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Nutraceutical value of *Carica papaya*: A review ☆

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ABSTRACT

Papaya (*Carica papaya* L.), one of the extensively studied plants, belongs to the family *Caricaceae*. Papaya is commonly known for its nutritional and medicinal value worldwide. Many parts of papaya plant such as roots, leaves, peels, fruits, and seeds have nutritional and therapeutic significance. The aim of this review is to consolidate the evidence-based information on papaya's functional activities, collected from online databases (Scopus, Dimensions, Google Scholar, ScienceDirect, and Web of Science) up to December 2020. A considerable literature is available detailing biomedical uses of different papaya plant parts which made papaya a treasured nutraceutical plant. Papaya plant possesses valuable phytochemicals such as phytosterols, tocopherols, flavonoids, alkaloids, and carotenoids. These compounds with interesting nutraceutical properties play key roles in ameliorating and treating some medical conditions such as inflammation, hyperglycemia, fertility-related complications, hypertension and possess anticarcinogenic activities. However, further studies are warranted to validate the dosage, mode of actions, and safety profile of papaya seeds, peels, and leaves when used as medicine.

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Background

Carica papaya Linn is a herbaceous plant which belongs to the *Caricaceae* family. The plants grow well in the tropics and can reach up to 10 m high [1]. In 2017, production of papaya reached 13 million metric tonnes with India and Brazil contributing more in the global share, trailed by Mexico, Indonesia, Dominican Republic, and Nigeria [2]. Papaya fruit is consumed either raw or in processed forms as jelly, candy, jam, and pickles [3]. More than 50 papaya varieties have been recorded, but pure breeding varieties are decreasing due to the uncontrolled papaya pollination [4,5]. Many parts of papaya plant such as roots, leaves, peels, latex, flowers, fruits, and seeds possess nutritional and medicinal significance [6]. The plant has been used as ethnomedicine for decades in tropics and subtropics where it is mostly grown [6,7]. The therapeutic motives for use vary, with probably the most common being anthelmintic and as a potential abortifacient agent [8–10]. Papaya seeds and leaves have been associated with amelioration of diabetes mellitus, hepatic and renal complications,

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Table 1
Nutritional value in papaya fruits, seeds, peels, and leaf (mg per 100 g).

Parameter	Nutritional value			
	Fruit [40–43]	Seed [5,21,23,25,28,33]	Peel [23,33,44,45]	Leaf [19,26,46,47]
Moisture	85.32–90.66	2.40–9.83	68.39–86.80	59.5–64.00
Ash	0.28–0.38	6.94–10.6	3.15–11.85	1.97–11.30
Carbohydrate	7.76–13.44	8.4–27.6	9.67–38.35	10.37–58.30
Protein	0.36–0.45	24.3–31.80	6.86–20.20	16.08–29.50
Lipid	0.20–0.29	20.97–30.1	0.23–2.44	2.70–6.31
Dietary fiber	0.37–0.60	17.0–22.6	9.67–34.70	1.27–2.13
β-carotene (µg/g)	208.67–4534.26	888.00	15.46–1940	–
Ascorbic acid (mg/g)	35.32–43.80	0.12–0.15	65.70–71.01	126.2
Sodium	6.79–9.53	39.80	9.61	0.03 g/kg
Potassium	18.36–24.78	743.30–1635.50	504.33–516.33	2.75
Iron	0.61–0.85	5.23–5.80	0.65–2.73	0.46–1.84
Calcium	27.88–32.48	725.00–8435.10	16.22–18.61	4.80–32.73
Zinc	–	5.00–6.17	1.94–1.97	0.04–0.05
Phosphorus	11.54–16.81	566.9	221.54	–
Copper	–	0.50–1.09	0.41	0.01–0.06
Manganese	–	2.50–3.10	–	0.12–0.66
Magnesium	9.45–13.63	218.80–332.50	19.11	16.18

'–' – data not available. Some data have been converted to be expressed as mg/100 g unless stated otherwise

fertility, hyperglycemia, amoebic dysentery, and recently antitumor activities [7,11–13]. The densely-packed phytochemicals in papaya seeds and leaves such as flavonoids, phytosterols, carotenoids, alkaloids, phenolic compounds, and the cyanogenic compounds (benzyl glucosinolate) are reported to be behind the therapeutic power of the plant [3,12,14–18].

About twenty per cent of the fresh mass of papaya fruit is seeds. Papaya seeds are usually discarded during fruit processing regardless of being therapeutically valuable [19]. The seeds are rich in unsaturated lipids and can be an alternative source of essential oil [20,21]. Both the seeds and leaves contain protein, dietary fibers, phytochemicals, antioxidants, and minerals [19,22,23]. A substantial quantity of protein in papaya leaves make them appropriate for the enhancement of the high-carbohydrate-foods while available fiber content may smoothen bowel movement [19,24] Furthermore, papaya seeds are used as a substitute for black pepper in food preparation due to its spicy and pungent taste.

For the last three decades, researchers have turned their attention to study the efficacy of ethnomedicines as a cure, the mode of actions by which they may be effective, and the possible bioactive compounds behind their functional effects [1,15–18]. The present review highlights therapeutic properties of *C. papaya* seeds, peels and leaves as linked to the molecular roles to determine their potential impacts on selected disease conditions as a nutraceutical food ingredient. It also identifies the knowledge gaps and provide a scientific base and course for prospective studies.

Methodology

We searched online databases (Scopus, Dimensions, Google Scholar, ScienceDirect, and Web of Science) using these keywords: chemical or nutritional composition; gastrointestinal ulcers; tumor or cancer; sickle-cell, helmithes; antimicrobial or antifungal; hypoglycemia or diabetes; liver or kidney; and infertility with "papaya" or "*Carica papaya*" in the search up to December 2020. We identified additional relevant papers from related review articles identified in the primary search. The disease conditions that were widely reported to be relieved or ameliorated with papaya or papaya-based products were discussed in this review. The available literature, published only in English, assessing the relationship between the chemical composition in papaya and disease conditions or ameliorative roles mentioned above were identified and used to compose this review.

Chemical composition of Carica papaya *fruits, seeds, peels, and leaves*

Papaya fruits, seeds, peels, and leaves have nutraceutical values, which make them important in human diets. These papaya parts are rich in macro- and micronutrients with varying degrees (Table 1). For example, the seeds and leaves contain 16–32% protein [5,19,21,23,25,26], regardless of the cultivars. The seeds contain a good amount of lipid (21–30%) [23,27,28], and carbohydrate (8–58%) in seeds and leaves [5,19,21,23,26] making them good alternative energy sources which may complement the undernourished populations.

Contrary to the fresh papaya seed with a strong spicy flavor, its oil has a unique aroma composition. The papaya seed oil (20.97–30.10%) is enriched with lipophilic phytochemicals and essential fatty acids such as oleic acid (70.84–79.10%) [5,21,27]. Oleic acid is widely identified as an anti-inflammatory agent and may even have positive effects on genes associated with tumor [29–31]. Palmitic, arachidic, linolenic, and stearic acids are other reported fatty acids in the seeds (Table 2). The high levels of lipid in papaya seeds offer economical attraction for industrial consumption relative to other oilseeds,

Table 2
Fatty acid profiles of C. papaya seed oil.

