Nutritional and bioactive profile of different parts of *Carica papaya* L. in relation to thrombocytopenia

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**ABSTRACT**

The aim of the present study was to elucidate the effect of different parts (fruit, leaves, and seed) of papaya on thrombocytopenia. For the Purpose, the papaya fruit, leaves, and seeds were procured from Botanical Garden of University of Agriculture Faisalabad. Afterwards, the papaya fruit, leaves, and seeds were converted to powder followed by extraction of polyphenol with various solvents (aqueous ethanol and methanol). The obtained extracts were characterized for total flavonoid contents, polyphenols as well as anti, nutritional compounds, such as tannins and saponins. Moreover, efficacy trials were carried out to explore the effect of papaya parts (fruit, leaves, and seed) on the platelets count of potassium bromate-induced (PBI) rats. The PBI rats were fed with extract enriched diet for a time period of 56 days. Results showed that maximum extraction was obtained with ethanol. In addition, a higher bioactive profile (polyphenols) was observed in papaya leaves extract followed by fruit and seed extracts. Papaya leaves extract (PLE) treatment showed a maximum increase in platelets count from 169.9 ± 2.1 × 10\(^3\)/L to 231.1 ± 6.1 × 10\(^3\)/L in PBI rats as well as WBCs and RBCs 521 ± 16.8 × 10\(^3\)/L to 594.5 ± 11.2 × 10\(^3\)/L and 469.2 ± 13.2 × 10\(^3\)/L to 562.2 ± 14.2 × 10\(^3\)/L. But for hemoglobin, the papaya fruit extract treatment showed a higher value of 6.4 ± 0.1 to 7.4 ± 0.2 (mg/dL). Conclusively, papaya leaves should be included in dietary regimens for health promotion to combat thrombocytopenia and related diseases.

**Introduction**

Therapeutic plants are a rich wellspring of bioactive phytochemicals. Phytochemicals present in various pieces of the plant, for example, in the roots, stems, leaves, seeds, and fruits. Phytochemicals are named essential or optional constituents, contingent upon their role in plant metabolism. Essential constituents consist of the normal sugars, amino acids, proteins, purines, pyrimidines, nucleic acids, and chlorophylls. Optional constituents are the leftover plant synthetic substances like alkaloids, terpenes, flavonoids, lignans, plant steroids, saponins, phenolics, flavonoids, and glucosides.\(^1\)

In this subcontinent, Malaysia could successfully control its rates and demise of patients utilizing elective prescription treatment principally ready from different parts of Carica papaya L. alongside legitimate consideration and hospitalization. Papaya leaves, their juice or concentrate, just as their various types of readiness have for quite some time been utilized customarily for treating dengue fever and its inconveniences to save patients’ lives. Despite the fact that it is suggested by conventional healers, and the overall population use Papaya leaves juice or their different arrangements in dengue fever.\(^2\)

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The most up and coming outbreak and contagious viral disease of human being is Dengue Fever,\(^1\) which causes major disturbance in global public health. Dengue fever is very common across the world specially in tropical and subtropical countries. It is most common in few countries (Africa, Middle East Caribbean, India, and China). It is recently estimate that Pakistan stands 12th overall in world with 0.27 million cases along with 5865 deaths till July 28, 2020.\(^{[3,4]}\) Dengue virus is transmitted to humans by the female Aedes mosquito (Aedes aegypti). From 2014 to 2020, Pakistan has reported 99,264 confirmed cases in almost all four major provinces of the country. Epidemiological data from last five years indicate that Pakistan has experienced major outbreaks from July to December with peak onset observed in October.\(^{[3,5]}\) The carrier mosquito spreads and gets dengue virus by biting infected individuals.\(^{[6]}\) There are four stereotypes of dengue virus named DEN-1, DEN-2, DEN-3, and DEN-4 coined about some 1000 years ago.\(^{[7]}\)

