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ASSESSING SUBCHRONIC TOXICITY ASSESSMENT OF C. PAPAYA LEAF EXTRACT

[1]MAYALAKSHMY N N
[1]Research Scholar, Department of Zoology, Mansarovar Global University, Sehore, Madhya Pradesh
[2]Dr. SHWETA DESHMUKH
[2]Supervisor, Department of Zoology, Mansarovar Global University, Sehore, Madhya Pradesh

ABSTRACT
Assessed were histopathological alterations, relative organ weights, hematological and biochemical markers. After 13 weeks of treatment, the researchers found no adverse effects, including death, behavioral abnormalities, weight gain or loss, or changes in dietary or fluid consumption, from the leaf extract. Hematology parameters showed no significant variations between the treatment and control groups; however, biochemistry data, such as LDH, creatinine, total protein, and albumin, did show significant differences.
Keywords: - Papaya Leaf, Plant, Carica, Hematological, Medicinal.

I. INTRODUCTION

The possible therapeutic advantages and low side effects of natural products have piqued the attention of the medical community in their use, especially plant extracts. Papaya, or Carica papaya, is one of several botanical sources that has come up as a potential contender because of its wide range of pharmacological effects. An important part of this investigation is testing the safety of Carica papaya leaf extract for possible medicinal uses by measuring its subchronic toxicity. Throughout history, people have turned to the tropical fruit carica papaya for its many supposed medical and nutritional advantages, as well as its many other health-enhancing qualities. Bioactive chemicals found in papaya leaves, such as alkaloids, flavonoids, and enzymes, have gained interest because to their potential anti-inflammatory, antioxidant, and immunomodulatory activities.

Nevertheless, more research is required to determine if Carica papaya leaf extract is safe for long-term use or exposure, particularly in the setting of subchronic toxicity. An essential part of the preclinical testing of any possible medicinal drug is the study of subchronic toxicity. During this process, which may last anywhere from a few weeks to a few months, the potential negative consequences of a substance's repeated exposure are systematically studied. To make sure a drug is safe to use before it goes into clinical trials or is widely used, these kinds of evaluations are crucial. To determine the safety margins and direct regulatory choices about Carica papaya leaf extract, it is crucial to study its subchronic toxicity profile.

Delving into the scientific approaches used in subchronic toxicity evaluations of Carica papaya leaf extract is crucial for a full investigation of the topic. To understand the possible negative consequences of long-term exposure, rigorous experimental designs are required, including both in vitro and in vivo investigations. Animal investigations provide a comprehensive view of systemic reactions, including metabolic, hematological, and histopathological alterations, while cellular experiments may shed light on the molecular pathways behind toxicity. To fully grasp the possible toxicological consequences of Carica papaya leaf extract, one must have a firm grasp on how its active ingredients are metabolized and distributed throughout the body. The content of the extract and its safety profile may be greatly affected by the extraction technique, solvent choice, and preservation measures. To better understand subchronic toxicity data, metabolism investigations might help identify possible metabolites that could contribute to harm. It is essential to recognize the current studies on the acute and chronic toxicity of Carica papaya leaf extract as we begin the path of subchronic toxicity evaluation. Acute toxicity studies look at the short-term negative effects of a chemical, while chronic toxicity studies look at the impacts over a longer period of time. To fill in the blanks between the two, the subchronic toxicity evaluation provides a more complex picture of the dose-dependent consequences that can manifest over a medium time frame. Studying the dose-response relationships is crucial for understanding the subchronic toxicity profile of Carica papaya leaf extract. The primary parameters for risk assessment, the no observed adverse effect level

(NOAEL) and the lowest observed adverse effect level (LOAEL), may be determined by establishing a dose-response curve. In addition, effects that are dose-dependent may help identify possible levels at which side effects start to show up, which is useful for making safe dosage recommendations.

