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The Papaya-Based Poly-Herbal Extract Eases Thrombocytopenia and Pyrexia in Rats

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Abstract: The beneficial role of papaya leaf juice against dengue infection is gaining popularity. However, most of these studies involve the fresh juice, decoction, or solvent extraction methods with limitations in terms of formulation development and retention of natural phytochemical balance. Hence, this study aimed at investigating the platelet-increasing and anti-pyretic effect of its powdered extracts with favorable attributes for developing finished pharmaceuticals. The former activity was performed on papaya leaves powder extract (PE) used to prepare the product, i.e., Re-Plat. However, both activities were assessed on the multi-ingredients extract (ME; composition was PE plus decoction of *Achillea millefolium*, *Zingiber officinale*, *Phyllanthus niruri* and *Piper nigrum*) used in the poly herbal formulation i.e. Re-Plat Plus. Briefly, the Carboplatin (50 mg/kg) was used to develop a rat model of thrombocytopenia, which is followed by the administration of PE and ME (150, 300, and 450 mg/kg). After five days, the blood was collected to measure platelet levels using a hematology analyzer. In case of anti-pyretic activity, the yeast-induced pyrexia model was used to induce pyrexia followed by administration of ME (150, 300, and 450 mg/kg). The rectal temperature was noted for 5 h. Our data showed that, at the tested doses of 150 and 300 mg/kg, both PE and ME caused significant increase in the platelet count compared to the control group. In case of anti-pyretic activity, in similarity with standard drug (paracetamol), the PE (300 and 450 mg/kg) did not allow time-dependent increase in the temperature. Hence, it can be deduced that the active extracts of the poly-herbal formulation (Re-Plat Plus) are endowed with the platelet increase and anti-pyretic potentials; the attributed clinically useful in the management of dengue fever.

Keywords: papaya, dengue, platelets, pyrexia, thrombocytopenia.

基于木瓜的多草药提取物可缓解大鼠的血小板减少症和发热

摘要：木瓜叶汁对登革热感染的有益作用越来越受欢迎。然而，这些研究大多涉及新鲜果汁、煎剂或溶剂提取方法，在配方开发和保持天然植物化学平衡方面存在局限性。因此，本研究旨在研究其粉末提取物的增加血小板和解热作用，具有开发成品药物的有利特性。前一个活动是在用于制备产品即重制的木瓜叶粉末提取物(聚乙烯)上进行的。 然而，这两种活性都是在多成分提取物（我；成分是聚乙烯加上荠菜、生姜、珍珠草和黑胡椒）中使用的多成分提取物（即重新平台加）上进行评估的。简言之，卡铂 (50 毫克/公斤) 用于建立血小板减少症大鼠模型，随后给予聚乙烯和我（150、300 和 450 毫克/公斤）。五天后，收集血液

以使用血液分析仪测量血小板水平。在解热活性的情况下，酵母诱导的发热模型用于诱导发热，然后施用我（150、300 和 450 毫克/公斤）。记录直肠温度 5 小时。我们的数据显示，在 150 和 300 毫克/公斤的测试剂量下，与对照组相比，聚乙烯和我均导致血小板计数显着增加。在解热活性的情况下，与标准药物（扑热息痛）相似，聚乙烯（300 和 450 毫克/公斤）不允许温度随时间升高。因此，可以推断，多草药配方（重制加）的活性提取物具有增加血小板和解热的潜力；归因于临床上对登革热的管理有用。

关键词：木瓜、登革热、血小板、发热、血小板减少症。

Introduction

Dengue fever has become a major health issue nowadays. It is caused by a virus of the flaviviridae family having four distinctive serotypes (DENV-1 to DENV-4) transmitted by a mosquito, primarily females of specie *Aedes aegypti* [1]. An estimated 400 million cases leading to 22000 mortalities are reported annually around the globe, including both tropical and subtropical regions [2]. Another estimate revealed that 3.9 billion are at risk of infected with dengue virus with 70% of this burden lies with Asia, primarily South-East Asian countries [3, 4]. It is of note the projection of infection for 2080 is 6.1 billion, which is extremely alarming [5]. In Pakistan, the dengue fever is also among the major challenges related to public health. The overall environment and sanitary conditions are favorable for the growth of the dengue viral vector. The World Health Organization estimated that 1 million were infected in 2020, leading to approximately 30,000 deaths [6]. It is worth mentioning that the number of cases and associated mortalities in the country are on the rise with each passing year [7]. Dengue infection manifests itself in different forms, including mild fever to dengue shock syndrome (DSS) characterized by hemostasis malfunction, i.e., hemorrhage associated with thrombocytopenia (low platelets) leading to hypovolemic shock [1]. It is of note that infection with a particular serotype provides lifelong immunity against that particular virus without much safety offering against the other types [8]. The first infection with any serotype is generally asymptomatic. However, the subsequent infection with another serotype may lead to a severe form of disease, which has been attributed to antibody-dependent enhancement [9]. The management of the disease is symptomatic, i.e., use of anti-pyretic for fever and platelet infusion in case of thrombocytopenia. Unfortunately, there is no anti-viral currently available against dengue; therefore, the vaccine development is a priority and many are under investigation nowadays [10].