Nutrient	Nutritional value	Reference
Fatty acid	%	
Lauric acid (C12:0)	0.01–0.40	[4,28]
Myristic acid (C14:0)	0.04–0.49	[4,20,21,25,28,48]
Palmitic acid (C16:0)	13.90–19.70	[4,16,28,33,48]
Palmitoleic (C16:1)	0.08–1.77	[20,21,25,28,48]
Margoric acid (C17:0)	0.10–0.13	[21,25,28]
Stearic acid (C18:0)	4.20–6.68	[16,19,28,33]
Oleic acid (C18:1)	70.84–79.10	[16,19–21,25,28]
Linoleic acid (C18:2)	0.04–6.06	[4,16,28]
Linolenic acid (C18:3)	0.17–0.90	[20,21,25,28]
Arachidic acid (C20:0)	0.38–1.10	[20,21,25,28,33]
Gadoleic acid (C20:1)	0.51	[48]

Table 3
Phytochemical profile of papaya seeds.

Phytochemical	**Nutraceutical value**	**Reference**
Phenolics	mg/ g	[49]
p-Coumaric acid	0.35	
Kaempferol-3-glucoside	0.12	
p-Hydroxybenzoic acid	0.39	
Quercetin-3-galactoside	0.16	
Caffeic acid	0.43	
Ferulic acid	0.62	
Phytosterols	mg /g	[20]
Campesterol	1.0	
Stigmasterol	0.6	
β-Sitosterol	5.4	
Other phytochemicals	%	[50]
Flavonoids	3.66	
Alkaloids	7.25	
Phytates	0.15	
Steroids	0.49	
Terpenoids	1.33	
Oxalates	2.33	
Glycosides	9.17	
Strobosteroids	0.28	
Carotenoids	19.75	
Anthraquinones	21.50	
Phlobatannins	0.38	

such as corn (4.2–6.0%) and soybean (17.0–21.0%) [32]. However, the edibility of this lipid is inconclusive so far, and therefore further characterization and safety studies are necessary before the commercialization of the oil for public consumption.

Studies have also revealed that the papaya seeds and peels are rich in minerals (K, Ca, P, and Mg) (Table 1). Minerals are necessary for the optimal functioning of the physiological and metabolic systems of the human body [23,33]. Intake of 100 g of papaya seeds may provide the human body with 15%, 120%, 35%, 80%, 130%, 60%, 80%, and 70% of K, Mg, Fe, Zn, Mn, Cu, P and Ca, respectively [34].

Papaya seeds and peels contain a notable amount of dietary fibers (Table 1). Dietary fibers are widely known for several health benefits; they remove toxins out of the digestive system, and lower the levels of cholesterol [29,35]. Papaya peels contain 68–87% moisture, 7.00–20.00% protein, 0.20–2.00% fat, and 3.00–12.00% ash [5,23,25]. These peels could also be considered as a source of macro-minerals and trace minerals (Table 1).

Papaya seeds are a good source of phytochemicals. They contain valuable phytochemicals such as phenolics, tocopherols, phytosterols, and carotenoids (Table 3). Phytochemicals generally offer an array of beneficial properties from antiproliferation of cancer cells to shielding against cellular oxidative injury; they also reduce the risk of non-communicable diseases' incidence [15]. Phenolics, isothiocyanates, terpenes, phytosterols, flavonoids, and anthraquinones can scavenge reactive molecules thus protecting the cellular environment against the damaging impacts of oxidative and inflammatory activities of carcinogens [14,15,36–39].

Gastroprotective activity

Ulcers are one of the gastrointestinal tract disorders affecting millions of people globally [51]. Gastrointestinal ulcers (GIU) are the result of erosion of the gastric or duodenal mucosa because of the excessive secretion of gastric acid or pepsin. The main risk factor linked to GIU is *Helicobacter pylori* infections. Other factors are smoking, stress, alcohol, nutritional

Table 4
Gastroprotective activities of extracts from different parts of C. papaya.

Model	Dosage	Significance	Reference
In vivo ethanol-, acetic acid- and indomethacin-induced gastric ulcer rat model	500 mg/kg methanolic PSE for 14 d	Reduced the gastric lesion with 82% inhibition in ethanol model; 81% inhibition in indomethacin model; and acetic acid model showed a reduction inulcerative symptoms by 84%	Pinto [53]
In vivo aspirin-induced ulcer mice	400 mg/kg aqueous extract of fresh, unripe, mature papaya fruits for 7 d	Lowered the ulcer index and lipid peroxide levels in the rats	Ologundudu [57]
In vivo ethanol- and indomethacin-induced gastric ulcer rats	300 mg/kg methanolic and aqueous green papaya extracts	Both methanol and aqueous extracts possessed antiulcerogenic properties and inhibited gastrointestinal propulsion. The methanolic extract showed more ameliorative effect against indomethacin-induced ulcers, while the aqueous extract demonstrated a better gastroprotective activity against ethanol-induced gastric ulcers with no toxicity	Ezike [56]
In vivo ethanol-induced peptic ulcer adult female albino rats	20 mL/kg ripe papaya juice mixed with 5 mL/kg cumin seed extract for 8 d	Extract combination displayed significant anti-ulcerogenic property	Nilugal [51]
In vivo ethanol-induced peptic ulcer adult male Sprague-Dawley rats	450 mg/kg of aqueous PLE for 30 min post-treatment	Showed significant reduction of oxidative damage and protection to the gastric mucosa in rats	Indran [54]
In vivo ethanol-induced ulcer adult albino male rat model	100 mg/kg of aqueous PSE for 14 d	Protected the gastric mucosa against ethanolic adverse actions. Also, lowered the gastric acidity	Okewumi and Oyeyemi [52]

deficiencies, the use of acetylsalicylic acid (ASA) and non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen have also long been implicated in causing gastric mucosal injury [51–53]. The management of *H. pylori* infection has improved drastically two decades ago; nevertheless, over the same period, the use of ASA and NSAIDs has correspondingly increased [52–54]. Ulcers not related to *H. pylori* infection or the use of NSAIDs are now also imposing considerable diagnostic and therapeutic challenges [53]. Gastrointestinal ulcers are a global problem with a lifetime risk of development ranging from 5 to 10% [51]. Suprisingly, the problem is four times more common in men than in women [53].

Several in vivo studies have shown the gastroprotective properties of papaya extracts on various ulcerogenic damages such as papaya seed extract (PSE) on peptic ulcers [55]. Similarly, papaya leaf extract (PLE) significantly reduced the alcohol-induced acute gastric ulcers and oxidative stress in rats [54]. In another study of thirty-two (32) male mice with ethanol-induced gastric ulcers were administered with PSE [52]. Findings revealed that the PSE shielded the mucosa destruction against alcohol damage. The same study reported that PSE substantially decreased the volume of gastric juice and gastric acidity in a dose-response fashion. The gastroprotective activity of *C. papaya* extracts is presented in Table 4. Another examination of gastroprotective potential of the methanolic PSE showed that PSE ameliorated the gastric lesion with increased mucus release and gastric pH and no signs of toxicity when rats with ethanol- and indomethacin-induced gastric ulcers were used in the study [53]. The study further reported that the sulfhydryl compounds in the extracts were probably responsible for these antiulcerogenic activities. Furthermore, Ezike [56] reported that both aqueous (AE) and methanol (ME) extracts of entire immature papaya fruit possess antiulcerogenic effects using indomethacin- (IIU) and ethanol- (EIU) induced ulcers models in mice. While the ME showed better ameliorative effect against IIU, the AE worked well against EIU. The extracts also notably prevented gastrointestinal propulsion, with ME displaying superior activity.

From the overview above, it can be noticed how papaya plant parts carry potential in amelioration and protection of some gastroduodenal ulcers in animal models. No lethality or signs of acute toxicity were reported in the animal model. This might inconclusively suggest the safety profile of the papaya extracts, though further investigations are warranted to approve the safety aspect of the PSE and PLE. Since preliminary examinations show promising results, there is a room for further studies of the gastroprotective potential of this plant in clinical setups. Furthermore, the molecular mechanisms involved in the gastroprotective activity of papaya extract are multifaceted, therefore several experimental models should be employed to profile the principal and specific anti-ulcerogenic agents and establish their gastroprotective mechanisms.

