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REVIEW ARTICLE

Therapeutic application of *Carica papaya* leaf extract in the management of human diseases

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Abstract

Introduction Papaya (*Carica papaya* Linn.) belongs to the family Caricaceae and is well known for its therapeutic and nutritional properties all over the world. The different parts of the papaya plant have been used since ancient times for its therapeutic applications. Herein, we aimed to review the anticancer, anti-inflammatory, antidiabetic and antiviral activities of papaya leaf.

Methods All information presented in this review article regarding the therapeutic application of *Carica papaya* leaf extract has been acquired by approaching various electronic databases, including Scopus, Google scholar, Web of science, and PubMed. The keywords *Carica papaya,* anticancer, anti-inflammatory, immunomodulatory, and phytochemicals were explored until December 2019.

Results The papaya plant, including fruit, leaf, seed, bark, latex, and their ingredients play a major role in the management of disease progression. *Carica papaya* leaf contains active components such as alkaloids, glycosides, tannins, saponins, and flavonoids, which are responsible for its medicinal activity. Additionally, the leaf juice of papaya increases the platelet counts in people suffering from dengue fever.

Conclusion The major findings revealed that papaya leaf extract has strong medicinal properties such as antibacterial, antiviral, antitumor, hypoglycaemic and anti-inflammatory activity. Furthermore, clinical trials are needed to explore the medicative potential of papaya leaf.

Keywords *Carica papaya.* Anticancer. Anti-inflammatory. Immunomodulatory. Phytochemical

Introduction

Plants and plant-based products have been employed to prevent various human diseases since ancient times. Overall, approximately 80% population of the world depends directly on plants for the primary health care [1]. In India, about 45,000 plant species have been reported to possess medicinal properties [2]. Natural product or compounds isolated from the plant have shown a major advantage over synthetic drugs such as cost-effective, easy availability and show negligible side effects [3]. Numerous studies have published the use of medicinal plants for the management of a wide range of Diseases. *carica papaya* Linn. from the Caricaseae family, is *indigenous* to Central America and South of Mexico, and commonly grown in India has been used for its medicinal properties around the world [4]. The papaya plant is perennial usually unbranched, smooth stem and long-stalked leaves are having 5–6 lobes and can grow up to 20 m in height [5]. Different parts of papaya plant viz. fruit, bark, roots, seeds, peel, pulp, and leaf have many known therapeutic uses around the world (Table 1) [6].

The papaya plant is a nutritionally abundant source of vitamins A, B and C and also a fair source of calcium and iron [10]. It contains enzyme papain, which helps in digestion and used to treat ulcers and in some microbial diseases where it is specifically effective against gram-negative bacteria at higher

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Table 1 Medicinal uses of different part of papaya plant [6–9]

Plant part	Medicinal uses
Ripe fruit	Sinuses, chronic forms of skin indurations in Caribe, Philippines; Chronic skin ulcers in Jamaica Stomachic, digestive, diuretic, expectorant, sedative and tonic, bleeding Piles and dyspepsia in India
Green fruit	Malaria, hypertension, diabetes mellitus, hypercholesterolemia, jaundice Intestinal helminthiasis in Nigeria
Latex	Dermatitis and psoriasis in Africa, Asia, Europe
Leaves	Heart tonic, febrifuge, vermifuge, colic, dengue fever, beriberi, abortion, asthma India, Stomach troubles, cancer in Australia
Flowers	Jaundice, cough, hoarseness, bronchitis, laryngitis, and tracheitis in Asia
Seeds	Anti-fertility. Antimicrobial, fungicidal, carminative, counter irritant
Roots/barks	Digestive, tonic, abortifacient in Australia, sore teeth in India, syphilis in Africa

doses [7]. The seed extract of papaya fruit contains benzyl isothiocyanate, which is bactericidal, bacteriostatic, and fungicidal at a single effective dose of 4–5 g seeds (25–30 mg BITC) [8]. Papaya possesses excellent antioxidant activity which play role in the neutralization of free radical generation and prevent the pathogenesis [11]. Latex is one of the most important constituents of papaya which contains papain, glycyl endopeptidase, chymopapain and caricain, and the abundance of these proteinases vary in different parts of papaya plant [12]. In recent years many scientific research have been performed to explore the therapeutic uses of papaya leaf. Papaya leaves have been used for remedies against various ailments, such as fever, asthma, colica, beriberi and jaundice [9]. Currently, various methods have been used for the preparation of papaya leaf extract (PLE), but most commonly aqueous extract, ethanol extract, methanol extract, and freeze-dried papaya leaf juice have been used for the prevention of several diseases [13–15]. Papaya leaf contains carbohydrates, vitamins, lipids, proteins, and thus, it can be used as a nutritional agent. These compounds varying in concentration including ascorbic acid 38.6%, protein 5.6%, phosphoric acid 0.225%, carbohydrates 8.3%, iron 0.0064% and minerals like magnesium 0.035% per 100 g of leaf portion [16]**.** The quantitative phytochemical analysis illustrated that aqueous PLE revealed the presence of 0.001% tannins, 0.022% saponins, 0.013% flavonoids, 0.011%, phenolics, 0.019% alkaloids and 0.004% steroids [17].

In addition, PLE has a therapeutic option for the prevention of dengue, which is a viral disease [18]. Recently, Otsuki and coworker have reported the effect of PLE on the growth of tumor cells and also showed that increased secretion of T_H1 type cytokines from human lymphocytes [19]. Currently, reported that papaya leaf has several active constituents which can enhance the antioxidant power in the blood and decrease lipid peroxidation level, like ascorbic acid, alpha-tocopherol, chymopapain, cyanogenic glucosides, cystatin, flavonoids, glucosinolates, and papain [20]. The structures of bioactive secondary metabolites derived from PLE were shown in Fig. 1. Many anecdotal references for the treatment of breast cancer [21], osteosarcoma [22], hepatocellular carcinoma, Burkitt's lymphoma, pancreatic epithelioid carcinoma, cervical carcinoma, mesothelioma, and lung adenocarcinoma [23] have been reported. Even various studies of the anticancer properties of PLE prepared by aboriginals in Australia have been subsequently documented [24]. Many scientific studies have been carried out to isolate and characterize the bioactive constituents from papaya leaves. The photochemical investigation suggested that young leaves contain alkaloids, saponin, tannin, flavonoid and glycosides, hence have therapeutic properties like antibacterial, anti-inflammatory, antiviral, hypoglycaemic antitumor and many others [25]. The review

