cordia dichotoma* at different concentrations of 3 mL (low), 4 mL (moderate), and 5 mL (high) for 21 days. Data expressed in mean ± standard deviation. None of the comparisons were statistically significant.

**Figure 4.** Body weight (g) of male Wistar rats treated with aqueous bark extract of *Cordia dichotoma* at different concentrations of 3 mL (low), 4 mL (moderate), and 5 mL (high) for 21 days. Data expressed in mean ± standard deviation. None of the comparisons were statistically significant.

***Histopathological analysis***

Figure 5 shows the effects of the aqueous leaf extract of *Cordia dichotoma* on the histopathological examination of the liver section in male Wistar rats after 21 days of treatment. All concentrations revealed hepatocytes that were granular but not swollen, with ongoing congestion in the central veins and sinusoids. In the groups receiving 4 mL and 5 mL concentrations, parts of Glisson’s capsule were thickened and infiltrated with neutrophils. Furthermore, liver sections from the 4 mL group showed slight lymphocytic infiltration in some periportal areas, along with focal hemorrhage (see Figure 5 (B)).

**Figure 5.** Photomicrograph of a rat’s liver cross-section treated with aqueous leaf extract of *Cordia dichotoma* (40x, H&E stained)

**A.**

**B.**

**C.**

Figure 6 shows the effects of the aqueous bark extract of *Cordia dichotoma* on the histopathological examination of the liver section in male Wistar rats after 21 days of treatment. All treated groups showed that the hepatocytes were slightly granular, and both the central veins and sinusoids were significantly congested. Mild lymphocytic infiltration was also observed in periportal areas (see Figure 6 (A-C)).

**A.**

**B.**

**C.**

**B.**

**Figure 6.** Photomicrograph of a rat’s sliver cross-section treated with aqueous bark extract of *Cordia dichotoma* (40x, H&E stained)

**C.**

Figure 7 shows the effects of the aqueous leaf extract of *Cordia dichotoma* on the histopathological examination of the spleen section in male Wistar rats at 21 days of treatment. The spleen sections from rats that received 4 mL and 5 mL concentrations displayed severe congestion, while the sections from rats given a 3mL concentration showed mild congestion. Notably, in the 3mL treatment group, hemosiderin-laden macrophages were present. Conversely, the 5 mL treatment group showed a thickened capsule with neutrophil infiltration (see Figure 7 (C)).

**A.**

**Figure 7.** Photomicrograph of a rat’s spleen cross-section treated with aqueous leaf extract of *Cordia dichotoma* (40x, H&E stained)

Figure 8 shows the effects of the aqueous bark extract of *Cordia dichotoma* on the histopathological examination of the spleen section in male Wistar rats at 21 days of treatment. Spleen sections from all groups continued to show lymphoid hyperplasia. However, at a 3 mL concentration, there was congestion, while the moderate and higher concentrations of 4 mL and 5 mL exhibited severe congestion. Additionally, a few megakaryocytes were observed scattered within the parenchyma at the 3mL concentration, whereas rats receiving the 5mL concentration showed hemosiderin-laden macrophages (see Figure 8 (A & C)).

**A.**

**B.**

**C.**

**Figure 8.** Photomicrograph of a rat’s spleen cross-section treated with aqueous bark extract of *Cordia dichotoma* (40x, H&E stained)

The observed similarities in the results and the concentration-dependent reactions across all tested groups indicate that the extract may induce mild adverse effects on the structure and function of the liver and spleen, while simultaneously enhancing the immunological responses in male rats. These effects are likely attributable to the anti-inflammatory activity and antioxidant potential of its constituent phenolic compounds, flavonoids, saponins, and alkaloids. Furthermore, the noted congestion in the central vein of most of the treated groups may be associated with an excessive influx of blood into the arteries or inadequate drainage into the veins. Microscopically, congestion is characterized by the dilatation of the arterial wall resulting from an increased blood volume in the central vein. If damage occurs, the major vein may dilate due to the lysis of endothelial cells. Elevated concentrations of compounds in the bloodstream can lead to altered blood distribution, causing muscular perfusion to be reallocated to the sinusoids, subsequently resulting in their widening (Zebua et al., 2023). According to Murad and Karbon (2020), at a concentration of 500 mg/kg, the protective action of both the aqueous and alcoholic extracts of *C. myxa* fruit has been confirmed, protecting liver tissue concerning the central vein, hepatocytes, hepatic sinusoids, and Kupffer cells. Additionally, Ali et al. (2015) reported that aqueous extracts of *Cordia myxa* can stimulate cell-mediated and immune responses in mice to protect soft organs such as the liver and spleen from a variety of harmful agents.

**CONCLUSION AND RECOMMENDATION**

In conclusion, the aqueous leaf and bark extracts of *Cordia dichotoma* exhibit beneficial properties that help protect the liver and spleen from oxidative stress and tissue damage by regulating free radicals and reducing toxicity. Nevertheless, it is important to note that the extract may also cause slight adverse effects, thereby potentially influencing both the structural integrity and functional capacity of these organs. Therefore, further studies are needed to clarify the precise mechanisms of action and to isolate the active compounds, which will help address any potential toxic effects associated with this plant.

**LIMITATION OF THE STUDY**

The decoction method was selected to extract the leaves and bark of *Cordia dichotoma*, as other extraction techniques were either unavailable or insufficient to yield the required volume of samples for the research. Consequently, the dosage of the extracted substance administered to the experimental rats was not determined based on their body weights; rather, it was calculated according to an appropriate volume suitable for rats with similar or nearly equivalent body weights. Furthermore, due to unexpected incidents of cannibalism among certain animal groups before the treatment period, the number of experimental animals required was reduced. The researchers faced significant challenges in replacing the deceased rats because there was a limited supply of animals that met the necessary age and size specifications. Consequently, no comparisons could be made between the control group and the treatment groups. Therefore, the findings obtained necessitate further investigation and validation.

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