Antitumor activity

Tumors result from irregular growth of tissue mass due to the uncontrolled cell cycle [58]. The irregular growth of cells demonstrates as either non-cancerous or cancerous tumors. Cancer killed about 9.6 million people globally in 2018 [59]. While 20% of men and 16.7% of women worldwide develop cancer during their lives, about 12.5% of men and 9% of women die from the disorder [60].

Table 5
Antitumor effects exerted by papaya extracts.

Cell line	Model	Dosage	Significance	References
Human preadipocytes (SW872) and Hepatocellular carcinoma (HepG2) cells	*In vitro* cultures	2 mg/mL of PSE	Showed cytoprotective effects against oxidative stress and inflammation	Somanah [62]
Benign tumor (BPH1) and prostate epithelial cells (RWPE 1)	*In vitro* cultures	0.01–1 mg/mL juice of papaya leaves	Demonstrated anti-proliferative activity. Significantly reduced the S phase cell cycle arrest	Pandey [75]
Human prostate carcinoma (LNCaP, DU145, PC3) cells	*In vitro* cultures	5, 10, 25 μl/mL aqueous PLE	Reversed the expression of cell cycle regulatory molecules cyclin D1 and cyclin B1. Also, induced apoptosis	Singh [7]
Human hepatoma (HepG2) cell lines	*In vitro* cultures	50–500 μg/mL of methanol and hexane PSE	Suppressed oxidative stress	Salla [65]
Prostate cancer PC-3 cell line (CRL-1435)	*In vitro* cultures	50–250 μg/mL aqueous and alcoholic PSE	Decreased cell proliferation of PC-3 cells. Also stimulates the growth of the pre-existing prostate cancer cells	Alotaibi [74]
Human skin Detroit 550 fibroblasts	*In vitro* cultures	50–250 μM aqueous PSE	Showed protection of fibroblasts from H_2O_2-induced oxidative stress	Panzarini [73]
Human erythrocytes	*In vitro* cultures	0.25–2.00 mg/mL methanol PSE	Inhibited cellular oxidative stress	Okoko and Ere [72]
Rat pancreatic cells	*In vitro* cultures	25 mL aqueous extract of green papaya peel and flesh	Inhibited the effect of Fe^{++}-induced lipid peroxidation	Oboh [71]
Liver cancer cell line (HepG2) and Chang liver cell line (normal cell)	*In vitro* cultures	0.30–30 mg/mL papaya fruit juice	Inhibited viability of liver cancer cell line HepG2 but did not affect normal cells.	Rahmat [64]
Acute promyelocytic leukemia (HL-60) cells	*In vitro* cultures	0.1–100 g/mL n-hexane extract of papaya seed	Inhibited the superoxide release and the viability of cells at a dose-response manner	Nakamura [11]
Breast cancer (MCF-7) cell line	*In vitro* cultures	50–640 μg/mL ethanolic extract of papaya pericarp.	Reserved cell growth	Jayakumar and Kanthimathi [69]
Breast cancer cell line (T47D) from papaya leaves	*In vitro* cultures	Protein isolate	Induced apoptosis	Hirose [67]
Acute promyelocytic leukemia HL-60 cells	*In vitro* cultures	50 μL aqueous PSE	Effective in impeding superoxide production. induced apoptosis	Nakamura [11]
Human lung cancer H69 cells	*In vitro* cultures	1.25–20 μmol/L BITC from papaya seeds	Anti-proliferative effect against H69 cells in a dose-response fashion	Li [66]
Tumor- associated macrophages	*In vitro* cultures	5, 10, 25 μl/mL aqueous PLE	Positively modulated production of NO, H_2O_2, TNF-a, and IL-6. Also, upregulated the costimulatory receptor CD80 in TAMs	Singh [17]
Breast cancer (ER-/Her-2) cell lines	*In vitro* cultures	50–250 μg/mL aqueous PSE and PLE	Showed anti-proliferative activity against ER-negative breast cancer	Hadadi [70]

Evidence suggests that phytochemical-extract-based trials of both human and animal trials demonstrated antitumor activities [61]. Papaya extracts are no exception. Studies over the past three decades have provided important information on antitumor properties of papaya extracts on an array of cancer cells such as Human pre-adipocytes (SW872) and Hepatocellular carcinoma (HepG2 and Huh-7) cells [62–65]; Tumor-associated macrophages [17]; Human lung cancer (H69) cells [66]; Acute promyelocytic leukemia (HL-60) cells [11]; Breast cancer (T47D) cells [67], Breast cancer (ER- and Her-2) cell lines [64,68–70]; Rat pancreatic cells [71]; Human erythrocytes [72]; Human skin Detroit 550 fibroblasts [73]. Prostate cancer (CRL-1435, LNCaP, DU145, PC-3) cell lines [74] and prostate epithelial (RWPE-1) cells [7,75]; and Lung adenocarcinoma (PC14) cells, Leukemia (K562) cells, T cell (Jurkat, Molt-4, Cervical carcinoma (Hela) cells and Human peripheral blood mononuclear (PBMC) cells [63]. We summarize the antitumor activities and respective molecular targets for extracts of different papaya parts in Table 5. In a nutshell, papaya extracts showed promising activities in eight forms of cancer; lung, prostate, skin, breast, blood, cervix, liver, and pancreas as highlighted above.

From the literature, it is evident that extracts of papaya leaves, seeds, and peels displayed anticancer potential through the suppression of tumor growth, induction of apoptosis, inhibition of cell proliferation, and metastasis in some studied

human cancer cells. The antitumor activity in seed, leaf, and peel extracts could be explained by the bioactive phytochemicals such as benzyl isothiocyanate (BITC); phenolics, carotenoids, glucosinolates; and flavonoids, α-tocopherol, and lycopene. Surprisingly, there is a limited number of studies that attempt to characterize the bioactive compounds responsible for antitumor properties and the mode of actions of the PSE and PLE so far in the available literature. This provides room for further investigations of the antiproliferative activity of PSE and PLE to identify the mechanism of action and evaluate their efficiency with novel models for exploring new treatment for tumor and cancer.

Anti-sickling activity

Sickle-cell disease is a hereditary blood condition which affects up to 3% of Africans [76]. The disease is caused by possessing a specific hemoglobin molecule known as hemoglobin S, which results from abnormal protein in which the glutamic acid at location six of its chain is substituted by valine [22,77–79]. Haemoglobin S forms polymers that aggregate to tube-like fibers when deoxygenated [22,78]. As a result, this causes a remarkably colossal number of immature erythrocytes cells with the crescent-shape, which prevents the oxygen from being effectively supplied throughout the body [80,81]. The patient would experience shortness of breath, anaemia, paleness, abdominal pain, heart palpitations and muscular pains [80].

The use of *C. papaya* in treating sickle cell patients has been described in several in vivo research studies. The five days of ethanolic fermentation of unripe *C. papaya* fruit pulp gave an average of 87% inhibition and 74% reversal activities on the erythrocyte's cells. The anti-sickling activity tends to increase with increased incubation time when the methanolic extract is used compared to chloroform [81]. Afolabi [80] documented the rise in the amount of normal erythrocytes cells by 98.7% in comparison to the sickle blood cells (1.3%) when the methanolic extract on the ripe fruit was used. In another study, there was no considerable difference in anti-sickling effect amidst the positive control with the ethanolic extract and NaOH extract of ripe *C. papaya* fruits [82]. When petroleum ether leaves extract was used, it lowered the frequency of erythrocytes cells lysis [83]. Moreover, the seed oil of *C. papaya* holds anti-sickling properties and likely to lessen suffering in sickle cell patients [79–81].