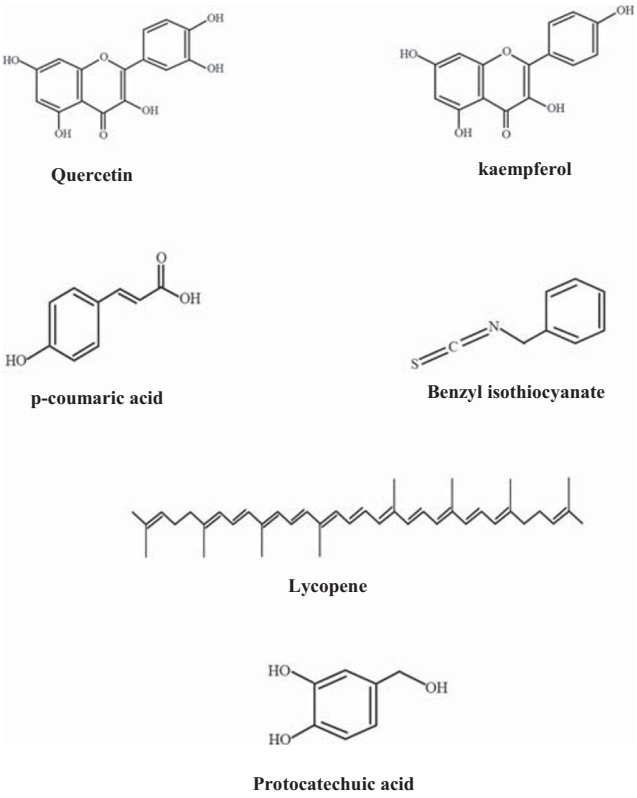

Fig. 1 *Carica papaya* leaf derived compounds

mainly emphasises on the therapeutic properties of *Carica papaya* leaf for the prevention and management of disease progression.

Therapeutic application of PLE

Papaya leaf extract (PLE) has a medicinal role in the treatment of various human diseases owing to the presence of rich source of phytochemicals, minerals and vitamins. Several literatures have been documented the implication of PLE for controlling various diseases since ancient time. Furthermore, the potential role of leaf in disease prevention summarized below is based on the current scientific investigations.

Mechanism of action of papaya leaf in health management

PLE is known to interact with a broad range of molecular targets and exert therapeutic activity against several diseases. The vital molecular targets involved in the anticancer prevention are suppression of the activity of DNA topoisomerase I/II, alteration of signalling pathways, downregulating gene expression of Bcl-2 and Bcl-XL, upregulating the gene expression of Bax, Bak, cleaved caspase 3 and increasing the expression of P53 [19, 26]. PLE treatment increased nitric oxide production (NO), costimulatory receptor (CD80), tumor necrosis factor-alpha (TNF-α), IL-12p40, IL-6, IL-12p70, IFN-γ, and decreased the secretion of IL-2, IL-4 [19, 27]. Further, PLE modulates the secretion of pro-inflammatory cytokines like IL-1β, IL-6, IL-1α, IL-8, and chemokine CCL7, CCL2, CCL8 [19, 28]. CPE treatment is reported to the beneficial effect on dengue patients through activation of expression of ALOX 12 and PTAFR gene [29]. Figure 2 illustrates the molecular mechanisms of action of PLE for the treatment of various diseases. Furthermore, freeze-dried *Carica papaya* leaf modulates the production of inflammatory cytokines CCL6/MRP-1, CCL17/TARC, CCL12/MCP-5, CCL8/MCP-2, IL1RN/IL1Ra, IL1R1, PF4/CXCL4, and NAMPT/PBEF1 in the dengue virus-infected mice AG129 [30]. PLE also regulates the β-cells for the release of insulin in diabetic rats [31].

Anti-cancer effect of PLE

Cancer is one of the most deadly diseases which arises due to the uncontrolled division of genetically unstable cells and significant causes of deaths that occur worldwide. Among different types of cancers including colon, cervix, liver, stomach, lung, pancreas and breast cancer reported in the human, lung cancer is the most prevalent cancer among males, followed by breast cancer in females [32]. Currently, depending upon the type, stage and location of cancer, there are many treatments available for cancer like surgery, chemotherapy, radiotherapy, immunotherapy, vaccinations and combination therapy, where chemotherapy is a widely used treatment for highly metastatic cancer [33]. Chemotherapeutic drugs like Irinotecan, vinblastine, doxorubicin, oxaliplatin, melphalan, carboplatin, cisplatin, cyclophosphamide, docetaxel, vincristine, and paclitaxel, etc. are significantly effective against a wide range of cancers, and have shown promising results alone or in combination with other cancer therapies [33, 34]. However, these drugs have their own limitations including limited bioavailability, toxicity, non-specificity and fast clearance [35]. These drugs are frequently linked with adverse effects like high cytotoxicity, neutropenia, sensory neuropathy, cardiovascular toxicity, pulmonary and hematologic toxicity, gastrointestinal toxicity, diarrhoea and nephrotoxicity, [33, 34]. Therefore, now researchers have focused on using alternative treatments against cancer with minimal or without any side effects [36]. Based on extensive research findings, plant extracts and their derived analogues are thought to be the most promising option for cancer treatment without any noticeable side effects of drugs during therapy [37].

Recently, the presence of a rich phytochemicals-based medicine system of several tropical plants including papaya has attracted the attention of researchers [38]. Several groups of scientists are working worldwide on a possible phytochemicals-based treatment with minimal side effect to cure the malaise of cancer. In 2008, Morimoto et al. reported that in many cases where patients suffering from blood, lung, liver, pancreatic and stomach cancer showed increased survival after consuming aqueous PLE, and that was later patented by him [39]. The most common process used throughout the world to prepare extracts from various parts of the papaya plant is cold juicing, where mortar and pestle are used [40, 41]. This method has been studied to release bioactive compounds having strong cytotoxic effects on cancer cells as compared to its aqueous and ethanol extracts [40, 41]. The extract isolated by this method has a very good anticancer effect against benign, malignant and normal cells of prostate origin when applied in vitro; however, if given orally, the same effect may not be observed in the animal [42].

