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Pharmaceutical features of herbal remedy *Carica papaya* in life threatening diseases and acceleration of thrombocytes count in dengue fever

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Abstract
Pakistan has various types of higher plants around 7,000. Which has been accounted for that 700 to 800 species as valuable for pharmaceutical drives. *Carica papaya* is one of them, also called pawpaw in Africa and the United Kingdom. *Carica papaya* is a spice like a tree with 17-34 feet in stature. Papaya currently developed in 50 countries involves tropical and sub-tropical around the world. The inception of (Caricaceae family) is Africa, around 35 (MYA) million years back the dispersal of the Caricaceae family from Africa to Central America occurred by the dispersal of vegetation might be with sea flows. Segments of spice (Fruit, seeds and leave) utilized as food just as a pharmaceutical solution for inconvenience/sickness. *C. papaya* has advantageous properties, for example, (healing wound, anti-inflammatory, and antioxidant activities). Generally, *C. papaya* has pharmacological significates and important restorative plants. Internationally, all constituents of papaya have been utilized in various ailments as a treatment for example dengue fever. It is utilized in the home as solutions for a treat the routine illness, for example, skin-illnesses, stomach-ulcer, male infertility, and loose bowels. It has been recommended in problematical illnesses, for example, disease (prostate, bosom, and cervical malignant growth), because it favored with enormous normal phytochemicals with solid adequacy. Arthropod-borne irresistible illness, for example, Dengue fever that transmits through vector called Aedes-albopictus and Aedes aegypti mosquitoes and is portrayed by hemorrhagic fever and stun. *Carica papaya* juice of leaves leads top over different chemotherapies. Scientists proposed a plant that can be utilized as an elective treatment for dengue patients. Clinically, broad examinations have been finished by utilizing (rodents) as subjects. In conclusion, *C. papaya* has been decided to treat dengue fever and dengue hemorrhagic fever.

Keywords: *C. papaya*, pharmacological properties of papaya, extraction method, dengue fever, thrombocytes, phytochemical

1. Introduction
Pakistan has different species of higher plants about 7,000. Which has been reported that 700 to 800 species as beneficial for pharmaceutical drives [2]. The rapid trend growing toward herbal remedies in Pakistani inhabitants, due to the use of 85% traditional medicinal plants has been reported in abundant ruler areas of the country. Such remedies are used as alternative chemotherapy. *Carica papaya* is one of them that belongs to a family called Caricaceae with polygamous, dicotyledonous, and diploid species [3], also called pawpaw in Africa and the United Kingdom. *Carica papaya* is found in the form of an herb like a tree (fig no.1) with 17-34 feet in height while the diameter of leaves is in 50-75 cm with deep seven lobes [4]. Papaya now cultivated in 50 countries comprises tropical and sub-tropical worldwide.

Fig 1: 4 Fresh slices, juice, and dried powder of papaya [5]

2. Origin and global distribution of *Carica papaya*

The origin of (Caricaceae family) is Africa where the occurrence of 2 extant species takes place. About 35 (MYA) million years ago the dispersal of the Caricaceae family from Africa to Central America took place by dispersal of vegetation that maybe with ocean currents. Between 19 to 27 million years ago(MYA) the shuffling of Caricaceae members from Central America to South America take place, At that time a land bridge form from Central America to facilitate South America with Mexico [6]. About 25 million years ago (MYA) it's reported sister clade of (*Carica papaya)* departed and (small clade) is limited in Mexico, Guatemala and El Salvador belong to it in which four species, the tree let (*Horovitzia cnidoscoloides),* endemic to Oaxaca in Mexico and 3 perennial herbs presents i.e. (*Jarilla chocola),(J. heterophylla),* and(*J. nana)*mainly occur in tropical seasonal forests, though the exact place of origin is not known, the(papaya plant)is thought to (Tropical America's native), maybe in Southern Mexico and Central America [7]. Commercial production that is successful nowadays is mainly in Australia, Hawaii, Tropical Africa, India, Ceylon, Malaysia, the Philippines, but South Africa and Latin America have small scale production, In India, (papaya) is grown in Bengal, Bihar, Haryana, Maharashtra, Punjab, Andhra Pradesh, Delhi and Uttar Pradesh [8].