Dengue fever is generally described by typical fever (about 103°F to 104°F), rashes on skin, ordinary pain (e.g., headache) and the most often muscular and joints pain, prostration, and lymphadenopathy. Oxidizing plasma protein and lowering sialic acid concentration can cause the oxidative stress in body.\(^{[8]}\) Classically, dengue fever though primarily occurs in non-indigenous individuals having less immunity level. It may cause illness in the case of those (e.g., children and adults) who are more prone to immune system disturbances even by little stimulation. The first and principal symptoms of dengue fever may appear in approximately 5–7 days of infection with the virus. However, in its postcomplications, dengue fever can lead toward several deficiency symptoms and other related complexities. The deficiency of vitamin A leads to immune system malfunctioning,\(^{[9,10]}\) while that of vitamin B12 causes abnormalities in central nervous system (CNS), which may upsurge the complexity,\(^{[11]}\) and immune system is destroyed, severely leading to other problems. There are also probabilities of mild-to-severe hepatitis on infection with dengue virus.\(^{[12]}\)

In fruits, the therapeutic approach can decrease inflammation, oxidation, and related complexities. Synergistic advantages are provided by them with no side effects. The utilization of vitamin C-rich fruit is increased day by day and interlinked with a reduced hazard of various ailments and neurological disorders.\(^{[13]}\) These possible advantages are described in the presence of enough amount of antioxidant substances such as carotenoids, vitamin E, vitamins C, and polyphenolic substances.\(^{[14,15]}\)

Phenolic acids are vastly dispersed in plants. Many of these are an essential part of diet. They can also be engaged as active ingredients during preparation of medicines. The health claims of photochemical investigation of different parts Papaya are due to their broader range of qualities, for example, alkaloids, saponin, tannin, flavonoid, and glycosides, and hence have therapeutic properties like antibacterial, anti-inflammatory, antiviral, hypoglycemic antitumor, and many others.\(^{[16,17]}\)

In the case of serious hemorrhagic manifestation, therapeutic platelets transfusions are employed to manage thrombocytopenia. Many reports of natural remedies to cure thrombocytopenia in dengue was observed. In most of the countries, oral administration of extract of different parts Carica Papaya was used as a natural remedy against dengue fever with thrombocytopenia. These extracts show erythrocyte stabilization potential that prevents the hemolysis and directly exerts the action on platelets. Keeping in view the bioactive and nutraceutical profile of different parts, Carica papaya extract, the present study was planned to address the thrombocytopenia in relation to dengue fever.

*Carica papaya* is an evergreen, giant herbaceous tree of the Caricaceae (papaya) family with origin in Central America. It is now grown in tropical areas worldwide for its large, sweet, melon-like fruits. Different parts of papaya plant, viz., fruit, bark, roots, seeds, peel, pulp, and leaf, have many known therapeutic uses around the world.\(^{[17]}\) There are many commercial products derived from different parts of the *C. papaya* plant, with the most prominent being papain and chymopapain, which is produced from the latex of the young fruits, stem, and the leaves. *C. papaya* leaves have been used in folk medicine for centuries. Shallow cuts on the surface of fully grown but unripe fruits cause a milky sap or latex to ooze that is collected, dried, and termed “crude papain.” Considering the above-mentioned facts and figures, the present study was designed to explore the nutraceutical and therapeutic worth of papaya leaf, fruit, and seed extracts against dengue fever.
Materials and methods

**Purchasing of raw materials**

Chemicals and standards (HPLC) were procured from Sigma-Aldrich. *Carica papaya* leaf, seed, and fruit were obtained from Botanical Garden of University of Agriculture Faisalabad. The featured kits used for various analyses were also obtained from Sigma-Aldrich.

**Preparation of sample**

Preparation of papaya fruit, leave, and seed was carried out as described in Ref. \(^\text{18}\) with slight modification. Initially, the papaya fruit was cleaned by water and peeled. After that, pulp was sliced into lesser parts and dried through sunlight. After drying, the pulp was ground well using mechanical blender into fine powder and transferred into an air-tight container with proper labeling for further studies.

For leaves, the collected leaves were cleaned, washed with water, and dried for 15 days under shade and at room temperature. Leaves were grounded into powdered and preserved in clean plastic containers, away from light, heat, and moisture until further studies. Seeds were washed followed by drying. At that point, seeds were dried at room temperature for about fourteen days and dried seeds were pounded into fine powder by utilizing a household electric blender and stuffed into little plastic envelopes.