Studies have shown that in vitro digested PLE by passing through key steps responsible for physiochemical changes during human digestion, retained anti-proliferative response, but with lower potency and efficacy as compared to the crude PLE [43]. The in vitro anticancer effect of PLE has been evaluated in several types of cancer cells summarized in Table 2. Further, PLE showed potential anticancer effect by decreasing proliferation of prostate cancer cells, only with negligible effect on the normal cells possibly by inducing cell cycle arrest and apoptosis [45]. It has been reported that the antitumor effect of PLE is due to the activation of caspase-3/7

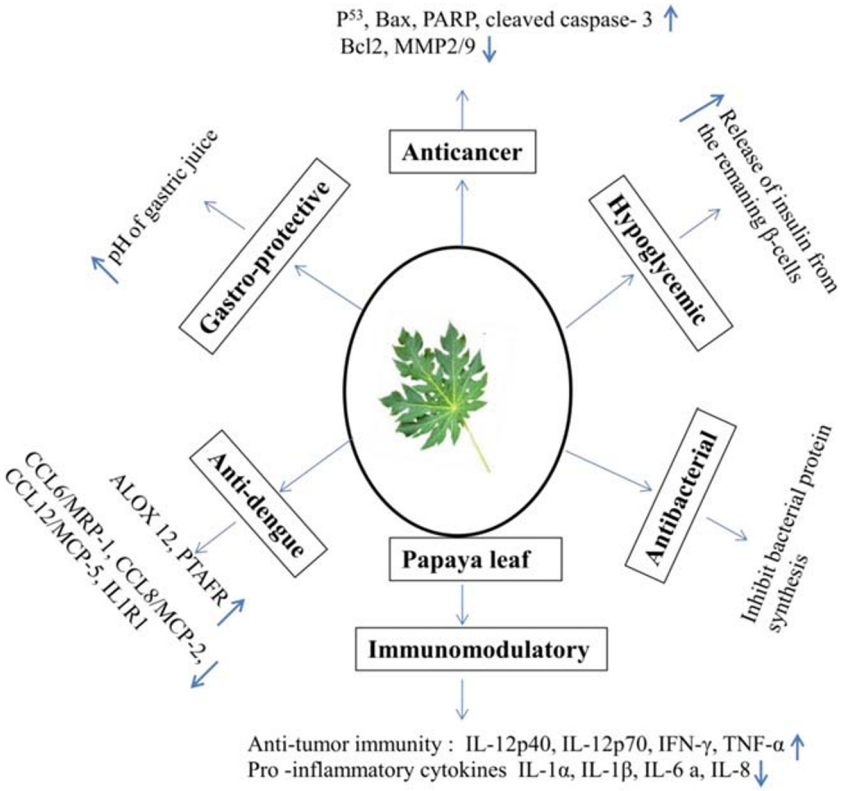

Fig. 2 Molecular mechanisms of action of underlying therapeutic properties of papaya leaf

and p53-dependent mitochondrial pathway [46], while another study showed that PLE arrests PCa cells in S phase followed by cell death as a mechanism for the antitumor activity of PLE fraction [42]. Further, PLE has been shown to decrease characteristic feature of metastatic cancer including adhesion, migration and invasion [44, 47] by reducing extracellular matrix (ECM) that acts as chemo-attractants for adhesion and migration of PC-3 cells [42, 48]. However, thorough investigations are required to explore the anti-metastatic potential of PLE and its compound(s) against different cancers. In vivo acute toxicity study found that orally administered of PLE at different doses from 5 to 2000 mg/kg body weight

Table 2 In vitro anticancer effect of papaya leaf extract

Papaya leaf (Dose)	Cell line	Mechanisms of action	References
Aqueous (1.25–27 mg/mL)	Stomach cancer cells (AGS), Pancreatic cancer cells (Capan-1), Colon cancer cells (DLD-1), Ovarian cancer cells (Dov-13), Lymphoma cells (Karpas), Breast cancer cells (MCF-7)	Papaya leaf extract significantly decreased the cell proliferation of each cancer cells and suppressed DNA synthesis	[39]
Aqueous (0.625–20 mg/mL)	Human peripheral blood mononuclear cells (PBMC), T cell lines (Jurkat, Molt-4, CCRF-CEM and HPB-ALL), Burkitt's lymphoma cell lines (Ramos and Raji), Leukemia cell line (K562), Cervical carcinoma cell line (Hela), Hepatocellular carcinoma cell lines (HepG2 and Huh-7), Lung adenocarcinoma cell line (PC14), Pancreatic epithelioid carcinoma cell line (Panc-1), Mesothelioma cell lines (H2452, H226, MESO-4)	Inhibited the cell growth in tumor cell lines. In human peripheral blood mononuclear cells, papaya extract decreased the production of IL-2, IL-4 and increased the production of cytokines L-12p40, IL-12p70, IFN-γ and TNF-α.	[19]
Juice (0.01-1 mg/mL)	Prostate epithelial cells (RWPE 1), Benign tumour (BPH1), Human prostate cancer cells (PC-3 &LNCaP)	Obtained results shown that significantly decrease the cell proliferation, S phase cell cycle arrest and induced apoptosis in prostate cancer cells	[42]
Aqueous (5,10,25 μl/ml)	Human prostate carcinoma cells (LNCaP, DU145, PC3)	Aqueous leaf extract of papaya down regulated the expression of cell cycle regulatory molecules CDK 4, cyclin D1, cyclin B1, PCNA and induced apoptosis by cleavage of caspase-3 and cleaved Poly (ADP-ribose) polymerase (PARP).	[44]

(BW) showed no significant toxicity effect in rats [49]. Further, consumption of PLE 2 g/kg BW for 13 weeks did not cause any toxicity effects in rats [50]. We have found that oral administration of PLE (0.25%, 0.5% and 1% *v*/v) in drinking water has not shown any significant changes in BW, water consumption and food intake as compared to the control group in C57BL/6 male mice [44].