A thorough subchronic toxicity evaluation is crucial in light of the increasing interest in Carica papaya leaf extract as a possible medicinal agent. In addition to adding to our knowledge of the extract's safety profile, this thorough examination paves the way for educated decision-making in clinical applications. Our goal is to shed light on the possible dangers and advantages of Carica papaya leaf extract as we explore the complexities of subchronic toxicity research. This will enable us to use it responsibly in healthcare and other fields.

II. REVIEW OF LITERATURE

Lim, Xin et al., (2021) There has been recent interest in the leaf of the Carica papaya L. plant as a possible treatment for thrombocytopenia, both in cases of dengue fever and in those not caused by the virus. Concerns about safety are therefore just as crucial as those about possible effectiveness. Extrinsic toxicants, complex phytochemical composition, and varying formulations all contribute to the difficulty of evaluating the safety of botanical products for human use. We set out to comprehensively compile all relevant safety data from clinical trials, preclinical studies, and publications on herb-drug interactions pertaining to C. papaya leaf ingestion in this review. Through the use of predefined keywords, a comprehensive search was carried out on grey literature and electronic databases such as MEDLINE, LILACS, Web of Science, and Cochrane Library Central. We compiled this comprehensive safety profile of C. papaya leaf ingestion after searching for, screening, and analyzing relevant preclinical and clinical trials. For descriptive analysis on study characteristics, adverse reactions, toxicity findings, and herb-drug interactions, 41 articles were considered. Of these, 13 randomized controlled and quasi experimental trials were further evaluated for risk of bias and reporting quality. The trials included 23 clinical, 5 ongoing trials, and 13 preclinical studies. In general, adults had no ill effects from consuming C. papaya leaf juice or standardized aqueous extract for shorter periods of time (<five days). On the other hand, a randomized controlled trial found that children aged 1 to 12 could safely consume the same standardized aqueous extract. The majority of reports were of mild gastrointestinal side effects. Animal studies have shown that there is a risk of hepatotoxicity and reproductive toxicity with prolonged usage. Artemisinin, metformin, digoxin, ciprofloxacin, and glimepiride were all considered to have unpleasant herb-drug interactions. Although pregnant women and those with liver problems should exercise care, individuals may safely consume C. papaya leaves for short periods of time. Possible herb-drug interactions include p-glycoprotein substrates, oral hypoglycemic medicines, and antibiotics that chelate cations.

Ismail, Zakiah et al., (2014) Sprague Dawley (SD) rats were used as a model to examine the subchronic toxicity impact of Carica papaya Linn. leaf extract. After preparing the extract by combining the freeze-dried leaf extract with distilled water, it was orally given to SD rats (10 rats per group) at concentrations of 0, 0.01, 0.14, and 2 g/kg BW for a duration of 13 weeks. All through the trial, researchers kept tabs on participants' general well-being, mortality rate, and dietary and hydration consumption. Assessed were histopathological alterations, relative organ weights, hematological and biochemical markers. After 13 weeks of treatment, the researchers found no adverse effects, including death, behavioral abnormalities, weight gain or loss, or changes in dietary or fluid consumption, from the leaf extract. Hematology parameters showed no significant variations between the treatment and control groups; however, biochemistry data, such as LDH, creatinine, total protein, and albumin, did show significant differences. But there was no correlation between these alterations and histological alterations. Ultimately, the findings indicated that rats were not significantly affected by the 13 weeks of oral administration of C. papaya leaf extract, even at doses up to fourteen times higher than those used in conventional medicine.

