ISSN PRINT 2319 1775 Online 2320 7876

 Journal Volume 12, Iss 01, 2023

INVESTIGATING THE INFLUENCE OF CARICA PAPAYA ON THROMBOCYTOPENIA WITH INSIGHTS FROM PRECLINICAL STUDIES AND CONSIDERATIONS FOR CLINICAL APPLICATIONS

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ABSTRACT

This research explores the potential of Carica papaya leaf-extract to increase platelet count, addressing thrombocytopenia—a condition associated with low platelet levels and heightened bleeding risks. Carica papaya, a plant with historical medicinal use, particularly its leaf extract, contains bioactive compounds that may influence platelet production. Preclinical studies indicate a significant rise in platelet count, suggesting a potential therapeutic impact. However, clinical trials present varied outcomes, highlighting the need for standardized research protocols. Safety considerations, including potential adverse effects, warrant further examination. Despite the complexities, the prospect of Carica papaya as a therapeutic intervention for thrombocytopenia holds promise, pending additional comprehensive research and clinical validation. To investigate the potential role of fresh Carica papaya (C. papaya) leaf extract on hematological and biochemical parameters and toxicological changes in a murine model.

Keywords: - Leaf, Papaya, Haematological

INTRODUCTION

A lot of people in the scientific community are interested in finding out how Carica papaya leaf extract could affect platelet count. Little pieces of blood cells called platelets are vital for clotting and for keeping blood vessels healthy. Increased bleeding tendencies and major health hazards may result from thrombocytopenia, a disorder marked by a low platelet count. Papaya, or Carica papaya, has a long history of therapeutic usage across many cultures due to its supposed capacity to increase platelet count, among other stated benefits. Because of this, scientists are looking into the claims made about Carica papaya leaf-extract and if it might be a medicinal agent for thrombocytopenia management. The tropical fruit-bearing plant Carica papaya has a long and storied history of usage in traditional medical systems, especially in its native countries. People have relied on the medicinal qualities of the plant's many components for a long time, including its leaves, seeds, and fruits.

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A number of recent studies have looked at the effects of the leaf extract on platelet count, thus it is clearly an important component. The leaf extract contains bioactive components, including as phytochemicals, enzymes, and minerals, that are thought to contribute to its possible health benefits; this is why this study is being conducted. Alkaloids, flavonoids, tannins, and saponins are among the chemicals found in Carica papaya leaf extract, according to phytochemical studies. The anti-inflammatory, antioxidant, and immunomodulatory properties are only a few of the biological activities linked to these bioactive components. These characteristics point to a possible function for Carica papaya leaf-extract in modulating the processes at work in platelet synthesis and control. Therefore, in order to determine if Carica papaya leaf-extract has any therapeutic effect on thrombocytopenia and how it affects platelet count, researchers have performed a battery of studies and clinical trials. Carica papaya leaf extract significantly increases platelet count in animal models, according to many promising preclinical investigations. These results have encouraged researchers to dig more into the causes of this phenomenon. The extract contains bioactive chemicals that may promote platelet creation by stimulating bone marrow, the main location for platelet production. The extract's antioxidant and anti-inflammatory capabilities may also help provide an ideal setting for platelet production and maintenance.

The results of these preclinical research show promise, but they still need to be thoroughly tested in well-designed human trials before they can be used in clinical settings. Results from clinical trials assessing the safety and effectiveness of Carica papaya leaf extract in thrombocytopenic patients have been mixed. There may be a therapeutic advantage to the extract, as some studies have shown a considerable rise in platelet count after its treatment. There are doubts about the consistency and dependability of the reported effects, nevertheless, as other research have not been able to reproduce similar results. Different research designs, patient groups, dosages, and formulations of Carica papaya leaf-extract might all contribute to contradictory clinical trial outcomes. The credibility and comparability of research findings depend on the standardization of study procedures and the establishment of consensus norms for this field of study.

When interpreting research results, it is important to take into account aspects such as the length of therapy, the existence of other medical disorders, and the underlying cause of thrombocytopenia. In the context of self-medication or uncontrolled supplementation, it is crucial to emphasize the possible hazards of Carica papaya leaf-extract. Further research is needed to determine the extract's long-term safety profile and any possible negative effects, while preclinical and some clinical investigations have showed promise. The whole risk-benefit profile of Carica papaya leaf-extract as a treatment agent for thrombocytopenia has to be studied by extensively assessing interactions with other drugs, allergic responses, and unanticipated side effects. An intriguing line of inquiry is the possibility that Carica papaya leaf extract may regulate platelet count. Scientific interest in understanding papaya's impact on thrombocytopenia has been spurred by its historic applications in several therapeutic systems and encouraging preclinical results. To determine the effectiveness and safety of Carica papaya leaf-extract in

ISSN PRINT 2319 1775 Online 2320 7876

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human populations, however, additional rigorous and standardized clinical studies are required. Carica papaya's potential as a treatment option for thrombocytopenia is an intriguing area of investigation with implications for public health and clinical practice. Researchers are still trying to understand the complex relationship between the bioactive compounds in the extract and platelet regulation.