Immunomodulatory effect of PLE

The experimental evaluation of different parts of papaya plant show that it has high medicinal values and beneficial in many pathological conditions including wound healing, cardiovascular diseases, dengue fever, cancer etc. [51, 52]. Recently, a strong immunomodulatory, antitumor and anti-inflammatory properties of PLE have been reported on several cancer cell lines [53–55]. However, with very few reports on peripheral blood mononuclear cells (PBMC) [19]. In 2010, a study showed the immunomodulatory potential of PLE and evaluated the cytokine profile of human PBMC by ELISA, and reported that PLE downregulates IL-4 and IL-2 secretion in culture supernatants in a dose-dependent manner, and assumed that PLE may induce apoptosis in PBMC, like similar effect on cancer cells [19]. However, secretion of Th1 type cytokines like IL-12p70, IL-12p40, TNF-α, or IFN-γ relevant to anti-tumor immunity was interestingly upregulated at a low dose of PLE, while slight effect on IL-15, IL-6, IL-5, and IL-10 production [19]. This finding suggests that there could be a significant correlation between elevated secretion of Th1 type cytokines and enhanced cytotoxicity, since IFN-γ, TNF-α, and IL-12 are potent in activating cell-mediated cytotoxicity [56], which could result in enhanced anti-tumor immunity [57]. It further enhances the possibility that PLE may promote the management of Th2-mediated allergic ailments, like bronchial asthma and allergic rhinitis, or as an adjuvant of various vaccines by stimulating a change from Th2 to Th1 type immune response [19].

Numerous in vitro findings have emphasized on the role of bioactive compositions present in PLE extracted with polar solvents, mainly alcohol and water, in modulating immune-inflammatory markers [58]. In 2014, Bertrand et al. have shown that bacterial endotoxin, lipopolysaccharide (LPS) activates innate immunity by modulating the production of various inflammatory mediators like IL-6, IL-1β, IFN-γ, and TNF-α in monocytes/macrophages [59]. TNF-α secreted by monocytes or macrophages induces secretion of additional pro-inflammatory cytokines namely IL-6, IL-1β and IFN-γ that play a vital role in the pathophysiology of inflammation [58]. This finding motivated the researchers to find out the agent that could block TNF-α activities during chronic inflammation. In 2014, Bertrand et al. showed that an ethanolic PLE significantly inhibited isopentenyl pyrophosphate (IPP) induced TNF-α release in LPS-induced dendritic cells [59]. Further, it was reported that methanol extract of papaya leaf decreased the secretion of pro-inflammatory IL-6, IL-1β, IL-1α, TNF-α, and IL-8 by 42.9%, 27.4%, 12.5%, 10.8%, and 8.4%, accordingly in LPS-stimulated human PBMCs [28]. Further, reduction of nitric oxide (NO) secretion in IFN-γ or LPS-activated murine macrophages cells (RAW 264.7 cell line) by methanolic PLE was reported in 2011 [60]. A study documented that an aqueous extract of unripe papaya fruit modulates the levels of malondialdehyde, catalase, glutathione and superoxide dismutase, and enhanced the immunoglobulin IgG and IgM levels significantly in acrylamide-treated rats [61].

Collectively, all in vitro findings discussed here indicate that papaya extracts have potential to modulate the expression of inflammatory markers in several cell types under stress. Many in vitro studies have employed polar solvent of papaya extracts and hence, the anti-inflammatory activity of nonpolar extracts needs further investigation. Animal studies are required to understand the biological effects and potential use of plant extracts for their pre-clinical significance. Table 3 demonstrates the activities of papaya for modulation of inflammatory markers, and enhancing of antioxidant enzymes and platelets in animals and humans when it is taken in the form of fruit, peel and leaf. Other in vivo findings on mice and humans have also founded the anti-inflammatory [60] and platelet increasing activities of PLE. The in vitro studies are limited which have analysed the immunomodulatory activity and mechanisms of papaya fruit, however, it has been studied in several animal experiments.

Anti-dengue effect of PLE

Dengue is an alarming disease that affects people globally and estimated to have 50–100 million cases every year [63]. Dengue is caused by dengue virus (DENV) 1–4, belongs to the Flaviviridae family and transmitted through the bite of infected mosquito, *Aedesaegypti* [63]. The symptoms of the disease appear within 4–7 days after incubation of dengue virus that include high fever, rash, headache, vomiting and muscular pain [64]. Thrombocytopenia, the decline in platelet count, is one of the main hallmarks of dengue and used for the diagnosis of dengue patients [65]. World Health Organization (WHO) reported that thrombocytopenia is a rapid decrease in platelet count and confirmed by a platelet count of below 150,000 per microliter of blood [67]. Currently, no vaccine or antiviral drugs are existed for the control of dengue disease. Only patients receive supportive treatment with blood, blood components, and fluids for the prevention of the disease or maintenance therapy. There is a ray of hope to have vaccine against dengue as several clinical trials are ongoing.

Alternatively, for tackling the nemesis of dengue, other options need to be explored. Many studies have been carried out to

Table 3 In vivo studies of effect of papaya leaf extracts on dengue fever

Leaf extract	Oral route of administration (dose)	Results	References
Juice	0.2 ml, 7 d	Platelet and RBC count were significantly increased after 21 d ($5.53X10^5$/ml to 11.3 × 105/ml), (6×10^6/ml to 9×10^5/ml) in mice.	[62]
Juice	25 ml, twice daily, 5 d	Significantly increased platelets, RBC, WBC and PMN in male dengue patient.	[63]
Ethanol (70%)	1.1 g, twice daily, 12 d	The results showed that CPC had significant increased the platelet count ($p < 0.05$), maintained stability of hematocrit in the normal level, shorten hospitalization ($p < 0.05$) in dengue fever patients	[64]
Juice	50 g, daily, 3 d	The ALOX 12 (FC = 15.00) and PTAFR (FC = 13.42) genes were highly expressed among those on the juice	[65]
Juice	0.72 ml/100 g	High dose of mature leaf concentrate of *C papaya* in thrombocytopenic rats significantly ($P < 0.05$) increased platelets by 76.5%, WBC by 30.51% and RBCs by 9.08%, when compared with controls	[66]
juice	1000 mg/kg BW	Significantly downregulated 8 inflammatory cytokine genes CL6/MRP-1, CCL8/MCP-2, CCL12/MCP-5, CCL17/TARC, IL1R1, IL1RN/IL1Ra, NAMPT/PBEF1 and PF4/CXCL4 were observed in the liver of infected AG129 mice.	[30]

exploit the herbal medicine for the alternative treatment of dengue complications. Recently, many studies explored the potential role of PLE in treating thrombocytopenia linked with dengue. These studies demonstrated that treatment with papaya leave extract significantly increases the platelet count which is decreased during the dengue infection [62]. A study showed the increase in platelet count of five dengue patients within 24 h after treatment of PLE [68]. Similarly, a randomized controlled study was conducted on 285 patients and observed that papaya leaf syrup enhanced the mean platelet count in comparison with control subjects [69]. Similar results have been observed in a study conducted on 228 patients in Malaysia [66]. Studies indicate that main causes of bleeding in dengue patients are associated with a decreased platelet count which is accompanied by an increased vascular permeability and plasma leakage [70].