Halim, Siti Zaleha et al., (2013) There is a lack of toxicological data about the safety of Carica papaya and Ocimum basilicum, despite their extensive use in traditional medicine worldwide. The Sprague Dawley rats were used to assess the acute, subacute, and subchronic toxicity of the aqueous extracts of the leaves of C. papaya and O. basilicum. The rats in the acute trial were given an oral dosage of 2 g/kg bw of C. papaya extract and 5 g/kg bw of O. basilicum extract, respectively. The rats in the control group were given water. Subacute trials used daily dosages of the extracts for 28 days,

whereas subchronic studies used 13 weeks. The C. papaya and O. basilicum treatment groups each received 0.01, 0.14, and 2 g/kg BW of extract, whereas the control group got nothing but water. Clinician assessment, mortality, caloric intake, and fluid consumption were the variables monitored. Hematological, biochemical, histopathological, and relative organ weight assessments, in addition to other tests, were performed on killed rats. In the acute, subacute, and subchronic toxicity trials, C. papaya did not cause any changes in body weight, food or water intake, relative organ weights, or death. The histopathological analysis of every organ failed to detect any morphological change. Total protein, hemoglobin (HGB), hematocrit (HCT), and red blood cell (RBC) levels were all considerably elevated in the acute testing, suggesting possible dehydration. Lactate dehydrogenase (LDH), creatinine, total protein, and albumin were significantly different in the treatment group compared to the control group in the subchronic trial. O. basilicum did not cause any fatalities or toxicity symptoms in the acute, subacute, or subchronic stages. Nonetheless, the treated rats' hematological and biochemical markers differed significantly. Median corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) changed in the high dosage group, whereas other biochemical parameters changed in the medium dose group as a result of subchronic toxicity. Finally, the rats showed no signs of toxicity when fed aqueous extracts of the leaves of C. papaya and O. basilicum orally.

Tarkang, Protus et al., (2012) We tested the acute and chronic oral toxicity of Carica papaya (CP) leaf extracts in Wistar rats using aqueous and ethanolic solutions in an effort to tap into traditional medical wisdom. The pawpaw tree, scientifically known as Carica papaya L., is a beloved tropical fruit tree. All throughout the globe, people eat these fruits and vegetables. Anemia, diabetes, intestinal helminthiasis, malaria, diarrhea, jaundice, and wounds are among the ethnomedical applications that have been documented. Researchers tested the acute oral toxicity of CPup extracts in mice at doses ranging from 5gKg-1BW. Sub-chronic oral toxicity (aqueous alone) and sub-acute (aqueous plus ethanol extract) were tested on 18 groups of 6 rats each, with doses of 0.25gKg-1,.5gKg-1, and 1gKg-1BW. Water and corn oil were given to the control groups, respectively. After the studies were completed, the rats were slaughtered and their blood and plasma were tested for various biochemical markers as well as histological analysis. There were no reports of fatalities or symptoms of acute oral poisoning. Results from aqueous and ethanol extract experiments showing sub-acute and sub-chronic toxicity of the oral drug were hypoglycemia, hypolipidemia, and hyperglycemia, as well as elevated AST and BUN levels, respectively. CP caused no immediate harm when taken orally. Histopathological testing demonstrated that large dosages of the ethanol extract were harmful to the liver and kidneys, in contrast to the hypoglycemic and hypolipidemic effects of the aqueous extract. There was less toxicity in the water-based extract compared to the alcohol-based one.

III. RESEARCH METHODOLOGY

Plant Material

Malaysian Agricultural Research and Development Institute (MARDI) bought the young leaves of Carica papaya L. "Sekaki" tree. The voucher specimen number 007/10 was used to validate a representative sample of this species at the Forest Research Institute Malaysia (FRIM), Kepong. We used a juicer (Panasonic, Shah Alam, Malaysia) to extract the juice from the leaves after collecting them, washing them under running water, and chopping them into tiny pieces. After extracting the juice, it was strained into a glass container and frozen. No water was used throughout the process. A dark green powder was produced by lyophilizing the juice, with a yield of 2.6% w/w. In order to create a chemical fingerprint, phytochemical analysis was performed. Rats' body weight (BW) used as the basis for dosage calculations in the toxicity research. To get concentrations of 0.01, 0.14, and 2 g/kg BW, the powder was dissolved in distilled water to create the test samples.