The immature fruit of *C. papaya* is described to contain possible anti-sickling compounds such as tyrosine, glycine, and phenylalanine. The anti-sickling activity of immature *C. papaya* fruit result from the presence of phenolic acids, aromatic amino acids, and antioxidant compounds [79,83]. Clinical trials and formulations of potential papaya bioactive compounds are important for the provision of relief to sickle cell patients.

Anti-thrombocytopenic and immunomodulatory activities

Immune thrombocytopenic purpura (ITP) is a common hematologic disorder in which the immune system act against platelets autoantigens and causes it to be below average, which can lead to internal hemorrhage [84]. The standard number of platelets in the blood is between 150,000 – 400,000 platelets per micro-liter [84]. The ITP can be the outcome of decreased thrombopoiesis in the bone marrow, amplified platelets exploitation in the liver, or platelet sequestration in the spleen [85–87]. This condition is also the second prevalent hematological problem in at least 10% of pregnant women as the result of physiological changes and obstetric conditions such as Low Platelet level syndrome, hemolytic uraemic syndrome, and amniotic embolism [88]. It can also be triggered by infections resulting from viruses such as Dengue fever (DF), fungus, or bacteria [89]. Dengue fever is an arthropod-borne flavivirus named dengue virus (DENV) spread by *Aedes aegypti* as the vector in which 40% of the global population is at risk [90]. Consuming drugs that have blood-thinning properties such as aspirin can also induce platelet aggregation in the blood plasma [91,92]. Although steroids are the first-line therapy for ITP, splenectomy is sometimes performed on patients as last resort to reduce platelet damage [86].

The use of *C. papaya* leaves extract has demonstrated to be a potential alternative for chronic ITP when given to 4 patients while waiting for the second-line treatments [93]. When ITP was induced through the injection of a carboplatin drug to Swiss albino mice, there was a substantial rise in platelets count among the group given the high concentration of *C. papaya* leaves extract compared to low concentration and the control (distilled water) [94]. A clinical randomized controlled trial revealed the significant increase in the platelets number ($p < 0.003$ [89], $p < 0.01$ [88], $p < 0.001$ [90] of dengue viral-infected patients when *C. papaya* leaves juice was administered in contrast to the positive control when the therapy was completed. In another study conducted in vivo on mice, there was a remarkable rise in platelet number ($p = 0.00004$), reaching four times higher on day 21 as to the comparison group [95]. Additionally, the increased synthesis of thrombopoietic cytokines was observed, that is, a protein that regulates the production of platelets when exfoliated human primary teeth were treated with immature *C. papaya* juice in vitro [96]. Ranasinghe [97] concluded that any compounds that have a stabilizing effect on the plasma membrane would be able to protect the platelets from destruction.

Clinical researches are necessary to evaluate the effect of PLE in chronic ITP and pregnancy-related thrombocytopenia. To minimize the number of patients requiring splenectomy, more research on how plants like *C. papaya* can regulate platelet sequestration in the spleen is needed. Moreover, there is a need to identify the active compounds and their potential sites, i.e., to increase thrombopoiesis in the bone marrow or reduce platelet sequestration in the spleen for ITP patients.

Table 6
Antiparasitic activities of C. papaya extracts on the different human parasites.

Parasite	Model	Dosage	Significance	Reference
Ascaris lumbricoides	Human clinical trial	20 mL of *C. papaya* seed powder	Parasite stool clearance rate was 71%. No harmful effects to the subjects were observed	Okeniyi [106]
Strongyloides stercoralis *Caenorhabditis elegans*	In vitro culture	20 mL of 0.06 seed crude extracts	Significant decrease in the viability of *Caenorhabditis elegans* by 90%.	Kermanshai [103]
Ancylostoma caninum	In-vivo albino mice	0.2 mL papaya extract	Reduced the number of larva within 24 h. Digested and removed the cuticle	Bi and Goya [101]
Haemonchus spp., *Trichostrongylus* spp., *Coöperia* spp. and *Oesophagostomum* spp.	In vivo test	350 mL of PLE and extract from unripe fruit of *C. papaya*	Fecal egg count reduction by 60%	Bastiaensen [108]
Haemonchus contortus	In vitro culture	300–1200 µg/mL PSE for eggs 1200–2400 µg/mL PSE for larval 1200–2400 µg/mL PSE for adult	Inhibited egg-hatching and morbidity of both larva and adult worms	Hounzangbe-Adote [99]
Trichostrongylus colubriformis	In vivo test	600 µg/mL PSE for larval 2500 µg/mL PSE for adult	Suppressed egg-hatching and morbidity of larva and adult in a dose-dependent style	Hounzangbe-Adote [99]
Trypanasoma cruzi	In vitro culture	50 mg/kg, 75 mg/kg chloroform PSE	Decreased the number of parasites in growth stages (blood trypomastigote and amastigote)	Odhong [18]
Entamoeba histolytica	In vitro culture	Minimum Inhibitory Concentration (MIC) $\leq$ 8.0 µg/mL maceration of mature seeds; 62.5 µg/mL decoction of immature seeds	Inhibit the growth of amoeba	Tona [1] Tona [109]

Antiparasitic activity

Anthelmintic properties

Intestinal parasites are among the global health issues with substantial economic implications, particularly in developing world. In traditional medicine, the seeds of *C. papaya* have been utilized in the management of helminthes [10,98]. The leave, seed, latex and fruit of *C. papaya* contain anthelmintic alkaloid and carpaine which are effective in expelling worms from human alimentary canal [99–101] (Table 6). Studies report that the latex from the immature fruit of *C. papaya* expelled the *Hemogmosomoides polygyrus* in a dose-dependent fashion in a study of infected mice conducted in-vivo [102]. In another study, PSE was potent in killing all the *Caenorhabditis elegans* after 12 h of administration [103]. Additionally, there was an in-vitro inhibition of eggs hutching (99%) and larvae (60%) when the dried leaves of *C. papaya* were used against the gastrointestinal nematodes in sheeps [18]. In addition to their alkaloid effect, benzyl isothiocyanate (BITC) could explain the parasiticidal properties of the seeds of *C. papaya* [104,105]. In another study, Okeniyi [106] stated a notable clearance of intestinal worms ($p = 0.00001$) in the fecal sample of Nigerian children when *C. papaya* seeds were mixed with honey when administered to the children compared to the control (honey alone). Although *C. papaya* seeds were successful in expelling the worms, it resulted in side effects such as nausea and loose stools without such experience when the control was used. These findings suggest that the papaya latex and seed extract have a potential anthelmintic property against interior nematodes of various mammalian hosts.

Anti-protozoal properties of C. papaya

The inhibitory effect of the *C. papaya* extracts in different solvents was evaluated against protozoa parasites. The antiparasitic activities of *C. papaya* extracts on the various human parasites are detailed in Table 6. Odhong [18] stated a substantial reduction in the number of *Trypanasoma cruzi* in an in-vivo study when the albino mice were treated with chloroform extract of *C. papaya* seed as compared to the positive control (allopurinol 8.5 mg/kg). Although *C. papaya* notably reduced the *T. cruzi* load, it did not eradicate the protozoa during its active infection phase. The PSE also kills amoeba parasites. In a study by Tona [1] reported that a Minimum Inhibition Concentration (MIC) of 7.81 µg/mL of PSE from mature seeds and MIC of 62.5 µg/mL of PSE from immature seeds destroyed the amoeba parasites. Among others, the bioactives contained in *C. papaya* seeds and leaves are benzyl isothiocyanate (BITC) and alkaloids, which is proven to hold anti-protozoal and anti-amoebic properties [104,105]. The BITC is thought to be specifically responsible for the mitochondrial dysfunction of amoeba [107].