The membrane stabilizing properties of *PLE* to protect blood cells against stress-induced destruction has been reported. Such activity can prevent the platelet lysis in dengue patients [71]. Freeze-dried *Carica papaya* leaf juice is also reported recently to significantly decrease the production of inflammatory cytokines viz. CCL12/MCP-5, CCL8/MCP-2,CCL17/TARC, CCL6/MRP-1, IL1RN/IL1Ra, IL1R1, PF4/CXCL4 and NAMPT/PBEF1 in the dengue virus-infected mice AG129 [30]. Currently, PLE was shown to decrease the expression of DENV NS1 envelop protein and cause upregulation of the expression of IFN-α in THP-1 cells [72]. These studies are encouraging and suggest that detailed investigations are needed involving animal models and clinical trials to standardize the use of PLE for the prevention and treatment of the dengue infection.

Hypoglycemic effect of PLE

Diabetes mellitus is a series of metabolic abnormalities characterized by hyperglycaemia and defect in insulin production. The incidence of diabetes is increasing due to various factors such as unhealthy diets, aging, obesity, sedentary lifestyle, and also promoted by malnutrition-related causes. According to the American Diabetes Association, an estimated 1.3% of the population was affected from diabetes around the world in 2017. India is considered as the diabetic centre of the world due to increasing number of diabetic patients [73]. The International Diabetes Federation estimated 40.9 million people with diabetes and predicted an increase in the number up to 69.9 million by 2025 [74]. Many investigations show that medicinal plants for example psyllium seeds, garlic and bittermelon have excellent antidiabetic properties [75].

A study demonstrated that papaya leaf has hypolipidemic and anti-hyperglycemic effects in diabetic rats. Similarly, the aqueous PLE enhances the release of more insulin from remaining β–cells [31]. The administration of the PLE induced a significant decrease in the plasma concentrations of glucose and triacylglycerol to 0.75 and 1.5 g/100 mL, respectively [31]. Furthermore, studies have shown that fermented papaya decreases both the basal and postprandial glycemia and enhances the lipid profile [76]. Furthermore, mechanistic research and clinical trials are required to explore the antidiabetic activity and molecular changes due to PLE.

Sickle cell anaemia and PLE

Sickle cell anaemia is a hereditary disorder affecting the shape and size of red blood cells (RBCs). Molecular investigations have established that mutation in haemoglobin causing replacement of valine for glutamic acid at the sixth position in the beta-globin chain alters the shape of normal RBCs to a sickle shape [77]. Haemoglobin plays a major role in oxygen transport. The major symptoms appear during sickle cell disease are anaemia, blockage of blood vessels and headaches [77]. Sickle cell incidence has been continuously increasing in under developing countries. In 2012, WHO accounted that

Nigeria people are largely affected by sickle cell disease worldwide [78].

A study showed that pre-treatment of SS cell suspensions with PLE suppressed the development of sickle cells in severe hypoxia, with only 0–2% sickle cells against untreated SS cell suspensions having 60% sickle cells. In another comparative study, the aqueous crude extract fraction decreased the sickle cell formation at different concentration of treatment (1, 3, 5–10 mg/ml), with the highest concentration showing a significant antisickling property as compared with crude methanol extract and the HbSS-sodium metabisulphite control [79]. The 5 and 10 mg/ml extract concentrations maintained discoidal shape cells whereas 80% of the SS cells have sickle shape [79]. The PLE also decreased the degree of hemoglobin polymerization and the osmotic fragility of human crescent RBCs [80]. Furthermore, investigations of PLE depicted the presence of amino acids like cysteine, glycine and glutamic acid as well as the fair source of mineral elements such as K, Mg, Ca, Fe, Mn and Na that protect the RBC membrane from lysis and destruction. Further investigations are lacking to examine the mechanism of PLE for the prevention of sickle cell disease.

Antibacterial activity of PLE

There are few studies showing that *Carica papaya* leaf extracts have antibacterial activity. A study performed by Suresh et al. indicated that among five plants extracts, the *Carica papaya* leaf extract presented the highest antibacterial activities [81]. PLE strongly inhibited the growth of the tested gram-positive bacteria (*Pseudomonas aeruginosa, Bacillus subtilis and Staphylococcus aureus*) and had lesser effect on gram-negative (*Klebsiella pneumoniae and Escherichia coli*) bacteria [81, 82]. The thick murein layer present in the outer membrane of gram-negative bacteria prevents the entry of plant extract inhibitor substance into the cell. In another study, papaya leaves extracted with ethanol, methanol, ethylacetate, acetone, chloroform or hot water extracts showed excellent bactericide action against *Bacillus cereus, Klebsiella pneumonia, Micrococcus luteus, Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus* [83]. In addition, methanolic extract of PLE exhibited antimicrobial activity versus *Candida albicans, Escherichia coli and Staphylococcus aureus* [84]. These studies appear to be preliminary warranting more investigations in the molecular alterations associated with its antibacterial activity.

Gastro-protective effect of PLE

Ulcers are a common gastrointestinal tract disorder that influences a massive population of human worldwide. Many risk factors could be associated with this disorder such as smoking, stress, alcohol, nutritional deficiencies, non-steroidal anti-inflammatory drugs (NSAIDs) and infections (*Helicobacter pylori*). Odo et al. [85] investigated the effect of ethanolic extract of papaya leaves in the treatment of experimentally caused gastric ulcer in rats. The result obtained shown the significant ($P < 0.05$) decreases in ulcer index and gastric juice volume, and increase in the pH of gastric juice in aspirin-induced gastric ulcer bearing rats [85]. Another finding confirmed that its aqueous leaf extract reduced the gastric ulcer index in alcohol-induced rat model [86]. Overall, the PLE can be useful as a therapeutic agent for the cure of gastric ulcer, however, more studies are needed for a broader insight.