3. Pharmacological distribution of *Carica papaya*;

Portions of herb (Fruit, seeds and leave) used as food as well as a pharmaceutical remedy for discomfort/illness [9]. *Carica papaya* is considered as a sophisticated content of (vitamin A, B, and C), and also rich mineral supplements in the diet [10]. *C. papaya* has beneficial properties, such as, (healing wound, anti-inflammatory, and antioxidant activities) [4, 11, 12]. Traditionally, *C. papaya* has pharmacological significates and valuable medicinal plants [13]. Globally, all constituents of papaya have been used in numerous diseases as treatment. It is used in the home as remedies to treat routine illnesses such as skin-diseases, stomach-ulcer, male infertility, and diarrhea [14]. It has been prescribed in problematical diseases such as cancer (prostate, breast, and cervical cancer), due to it blessed with gigantic natural phytochemicals with strong efficacy. Extracts of papaya seeds, fruit as well as leaves have been selected for liver-cancer, blood-cancer and cancer cell lines. Hence, papaya has substantial activities cytotoxicity against all of these [15]. It was measured by (titrimetric method) that it has antiobesity activity due to the presence of flavonoids, tannins, and Saponins. Seeds of papaya in the form of powder were used as inhibitors with powerful efficacy against pancreatic lipase [16]. Recently, newly hybrid papaya has been launched in the market with superior vitamin constituent. It has a massive volume of β-carotene and ascorbic-acid thus increased the consumption of such papaya and become a brand commercially [17]. A more interesting efficacy of papaya in dengue is to increase the volume of platelet by boosting its production.

4. General Procedures and extraction methods for *C. papaya*

For the process, about 250 grams fresh *C. papaya* latex was stored in a glass cylindrical jug or flask for extract preparation and then dried it [18]. Isolated latex was boiled at (70 C) in pure or non-mineralized water then wash it with distilled water about 25-30 mints and handle it with care. Now it was ready for syrup Extracted syrup was tried in the oven with a suitable temperature, after oven-dry about (50 grams) of crude papaya leaves extracts were obtained and stored it at 20C temperature [19, 20].

5. Phytochemical substances of *C. papaya*

Fig 1: Appearance of *C. Papaya*

6. Medicinal properties of *Carica papaya*

(C. Papaya) has been recognized as a food or drug. Its pharmacological properties are wide consumption owing's [21] and maybe utilized traditionally as a remedy in various diseases. It has various forms of antioxidants and immune-stimulating mediators [22, 23]. The pulp of Papaya is utilized in Africa's clinics for the healing of wounds and burns curing [24] because controlling (non-healing chronic ulcers) have many trouble and medical problems. In conducting enzymatic wound debridement papain-urea union has been effectively recognized [25]. For curing dyspepsia and external use on burns and scalds (*Papaya Carica*) latex is very useful and also treats diarrhea, bleeding hemorrhoids, and cough. Infections of the colon can be treated with Papaya juice by clearing away the mucus, any infection, and puss [26]. The (mature fruit) of Papaya has sedative, expectorant, carminative, diuretic, and perform role against dysentery, skin diseases, psoriasis and ringworm. Against various pathological disorders therapeutic assets are also property of Papaya. The remedy for impotence and ulcers is unripe fruit of Papaya [27]. Bacteriostatic activity against enteric pathogens of humans is also characteristic of (*Papaya Carica*) [28]. It promotes normal menstruation course in females and helps in menstrual irregularities. In severe hair dandruff problem, it has been suggested as a solution to dandruff. The juvenile leaf that is green in color has many essential nutrients while the yellow leaf provides iron [29]. The liver and enlarged spleen can be reduced by the synergistic action of Papaya and it is used to remove poison in case of snakebite. Some antioxidant and immune-stimulating agents are thought to be present in Papaya fruit [22]. Its juice is suggested to treat gastrointestinal maladies.

6.1. Dengue fever and hemorrhagic fever

Arthropod-borne infectious disease such as Dengue fever that transmits via vector called Aedes-albopictus and *Aedes aegypti* mosquitoes (fig no.2). It belongs to the family Flaviviridae and species is a flavivirus with four serotypes namely den-1, den-2, den-3, den-4.it is characterized by

hemorrhagic fever and shock [30]. Initial Symptoms are myalgia (muscle pain), headache retro-orbital pain (pain behind or around the eyes), and arthralgia (joint pain). Dengue virus causes complications such as (hepatitis, organ failure, maculopathy, rhabdomyolysis, neurological and myocardial impairment [31]. From the year 2019, the Pakistan national institute of health had been reported 20,000 cases of dengue virus infections and over 31 deaths till October [32]. In Pakistan, the most circulating and prevalent serotype is the DEN-2 serotype, while cases of DEN-3 serotype reported rarely [32], due to the unavailability of specific anti-viral chemotherapy for the dengue virus. Accordingly, dengue infected patients obtain supportive-management with fluids, blood, and blood-products submitting by (MHCPGs) ministry of health clinical practices guideline 2010. The clinical presentation of dengue has sudden onset monitored by 3 periods such as (febrile-period, critical-period, and recovery-period), thus in critical-period thrombocytopenia characterized by lesser platelet count lees than (100,000 permm3) from normal value and induces haemoconcentration by an increase of 20% hematocrit [33].