**Preparation of papaya fruit, leaves, and seed extract**

Extraction of bioactive compounds was carried out as described by Thakor *et al.*\(^\text{19}\) Purposely, papaya fruit leaves and seed extract were prepared by hydroalcoholic solvent. A volumetric flask containing 50 gm of sample was filled with 250 ml of solvent. Later on, the volumetric flask containing sample were kept in an orbital shaker for 30 min. Cellulose filter paper was used to filter the all leftover. A Rotary Evaporator at a temperature of 45°C for time 3 hours under controlled pressure was used to evaporate the filtrate from the solvent. Sealed bottles were used to store the extracts for further analysis. \(^\text{20}\)

**Phytochemical analysis of Papaya fruit leaves and seed extract**

Papaya fruit, seeds, and leaves extracts were analyzed qualitatively as well as quantitatively by using methods reported by Ref. \(^\text{18}\)

**Chromatographic analysis**

The ethanolic extracts of papaya fruit, leaves, and seed were found to have total flavonoids. HPLC was used for further quantification of flavonoids in the extracts by the method reported by Ghaffar *et al.*\(^\text{21}\)

**Bioefficacy study**

Male rats were procured from the University of Agriculture, Faisalabad, Pakistan, for bioefficacy trials. All the rats were acclimatized. The recent research was bringing out on 70 Sprague Dawley rats. During experiment of rodent feed, global guidelines for laboratory animals were used. At the starting point, the baseline values were obtained by sacrificing some rats. Two parallel studies carried out, Study I and Study II, consist of thrombocytopenic and normal rats. In current experiment, the rats were divided into four groups based on treatment. The control group was fed on control diet, while three of them gave experimental diet containing papaya fruit, leaves, and seed extract, respectively. In
Study I, rats were fed on basal diet to familiarize with the environment. After that, experimental diet consisted of normal diet: 80% (corn-flour), casein (4%), 10% (Corn oil), mineral mixed (2.5%), and mixed vitamins (1%) and by adding of papaya fruit, leave, and seed extract for 60 days. In Study II, at the 1st week, normal diet (flour 80%), 10% (Corn oil), casein (4%), mixed minerals (2.5%), and mixed vitamins (1%) was provided to the rats to familiarize them to the environment. In order to decrease the platelets (thrombocytopenic), the rats were given 83 mg/kg of KBrO3 body weight. The obtained values were considered as the initial platelets count. In conclusion, the nighttime starved rats were sacrificed to analyze the impacts of particular treatments on the selected parameters, i.e., platelet count, hemoglobin levels, white blood cells, and red blood cells.

**Hematological analysis**

Anticoagulant containers were used for the collection of blood samples of all treated rats for hematological studies reported by Cheesbrough. As collected blood samples were analyzed for Platelet’s count, White Blood Cells, Red Blood cells, and Hemoglobin.

**Data analysis**

The data obtained for each parameter were subjected to statistical design and subsequently the statistical procedures. ANOVA and DMR applied to sample results to analyze the difference between the diets by using SPSS 17.

**Results and Discussion**

**Phytochemical assessment of Papaya fruit, leaves, and seed extract**

Papaya (*Carica papaya*) fruit is famous all over the world due to its highly nutritious and medicinal point of view. Scientific research proved that papaya-rich diet has a great number of benefits for health. Papaya seeds, leaves, and fruits are a rich source of different bioactive compounds. Different parts of papaya (leaves, seeds, roots, stem, and fruits) have been reported as an alternative source of medicine. The stem and roots are being used for glucose lowering effect, and anti-inflammatory agents and leaves are being used as a covering for septic wounds. The screening of phytochemicals of fruit, leaves, and seeds of *Carica papaya* is shown in **Table 1**. The results indicate that flavonoids and polyphenols was present in all types of extracts, while tannin was only present in leaves and seed extract. Additionally, saponins were only reported in fruit and seed extracts. The same results were observed by Khadam et al. who conduct the study on different parts of *Carica papaya*. As far as the