Animals

This research included male and female Sprague Dawley (SD) rats that were six to seven weeks old and weighed 90 to 100 g. The SD rats came from the Medical Resource Research Center, Laboratory Animal Resource Unit, and Institute for Medical Research (IMR) in Kuala Lumpur. The research was authorized by the Institutional Animal Care and Use Committee (IACUC) (ACUC number ACUC/KKM 02 (1/2009)) for the use of laboratory animals. During the whole experiment, we adhered to the Malaysian Ministry of Health's Guidelines for the Proper Care of Laboratory Animals.

The animals were kept separately in a wire-mesh cage made of stainless steel, measuring 6H × 11D × 16W cm. The temperature was kept at room temperature (27 ± 2°C), the humidity was kept at 65.85 ± 6.76 percent, and there was a 12-hour cycle of natural and artificial light and dark.

A temperature datalogger (TempRH Datalogger BG-DL-01/01B) was used every day to record the room temperature and relative humidity. A cage card was used to identify each animal. Their nutrition consisted of pellets made with irradiated auto wafer feeds from Zeigler Rodent (Zeigler Bros, Pennsylvania, USA) and an endless supply of reverse osmosis water. Before the studies, the animals were kept in the lab for seven days to become used to the environment.

Experimental Design

With minor adjustments, the subchronic toxicity study followed the OECD Guidelines for the "Repeated Dose 90-day Oral Toxicity Study in Rodents," no. 408. Changes were made to the room's humidity and temperature.

Each of the four groups—a control group, three treatment groups, and a fifth group for each sex—consists of twenty rats, twenty males and twenty females, chosen at random. Lyophilized C. papaya leaf juice was diluted in water to the appropriate dose for the treatment group, while water was administered alone to the control group.

Parameters Measured during the Study

- General Observation and Mortality
- Body Weight and Food and Water Consumption
- Hematological and Biochemical Analysis
- Gross Findings and Organ Weights
- Histopathology

Statistical Analysis

The statistical package SPSS, version 14, was used for the data analysis. We used Tukey's HSD for multiple comparisons after doing a one-way analysis of variance (ANOVA) to look for statistically significant differences between the experimental groups. When one or more of the variables did not follow a normal distribution, nonparametric testing was used. The Kruskal-Wallis test was used for pairwise comparison as a nonparametric approach. Statistical significance was determined for results where the p-value was less than 0.05. For every measurable variable, the findings were presented as the mean value (x) with standard deviation (SD).

IV. DATA ANALYSIS AND INTERPRETATION

Hematology and Biochemistry

Table 1.During the subchronic toxicity research, the blood counts of both the control group and the rats treated with C. papaya leaf extract were recorded.

Male rats	**Control**	**0.01 g/kg BW**	**0.14 g/kg BW**	**2 g/kg BW**
WBC (10^3/μL)	4.71 ± 2.03	6.01 ± 2.73	3.69 ± 1.44	6.24 ± 2.42
RBC (106×μL)	7.87 ± 0.41	7.96 ± 0.12	7.88 ± 0.12	8.03 ± 0.26
HGB (g/dL)	16.31 ± 0.48	16.13 ± 0.12	16.27 ± 0.10	16.34 ± 0.62
HCT (%)	40.02 ± 1.43	39.83 ± 1.78	40.11 ± 1.78	39.97 ± 1.75
MCV (fL)	50.74 ± 1.58	49.98 ± 1.12	50.94 ± 1.78	49.79 ± 1.44
MCH (pg)	20.58 ± 0.65	20.24 ± 0.78	20.67 ± 0.12	20.38 ± 0.45
MCHC (g/dL)	40.62 ± 0.49	40.51 ± 0.12	40.58 ± 0.38	40.93 ± 0.12
PLT (10^3/μL)	637.23 ± 100.03	697.88 ± 69.78	563.44 ± 209.12	718.67 ± 111.32
Female rats	**Control**	**0.01 g/kg BW**	**0.14 g/kg BW**	**2 g/kg BW**
WBC (10^3/μL)	2.13 ± 0.78	1.71 ± 0.85	1.65 ± 1.12	3.40 ± 2.21
RBC (106×μL)	7.22 ± 0.42	7.05 ± 0.01	6.89 ± 0.15	6.85 ± 0.54
HGB (g/dL)	15.57 ± 0.75	15.16 ± 0.27	14.61 ± 1.18	14.38 ± 1.15
HCT (%)	37.57 ± 1.25	36.55 ± 0.84	35.45 ± 2.45	34.70 ± 3.18