Fig 2: *Aedes aegypti* vector of dengue fever

6.2 Mode of action of the medication on dengue virus;

Among all serotypes 60% homology is found based on surface antigen, the dengue virus is single-stranded RNA multiples on the endo-plasmic-reticulum membrane with the help of the largest NSP (non-structural-protein) of RNA. Improvement of a couple of immunizations base upon live constricted infection has been done yet the serious issues are the drag out portion plan, the reactivity of immunization, and its seroconversion rate. The mode of actions of different therapies has been exemplified in (fig no.3) [34]

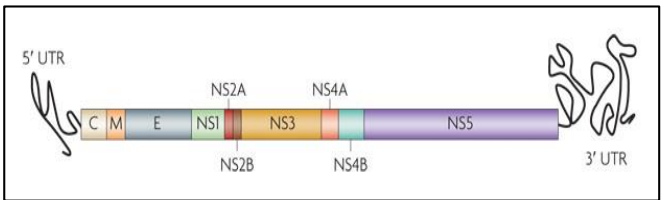

Fig 3: Genomic presentation of dengue virus which comprises on (C-capsid), (M-membrane), (E-envelope), and (seven non-structural proteins NS1, NS2, NS3, NS4, NS5, NS6, NS7) [35].

Fig 4: Fresh slices, juice, and dried power of papaya [5].

6.3 Effect of freeze-dried *Carica papaya* leaf juice on inflammatory cytokines production during dengue virus infection

In dengue infection pathogenesis, host specific-immune rejoinders producing secretion of chemokines and cytokines and immune cell activation which results in the development of inflammatory-mediators and auto-immunity [36]. For instance, the frequency rate of pro-inflammatory cytokines become higher as well as IL-6 and IL-8 and TNF-α were screened during viral-clearance that leads to vascular-leakage and endothelial-activation [37]. Due to the unavailability of suitable anti-viral chemotherapy [38] to treat the dengue, several traditional treatments show its positive efficacy in which *Carica papaya* juice of leaves lead top over other chemotherapies [38]. Researchers proposed that it is the only plant that can be used as an alternative therapy for dengue patients. Clinically, extensive studies have been done by using (rodents) as subjects [39]. Lastly, *C. papaya* has been chosen to treat dengue fever and dengue hemorrhagic fever. The beneficial consequences of papaya-extract that increase and boosted the volume of platelets in a rodent. From the previous decade, clinical trials and cases on the dengue individuals platelets increasing properties of *Carica papaya* have been reported by apply extract of papaya [40, 41].

7. Clinical efficacy of *C. papaya* in dengue fever

Numerous studies were directed to examine the thrombocyte inducing stuff of *C. papaya* juice in individuals with dengue fever and dengue hemorrhagic fever. Patients were consumed juice at least for three days regularly, then after 12 to 48 hours, their blood was observed. So, they have increased their thrombocytes count in the blood. Hence, the scientist concluded that *C. papaya* and its derivatives are helpful for the production of thrombocytes especially in dengue patients, and recommended it as an alternative remedy to treat the dengue [42].

8. Efficacy of *C. papaya* in leukocytes production

In-vivo and in-vitro extract/juice of papaya leaf were studied for their immunomodulatory activities and antioxidant [43, 44]. In-vitro leaves extract has been appeared to direct certain cytokine generation in enacted human peripheral blood mononuclear cells [45]. The treatment of *Carica papaya* leaves extracts condensed the inflammatory-effect in (paw edema induced rats) [46]. Juice of papaya leaf has also shown increased the production of TNF-α and induced the phagocytic-keys thus, prevented the reduction of white blood cells count in cyclophosphamide-induced neutropenia rats [47, 48]. Furthermore, in healthy mice, the activity of bone-marrow cells, splenocyte-count, and leukocytes-count, as well as macrophages-phagocytic, were induced by employing *C. papaya* leaf extract [49]. It likewise delivered restorative gainful impacts in patients with the fiery issue of the liver, digestive system, and eye [50].

9. Traditional uses of *Carica papaya*

An (active principle) that is papain is present in milky juice present in (Papaya fruits) as well as any part of the Papaya plant. Apart from its importance as a remedy in ailments and dyspepsia, it has been utilized for the clarification of beer. When the seed of Papaya is chewed it expels the intestinal worms, when chewed the roots and swallowed the juice of roots relief in cough, bronchitis, and many respiratory diseases. The (immature fruit of Papaya) is utilized for treatment or as a remedy of ulcer and impotence [51]. In Nigeria, the traditional medicine practitioners used the plant in diabetes management [52] and utilized in malaria and fungal and helminthic infections. Traditionally, various fragments of (*C. papaya*) including its roots, fruits, barks, leaves, and seeds of Papaya plant have various medicinal properties. The ripe fruit of Papaya in Jamaica is utilized in ulcers to initiate granulation, healing, de sloughing, and reducing odor in chronic skin cancers [53].

9.1Anti-Inflammatory Activity

Seeds of papaya were also described in the literature for its best effects against inflammation while the leaves of papaya were not so effective as the fruit and seeds [54].

9.2 Antifungal Activity

Papaya can perform against fungal diseases. Papaya leaf extract has secondary metabolites and properties against fungi [55].

9.3 Anti-Hypertensive Activity

Papaya leaves served as an anti-hypertensive agent. In West Africa, an Agboville villager worked on the anti-hypertensive effect of extract of leaves of papaya by oral management [56].