| Extracts     | Phytochemical analyzed in samples |
|--------------|-----------------------------------|
|              | Flavonoids | Polyphenols | Tannins | Saponins |
| Leaves       |            |             |         |          |
| extract      |            |             |         |          |
| Ethanol      | +          | +           | +       | -        |
| Methanol     | +          | +           | +       | -        |
| Aqueous      | +          | +           | +       | +        |
| Fruits       |            |             |         |          |
| extract      |            |             |         |          |
| Ethanol      | +          | +           | -       | +        |
| Methanol     | +          | +           | -       | +        |
| Aqueous      | +          | +           | -       | +        |
| Seed         |            |             |         |          |
| extract      |            |             |         |          |
| Ethanol      | +          | +           | -       | +        |
| Methanol     | +          | +           | +       | -        |
| Aqueous      | +          | +           | +       | +        |

(Detected (+); Not Detected (-))
quantitative analysis for phytochemical is concerned. It can be shown in Table 2 that the highest flavonoids were found in leaves (48.23 ± 2.14) followed by fruit (47.94 ± 1.30) and seed (41.62 ± 1.39). Flavonoid content in this study was found to be higher than that reported previously by Ref. 18. Additionally, ethanolic extraction showed a higher yield compared to others. The results regarding polyphenols indicated the same trend. The highest were present in leaves (46.17 ± 2.13) followed by fruit (45.28 ± 1.20) and seed (38.63 ± 2.29). The results of the present study regarding phytonutrients obtained were comparable with results reported earlier by different authors. The results are also in line with the experiment study by Khadam et al., 18 who reported that Carica papaya leaves are rich source of phytochemicals.

**Hematological investigation**

During this research, as demonstrated by the biochemical tests, no adverse outcomes were observed in the experimental models. Hereafter, interventions to find out detrimental and beneficial effects of papaya fruit, leaves, and seed extracts the whole experimental period, the animals kept on healthy, which are included or present in papaya fruit, leaves, and seed among experimental animals, will provide a basis for further exploration in this prospect.

**Platelet count**

The statistical analysis of extract-enriched diet showed a significant increase in platelets of treated rats. The recorded values regarding platelet counts for both (normal and treated rats) are shown in Table 1. The results showed that after an interval of 56 days, a significant increase in platelets was observed in study II from 164.1 ± 3.2 to 223.9 ± 6.7 × 10^9, 167.5 ± 2.7 to 218.2 ± 5.4 × 10^9, and 169.9 ± 2.1 to 231.1 ± 6.1 × 10^9 for PFE, PSE, and PLE, respectively. It was seen that the platelet count raised with that sequence PLE>PFE>PSE, respectively. The results are in line with the experimental study of Khadam et al., 18 who reported that papaya leaves extract significantly increased the platelet contents as compared to papaya fruit and seed extracts.

**White blood cells**

White Blood cells play a vital role in the immune system of the body. Time and treatment showed a significant effect on WBC of the treated and normal rats shown in Table 2. The results showed that after an interval of 56 days, a significant enhancement was detected in study II from 511 ± 14.8 to 591 ± 13.2 × 10^7, 517 ± 12.2 to 579 ± 14.9 × 10^7, and 521 ± 16.8 to 594.5 ± 11.2 × 10^7 for PFE, PSE, and PLE, respectively. Furthermore, PFE enhanced the WBC count to 9.52 and 15.07% in both (normal and treated rats), respectively. However, PSE enhanced the white blood cells count to 7.08 and 10.90% in both (normal and treated rats) and for PLE, the WBC count raised to 8.03 to 11.3%, respectively. The same results were observed in the study by Veronika Buxhofer-Ausch et al., 26 who worked on the different parts of Carica papaya that the papaya leaves extract was helpful in increasing in WBCs.
Table 3. Influence of diet and time intervals on platelets (×10^9) of rat.