Conclusions and future perspectives

Overall, this review summarized the therapeutic medicinal potential of papaya leaf for various diseases. The studies discussed above provided evidence for the presence of bioactive phytochemicals in papaya leaf, which could be playing roles in the prevention and cure of the diseases. Under the circumstances, phytomolecules are expecting to revolutionize cancer prevention and treatment in the next decade and will provide a promising and effective alternative to conventional drugs. To evaluate the possible therapeutic applications of these phytochemicals, extensive in vitro or in vivo studies are required, before going to the clinics. In spite of the promising data available, from a number of biochemical, cell culture, animal, and few human studies, there is a need for in depth studies and clinical trials to investigate the potential role of papaya in the management of various human diseases.

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Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest.

References

1. Tripathi L, Tripathi JN. Role of biotechnology in medicinal plants. Trop J Pharm Res. 2003;2(2):243–53.
2. Jain SK. Ethnobotany and research in medicinal plants in India. Ethnobot Search New Drugs. 1994;185:153–68.
3. Wang MW, Hao X, Chen K. Biological screening of natural products and drug innovation in China. Philos Trans R SocLond B Biol Sci. 2007;362(1482):1093–105.
4. Aravind G, Bhowmik D, Duraivel S, Harish G. Traditional and medicinal uses of Carica papaya. J Med Plants Stud. 2013;1(1):7–15.
5. Owoyele BV, Adebukola OM, Funmilayo AA, Soladoye AO. Anti-inflammatory activities of ethanolic extract of Carica papaya leaves. Inflammopharmacol. 2008;16(4):168–73.

6. Vij T, Prashar Y. A review on medicinal properties of Carica papaya Linn. Asian Pac J Trop Dis. 2015;5(1):1–6.
7. Leader B, Baca QJ, Golan DE. Protein therapeutics: a summary and pharmacological classification. Nat Rev Drug Discov. 2008;7(1): 21–39.
8. Tang CS. Benzyl isothiocyanate of papaya fruit. Phytochemistry. 1971;10(1):117–21.
9. Krishna KL, Paridhavi M, Patel JA. Review on nutritional, medicinal and pharmacological properties of papaya (Carica papaya Linn.). Nat Prod Radiance. 2008;7(4):364–73.
10. Wall MM. Ascorbic acid, vitamin a, and mineral composition of banana (Musa sp.) and papaya (Carica papaya) cultivars grown in Hawaii. J Food Compos Anal. 2006;19(5):434–45.
11. Rahmani AH, Aldebasi YH. Potential role of carica papaya and their active constituents in the prevention and treatment of diseases. Int J Pharm Pharm Sci. 2016;8(1):11–5.
12. Paul BI, Nasreen MA, Sarker AN, Islam MR. Isolation, purification and modification of papain enzyme to ascertain industrially valuable nature. Int J Biotechnol Res. 2013;3(5):11–22.
13. Patil T, Patil S, Patil A, Patil S. Carica papaya leaf extracts–an Ethnomedicinal boon. Int J Pharmacogn Phytochem Res. 2014;6(2):260–5.
14. Hu T, Guo YY, Zhou QF, Zhong XK, Zhu L, Piao JH, et al. Optimization of ultrasonic-assisted extraction of total saponins from Ecliptaprostrasta L. using response surface methodology. J Food Sci. 2012;77(9):C975–82.
15. Longdet IY, Adoga EA. Effect of methanolic leaf extract of Carica papaya on plasmodium berghei infection in albino mice. Eur J Med Plants. 2017;20(1):1–7.
16. Saran PL, Choudhary R. Drug bioavailability and traditional medicaments of commercially available papaya: a review. Afr J Agric Res. 2013;8(25):3216–23.
17. Bamisaye FA, Ajani EO, Minari JB. Prospects of ethnobotanical uses of pawpaw (Carica papaya). J Med Plants. 2013;1(4):171–7.
18. Sarala N, Paknikar SS. Papaya extract to treat dengue: a novel therapeutic option?.Ann Med Health Sci Res. 2014;4(3):320–4.
19. Otsuki N, Dang NH, Kumagai E, Kondo A, Iwata S, Morimoto C. Aqueous extract of Carica papaya leaves exhibits anti-tumor activity and immunomodulatory effects. J Ethnopharmacol. 2010;127(3):760–7.
20. Seigler DS, Pauli GF, Nahrstedt A, Leen R. Cyanogenicallosides and glucosides from Passifloraedulis and Carica papaya. Phytochemistry. 2002;60(8):873–82.
21. Hadadi SA, Li H, Rafie R, Kaseloo P, Witiak SM, Siddiqui RA. Anti-oxidation properties of leaves, skin, pulp, and seeds extracts from green papaya and their anti-cancer activities in breast cancer cells. J Cancer Metastasis Treat. 2018;4:25.
22. Liew SY, Stanbridge EJ, Yusoff K, Shafee N. Hypoxia affects cellular responses to plant extracts. J Ethnopharmacol. 2012;144(2): 453–6.
23. Saranya V, Malathi N. Evidence-based review on anticancer effects of commonly used herbs. J AdvClin Res Insights. 2014;1(2):73–7.
24. Webb LJ. The use of plant medicines and poisons by Australian aborigines. Aust J Anthropol. 1969;7(2):137–46.
25. Nugroho A, Heryani H, Choi JS, Park HJ. Identification and quantification of flavonoids in Carica papaya leaf and peroxynitrite-scavenging activity. Asian Pac J Trop Biomed. 2017;7(3):208–13.
26. Rumiyati S. Effect of the protein fraction of Carica papaya L. leaves on the expressions of P53 and BCL-2 in breast cancer cells line. Maj Farm Indones. 2006;17:170–6.
27. Singh SP, Kumar S, Tomar MS, Singh RK, Verma PK, Kumar A, et al. Aqueous extract of Carica papaya leaf elicits the production of TNF-α and modulates the expression of cell surface receptors in tumor-associated macrophages. Biosc Biotech Res. 2019;4:1115–22.
28. Salim E, Kumolosasi E, Jantan I. Inhibitory effect of selected medicinal plants on the release of pro-inflammatory cytokines in lipopolysaccharide-stimulated human peripheral blood mononuclear cells. J Nat Med. 2014;68(3):647–53.
29. Siddique O, Sundus A, Ibrahim MF. Effects of papaya leaves on thrombocyte counts in dengue–a case report. JPMA J Pak Med Assoc. 2014;64(3):364–6.
30. Norahmad NA, Razak MR, Misnan NM, Jelas NH, Sastu UR, Muhammad A, et al. Effect of freeze-dried Carica papaya leaf juice on inflammatory cytokines production during dengue virus infection in AG129 mice. BMC Complement Altern Med. 2019;19(44): 1–10.
31. Juárez-Rojop IE, Díaz-Zagoya JC, Ble-Castillo JL, Miranda-Osorio PH, Castell-Rodríguez AE, Tovilla-Zárate CA, et al. Hypoglycemic effect of Carica papaya leaves in streptozotocin-induced diabetic rats. BMC Complement Altern Med. 2012;12(1):236.
32. Society AC. Cancer facts & figures. Am Cancer Soc. 2016.
33. Weaver BA. How Taxol/paclitaxel kills cancer cells. Mol Biol Cell. 2014;25(18):2677–81.
34. Caruso M, Colombo AL, Fedeli L, Pavesi A, Quaroni S, Saracchi M, et al. Isolation of endophytic fungi and actinomycetestaxane producers. Annales de Microbiologie. 2000;50(1):3–13.
35. Patra CR, Mukherjee S, Kotcherlakota R. Biosynthesized silver nanoparticles: a step forward for cancer theranostics. Nanomed. 2014;9(10):1445–8.
36. Chua LK, Lim CL, Ling AP, Chye SM, Koh RY. Anticancer potential of Syzygium species: a review. Plant Foods Hum Nutr. 2019;74(1):18–27.
37. Singh S, Sharma B, Kanwar SS, Kumar A. Lead phytochemicals for anticancer drug development. Front Plant Sci. 2016;7:1–13.
38. Rasmann S, Agrawal AA. Latitudinal patterns in plant defense: evolution of cardenolides, their toxicity and induction following herbivory. Ecol Lett. 2011;14(5):476–83.
39. C Morimoto, N Dang, inventors; Dang Nam H, assignee. Compositions for cancer prevention, treatment, or amelioration comprising papaya extract. United States patent application US 11/631,655. 2008.
40. Nguyen TT, Parat MO, Hodson MP, Pan J, Shaw PN, Hewavitharana AK. Chemical characterization and in vitro cytotoxicity on squamous cell carcinoma cells of Carica papaya leaf extracts. Toxins. 2016;8(1):1–11.
41. Nguyen TT, Parat MO, Shaw PN, Hewavitharana AK, Hodson MP. Traditional aboriginal preparation alters the chemical profile of Carica papaya leaves and impacts on cytotoxicity towards human squamous cell carcinoma. PLoS One. 2016;11(2):1–15.
42. Pandey S, Walpole C, Cabot PJ, Shaw PN, Batra J, Hewavitharana AK. Selective anti-proliferative activities of Carica papaya leaf juice extracts against prostate cancer. Biomed Pharmacother. 2017;89:515–23.
43. Bouayed J, Hoffmann L, Bohn T. Total phenolics, flavonoids, anthocyanins and antioxidant activity following simulated gastrointestinal digestion and dialysis of apple varieties: bioaccessibility and potential uptake. Food Chem. 2011;128(1):14–21.
44. SP Singh, SV Mathan, A Dheeraj, D Tailor, RP Singh, A Acharya. Anticancer effects and associated molecular changes of *Carica papaya* against prostate cancer. AACR; Cancer Res. 2019; 79(13): Abstract nr 3004.
45. Cragg GM, Newman DJ. Plants as a source of anti-cancer agents. J Ethnopharmacol. 2005;100(1–2):72–9.