9.4 Anti-bacterial Activity

Papaya seeds have an antibacterial agent. Escherichia coli, Klebsiella pneumonia subtilis, Proteus Vulgaris, Enterobacter cloacae, salmonella typhi, staphylococci, and pseudomonas aeruginosa were normally used. Gram-negative and gram-positive bacteria were verified under various conditions while gram-negative bacteria presented more good results [57].

9.5 Anticancer activity

The myrosin, dehydrocarpaines, saponins, pseudocarpaine enzymes, and ascorbic acid are ingredients of Papaya leaf, that can perform immunomodulatory and theatrical properties of cancer-fighting against tumors, it also acts as a tumor-destroying agent [3]. The papaya leaf has cytotoxic effects, that support the fact of saponins presence in it [58] while for treatment of prostate cancer ascorbic acid indicates the *(Papaya Carica)* plant to be utilized in homeopathic (herbal) medicine [59]. Moreover, on liver cancer cells Papaya's juice has an anti-proliferative effect. According to an anticipated biosynthetic trail, the central and key compound is lycopene that is the copious carotenoids, which show the high stimulus at the ripening stage during its upstream step. Papaya performs protective action against prostate cancer, rheumatoid, failure of kidney, and arthritis [60, 61]. It has an effective role against oxidant so, neutralizes the free radicals, giving resistance against a different form of cancer like atherosclerosis, prostate cancer, cancer of the breast and related coronary artery disorder as well [62].

9.6 Anti-helminthic Activity of *Carica papaya*

At the point when any aspect of the body is tainted with worms, for example, roundworm, pinworm, or tapeworm, such illness is called (Helminthiasis). The worms present in a lot of the gastro digestive system and structure a gap in the liver and different structures. They harm the host by food depriving, by toxins secretions, and lead to blood loss. The drugs that are locally used to expel parasitic worm from the gastrointestinal tract are known as (Anthelmintic). Seeds of *(Papaya Carica)* are used as anthelmintic [64]. In recent years, pharmacy and new chemical synthesis (latex of papaya) and its commercial products have been widely applied in the baking and beverage industries. Due to its anatomical and physiological resemblance with the (intestinal roundworm parasite) of human beings, the *(C. papaya)* has (anthelmintic properties) on Pheretima silvvlae and adult Indian earthworm. For the initial evaluation of anthelmintic compounds *in vitro*, earthworms have been broadly used because of their easy accessibility [65].

9.7 Anti-diabetic Activity

A Study of the Assessment of Antidiabetic Activity of (*Carica papaya*) leaf extract in an Experimental Rat Model. The chloroform extract which consisted of steroid and quinines was administered at several dose levels in streptozotocin-induced diabetic and non-diabetic rats. After 20 days of treatment, the cost was done and the biochemical histology of granulation tissue were the assessment criteria. The insignificant wound contraction was noticed. But significant wound closure and fibroblast cell count were observed in the *Carica papaya* L. leaves powder treated group. As a conclusive remark, this study provides a scientific background for leaves of *Carica papaya* L. having remarkable wound healing potential [71].

10 Therapeutic potential of *Carica papaya*

Biological membrane maintenance possessions of the (Papaya leaf) extract that inhibiting the plasma membrane stress-induced annihilation. Papaya leaf extracts compound such that (phenolic and Flavonoids) proved the action by inhibiting internal bleeding in the blood vessels and membrane-stabilizing property [72]. The flavonoid present in *(Carica papaya)* inhibits thereby prevents the DEN-2 Virus assembly [73]. It is also reported that papaya leaf juice significantly increases platelet count [74, 75]. Anti-oxidant vitamins and minerals present in (Papaya leaf) help in the increment of thrombocytes, hematocrit, the hemoglobin, and total protein components [76, 77] (Vitamin B9) support the blood DNA synthesis, growth of the cell and also the development.

The normal count of thrombocytes is maintained by (Vitamin B12) and (Vitamin A) helps in keeping bile production normal that function is to defend against thrombocytopenia [78]. (Vitamin C) acts as an (anti-oxidant) to search the oxygen radicals that are superoxide, hydroxyl, peroxyl Sulphur radicals, and nitrogen-oxygen radicals [79]. Minerals present in the leaves of Papaya play an important role in fighting DENV infection. Ions of calcium support in lymphocyte cell proliferation, playing a key role in platelet aggregation when combined with vitamin D and prevents thrombocytopenia [80, 81]. Magnesium ions progress erythrocyte hydration. Ions of Sodium prevent hyponatremia during dengue infection and help in maintaining electrolyte balance. Ions of Potassium maintain potassium levels in the human body and help in the

prevention of acute hypokalaemic quadriparesis during dengue infection [82, 85].

Conclusion; a mention literature review concluded that *C. papaya* has potential aspects in multitudinous diseases, such as malignancy growth, diabetes, dengue fever, and infertility so forth it is utilized as a conventional medication in different continentals because of its phytochemical constituents and pharmacological highlights. *Carica papaya* is utilized by a large portion of the inhabitants for an acceleration of platelet, especially in dengue fever. Clinically, papaya is utilized as an alternative treatment or medicine in dengue fever and dengue hemorrhagic fever.