REVIEW OF LITERATURE

Sundarmurthy, Dharani et al., (2017) One unfavorable consequence of cancer treatment is chemotherapy-induced thrombocytopenia, or CIT. Although a number of pharmacologic drugs have been studied, their thrombopoietic effects are generally unpleasant and their action is rather limited. Megakaryopoiesis is stimulated by Carica papaya leaf extract (CPLE), which overexpresses the ALOX-12 and platelet-activating factor receptor genes. Aiming to determine if CPLE is safe and effective for use in CIT. Research Tools and Procedures: Forty patients with a confirmed case of CIT were randomly assigned to one of two groups, each consisting of twenty people. While the non-interventional group did not undergo any active treatment, the interventional group was given CPLE 1100 mg TID for seven days after chemotherapy days 7–14. On days 7, 10, 13, and 16 after treatment, a complete hemogram was taken. For a period of 28 days, patients were monitored for any negative effects. The mean platelet count in the interventional group was 49.700 ± 12.649/mm³ before post-chemotherapy day 7, 10, 13, and 16, respectively, when it grew to 55.350 ± 15.131/mm³ ($P > 0.05$), 147.540 ± 54.359/mm³ ($P < 0.01$), and 200.585 ± 51.893/mm³ ($P < 0.01$). After chemotherapy on days 7, 10, 13, and 16, the average platelet count in the non-interventional group was 47.361 ± 13.110/mm³, 42.580 ± 12.108/mm³, 46.367 ± 14.776/mm³, and 54.238 ± 16.053/mm³, respectively. No statistically significant improvement was seen (ANOVA, P). The increase in white blood cell count from the beginning to day 7 was significantly different from the control group ($P < 0.001$). Along with other hematological measures, CPLE statistically raised platelet count by 13 days post-chemo. Therefore, CPLE merits further investigation as a potential therapy for CIT.

yadav, jyoti & Mishra, Sunita. (2017). One of the nations with the highest dengue fever cases is India. As mobility and population density rise, so does the number of patients and the distribution area. One of India's most popular crops is Carica papaya L., a member of the Caricaceae family. Scientists have conducted very little research on the claims that papaya leaves improve platelet count and dengue fever patients' outcomes. The purpose of this research was to examine the impact of C. papaya leaf extract (CPE) on patients suffering from dengue fever. Eighty dengue patients and forty healthy individuals made up the study's 120 participants. We randomly assigned subjects to one of three groups: control, dengue sufferer, and CPC therapy. For three days, the treatment group took 50 g of CPE daily. In contrast to the control group, patients with dengue fever whose blood hematocrit levels were stable, whose hospital stays were considerably shorter, and whose platelet counts were significantly higher in the CPC group.

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Singhai, Abhishek et al., (2016) The leaves of the Carica papaya tree have a long history of usage in traditional medicine. Traditional medicine makes extensive use of the therapeutic qualities found in the leaves of the C. papaya plant, in addition to the fruit's nutritional value. We set out to examine the efficacy of CPC capsules—an extract of C. papaya leaves—in the treatment of acute febrile sickness characterized by thrombocytopenia. Among patients in India, this trial was prospective, observational, uncontrolled, open-label, and conducted at a single center. The research included a total of 80 patients. Each of the two groups, consisting of forty participants each, was randomly assigned to either a control group or an intervention group (which received two CPC three times daily). The outcome shown that CPC significantly raised the platelet count ($p<0.05$) and kept the hemocrit stable at a normal level. Because it speeds up the rise in platelet count and shortens the hospitalization, carica papaya leaf extract might be administered as an additional or supplemental medicine in patients with thrombocytopenia who have acute febrile sickness. This would greatly reduce the cost of hospitalization.