Table 7
Antimicrobial and antifungal effect of C. papaya extracts on different strains of microorganism

Antibacterial activity Strain	Model	Dosage	Significance	Reference
Salmonella typhi	In vitro culture	50–200 mg/mL ethanolic PLE and root extract (PRE)	Exhibited the highest antimicrobial activity	Nirosha and Mangalanayaki [113]
Salmonella typhi Pseudomonas aeruginosa Proteus mirabilis	In vitro assay	50–200 mg/mL papaya root methanol extracts	Proved the highest antibacterial activity	Doughari [111]
Bacillus subtilis Escherichia coli Klebsiella pneumoniae Pseudomonas aeruginosa Staphylococcus aureus	Invitro agar well diffusion method	25–75 µL aqueous PLE	Significantly prevented growth by 60% of tested microorganisms	Suresh [114]
Pseudomonas aeruginosa	In vitro broth dilution method	50 mg/mL (MIC) methanolic root extract (PRE)	Demonstrated higher antibacterial activities	Anibijuwon and Udeze [110]
Escherchia coli	In vitro culture	0.5 mg/mL hot aqueous extract of the ripe papaya peels	Exhibited antibacterial activity	Khanja [129]
Antifungal activity				
Candida albicans Candida parapsilosis	In vitro broth dilution method	4 – 16 µg/mL (MIC) and 16 – 64 µg/mL (MFC) of papaya seed oil (PSO)	Exhibited inhibitory effect of 19.4 mm and 33.2 mm, respectively	He [118]
Candida albicans Aspergillus flavus Penicillium citrinium	In vitro agar diffusion bioassay	5, 10 and 20 µg/mL methanolic PSE	Displayed inhibition activity	Singh and Ali [126]
Candida albicans	Turbidimetry assay	16 – 32 µg/mL PSE	Exhibited apoptosis of *C. albicans* cell in a dose-dependent manner	Collignon [130]

MIC - minimum inhibitory concentration
MFC - minimum fungicidal concentration

Antimicrobial and antifungal activities

Antimicrobial activity

Several studies show that PSE and PLE have antibacterial activity media [110–113]. Suresh [114] demonstrated that amongst five plant extracts, the PLE offered the uppermost antibacterial activities. The PLE strongly suppressed the development of the tested Gram-positive bacteria (*Staphylococcus aureus Bacillus subtilis* and *Pseudomonas aeruginosa*) and reduced outcome on gram-negative (*Escherichia coli* and *Klebsiella pneumoniae*) bacteria [113,114]. The impenetrable murein coat existing in the external membrane of gram-negative bacteria prohibits the entrance of plant extract into the cell [114]. The microbial effect of *C. papaya* on gram-positive and negative strains of microbes is presented in Table 7. Some other study where hot water, methanol, ethyl acetate, chloroform, ethanol, and acetone, and PLE were used. Papaya leaf extracts exhibited exceptional bactericide effect against *Micrococcus luteus, Bacillus cereus, Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus* and *Pseudomonas aeruginosa* [115]. Furthermore, methanolic PLE displayed antimicrobial action against *Escherichia coli, Candida albicans* and *Staphylococcus aureus* [116]. The mechanism of action of *C. papaya* is thought to involve the distortion of the morphology of the cells on both bacteria cells which resulted in the irregular cell wall thus resulting in inhibition of their growth [117]. The reviewed articles justify for more research in the molecular alterations linked to antibacterial activities.

Antifungal activity

Fungi can be detrimental to innumerable parts of the human body, including the skin, nail, reproductive parts, gastrointestinal canal, cardiovascular, and nervous system [118]. Some of the fungal infections, such as candida can be severe and even deadly for immunocompromised patients [119,120]. There is an increase of drug-resistant to infectious fungi for decades as the result of extensive usage of broad-spectrum antifungal drugs such as fluconazole, ketoconazole, and itraconazole [121]. Some of the antifungal drugs have proved to be toxic and result in profound side effects to patients, e.g. Amphotericin B [122]. This had led the researchers to look back into the natural and safe alternatives that are locally available to fight off the fungal resistance strains in the fight of infections [123–125]. The antifungal effects of *C. papaya* extracts on several strains of fungus are highlighted in Table 7.

The antifungal effects of bioactive compounds in papaya extracts are well explained in traditional medicine research articles [22,112,118,121,126,127]. Aqueous and alcoholic extracts of papaya seeds, leaves, peels and roots, are acknowledged to contain antifungal activity against *Penicillium citrinium, Aspergillus flavus, Colletotrichum gloeosporioides, Fusarium* spp. and *Candida albicans* [118,128]. The leaf extract exhibits wide-ranging activity. The MIC_{50} for the PLE was 0.625 mg/mL for *Fusarium* spp. and more than 10 mg/mL for *C. gloeosporioides*, with a total of 20% mycelial spread prohibited [128].

Few studies to test the effectiveness of *C. papaya* in treating fungus-related ailments are listed in Table 7. The generation of oxygen radicals could explain the antifungal properties of PSE, breakdown of mitochondrial membrane potential (MMP) and reduces the activities of the mitochondria respiratory chain enzymes [127]. Benzyl isothiocyanate (BITC) compound in the *C. papaya* seed is said to be responsible for the inhibitory effect [118]. However, more researches are essential prior to promoting extensive therapy.

Hypoglycemic and antidiabetic activities

Diabetes mellitus is a severe chronic disease resulting from the failure of the pancreas to create adequate insulin (type 1), or when the body fails to utilize the insulin effectively, it makes (type 2) hence causing the aggregation of blood glucose [131]. The frequency of diabetes is snowballing owing to numerous influences such as obesity, unhealthy diets, an inactive lifestyle, ageing as well as malnutrition. Shaw [132] projected 285 million people with diabetes in 2010 and foresaw an upsurge in the figure up to 439 million in 2030. The same authors estimated that amid 2010 and 2030, there will be an increase in diabetes by 69% in developing countries and 20% in developed countries among adults. The number of individuals affected by type 2 has driven drastically, and now it affects even the children, which was not the case in the past decades [131,133]. The increase of type 2 diabetes is associated with obesity, a sedentary lifestyle, and unhealthy diety. The prevalence of diabetes is high in urban areas compared with rural areas. It is estimated that half of the people living with type 2 diabetes are not aware of their illness [131]. All types of diabetes may result in complications involving leg amputation, nerve damage, kidney failure, vision loss, and heart attack [131,133].

Many studies have been carried out to exploit traditional medicine as a substitute for the pharmaceutic drug in the management of diabetes. Lately, several herbs have been explored to be useful in treating and easing the symptoms related to diabetes [134]. Juárez-Rojop [135] and Olubodun [136] reported the antihyperglycemic and hypolipidemic effects of PLE and PSE in diabetic induced Wistar rats. In another study, the potential of PLE was proven to decreased serum glucose [137]. The PLE brought a substantial reduction in glucose and triacylglycerol concentration to 0.75 and 1.5 g/100 mL, correspondingly [13]. Moreover, there was improved lipid profile with the decrease in both basal and postprandial glycemia when fermented papaya fruit was administered Aruoma [138].