Ethics approval and consent to participate; it is a literature review and does not contain any patients while it is a case review of clinical presentation and analysis, therefore no ethical approval is needed.

Consent for publication; Not applicable because the study is simply a chart review, hence the manuscript does not contain data from any person. It is a literature review comprising the clinical presentation of researchers.

Availability of data and materials; not applicable

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References

1. Shaz S. Contribution of viruses to cancer and its global burden. Glob J Cancer Ther. 2019; 5(1):012-5.
2. Shinwari ZK. Medicinal plants research in Pakistan. Journal of medicinal plants research. 2010; 4(3):161-76.
3. Fernandez G, Chitra M, Sudha P, Kiruthiga D, Jayakumar D. Spectrophotometric method of Ascorbic acid in *Carica papaya* L. extracts: An *in vitro* study. Journal of Pharmacognosy and Phytochemistry. 2019; 8(6):119-23.
4. Nakhate YD, Talekar KS, Giri SV, Vasekar RD, Mankar HC, Tiwari PR. Pharmacological and chemical composition of *Carica papaya*: On overview, 2019.
5. Jarisarapurin W, Sanrattana W, Chularojmontri L, Kunchana K, Wattanapitayakul SK. Antioxidant Properties of Unripe *Carica papaya* Fruit Extract and Its Protective Effects against Endothelial Oxidative Stress. Evidence-Based Complementary and Alternative Medicine, 2019.
6. Carvalho FA, Renner SS. IV. A Dated Phylogeny of the Papaya Family (Caricaceae) Reveals the Crop's Closest Relatives and the Family's Biogeographic History §. Molecular phylogeny, biogeography and an e-monograph of the papaya family (Caricaceae) as an Example of Taxonomy in the Electronic Age: Springer, 2015, 49-81.
7. Iipinge LN. Effect of pawpaw (*Carica papaya*) seed meal on growth performance, feed utilization, survival and masculinization of sexualy undifferentiated three spotted Tilapia (*Oreochromis andersonii*) fry: University of Namibia, 2019.
8. Aravind G, Bhowmik D, Duraivel S, Harish G. Traditional and medicinal uses of *Carica papaya*. Journal of Medicinal Plants Studies. 2013; 1(1):7-15.
9. Heena D, Sunil T. *Carica papaya*: Potential Implications in Human Health. Current Traditional Medicine. 2019; 5(4):321-36.
10. Bhatnagar P, Rathi N, Singh S. Medicinal properties of banana and papaya: A review. Energy. 2019; 163:39kCal.
11. Castro-Vargas HI, Baumann W, Ferreira SR, Parada-Alfonso F. Valorization of papaya (*Carica papaya* L.) agroindustrial waste through the recovery of phenolic antioxidants by supercritical fluid extraction. Journal of food science and technology. 2019; 56(6):3055-66.
12. Hasanah F, Hidayah N. Test of Anti-Inflammation activities of pepaya leaf (*Carica papaya* L.) Extract on male wistar rats induced by caragenan 1%. Jurnal Natural. 2019; 19(3):54-7.
13. So'aib MS, Salihon J, editors. Simulation and Optimisation of Anti-Dengue Nutraceutical Drink Production Plant for Medic IG Biopharma. Key Engineering Materials; Trans Tech Publ, 2019.
14. Hossain MA, Hitam S, Ahmed SHI. Pharmacological and toxicological activities of the extracts of papaya leaves used traditionally for the treatment of diarrhea. Journal of King Saud University-Science, 2019.
15. Reddy PRK, Thiruvanavukkarasu P, Hari R. Free radicals scavenging and antiproliferative activity of ethanolic and methanolic extracts of *Carica papaya* leaves in PA-1 cell line. International Journal of Research in Pharmaceutical Sciences. 2019; 10(1):339-45.
16. Nurowidah A, editor The Potency of *Carica papaya* L. Seeds Powder as Anti-Obesity 'Coffee'Drinks. IOP Conference Series: Materials Science and Engineering;: IOP Publishing, 2019.
17. Nishimwe G. Characterization of Morphological and Quality Characteristics of New Papaya (*Carica papaya* L) Hybrids Developed at JKUAT: JKUAT-AGRICULTURE; 2019.
18. Urgessa OE, Itana DD, Raga TO. Extraction of Papain from Papaya (*Carica papaya* L.) Fruit Latex and Its Application in Transforming Tannery Raw Trimming. Ethiopian Journal of Sciences and Sustainable Development. 2019; 6(2):22-32.
19. Saravana Kumaar A, Senthilkumar A, Sornakumar T, Saravanakumar S, Arthanariesewaran V. Physicochemical properties of new cellulosic fiber extracted from *Carica papaya* bark. Journal of natural fibers. 2019; 16(2):175-84.
20. Khadam S, Afzal U, Gul H, Hira S, Satti M, Yaqub A, *et al*. Phytochemical screening and bioactivity assessment of leaves and fruits extract of *Carica papaya*. Pakistan Journal of Pharmaceutical Sciences, 2019, 32(5).
21. De Oliveira JG, Vitória AP. Papaya: Nutritional and pharmacological characterization, and quality loss due to physiological disorders. An overview. Food Research International. 2011; 44(5):1306-13.
22. Aruoma OI, Colognato R, Fontana I, Gartlon J, Migliore L, Koike K *et al*. Molecular effects of fermented papaya preparation on oxidative damage, MAP Kinase activation and modulation of the benzo [a] pyrene mediated genotoxicity. Biofactors. 2006; 26(2):147-59.
23. Mehdipour S, Yasa N, Dehghan G, Khorasani R, Mohammadirad A, Rahimi R *et al*. Antioxidant potentials of Iranian *Carica papaya* juice *in vitro* and *in vivo* are comparable to α-tocopherol. Phytotherapy Research: An