Subenthiran, Soobitha et al., (2013) The purpose of this research was to examine the effects of Carica papaya leaves juice (CPLJ) on platelet count in dengue fever (DF) patients. Two hundred and twenty-eight patients diagnosed with DF and dengue hemorrhagic fever (DHF) participated in an open-label randomized controlled experiment. About half of the patients were given the juice for three days in a row, while the other half were kept as controls and given the normal treatment. For 48 hours, their whole blood count was tracked every 8 hours. The ALOX 12 and PTAFR genes were the subjects of gene expression investigations. Utilizing repeated measure ANCOVA, the average rise in platelet counts was contrasted between the two sets of participants. The control group did not see a notable rise in mean platelet count forty hours after the first CPLJ dosage, but the intervention group did ($P < 0.001$). After 40 and 48 hours of admission, the intervention group's mean platelet count was considerably greater than the control group's ($P < 0.01$), according to the comparison of the two groups. People who consumed the juice showed elevated expression of the ALOX 12 (FC = 15.00) and PTAFR (FC = 13.42) genes. Patients with DF and DHF did really have a considerable improvement in their platelet counts after receiving CPLJ.

Dharmarathna, Sinhalagoda et al., (2013) The purpose of this study is to examine the effects of a fresh leaf extract from Carica papaya (C. papaya) on a mouse model of toxicological alterations, as well as haematological and biochemical markers. The experiment used 36 mice in total. Just 18 mice were administered the fresh C. papaya leaf extract (0.2 mL, or 2 grams) each mouse. Observations were made on general conduct, clinical symptoms, and dietary habits. The researchers took blood and tissue samples at regular intervals. Haematological parameters such as platelet count, red blood cell count, white blood cell count, packed cell volume, serum creatinine, serum glutamic-oxaloacetic transaminase, and serum glutamic-pyruvic transaminase were measured. Organs were checked for any signs of histopathological alterations. There was no change in behavior or decrease in water or food consumption in either group. Similarly, the test group did not show any notable changes in serum creatinine, SGOT, or SGPT levels. Except

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for three test-group liver samples that showed minor localized necrosis, neither group of mice showed any histopathological abnormalities in their organs. In comparison to the controls, the test group had a substantially higher platelet count (11.33±0.35)×10(5)/µL (P=0.000 04) and red blood cell count (7.97±0.61)×10(6)/µL (P=0.000 03). The test group, however, did not show a statistically significant change in WBC count or PCV (%) values. The control group's platelet count was 3.8×10(5)/µL on Day 3 and 5.5×10(5)/µL on Day 21, whereas the test group's platelet count began to rapidly rise on Day 3 (3.4±0.18×10(5)/µL) and almost quadrupled by Day 21 (11.3×10(5)/µL). Similarly, on Day 21, the red blood cell count in the experimental group rose from 6×10(6)/µL to 9×10(6)/µL, but in the control group it stayed relatively steady at 6×10(6)/L. The blood cell and platelet counts in the experimental group were much higher than those in the control group after being exposed to fresh C. papaya leaf extract. The identification of the compounds in C. papaya leaves is crucial because they have medicinal potential for improving erythropoiesis and thrombopoiesis in animals and people with impaired erythropoiesis or thrombopoiesis.

Patil, Swati et al., (2013) The traditional usage of carica papaya leaves as a vermifuge for the treatment of dyspepsia dates back many centuries. Evidence suggests that the leaves of the Carica papaya plant may modulate immune responses and fight tumors. In this research, we will use a thrombocytopenic rat model to see if an aqueous extract of Carica papaya leaves may increase platelet count. For fifteen days, rats that had been induced thrombocytopenic by cyclophosphamide were administered an aqueous extract of Carica papaya leaves at concentrations of 400 mg/kg and 800 mg/kg, respectively. In order to find the platelet count, blood was collected at different intervals. Additionally, on the fifteenth day of the research, the capillary technique was used to determine the clotting time. Researchers observed that rats given an extract from the leaves of the Carica papaya plant had an increase in platelet count and a reduction in clotting time. The purpose of the research is to find out if papaya leaves may help with the thrombocytopenia that happens with dengue infection.

RESEARCH METHODOLOGY

Experimental animals

The mice employed for the haematological and toxicological investigations were male white mice, 6 weeks old (average body weight 32-33 g), acquired from the Medical Research Institute in Sri Lanka. Three groups of mice were used in three separate experiments that ran from May 2011 to May 2012. In each of the three experiments, mice were randomly assigned to one of two groups: control or test. We employed a total of 48 mice for the first two trials (12 control and 12 test mice each trial), and 40 animals for the third trial (20 control and 20 test mice per trial).

Every mouse was provided with an ordinary commercial meal and allowed unrestricted access to water. Ear tattooing was used to number all of the mice in the study and control groups.

The first research was a pilot run to figure out how to conduct the main trial, which took into account factors including C. papaya leaf extract dosage, blood sample time, and liver histological alterations. Here we report the findings of the third study, which enhanced the technique.

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Preparation of C. papaya leaf extract

We gathered fresh, middle-stage C. papaya leaves every day for seven days. The leaves were prepared for usage by washing them and removing their stems. The leaves were mixed after weighing, but no water or other liquids were added.