| Studies  | Diet   | Study Days Interval |
|----------|--------|---------------------|
|          |        | 0       | 30       | 60       |
| Study I  | Control| 342.5 ± 5.9 | 346 ± 3.2 | 349.9 ± 4.2 |
|          | PFE    | 359 ± 6.2  | 362.8 ± 7.2 | 375 ± 5.7* |
|          | PSE    | 369.5 ± 10.9 | 372 ± 4.8 | 365.5 ± 6.9 |
|          | PLE    | 375 ± 8.2  | 377.2 ± 7.2 | 379.1 ± 8.1** |
| Study II | Control| 351 ± 7.2  | 353 ± 8.1  | 358.6 ± 4.2 |
|          | PFE    | 164.1 ± 3.2 | 192 ± 3.9  | 223.9 ± 6.7* |
|          | PSE    | 167.5 ± 2.7 | 199 ± 4.8  | 218.2 ± 5.4 |
|          | PLE    | 169.9 ± 2.1 | 201.4 ± 5.6 | 231.1 ± 6.1** |

*Mean ± S.D (n = 10 in each group), *p < 0.05; **p < 0.01) between the means of different diets (control, PFE, PLE, and PSE).

PFE = Papaya fruit extract-enriched diet; PSE = Papaya seed extract-enriched diet; PLE = Papaya leaves extract-enriched diet.

Table 4. Influence of diet and time intervals on White Blood cells (×10^9) of rat.

| Studies  | Diet   | Study Days Interval |
|----------|--------|---------------------|
|          |        | 0       | 30       | 60       |
| Study I  | Control| 729.5 ± 15.9 | 734 ± 14.2 | 741.9 ± 13.2 |
|          | PFE    | 739.5 ± 13.1 | 779 ± 15.5 | 807.4 ± 14.4* |
|          | PSE    | 724.5 ± 18.1 | 749 ± 15.5 | 767.4 ± 14.4 |
|          | PLE    | 745 ± 16.3  | 785 ± 12.3 | 811 ± 11.3** |
| Study II | Control| 711.2 ± 13.3 | 715 ± 14.3 | 721.2 ± 15.3 |
|          | PFE    | 511 ± 14.8  | 559 ± 15.8 | 591 ± 13.2* |
|          | PSE    | 517 ± 12.2  | 549 ± 13.2 | 579 ± 14.9 |
|          | PLE    | 521 ± 16.8  | 561.4 ± 14.1| 594.5 ± 11.2** |

*Mean ± S.D (n = 10 in each group), *p < 0.05; **p < 0.01) between the means of different diets (control, PFE, PLE, and PSE).

PFE = Papaya fruit extract-enriched diet; PSE = Papaya seed extract-enriched diet; PLE = Papaya leaves extract-enriched diet.

Red blood cells

Treatment and time interval showed a significant effect on the RBC of normal and treated rats. The recorded values are shown in Table 3. The results showed that after an interval of 56 days, a significant enhancement was detected in study II from 452.1 ± 12.3 to 553.2 ± 13.2 × 10^10/L, 461.2 ± 15.2 to 542.4 ± 12.2 × 10^10/L, and 469.2 ± 13.2 to 562.2 ± 14.2 × 10^10/L for PFE, PSE, and PLE, respectively. It was observed that PFE increases the RBC count to 15.52 and 21.07% in both (normal and treated rats), respectively. However, PSE raised the RBC count to 17.08 and 22.90% in both (normal and treated rats) and for PLE, the RBC count raised to 11.03 to 16.3%, respectively. The results are in line with the experimental study by Kaushik et al. who reported that papaya leaves extract significantly increased the platelet contents as compared to papaya fruit and seed extracts Table 5.