International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2006; 20(7):591-4.
24. Starley IF, Mohammed P, Schneider G, Bickler SW. The treatment of paediatric burns using topical papaya. Burns. 1999; 25(7):636-9.
25. Vijaykumar H, Pai SA, Pandey V, Kamble P. Comparative study of collagenase and papain-urea based preparations in the management of chronic nonhealing limb ulcers. Indian Journal of Science and Technology. 2011; 4(9):1096-100.
26. Reed C. Information summaries on 1000 economic plants. Typescripts submitted to the USDA, 1976, 102-3.
27. Kafaru E. Immense Help from Nature's Workshop: Guidelines on how to Use Herbs to Achieve a Healthy Living, as Health is an Individual Responsibility: Elikaf Health Services Limited, 1994.
28. Osato JA, Santiago LA, Remo GM, Cuadra MS, Mori A. Antimicrobial and antioxidant activities of unripe papaya. Life sciences. 1993; 53(17):1383-9.
29. Ayoola P, Adeyeye A. Phytochemical and nutrient evaluation of *Carica papaya* (pawpaw) leaves. Ijrras. 2010; 5(3):325-8.
30. Rozera R, Verma S, Kumar R, Haque A, Attri A. Herbal remedies, vaccines and drugs for dengue fever: Emerging prevention and treatment strategies. Asian Pacific Journal of Tropical Medicine. 2019; 12(4):147.
31. Hapugaswatta H, Amarasena P, Premaratna R, Seneviratne KN, Jayathilaka N. Differential expression of selected microRNA and putative target genes in peripheral blood cells as early markers of severe forms of dengue. Med Rxiv, 2019, 19002725.
32. Fatima Z. Dengue infection in Pakistan: not an isolated problem. The Lancet Infectious Diseases. 2019; 19(12):1287-8.
33. Subenthiran S, Choon TC, Cheong KC, Thayan R, Teck MB, Muniandy PK *et al*. *Carica papaya* leaves juice significantly accelerates the rate of increase in platelet count among patients with dengue fever and dengue haemorrhagic fever. Evidence-Based Complementary and Alternative Medicine, 2013.
34. Saisuk W, Srisawat C, Yoksan S, Dharakul T. Hybridization Cascade Plus Strand-Displacement Isothermal Amplification of RNA Target with Secondary Structure Motifs and Its Application for Detecting Dengue and Zika Viruses. Analytical chemistry. 2019; 91(5):3286-93.
35. Huber RG, Lim XN, Ng WC, Sim AY, Poh HX, Shen Y *et al*. Structure mapping of dengue and Zika viruses reveals functional long-range interactions. Nature communications. 2019; 10(1):1408.
36. Tian Y, Grifoni A, Sette A, Weiskopf D. Human T Cell Response to Dengue Virus Infection. Frontiers in immunology. 2019; 10:2125.
37. Patra G, Mallik S, Saha B, Mukhopadhyay S. Assessment of chemokine and cytokine signatures in patients with dengue infection: A hospital-based study in Kolkata, India. Acta tropica. 2019; 190:73-9.
38. Madjos GG, Luceño AM. Comparative Cytotoxic Properties of Two Varieties of *Carica papaya* leaf extracts from Mindanao, Philippines using Brine Shrimp Lethality Assay. Bull Env Pharmacol Life Sci. 2019; 8:113-8.