46. Rumiyati S. Effect of the protein fraction of Carica papaya L. leaves on the expressions of P53 and BCL-2 in breast cancer cells line. Maj FarmIndones. 2006;17:170–6.
47. Fauziya S, Krishnamurthy R. Papaya (Carica papaya): source material for anticancer. CIBTech J Pharm Sci. 2013;2(1):25–34.
48. Nguyen TT, Shaw PN, Parat MO, Hewavitharana AK. Anticancer activity of Carica papaya: a review. Mol Nutr Food Res. 2013;57(1):153–64.
49. Ismail Z, Halim SZ, Abdullah NR, Afzan A, Rashid A, Amini B, et al. Safety evaluation of Oral toxicity of Carica papaya Linn. Leaves: a subchronic toxicity study in Sprague Dawley rats Evid Based Complement. 2014;2014:1–10.
50. Halim SZ, Abdullah NR, Afzan A, Rashid BA, Jantan I, Ismail Z. Acute toxicity study of Carica papaya leaf extract in Sprague Dawley rats. J Med Plant Res. 2011;5(10):1867–72.
51. Cooper CR, McLean L, Walsh M, Taylor J, Hayasaka S, Bhatia J, et al. Preferential adhesion of prostate cancer cells to bone is mediated by binding to bone marrow endothelial cells as compared to extracellular matrix components in vitro. Clin Cancer Res. 2000;6(12):4839–47.
52. Maniyar Y, Bhixavatimath P. Antihyperglycemic and hypolipidemic activities of aqueous extract of Carica papaya Linn. Leaves in alloxan-induced diabetic rats. J Ayurveda Integr Med. 2012;3(2): 70–4.
53. Imaga NA, Gbenle GO, Okochi VI, Adenekan S, Duro-Emmanuel T, Oyeniyi B, et al. Phytochemical and antioxidant nutrient constituents of *Carica papaya* and Parquetinanigrescens extracts. Sci Res Essays. 2010;5(16):2201–5.
54. Gurung S, Škalko-Basnet N. Wound healing properties of Carica papaya latex: in vivo evaluation in mice burn model. J Ethnopharmacol. 2009;121(2):338–41.
55. Anjum V, Arora P, Ansari SH, Najmi AK, Ahmad S. Antithrombocytopenic and immunomodulatory potential of metabolically characterized aqueous extract of Carica papaya leaves. Pharm Biol. 2017;55(1):2043–56.
56. Foulds KE, Wu CY, Seder RA. Th1 memory: implications for vaccine development. Immunol Rev. 2006;211(1):58–6.
57. Baxevanis CN, Voutsas IF, Tsitsilonis OE, Gritzapis AD, Sotiriadou R, Papamichail M. Tumor-specific CD4+ T lymphocytes from cancer patients are required for optimal induction of cytotoxic T cells against the autologous tumor. J Immunol. 2000;164(7):3902–12.
58. Pandey S, Cabot PJ, Shaw PN, Hewavitharana AK. Anti-inflammatory and immunomodulatory properties of Carica papaya. J Immuno toxicol. 2016;13(4):590–602.
59. Sagnia B, Fedeli D, Casetti R, Montesano C, Falcioni G, Colizzi V. Antioxidant and anti-inflammatory activities of extracts from Cassia alata, Eleusine indica, Eremomastax speciosa, Carica papaya and Polyscias fulva medicinal plants collected in Cameroon. PLoS One. 2014;9(8):1–10.
60. Lee KH, Padzil AM, Syahida A, Abdullah N, Zuhainis SW, Maziah M, Sulaiman MR, Israf DA, Shaari K, Lajis NH. Evaluation of anti-inflammatory, antioxidant and antinociceptive activities of six Malaysian medicinal plants. J Med Plant Res 2011 Oct 23;5(23): 5555–5563.
61. Sadek KM. Antioxidant and immunostimulant effect of Carica papaya Linn. Aqueous extract in acrylamide intoxicated rats. Acta Inform Med. 2012;20(3):180–5.
62. Dharmarathna 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):720–4.
63. Ahmad N, Fazal H, Ayaz M, Abbasi BH, Mohammad I, Fazal L. Dengue fever treatment with Carica papaya leaves extracts. Asian Pac J Trop Biomed. 2011;1(4):330–3.
64. Yunita F, Hanani E, Kristianto J. The effect of Carica papaya L. leaves extract capsules on platelets count and hematocrit level in dengue fever patient. Int J Med Aromat Plants. 2012;2(4):573–8.
65. 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. Evid Based Complement Alternat Med. 2013;2013:1–7.
66. Gammulle A, Ratnasooriya WD, Jayakody JR, Fernando C, Kanatiwela C, Udagama PV. Thrombocytosis and anti-inflammatory properties and toxicological evaluation of Carica papaya mature leaf concentrate in a murine model. Online Int J Med Plant Res. 2012;1(2):21–30.
67. Oishi K, Saito M, Mapua CA, Natividad FF. Dengue illness: clinical features and pathogenesis. J Infect Chemother. 2007;13(3): 125–33.
68. Kala CP. Leaf juice of Carica papaya L. a remedy of dengue fever. Med Aromat Plants. 2012;1(6):1–2.
69. Srikanth BK, Reddy L, Biradar S, Shamanna M, Mariguddi DD, Krishnakumar M. An open-label, randomized prospective study to evaluate the efficacy and safety of Carica papaya leaf extract for thrombocytopenia associated with dengue fever in pediatric subjects. Pediatric Health Med Ther. 2019;10:5–11.
70. Srikiatkhachorn A. Plasma leakage in dengue haemorrhagic fever. Thromb Haemost. 2009;102(12):1042–9.
71. Ranasinghe P, Ranasinghe P, Abeysekera WK, Premakumara GS, Perera YS, Gurugama P, et al. In vitro erythrocyte membrane stabilization properties of Carica papaya L. leaf extracts. Pharmacogn. Res. 2012;4(4):196–202.
72. Sharma N, Mishra KP, Chanda S, Bhardwaj V, Tanwar H, Ganju L, et al. Evaluation of anti-dengue activity of Carica papaya aqueous leaf extract and its role in platelet augmentation. Arch Virol. 2019;164(4):1095–110.
73. Pandey SK, Sharma V. World diabetes day 2018: battling the emerging epidemic of diabetic retinopathy. Indian J Ophthalmol. 2018;66(11):1652–3.
74. Gupta M, Prabhu K, Parijatham BO, Kalaiselvi VS, Rajendran SM, Rose J. Prevalence of diabetes mellitus in South India: a retro spective analysis. JIMSA. 2012;25(4):239–40.
75. Fakeye TO, Oladipupo T, Showande O, Ogunremi Y. Effects of coadministration of extract of Carica papaya Linn (family Cariaceae) on activity of two oral hypoglycemic agents. Trop J Pharm Res. 2007;6(1):671–8.
76. Aruoma OI, Somanah J, Bourdon E, Rondeau P, Bahorun T. Diabetes as a risk factor to cancer: functional role of fermented papaya preparation as phytonutraceutical adjunct in the treatment of diabetes and cancer. Mutat Res. 2014;768:60–8.
77. Gardner RV. Sickle cell disease: advances in treatment. Ochsner J. 2018;18(4):377–89.
78. Ambe JP, Mava Y, Chama R, Farouq G, Machoko Y. Clinical features of sickle cell anaemia in northern nigerian children. West Afr J Med. 2012;31(2):81–5.
79. Imaga NO, Gbenle GO, Okochi VI, Akanbi SO, Edeoghon SO, Oigbochie V, et al. Antisickling property of Carica papaya leaf extract. Afr J Biochem Res. 2009;3(4):102–6.
80. Nurain IO, Bewaji CO, Johnson JS, Davenport RD, Zhang Y. Potential of three Ethnomedicinal plants as Antisickling agents. Mol Pharm. 2017;14(1):172–82.