Male rats	**Control**	**0.01 g/kg BW**	**0.14 g/kg BW**	**2 g/kg BW**
MCV (fL)	52.08 ± 1.72	51.87 ± 0.85	51.45 ± 1.25	50.70 ± 1.70
MCH (pg)	21.59 ± 0.23	21.52 ± 0.35	21.23 ± 0.78	21.04 ± 0.45
MCHC (g/dL)	41.47 ± 0.71	41.49 ± 0.37	41.29 ± 0.59	41.54 ± 0.25
PLT (10^3/μL)	708.40 ± 117.35	681.70 ± 56.13	464.50 ± 272.28	535.00 ± 290.59

Hematological parameters of male and female rats exposed to various dosages of a drug are shown in the table. The white blood cell (WBC) and platelet count (PLT) in male rats were shown to be raised at dosages of 0.01 g/kg BW, 0.14 g/kg BW, and 2 g/kg BW, respectively. There was some variance but no discernible trend in the following parameters: red blood cell counts (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). The substance's effects on white blood cell (WBC) and platelet lysate (PLT) levels were more noticeable in female rats, who showed a dose-dependent reduction in WBC and variable effects on PLT. There were dose-dependent variations in RBC, HGB, HCT, MCV, MCH, and MCHC, suggesting possible hematological abnormalities caused by the substances. The data in the table point to possible gender differences in the substance's effects on rat hematological parameters, which calls for more research into the substance's toxicity and physiological consequences.

Table 2. Results from the subchronic toxicity research measuring the biochemistry of rats treated with C. papaya leaf extract and those in the control group.

Female rats	**Control**	**0.01 g/kg BW**	**0.14 g/kg BW**	**2 g/kg BW**
Liver profile				
Total protein (g/L)	71.80 ± 4.02	71.33 ± 3.75	89.00 ± 18.12*	87.33 ± 6.92*
Albumin (g/L)	44.84 ± 2.02	44.43 ± 2.16	34.92 ± 5.17*	32.58 ± 2.23*
ALP (U/L)	119.20 ± 53.77	169.78 ± 80.11	70.30 ± 51.12	95.78 ± 40.7
AST (U/L)	274.20 ± 47.28	276.78 ± 83.18	268.80 ± 147.1	215.89 ± 72.39
ALT (U/L)	70.80 ± 18.04	85.89 ± 21.12	63.10 ± 33.10	52.33 ± 25.27
Renal profile				
Urea (mmol/L)	9.21 ± 1.42	8.78 ± 1.	7.51 ± 2.10	7.38 ± 2.42
Creatinine (μmol/L)	78.56 ± 10.73	83.56 ± 14.02	69.70 ± 14.08	57.67 ± 8.01*
Uric acid (μmol/L)	277.52 ± 119.1	440.73 ± 185.4	359.33 ± 195.1	247.36 ± 97.78
Cardiac profile				
CK (U/L)	1675.89 ± 364	1514.75 ± 517	1530.30 ± 671.41	1739.11 ± 1163.78
LDH (U/L)	1481.50 ± 871	2265.50 ±52.88	1561.70 ± 593.75	1683.11 ± 668.43
HBDH (U/L)	1027.78 ± 302	867.00 ± 171.1	888.50 ± 123.12	817.25 ± 148.07
Lipid profile				
Cholestrol (mmol/L)	1.62 ± 0.21	1.56 ± 0.2	1.79 ± 0.10	1.57 ± 0.12
Triglycerides (mmol/L)	1.31 ± 0.10	1.47 ± 0.10	1.43 ± 0.72	1.48 ± 0.10
Glucose (mmol/L)	8.88 ± 5.10	15.17 ± 5.10*	9.24 ± 3.78	6.85 ± 1.12
Male rats	**Control**	**0.01 g/kg BW**	**0.14 g/kg BW**	**2 g/kg BW**
Liver profile				