39. Nafiu AB, Alli-Oluwafuyi A-m, Haleemat A, Olalekan IS, Rahman MT. Papaya (*Carica papaya* L., Pawpaw). Nonvitamin and Nonmineral Nutritional Supplements: Elsevier, 2019, 335-59.
40. Mohiuddin A. Dengue Epidemic Situation in Bangladesh. J Clin Case Stu, 2019, 4(3).
41. Husin F, Ya'akob H, Rashid SNA, Shahar S, Soib HH. Cytotoxicity study and antioxidant activity of crude extracts and SPE fractions from *Carica papaya* leaves. Biocatalysis and Agricultural Biotechnology. 2019; 19:101130.
42. Nesar S, Omer KR, Rizvi S, Ali A, Mumtaz T, Usmani MSA. *Carica papaya*; A Paired and Alternative Therapy of Dengue Fever. 2018.
43. Jagtap NS, Wagh RV, Chatli MK, Kumar P, Malav O, Mehta N. Optimisation of extraction protocol for *Carica papaya* L. to obtain phenolic rich phyto-extract with prospective application in chevon emulsion system. Journal of food science and technology. 2019; 56(1):71-82.
44. Pham HNT, Sakoff JA, Van Vuong Q, Bowyer MC, Scarlett CJ. Phytochemical, antioxidant, anti-proliferative and antimicrobial properties of Catharanthus roseus root extract, saponin-enriched and aqueous fractions. Molecular biology reports. 2019; 46(3):3265-73.
45. Amin AH, Bughdadi FA, Abo-Zaid MA, Ismail AH, El-Agamy SA, Alqahtani A, *et al*. Immunomodulatory effect of papaya (*Carica papaya*) pulp and seed extracts as a potential natural treatment for bacterial stress. Journal of Food Biochemistry, 2019.
46. Devi G, Harikrishnan R, Paray BA, Al-Sadoon MK, Hoseinifar SH, Balasundaram C. Effects of aloe-emodin on innate immunity, antioxidant and immune cytokines mechanisms in the head kidney leucocytes of Labeo rohita against Aphanomyces invadans. Fish & shellfish immunology. 2019; 87:669-78.
47. Zargar OA, Bashir R, Ganie SA, Hamid R. The effect of Elsholtzia densa methanolic extract modulates inflammation *in vitro* and *in vivo*. Oriental Pharmacy and Experimental Medicine. 2019; 19(1):49-58.
48. Shahid H, Shahzad M, Shabbir A, Saghir G. Immunomodulatory and Anti-Inflammatory Potential of Curcumin for the Treatment of Allergic Asthma: Effects on Expression Levels of Pro-inflammatory Cytokines and Aquaporins. Inflammation. 2019; 42(6):2037-47.
49. Wadkhien K, Pongimitprasert N. Anti-Inflammatory Effects of Rhein Anthraquinone and Crude Extracts from *Cassia alata* Linn. In Hacat Cells: Silpakorn University, 2019.
50. Mogahed HE, El-Rhman AA, El-Sheikh NM, Barakat H. Protective effects of cactus and/or papaya juices against hepatic and testicular toxicity induced by chlorpyrifos in albino rats, 2019.
51. Gbolade AA. Inventory of antidiabetic plants in selected districts of Lagos State, Nigeria. Journal of Ethnopharmacology. 2009; 121(1):135-9.
52. Okpe O, Habila N, Ikwebe J, Upev VA, Okoduwa SI, Isaac OT. Antimalarial Potential of *Carica papaya* and *Vernonia amygdalina* in Mice Infected with Plasmodium berghei. Journal of tropical medicine, 2016.
53. Hewitt H, Whittle S, Lopez S, Bailey E, Weaver S. Topical use of papaya in chronic skin ulcer therapy in Jamaica. The west Indian medical journal. 2000;