81. Suresh K. Antimicrobial and phytochemical investigation of the leaves of Carica papaya L., Cynodondactylon (L.) Pers., Euphorbia hirta L., Meliaazedarach L. and Psidiumguajava L. Ethnobot Leaflets. 2008;12:1184–91.
82. Nirosha N, Mangalanayaki R. Antibacterial activity of leaves and stem extract of Carica papaya L. Int J Adv Pharm Biol Chem. 2013;2(3):473–6.
83. Baskaran C, Velu S, Kumaran K. The efficacy of Carica papaya leaf extract on some bacterial and a fungal strain by well diffusion method. Asian Pac J Trop Dis. 2012;2:S658–62.
84. Tewari BB, Subramanian G, Gomathinayagm R. Antimicrobial properties of Carica papaya (papaya) different leaf extract against E. coli, S. aureus and C. albicans. Am J Pharmacol Pharmacother. 2014;1(1):025–39.
85. Odo CE, Odo AI. Ethanol extract of the leaves of Carica papaya affords protection against aspirin-induced gastric ulcer in rats. J Pharm Res. 2017;11(8):1025–9.
86. Indran M, Mahmood AA, Kuppusamy UR. Protective effect of Carica papaya L leaf extract against alcohol induced acute gastric damage and blood oxidative stress in rats. W Indian Med J. 2008;57(4):323–6.