Humans are provided with wealth of natural substances (flora and fauna) for healing purposes, and there has been an increasing trend in the use of these natural products for medicinal purposes. In this regard, along with the prevailing incidences of dengue infection, the popularity of papaya leaf (*Carica papaya*) juice as a remedy also increased and has caught significant attention of the scientific community. Papaya leaf juice (approximately 10 ml twice a day for adults) has been traditionally used to treat thrombocytopenia (decreased platelets count) associated with dengue fever [11]. A more recent review, including pre-clinical, clinical, and ethnobotanical work, revealed the beneficial role of papaya leaf juice against dengue owing to its platelet-increasing and immunomodulatory actions [12]. There are concerns about the safety of these preparations too [13]. Hence, there is an intense need to regulate the use the papaya preparations through validated formulations. Thus, this study was designed to pre-clinically assess the efficacy of various papaya powder extracts with favorable attributes for developing finished pharmaceuticals.

1. Materials and Methods

1.1. Chemicals

The following chemicals were used: carboplatin (Pfizer, Pakistan), Pentothal Sodium (Abbott Laboratories, Pakistan), and sodium chloride (Sigma Aldrich, USA).

1.2. Animals

Animals (Wistar rats; 150–250 g) of either sex were obtained from the Animal Resource Facility of Herbion Pakistan (Pvt.) Limited. They were housed in controlled and standard environmental conditions, i.e., 25˚C ± 1˚C, 12/12-h dark/light cycle, and free access to food and water. All experiments were performed as per guidelines for the care and use of laboratory animals (Animals Scientific Procedure Act, 1986, UK).

1.3. Flow Diagram of the Research Methodology

The main steps of the research process are summarized in Fig. 1.

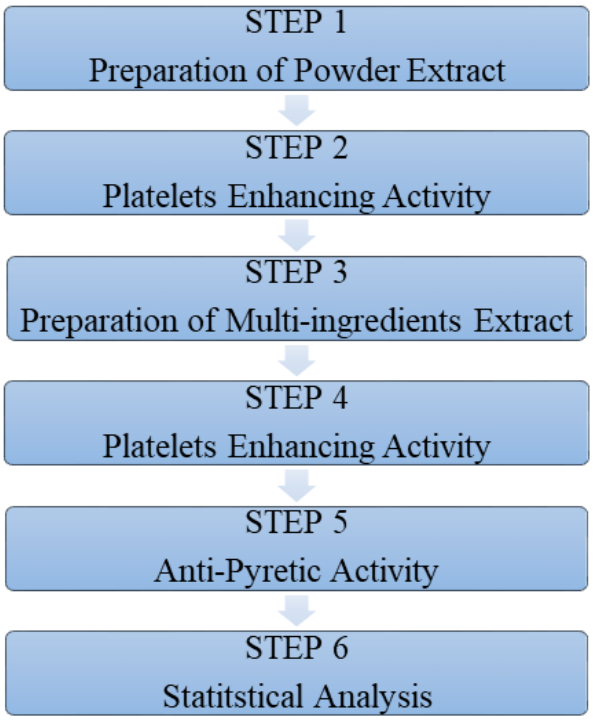

Fig. 1 Flowchart of the research methodology

1.4. Preparation of Extracts

Two types of extracts were prepared as follows:

1.4.1. Powder Extract (PE)

The concentrated dilution was fed in the tank of drying. As soon as the dryer reached 183 ± 2ºC, the dilution was started fed into it. After spray drying, the powder extract was blended in a blender at the speed of 20 ± 2 RPM. This active extract is used for the preparation of finished product i.e. Re-Plat (Herbion Pak. Pvt. Ltd).

1.4.2. Multi-Ingredient Extract (ME)

All herbs (*Achillea millefolium*, *Zingiber officinale*, *Phyllanthus niruri* and *Piper nigrum*) were extracted separately in different containers with specified amounts of purified water. Afterwards, the excess water was evaporated, and all decoctions were combined, while reducing and maintaining temperature at 90-100°C for 30 minutes. When the decoctions were approximately half of the initial volume, the flame was removed followed by filtration (100 no. mesh). After filtration, the filtrate was transferred to a separate container and heated (100-110°C) for 25 minutes to yield the concentrated decoction which was mixed with powder extract (PE) of papaya leaves. This active extract is used in the preparation of poly-herbal formulation, i.e., Re-Plat Plus (Herbion Pakistan Pvt. Ltd.).