The prohibition of α-glucosidase and α-amylase enzyme in type 2 diabetes could be answerable for the antidiabetic activity of PLE and PSE [137]. The flavonoids, quercetin, steroids, quinones, and kaempferol have also been reported to have a substantial hypoglycemic property through regenerating pancreatic beta cells and increase insulin secretion [135,136].

Limited research investigating the antidiabetic potential of papaya seeds, leaves, and peels were reported in the available literature. Hence, further studies are necessary to characterize the bioactive phytochemicals and explore the hypoglycemic and anti-diabetic properties of papaya seeds, leaves, and peels in scientifically validated experimental models to advance the value of papaya as a functional food ingredient.

Hepato- and reno-protective activities

Because of the recurrent cause of severe liver injury resulting from an overdose of cytotoxic agents, the ameliorative and medicinal effects of papaya seeds were studied and compared with the existing hepatic protectants. Papaya seeds showed a significant reduction of oxidative stress in liver [139,140]. The studies reported that papaya extract showed significant hepatoprotective roles against APAP- and CCl_4-induced liver injury. In another study, papaya has also shown its inhibitory potential in the of CCl_4-induced hepatic fibrosis in mice by noticeably increasing the glutathione peroxidase activities while lowering the amount of liver hydroxyproline and malondialdehyde [141]. Another study revealed that the hepatoprotective activity of papaya leaves against ethanol-induced hepatic injury significantly reduced the levels of serum markers in rats [142].

Similarly, PSEs have shown nephro- or reno-protective activities. One in vivo study showed the protective activities of papaya seeds $KBrO_3$-induced nephrotoxicity in rats. In this study, a methanolic PSE of 500 mg/kg for 2 days impeded $KBrO_3$-induced oxidative stress in a dose-response fashion [143]. Another study investigated the protective and ameliorative effects of 500 mg/kg aqueous PSE against paracetamol-induced nephrotoxicity in mice. The extract protected the damaging impact of paracetamol by reversing the changes caused in renal structure [144]. Gheith and El-Mahmoudy [145] evaluated the nephroprotective potential of PLE against nephrotoxicity induced by gentamicin in forty-five male albino rats. Findings showed that the PLE convincingly sheltered the kidney tissues against gentamicin nephrotoxic effects shown by a decline of both the novel and the traditional biomarkers in a dose-response fashion. The study further reported that PLE-mediated protection was attributed to its antioxidant potential indicated by significant inhibition of malondialdehyde (MDA) levels in both serum and kidney homogenates. Furthermore, Olagunju [146] investigated the nephroprotective effects of the aqueous PSE against renal CCl_4-induced damage in rats. Results revealed that the measured biochemical parameters (creatinine, urea, and uric acid) were significantly diminished in rats, in a time and dose-related fashion.

The connotation between these biological mechanisms proposes that papaya extracts possess free radical scavenging potential, particularly in inhibiting liver and kidney lipid peroxidation. Only baseline investigations on papaya's potential in treating liver and kidney oxidative damages were conducted. This offers a window of opportunities to further testing the *C. papaya* activities in experimental and clinical models to establish its full potential and therapeutic application in the treatment of liver and kidney complications in humans.

Table 8
Infertility and contraceptive activities of C. papaya seeds.

Model	Dosage	Significance	Reference
In vivo male Wistar rats	100 mg/kg of N-hexane, ethyl acetate, and ethanol-water papaya seed fraction for 24 d	Reduced testicular and epididymis. Also, significantly reduced sperm quality	Nita [148]
In vivo male albino rats	100 mg/kg of alcoholic PSE for 15 d	Induced infertility by inhibiting spermatogenesis in testes	Verma and Chinoy [154]
In vivo male albino rats	0.5 mg/kg of PSE for 7 d	Reduced the contractile response of epididymal tubules	Verma and Chinoy [154]
In vivo female albino rats	200 mg/kg of PSE for 21 d	Caused infertility, abortion, and anti-implantation decreasing progesterone levels	Memudu and Oluwole [147]
In vivo female albino rat uterus	200 mg/kg of PSE for 21 d	Triggered abortion by inducing contractions of the isolated rat uteri in a dose-response fashion	Airaodion [156]
In vivo male mice	20 mg/kg of PSE	Lowered sperm concentrations, motility, and viability	Wiryawan [157]
In vivo male rats	50 or 150 mg/kg of alkaloid PSE	Blocked fertilization and lowered sperm count	Udoh [158]
Female albino rats	100 mg/kg of chloroform PSE	Inhibited estrogen secretion, thus interfere with a normal oestrous cycle	Raji [159]
Albino male rats	250 mg/kg of PSE for 52 weeks	Adverse effects on the process of spermatogenesis	Goyal [155]

Infertility and contraceptive activities

The increasing burden in raising children, unplanned pregnancies, high number of street children, and the need to protect our environment from the ever-increasing population has introduced the need for family planning in the 21st century [147,148]. The family planning agenda has also aimed at reducing maternal and child mortality as well as reducing hunger and poverty, especially in developing countries [149]. Different birth control methods have been used in family planning such as oral contraceptives, intrauterine devices, diaphragm, hysterectomy, vasectomy, tubal ligation, condom, foams, gel, and rhythm [150,151]. More often than not, these birth control methods have been described to have adverse effects, such as permanent infertility, unsafe, ineffective, irregular menses, abdominal and pelvic pain, bleeding, permanent infertility, not to mention weight gain and loss of libido [150]. Due to numberless complaints about modern contraception, the use of traditional herbs with negligible or fewer side effects has been researched. Papaya was not excluded. *Carica papaya* has shown to be relatively effective in family planning as a contraceptive in both males and females.

The preliminary studies on PSE and PLE suggest that *C. papaya* extracts have beneficial effects as male contraceptives (Table 8). The extracts may cause reversible infertility through reducing sperm motility, viability, quantity, and interfering with their morphology when it was tested on Wistar male rats with no or negligible side effects [148,152]. A 1,2,3,4-tetrahydropyridin-3-yl-octanoate is reported to be the compound behind contraceptive activity by inhibiting spermatogenesis in testes [153]. Furthermore, the extracts induced a significant reduction of contractile response of epididymal tubules and sperm count and quality male rats [148,154]. It caused infertility by significantly inhibiting spermatogenesis in testes [154,155]. The PSEs also induced abortion, caused interference of a normal estrous cycle, and reduced progesterone levels in female rats considerably [148,157–160].

Studies suggest that PSE and PLE may possess contraceptive properties that work in both male and female mice. Therefore, it is worth to carry out further clinical studies to investigate the activity and quantify efficacy on both male and female humans using the validated experimental models. Furthermore, the phytochemical characterization of *C. papaya* extracts with the investigation into the biological activity of the resultant products is warranted to unravel the bioactives in the extract with both female and male reproductive system.

Concluding remarks

In a nutshell, many studies on seeds, leaves and peels of *C. papaya* worldwide have attempted to examine the activities of their bioactive compounds and reported to possess anticancer, gastroprotective, antioxidant, antifungal, antiparasitic, hypoglycemic, antimicrobial, contraceptive, and hepatoreno-protective activities. Existing data shows that papaya nutraceuticals hold promise for the management of mild and deadly health conditions. At the same time, some research gaps were identified in the available literature on papaya (seed, peel, and leaf) bioactives to be proven for their claimed biological mechanisms and confirm their safety profiles as nutraceutical food using the recently developed models.

Limited literature is documented on the identification, characterization, and pharmacokinetics of papaya's bioactives and metabolites. Further investigation is necessary to associate pharmacodynamics with the pharmacokinetics of papaya's bioactives and their metabolites.