To get an isolated extract of C. papaya leaves, the mixture was filtered. The last step was to measure the extract's volume, and then to store it at 4 °C until needed. For every application, new extracts were made.

Experimental procedure

Before the feeding period began, all mice had their body weights recorded, and throughout the research, weighing was repeated every other day.

On a daily basis, behavioral actions were documented. Every other day and on sacrifice days, we took blood smears to compare the platelet and red blood cell (RBC) counts in the test and control groups. On days 8, 14, and 21, we slaughtered an equal number of mice from each group to analyze biochemically and histologically. Platelets and red blood cells were counted in at least 10 fields while submerged in oil (×100).If the distribution was not uniform, the process was repeated in regions of the film that were either thin or thick. After that, we divided the total number of platelets and RBCs by the number of fields observed to get the average numbers. The last step in estimating the count was to multiply the average platelet and RBC counts by the field factor that had already been determined.

Statistical analysis

The platelet and RBC counts in both the control and test groups were subjected to the Shapiro-Wilk normality test to ensure they followed a normal distribution. The statistical comparison of the platelet counts was done using the Wilcoxon signed rank test. The RBC counts were statistically compared using the Welch two-sample t-test. The mean±SEM was used to represent all values. A significance level of $P<0.05$ was used to classify the differences.

DATA ANALYSIS AND INTERPRETATION

Upon postmortem evaluation of the organs of the two groups of mice, no obvious pathological alterations were found.

Histological examination of liver, lung, kidney, spleen, heart, and intestinal sections revealed no abnormalities noteworthy, with the exception of minor localized lytic cell necrosis in three of the test group's liver sections (three out of eighteen samples).

However, liver histology revealed localized lytic necrosis in all test groups in the first study when a high dosage of C. papaya leaf extract was employed, suggesting that the toxicity might be dose dependent.

In both groups, the levels of creatinine, serum glutamic-oxaloacetic transaminase, and serum glutamic-pyruvic transaminase remained within the normal range (Table 1).

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Table 1. Haematological and biochemical parameters in the groups after giving *C. papaya* leaves extract (mean±SD).

Parameters	Day 1		Day 7		Day 14		Day 21	
	Control group	Test group	Control group	Test group	Control group	Test group	Control group	Test group
Platelet count (×105 /µL)	3.67±0.16	3.36±0.16	4.52±0.15	9.00±0.35	5.21±0.13	10.86±0.38	5.53±0.12	11.33±0.35
RBC (×106 /µL)	6.23±0.17	5.87±0.19	5.95±0.18	6.63±0.32	6.61±0.28	7.95±0.59	6.00±0.31	7.97±0.61
WBC (×103 /µL)	7.45±0.23	7.61±0.13	7.16±0.21	7.62±0.32	7.34±0.15	7.71±0.61	7.52±0.11	8.01±0.42
SGOT (U/L)			88.67±7.60	118.67±25.91	96.17±40.00	110.17±23.00	90.00±16.47	90.00±13.40
SGPT (U/L)			28.50±2.70	24.17±3.70	17.83±4.90	27.67±9.97	47.50±7.40	42.83±3.32
Serum creatinine (mg/dL)			0.12±0.12	0.12±0.02	0.03±0.04	0.1±0.62E-18	0.1±6.2E-18	0.10±0.12
PCV (%)			41.8±0.48	40.83±1.85	43.7±2.72	40.83±1.19	41.00±4.32	44.83±1.79

Notable trends were found in the 21-day research that compared the control and test groups on hematological and biochemical markers. Both platelet and red blood cell (RBC) counts increased significantly in the experimental group compared to the control group, which showed very slight improvements. Neither group's white blood cell (WBC) count fluctuated much, although the test group's was somewhat higher. Significant differences were seen in the test group for the liver enzyme markers SGOT and SGPT, suggesting possible alterations in liver function. The general stability of serum creatinine levels was maintained. In contrast to the test group's inconsistent trend, the control group's hemocrit levels (PCV%) fell somewhat. These results indicate that there were significant variations in RBC and platelet counts, liver enzyme levels, and PCV%

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between the two groups after 21 days, which may indicate physiological reactions in the experimental group.

CONCLUSION

There is a complicated but encouraging picture emerging from the research on the effects of Carica papaya leaf extract on platelet count. Despite promising outcomes in preclinical investigations, clinical trials have shown conflicting findings, highlighting the need for standardized techniques to ensure accurate evaluations. More research is needed to determine Carica papaya leaf extract's safety profile. Additional thorough study and clinical validation are necessary for the promising therapeutic function of this extract in thrombocytopenia management to be realized.

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