Hemoglobin

The statistical analysis of extract-enriched diet showed a significant increase in hemoglobin of treated rats. The data regarding (Hb) hemoglobin values for both (normal and treated rats) are depicted in Table 4. The results showed that after an interval of 56 days, a gradual enhancement was recorded in study II from 6.4 ± 0.1 to 7.4 ± 0.2 g/dL, 6.6 ± 0.1 to 7.2 ± 0.1 g/dL, and 6.2 ± 0.2 to 6.9 ± 0.2 g/dL for PFE, PSE and PLE, respectively. It was seen that PFE enhanced the Hb to 6.82 and 12.07% in normal and treated rats, respectively. But PSE raised the Hb to 5.08 and 8.90% in both (normal and treated rats) and for PLE, the Hb raised to 6.03 to 11.03%, respectively. The same results were observed in the experimental study of Sharma et al. who reported that papaya leaves extract significantly increased the hemoglobin contents as compared to papaya fruit and seed extracts Table 6.
**Table 5.** Influence of diet and time intervals on Red Blood Cells (×10^15) of rat.

| Studies | Diet     | Study Days Interval |
|---------|----------|---------------------|
|         |          | 0       | 30       | 60       |
| Study I | Control  | 615.5 ± 12.9 | 629.1 ± 14.2 | 637.9 ± 14.2 |
|         | PFE      | 631 ± 9.2  | 688.1 ± 11.2 | 736.2 ± 12.2* |
|         | PSE      | 651.1 ± 11.2 | 676.2 ± 17.2 | 721.1 ± 15.2 |
|         | PLE      | 669.3 ± 14.1 | 711.3 ± 12.3 | 752 ± 14.3** |
| Study II| Control  | 635.2 ± 11.2 | 645.2 ± 8.1  | 653.2 ± 14.2 |
|         | PFE      | 452.1 ± 12.3 | 502.3 ± 15.2 | 553.2 ± 13.2* |
|         | PSE      | 461.2 ± 15.2 | 492.3 ± 12.4 | 542.4 ± 12.2 |
|         | PLE      | 469.2 ± 13.2 | 512.4 ± 16.3 | 562.2 ± 14.2** |

*Mean ± S.D (n = 10 in each group), *p < 0.05; **p < 0.01 between the means of different diets (control, PFE, PLE, and PSE).
PFE = Papaya fruit extract-enriched diet; PSE = Papaya seed extract-enriched diet; PLE = Papaya leaves extract-enriched diet.

**Table 6.** Influence of diet and time intervals on Hb (mg/dL) of rat.

| Studies | Diet     | Study Days Interval |
|---------|----------|---------------------|
|         |          | 0       | 30       | 60       |
| Study I | Control  | 10.6 ± 0.2 | 10.7 ± 0.1 | 10.8 ± 0.1 |
|         | PFE      | 10.2 ± 0.3 | 10.4 ± 0.3 | 10.6 ± 0.2 |
|         | PSE      | 10.3 ± 0.1 | 10.6 ± 0.2 | 10.8 ± 0.1* |
|         | PLE      | 10.4 ± 0.1 | 10.7 ± 0.1 | 10.9 ± 0.1* |
| Study II| Control  | 10.3 ± 0.1 | 10.5 ± 0.2 | 10.8 ± 0.2 |
|         | PFE      | 6.4 ± 0.1  | 6.9 ± 0.1  | 7.4 ± 0.2* |
|         | PSE      | 6.6 ± 0.1  | 6.8 ± 0.1  | 7.2 ± 0.1* |
|         | PLE      | 6.2 ± 0.2  | 6.6 ± 0.2  | 6.9 ± 0.2 |

*Mean ± S.D (n = 10 in each group),
PFE = Papaya fruit extract-enriched diet
PSE = Papaya seed extract-enriched diet
PLE = Papaya leaves extract-enriched diet.
*p < 0.05; **p < 0.01 between the means of different diets (control, PFE, PLE, and PSE).

**Conclusion**

Papaya significantly increased the platelet count, hemoglobin level, white blood cells, and red blood cells as papaya fruit, leaves, and seeds are rich in polyphenolic compounds. However, the administration of PLE and PFE in thrombocytopenia is safe and does tempt the rapid increase in the platelet count or in hematological parameters. The study demonstrates that PLE treatment significantly increases the platelet count in severe thrombocytopenia in dengue. It might be helpful to play a valuable role in the managing or controlling of Dengue fever and cost-effective in the resource-limited dengue pandemic regions. Due to lack of the vaccine and antiviral agents, extract from *Carica Papaya* play a major role in inhibiting the dengue.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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