1.5. Platelet-Increasing Activity

An animal model of carboplatin-induced thrombocytopenia [14] was used for evaluating the platelet-increasing potential of various test substances. The rats (n = 5/dose) were divided into the following groups:

Naïve/baseline control: Animals obtained were directly sacrificed, without any treatment, for the quantification of basal platelets levels.

Animal model of carboplatin-induced thrombocytopenia: The animals were intra-peritoneally (*i.p.*) injected with 50 mg/kg of carboplatin once followed by platelet quantification after one week to observe thrombocytopenia.

Test (curative) group: One week after carboplatin treatment, animals were orally administered with test extracts (PE & ME; 150, 300, and 450 mg/kg) for five days. On the last day, one hour after treatment, blood was collected for platelet count as described.

The animals were anesthetized (Pentothal sodium, 60 mg/kg, i.p.) and blood (0.5 ml minimum) was collected intra-cardially with syringe (1 ml, 26 G) and transferred into a vacutainer (purple EDTA tube, 3 ml). Later, the platelet count was performed using a hematology analyzer.

1.6. Anti-Pyretic Activity

Before inducing pyrexia, the initial rectal temperatures of rabbits were recorded using a digital thermometer. Care was taken to insert the thermometer to the same depth each time (about 1.5 cm). Pyrexia was induced by intra-peritoneal injection of 20% yeast suspension as described earlier [15]. Animals were divided into four groups, i.e., normal saline control, model group (yeast only), positive control (paracetamol), and treated (multi-ingredients extracts). All groups were administered yeast to induce pyrexia before the respective treatment. Temperature was measured after 1, 2, 3, 4, and 5 hours of drug administration.

1.7. Statistical Analysis

The data are presented as mean ± S.E.M (n = 5/dose). Differences between various means are evaluated by one-way ANOVA followed by the least significant difference (LSD), using SPSS (Statistical Package for the Social Sciences) software (Version 20, SPSS Inc, Chicago, IL, USA). The minimum level of significance was set at $p < 0.05$.

2. Results

2.1. Platelet-Increasing Activity

Our data showed that carboplatin treatment (50 mg/kg) caused significant ($p < 0.001$) decline in the platelets in rat plasma compared to control (Fig. 2). Furthermore, both powdered extract (PE) and multi-ingredient extract (ME) showed significant dose-dependent increase in the platelets count at the doses of 150 and 300 mg/kg followed by the decline at the highest test dose of 450 mg/kg, when compared with the carboplatin group.

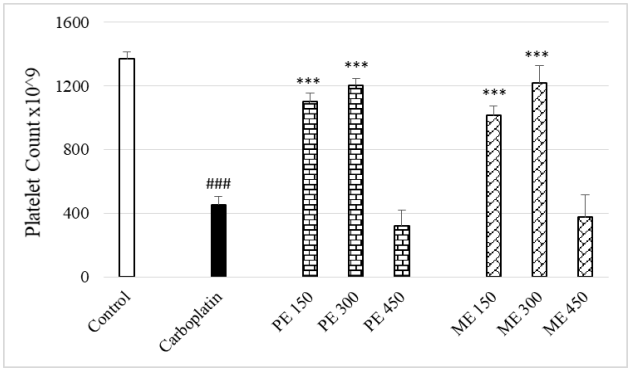

Fig. 2 Effect of carboplatin, powder, and multi-ingredients extracts on the platelet count in rats

Notes: The figure shows the mean ± SEM of platelet levels (n = 5 per group) following various treatments. The carboplatin treatment caused a significant decline in platelets. However, the powder and multi-ingredients extract treatment significantly raised the platelet levels at the doses of 150 and 300 mg/kg. The hash (###) and asterisks (***) represent statistical differences compared to the control and carboplatin groups, respectively.

2.2. Anti-Pyretic Activity

Our data showed that the yeast administration caused a significant time-dependent rise in the temperature compared to the zero (T°) temperature (Table 1). The standard drug (paracetamol) did not allow the increase in this temperature. In case of ME, a significant time-dependent increase in the temperature was noted at the lowest test dose of 150 mg/kg. However, in similarity with standard drug, the ME at the doses of 300 and 450 mg/kg did not exhibit any increase in the temperature with time.