Despite the considerable progress made in papaya bioactives' researches over decades, more data of mode of actions and animal and human clinical trials are needed to validate the safety and efficacy of papaya seeds, peels, and leaves using advanced approaches, not to mention the dosage, duration, mode of administration which are equally important to prevent possible adverse health effects and improve their nutraceutical potential.

This review highlights various nutraceutical activities of *C. papaya* bioactives that would be useful for researchers to further examine the potential of *C. papaya* seeds, peels, and leaves as a functional food.

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References

[1] L. Tona, K. Kambu, N. Ngimbi, K. Cimanga, A.J. Vlietinck, Antiamoebic and phytochemical screening of some congolese medicinal plants, J. Ethnopharmacol. 61 (1) (1998) 57–65, doi:10.1016/S0378-8741(98)00015-4.
[2] S. Altendorf, in: Major Tropical Fruits Market Review, FAO, 2019, pp. 1–10. 2017Ed. FAO, Rome. Italy.
[3] C.X. Tan, S.T. Tan, S.S. Tan, An overview of papaya seed oil extraction methods, Int. J. Food Sci. Technol. 55 (4) (2020) 1506–1514, doi:10.1111/ijfs.14431.
[4] S. Samaram, H. Mirhosseini, C.P. Tan, H.M. Ghazali, Ultrasound-assisted extraction (UAE) and solvent extraction of papaya seed oil: yield, fatty acid composition and triacylglycerol profile, Molecules 18 (10) (2013) 12474–12487, doi:10.3390/molecules181012474.
[5] L. Azevedo, P. Campagnol, Papaya seed flour (*Carica papaya*) affects the technological and sensory quality of hamburgers, Int. Food Res. J. 21 (6) (2014) 2141.
[6] A. Ali, S. Devarajan, M. Waly, M.M. Essa, M. Rahman, "Nutritional and medicinal value of papaya (*Carica papaya* L.)," in Natural Products and Bioactive Compounds in Disease Prevention, Nova Science Publishers (2011) 34–42. https://squ.pure.elsevier.com/en/publications/nutritional-and-medicinal-values-of-papaya-carica-papaya-l (Accessed 14 August 2021).
[7] S.P. Singh, S.V. Mathan, A. Dheeraj, D. Tailor, R.P. Singh, A. Acharya, Anticancer Effects and Associated Molecular Changes of Carica Papaya Against Prostate Cancer, In American Association for Cancer Research Annual Meeting, DOI, American Association for Cancer Research, 2019, doi:10.1158/1538-7445.AM2019-3004.
[8] C. Pop-Eleches, The supply of birth control methods, education, and fertility: Evidence from Romania, J. Hum. Resour. 45 (4) (2010) 971–997, doi:10.3368/jhr.45.4.971.
[9] M. Kugo, L. Keter, A. Maiyo, J. Kinyua, P. Ndemwa, G. Maina, P. Otieno, E.M. Songok, Fortification of Carica papaya fruit seeds to school meal snacks may aid Africa mass deworming programs: a preliminary survey, BMC Complement. Altern. Med. 18 (1) (2018) 1–7, doi:10.1186/s12906-018-2379-2.
[10] A.K. Srivastava, V.K. Singh, Carica Papaya- a herbal medicine, Int. J. Res. Stud. Biosci. 4 (11) (2016) 19–25, doi:10.20431/2349-0365.0411004.
[11] Y. Nakamura, M. Yoshimoto, Y. Murata, Y. Shimoishi, Y. Asai, E.Y. Park, K. Sato, Y. Nakamura, Papaya seed represents a rich source of biologically active isothiocyanate, J. Agric. Food Chem. 55 (11) (2007) 4407–4413, doi:10.1021/jf070159w.
[12] T.N. Archampong, R.H. Asmah, C.J. Richards, V.J. Martin, C.D. Bayliss, E. Botão, L. David, S. Beleza, C. Carrilho, Gastro-duodenal disease in Africa: literature review and clinical data from accra, Ghana, World J. Gastroenterol. 25 (26) (2019) 3344–3358 10.37482Fwjg.v25.i26.3344.
[13] I.E. Juárez-Rojop, J.C. Díaz-Zagoya, J.L. Ble-Castillo, P.H. Miranda-Osorio, A.E. Castell-Rodríguez, C.A. Tovilla-Zárate, A. Rodríguez-Hernández, H. Aguilar-Mariscal, T. Ramón-Frías, D.Y. Bermúdez-Ocaña, Hypoglycemic effect of *Carica papaya* leaves in streptozotocin-induced diabetic rats, BMC Complement. Altern. Med. 12 (2012) 236, doi:10.1186/1472-6882-12-236.
[14] X. Wang, M.D.M. Contreras, D. Xu, C. Xing, L. Wang, D. Yang, Different distribution of free and bound phenolic compounds affects the oxidative stability of tea seed oil: a novel perspective on lipid antioxidation, LWT 129 (2020) 109389, doi:10.1016/j.lwt.2020.109389.
[15] M. Olcum, B. Tastan, I. Ercan, I.B. Eltutan, S. Genc, Inhibitory effects of phytochemicals on NLRP3 inflammasome activation: a review, Phytomedicine 75 (2020) 153238, doi:10.1016/j.phymed.2020.153238.
[16] M.T.N. Doan, M.C. Huynh, A.N.V. Pham, N.D.Q. Chau, P.T.K. Le, Extracting seed oil and phenolic compounds from papaya seeds by ultrasound-assisted extraction method and their properties, Chem. Eng. Trans. 78 (2020) 493–498, doi:10.3303/CET2078083.
[17] S.P. Singh, S. Kumar, M.S. Tomar, R.K. Singh, P.K. Verma, A. Kumar, S. Kumar, A. Acharya, Aqueous extract of *Carica papaya* leaf elicits the production of TNF-α and modulates the expression of cell surface receptors in tumor-associated macrophages, Biosci. Biotechnol. Res. Commun. 12 (4) (2019) 115–1122, doi:10.21786/bbrc/12.4/35.
[18] C. Odhong, R.G. Wahome, M. Vaarst, S.W. Nalubwama, M. Kiggundu, N. Halb, S. Githigia, *In vitro* anthelmintic effects of crude aqueous extracts of Tephrosia vogelii, tephrosia villosa and *Carica papaya* leaves and seeds, Afr. J. Biotechnol. 13 (52) (2014) 4667–4672, doi:10.5897/A.
[19] O. Oche, A. Rosemary, O. John, E. Chidi, S.M. Rebecca, U.A. Vincent, Chemical constituents and nutrient composition of *Carica papaya* and Vernonia amygdalina leaf extracts, J. Complement. Altern. Med. Res. (2017) 1–8, doi:10.9734/JOCAMR/2017/29402.
[20] W.J. Lee, M.H. Lee, N.W. Su, Characteristics of papaya seed oils obtained by extrusion–expelling processes, J. Sci. Food Agric. 91 (13) (2011) 2348–2354, doi:10.1002/jsfa.4466.
[21] T. Puangsri, S.M. Abdulkarim, H.M. Ghazali, Properties of *Carica papaya* L. (papaya) seed oil following extractions using solvent and aqueous enzymatic methods, J. Food Lipids 12 (1) (2005) 62–76, doi:10.1111/j.1745-4522.2005.00006.x.
[22] C.G. Mahendra, D.A. Nikhil, Nutritional, medicinal and pharmacological properties of papaya (*Carica papaya* linn.): a review, J. Innov. Pharm. Biol. Sci. 3 (1) (2016) 162–169.
[23] C.M.D. Santos, C.M.P.D. Abreu, J.M. Freire, E.D.R. Queiroz, M.M. Mendonça, Chemical characterization of the flour of peel and seed from two papaya cultivars, Food Sci. Technol. 34 (2) (2014) 353–357, doi:10.1590/fst.2014.0048.
[24] J. Dotto, A.O. Matemu, P.A. Ndakidemi, Nutrient composition and selected physicochemical properties of fifteen Mchare cooking bananas: a study conducted in northern Tanzania, Sci. Afr. 6 (2019) e00150, doi:10.1016/j.sciaf.2019.e00150.
[25] C.R. Malacrida, M. Kimura, N. Jorge, Characterization of a high oleic oil extracted from papaya (*Carica papaya* L.) seeds, Food Sci. Technol. 31 (2011) 929–934, doi:10.1590/S0101-20612011000400016.
[26] N. Dev, A. Iqbal, Processing and quality evaluation of green papaya (*Carica papaya* L.) leaf tea, J.Agric. Crop Sci. 2 (2015) 01–06.
[27] V. Briones-Labarca, M. Plaza-Morales, C. Giovagnoli-Vicuña, F. Jamett, High hydrostatic pressure and ultrasound extractions of antioxidant compounds, sulforaphane and fatty acids from Chilean papaya (*Vasconcellea pubescens*) seeds: Effects of extraction conditions and methods, LWT Food Sci. Technol. 60 (1) (2015) 525–534, doi:10.1016/j.lwt.2014.07.057.