Total protein (g/L)	57.22 ± 2.33	59.13 ± 4.57	59.11 ± 5.37	60.89 ± 8.81
Albumin (g/L)	27.51 ± 2.12	28.60 ± 2.69	32.32 ± 2.91*	29.67 ± 1.57
ALP (U/L)	147.38 ± 33.12	173.13 ± 61.36	192.89 ± 60.88	218.22 ± 98.34
AST (U/L)	186.38 ± 28.75	166.63 ± 41.10	169.67 ± 37.35	158.22 ± 39.25
ALT (U/L)	49.50 ± 8.12	46.75 ± 7.10	61.22 ± 23.36	60.78 ± 29.28
Renal profile				
Urea (mmol/L)	6.75 ± 0.15	6.14 ± 1.21	6.73 ± 0.86	5.73 ± 1.11
Creatinine (μmol/L)	56.25 ± 8.77	51.75 ± 7.31	49.89 ± 8.01	40.33 ± 16.83*
Uric acid (μmol/L)	117.23 ± 50.12	81.53 ± 25.50	161.33 ± 98.82	95.80 ± 43.21
Cardiac profile				
CK (U/L)	1408.250 ± 534.19	1187.25 ± 208.45	1589.11 ± 588.35	1448.78 ± 478.48
LDH (U/L)	2014.67 ± 500.86	2187.38 ± 875.36	2706.00 ± 645.58	2952.78 ± 259.68*
HBDH (U/L)	648.33 ± 119.29	612.63 ± 199.59	648.00 ± 161.36	589.00 ± 106.47
Lipid profile				
Cholesterols (mmol/L)	1.39 ± 1.81	1.12 ± 0.35	1.21 ± 0.12	1.27 ± 0.12
Triglycerides (mmol/L)	0.97 ± 0.15	0.80 ± 0.03	1.27 ± 0.11	1.26 ± 0.12
Glucose (mmol/L)	7.97 ± 2.78	6.96 ± 2.01	10.31 ± 5.74	7.68 ± 2.24

Male and female rats' lipid, renal, cardiac, and liver profiles were examined at different dosages, as shown in the table. Significant changes in liver function, as seen by increased total protein and decreased albumin levels, occurred in female rats when dosages were increased. Even at the maximum dosage, renal markers like creatinine and uric acid levels dropped, which might indicate that your kidneys are getting better. Even at the maximum dosage, the heart profile showed elevated lactate dehydrogenase (LDH) levels. Elevated glucose levels were one of the lipid profile abnormalities seen at the intermediate dosage. Liver function in male rats was rather constant, with the exception of albumin, which increased with increasing doses. Even at the maximum dosage, renal function tests showed that creatinine levels were dropping. At the maximum dosage, cardiac indicators, especially LDH, rose sharply. At the lowest dosage, lipid profiles showed a tendency toward lower cholesterol levels among others. The results indicate that the chemical may have different effects on the sexes, which calls for more research into how it affects the rat metabolic processes and organ function.

V. CONCLUSION

Important for determining if Carica papaya leaf extract is safe for possible medicinal uses is the subchronic toxicity evaluation. Researchers may provide useful insights into the possible detrimental consequences of extended exposure via doing sophisticated dose-response analyses and using robust experimental designs. A thorough comprehension of the subchronic toxicity profile of this natural extract will help with both regulatory considerations and the prudent and educated incorporation of it into healthcare practices as scientists work to uncover its therapeutic potential. Investigating this further not only adds to our general knowledge of the safety of natural goods, but also highlights the need of thorough study in using botanical resources for human health.

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