Table 1 Antipyretic effect of paracetamol and the multi-ingredient extract

Group	**Dose**	**Temperature (◦F)**					
		T◦	**1**	**2**	**3**	**4**	**5**
Control	~	99.7 ± 0.2	98.9 ± 0.2	99.6 ± 0.5	100 ± 0.2	100 ± 0.6	99.9 ± 0.4
Yeast (20%; ml/Kg)	1	98.9 ± 0.3	99.4 ± 0.6	99.7 ± 0.6	101 ± 0.6*	101 ± 0.6**	102 ± 0.4***
Paracetamol (mg/Kg)	150	99.9 ± 0.5	101 ± 0.5	100 ± 0.3	100 ± 0.3	100 ± 0.1	100 ± 0.1
Multi-ingredient extract (mg/Kg)	150	99.2 ± 0.3	99.7 ± 0.4	99.8 ± 0.8	101 ± 0.5	102 ± 0.5***	103 ± 0.6***
	300	98.2 ± 0.8	97.1 ± 0.7	97.9 ± 0.8	97.9 ± 1.1	98.9 ± 0.9	98.7 ± 0.6
	450	99.9 ± 0.9	98.4 ± 0.9	99.2 ± 0.5	99.6 ± 0.2	99.7 ± 1.1	100 ± 1.2

3. Discussion

Dengue fever has become a major health issue nowadays, leading to both mortality and morbidity. This study assessed the therapeutic potential of various papaya leaf-based extracts for managing characteristic features of this disease, i.e., thrombocytopenia and pyrexia.

In our research, the platelet-increasing effect was studied using an animal model of carboplatin-induced thrombocytopenia. In line with the existing literature [16], our data demonstrated a significant reduction in platelet count following carboplatin administration (Fig. 1). The literature search revealed an increasing pool of both preclinical [17-19] and clinical studies [20-22] supporting the traditional usage of papaya leaf as a platelet-increasing agent. This platelet increase has been attributed to enhanced expression of platelet production genes, i.e., ALOX 12 (Arachidonate 12-lipoxygenase) and PTAFR (Platelet-Activating Factor Receptor) [23], thrombopoietin elevation [24], and anti-viral potential [25, 26]. It is of note that most of these studies involve the fresh juice, decoction, or solvent extraction methods with limitations in terms of formulation development and retention of natural phytochemical balance. Hence, our study involved the preparation of powder extract (PE) favorable from a commercial formulation viewpoint. Notably, our data exhibited the platelet-increasing action of PE in rats at tested dose of 150 and 300 mg/kg. However, at the highest tested dose of 450 mg/kg, a remarkable decline in the platelet count was noted, the phenomenon which can be attributed to the hormesis (bi-phasic response) observed in natural substances [27]. Hence, powder extract of papaya leaves with favorable attributes for pharmaceutical developments is also endowed with platelet-increasing potential; this notion is worth further investigation in the clinic.

Dengue fever is often accompanied with body aches alongside high-grade fever. Therefore, to address these concomitant issues, some potential herbal extracts (*Achillea millefolium*, *Zingiber officinale*, *Phyllanthus niruri* and *Piper nigrum*) were added in PE for the preparation of ME owing to their analgesic and anti-pyretic properties [28-31]. This ME was subsequently tested for both platelet enhancing and anti-pyretic actions. Our data showed that the platelet-increasing potential of ME was similar to that of PE (Fig. 2). This suggests that the presence of other extracts did not mask the therapeutic potential PE in case of ME. Furthermore, ME was tested for antipyretic action using a yeast-induced pyrexia model. Our data showed the anti-pyretic potential of ME at the doses of 300 and 450 mg/kg (Table 1).

Phytochemical analysis of the juice revealed the presence of phenolic compounds [32], saponins, cardiac glycoside alkaloids, vitamins, and minerals [33] and requires individually evaluating for the aforementioned effects to obtain more insight on the medicinal values of papaya leaves.

4. Conclusion

This study concludes that the active extract (ME) of the poly-herbal formulation (Re-Plat Plus) is endowed with the ability to enhance platelets and decrease

pyrexia at pre-clinical levels. Hence, the novel poly-herbal extract also retained the beneficial platelet-increasing effect along with value addition of anti-pyretic action. This additional action shall enhance the patient compliance in terms of taking fewer medicines for managing dengue fever. The major limitation of the study was that we considered limited constituents (active moiety) and obtained the desired results as indicated, but we believe that if we made our studies broader in terms of more active constituents present in our selected herbs, we could achieve promising results. Hence, the product is worthy of further investigation in patients with dengue fever (eased thrombocytopenia and pyrexia) to establish its efficacy in clinical settings.

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