49(1):32-3.
54. Shahid S, Fatima U. Pharmacological Activities of *Carica papaya* Linn. Journal of Basic and Applied Sciences. 2018; 14:210-6.
55. Chávez-Quintal P, González-Flores T, Rodríguez-Buenfil I, Gallegos-Tintoré S. Antifungal activity in ethanolic extracts of *Carica papaya* L. cv. Maradol leaves and seeds. Indian journal of microbiology. 2011; 51(1):54-60.
56. Koffi N, Solange T, Emma A, Noel Z. Ethanobotanical study of plants used to treat arterial hypertension, in traditional medicine. European J Scient Res. 2009; 1(1):1-10.
57. Sagadevan P, Selvakumar S, Raghunath M. Medicinal properties of *Carica papaya* Linn: Review. Madridge J Nov Drug Res. 2019; 3(1):120-5.
58. El-Amier YA, Al Borki AE-NS, Elagami SA. Potential of wild plant *Artemisia judaica* L. as sustainable source of antioxidant and antimicrobial compounds. Journal of Experimental Sciences, 2019.
59. Amadi G, Iwuji SC, Azeez TO, Nwaokoro CJ, Wodu CO. Biochemical Effects of Piper Guineense (African Black Pepper) in Female Diabetics: Opportunities for Diabetes Treatment. International Journal of Translational Medical Research and Public Health. 2019; 3(1):59-65.
60. Barreto GP, Fabi JP, De Rosso VV, Cordenunsi BR, Lajolo FM, do Nascimento JR *et al*. Influence of ethylene on carotenoid biosynthesis during papaya postharvesting ripening. Journal of Food Composition and Analysis. 2011; 24(4-5):620-4.
61. Sharma N, Goswami UC, editors. Functioning of lycopene in mammalian system: A review. Proceedings of the Zoological Society Springer, 2011.
62. González-Stuart A. Potential chemopreventive effects of fruits, vegetables, and spices consumed in Mexico. Nutrients, Dietary Supplements, and Nutriceuticals: Springer, 2011, 287-300.
63. Raju NJ, Yesuf EA. Evaluation of anthelmintic activities of *Rumex abyssinicus* Jacq and *Rumex nervosus* vahl. (polygonaceae). International Journal of Pharmaceutical Sciences Review and Research. 2010; 5(2):55-7.
64. Dwivedi G, Bairagi M, Rawal D, Rawal S. Anthelmintic activity of *Myristica fragrans* (Nutmeg) extract. Res J Pharm Biol Chem Sci. 2011; 2(3):315.
65. Ortega MG. Effect of proteolytic enzyme and fiber of papaya fruit on human digestive health: University of Illinois at Urbana-Champaign, 2012.
66. Ukoba O, Adfisan IE and Aguawa US: The wound healing effect of powdered *Carica papaya* leaves. IMPACT: International Journal of Research in Applied, Natural and Social Sciences (IMPACT: IJRANSS). 2016; 4(3):1-10.
67. Ranasinghe P, Kaushalya WP, Abeysekera M, Sirimal Premakumara GA, Perera YS, Gurugama P, Gunatilake SB. *In vitro* erythrocyte membrane stabilization properties of *Carica papaya* L. leaf extracts. Pharmacognosy Res. 2012; 4(4):196-202.
68. Senthilvel P, Lavanya P, Kumar KM, Swetha R, Anitha P, Bag S *et al*. Flavonoid from *Carica papaya* inhibits NS2B-NS3 protease and prevents Dengue 2 viral assembly. Bioinformation. 2013; 9(18):889-895.
69. Subenthiran S, Choon TC, Cheong KC, Thayan R, Teck MB, Muniandy PK *et al*. *Carica papaya* Leaves Juice Significantly Accelerates the Rate of Increase in Platelet Count among Patients with Dengue Fever and Dengue Haemorrhagic Fever, 2013. Evidence-Based Comp. Alter. Med. http://dx.doi.org/10.1155/2013/616737
70. D harmarathna SL, Wickramasinghe S, Waduge RN, Rajapakse RP, Kularatne SA. Does *Carica papaya* leaf-extract increase the platelet count? An experimental study in a murine model. Asian Pac. J Trop. Biomed. 2013; 3(9):720-724.
71. Kathiresan S, Surash R, Sharif M, Mas Rosemal N, Walther H. Thrombocyte couts in mice after the administration of papaya leaf suspension. Wien. Klin. Wochenschr. 2009; 121(3):19-22.
72. Halim S, Abdullah R, Afzan A, Abdul R, Jantan I, Ismail Z. Acute toxicity study of *Carica papaya* leaf extract in Sprague Dawley rats. J Med. Plants Res. 2011; 5:1867-1872.
73. Betty A, Wu H, Yu T, Hsuen C. Dengue haemorrhage in a mouse model. Ann. NY Acad. Sci. 2009; 1171:E42-E47.
74. Sebastian J, Arie K, Yaohui W, Peter E, Oran K, Je H *et al*. Vitamin C as an antioxidant: evaluation of its role in disease prevention. J Am. Coll. Nutr. 2003; 22(1):18-35.
75. Shaz SK, Ullah N, Rafique I. Prevalence of Hepatitis B and C in District Dir Upper, Khyber Pakhtunkhwa, Pakistan. Glob J Clin Virol. 2019; 4(1):008-18.
76. Cabrera-Cortina J, Sanchez-Vakdez E, Cedas-DeLezama D, Ramirez-Gonzalez M. Oral calcium administration attenuates thrombocytopenia in patients with dengue fever, Report of a pilot study. Proc. West. Pharmacol. Soc. 2008; 51:38-41.
77. Emilio S, Melissa D, Jose A, Jose M. Clinical response in patients with dengue fever to oral calcium plus vitamin D administration: study of 5 cases. Proc. West. Pharmacol. Soc. 2009; 52:14-17.
78. Jutrat M, Ausaneya S, Harutai T, Thaworn C, Thamrongprawat C, Chitsanu P. Serum and urine sodium levels in dengue patients. The Southeast Asian J Trop. Med. Public Health. 2005; 36:197-199.
79. Sanjeev J, Ansari M. Dengue infection causing acute hypokalemic quadriparesis. Neurol. India. 2010; 58:592-594.
80. Amitava R, Anil K, Shailendra PV, Himanshu R, Nirdesh J. Acute hypokalaemic quadriparesis in dengue fever, 2011. BMJ Case Reports. doi:10.1136/bcr.11.2010.3514
81. Harmanjith S, Amandeep K, Anuj S. Acute neuromuscular weakness associated with dengue infection. J. Neurosci. Rural Pract. 2012; 3(1):36-39.
82. Zeb S. Threats of Bioterrorism in Public Health, Epidemiological Clue, Detection and Safety Pre-cautions Deliberate by CDCs.