[28] N.A. Manaf Yanty, J.M. Nazrim Marikkar, B.P. Nusantoro, K. Long, H.M. Ghazali, Physico-chemical characteristics of papaya (*Carica papaya* L.) seed oil of the Hong Kong/Sekaki variety, J. Oleo Sci. 63 (9) (2014) 885–892, doi:10.5650/jos.ess13221.

[29] A. Basu, S. Devaraj, I. Jialal, Dietary factors that promote or retard inflammation, Arterioscler. Thromb. Vasc. Biol. 26 (5) (2006) 995–1001, doi:10.1161/01.atv.0000214295.86079.d1.

[30] S. Yoneyama, K. Miura, S. Sasaki, K. Yoshita, Y. Morikawa, M. Ishizaki, T. Kido, Y. Naruse, H. Nakagawa, Dietary intake of fatty acids and serum C-reactive protein in Japanese, J. Epidemiol. 17 (3) (2007) 86–92, doi:10.2188/jea.17.86.

[31] J.A. Menendez, L. Vellon, R. Colomer, R. Lupu, Oleic acid, the main monounsaturated fatty acid of olive oil, suppresses Her-2/neu (erbB-2) expression and synergistically enhances the growth inhibitory effects of trastuzumab (Herceptin) in breast cancer cells with Her-2/neu oncogene amplification, Ann. Oncol. 16 (3) (2005) 359–371, doi:10.1093/annonc/mdi090.

[32] S.S. Tan, M. Ramadan, Papaya (*Carica papaya* L.) seed oil. fruit oils, in: Fruit Oils: Chemistry and Functionality, Springer, 2019, pp. 615–626, doi:10.1007/978-3-030-12473-1_31.

[33] D.R. Morais, E.M. Rotta, S.C. Sargi, E.G. Bonafe, R.M. Suzuki, N.E. Souza, M. Matsushita, J.V. Visentainer, Proximate composition, mineral contents and fatty acid composition of the different parts and dried peels of tropical fruits cultivated in Brazil, J. Braz. Chem. Soc. 28 (2017) 308–318, doi:10.5935/0103-5053.20160178.

[34] O. Kadiri, B. Olawoye, O.S. Fawale, O.A. Adalumo, Nutraceutical and antioxidant properties of the seeds, leaves and fruits of *Carica papaya*: potential relevance to humans diet, the food industry and the pharmaceutical industry-a review, Turk. J. Agric. Food Sci. Technol. 4 (12) (2016) 1039–1052, doi:10.24925/turjaf.v4i12.1039-1052.569.

[35] D.D. Wulansari, D.D. Wulandari, R.R. Risthanti, A. Kirtishanti, Ameliorative effect of *Carica papaya* seed extract on diabetic rat model with muscle atrophy, Media Pharm. Indones. 2 (4) (2019) 208 (MPI), doi:10.24123/mpi.v2i4.2184.

[36] D. Enriquez-Ochoa, C. Sánchez-Trasviña, B. Hernández-Sedas, K. Mayolo-Deloisa, J. Zavala, M. Rito-Palomares, J.E. Valdez-García, Aqueous two-phase extraction of phenolic compounds from sedum dendroideum with antioxidant activity and anti-proliferative properties against breast cancer cells, Sep. Purif. Technol. 251 (2020) 117341, doi:10.1016/j.seppur.2020.117341.

[37] A. Gupta, C.K. Narkowicz, H.A. Al-Aubaidy, H.F. Jelinek, D.S. Nichols, J.R. Burgess, G.A. Jacobson, Phytosterol supplements do not inhibit dipeptidyl peptidase-4, Diabetes Metab. Syndr. 14 (5) (2020) 1475–1478 Clinical Research and Reviews, doi:10.1016/j.dsx.2020.07.019.

[38] Y. Cen, X. Zou, L. Li, S. Chen, Y. Lin, L. Liu, S. Zheng, Inhibition of the glutathione biosynthetic pathway increases phytochemical toxicity to Spodoptera litura and Nilaparvata lugens, Pestic. Biochem. Physiol. (2020) 104632, doi:10.1016/j.pestbp.2020.104632.

[39] Y. Nakamura, M. Yoshimoto, Y. Murata, Y. Shimoishi, Y. Asai, E.Y. Park, K. Sato, Y. Nakamura, Papaya seed represents a rich source of biologically active isothiocyanate, J. Agric. Food Chem. 55 (11) (2007) 4407–4413, doi:10.1021/jf070159w.

[40] C.F. Iroka, E.E. Akachukwu, R.N. Adimonyemma, N.C. Okereke, C.O. Nwogiji, Effects of induced ripening on the proximate, biochemical and mineral compositions of *Carica papaya* (Pawpaw Fruit), Eur. J. Med. Plants (2016) 1–10, doi:10.9734/EJMP/2016/26260.

[41] Z. Jiao, J. Deng, G. Li, Z. Zhang, Z. Cai, Study on the compositional differences between transgenic and non-transgenic papaya (*Carica papaya* L.), J. Food Compos. Anal. 23 (6) (2010) 640–647, doi:10.1016/j.jfca.2010.03.004.

[42] H.V. Annegowda, R. Bhat, M.S.J. Simmonds, V.R. Preedy, in: Composition of Papaya Fruit and Papaya Cultivars, in Nutritional Composition of Fruit Cultivars, Academic Press, 2016, pp. 497–516. San Diego.

[43] G. Jing, T. Li, H. Qu, Z. Yun, Y. Jia, X. Zheng, Y. Jiang, Carotenoids and volatile profiles of yellow- and red-fleshed papaya fruit in relation to the expression of carotenoid cleavage dioxygenase genes, Postharvest Biol. Technol. 109 (2015) 114–119, doi:10.1016/j.postharvbio.2015.06.006.

[44] A.K. Martial-Didier, K.K. Hubert, K.E.J. Parfait, T. Kablan, Phytochemical properties and proximate composition of papaya (*Carica papaya* L.) peels, Turk. J. Agric. Food Sci. Technol. 5 (6) (2017) 676–680, doi:10.24925/turjaf.v5i6.676-680.1154.

[45] P.D. Pathak, S.A. Mandavgane, B.D. Kulkarni, Waste to wealth: a case study of papaya peel, Waste Biomass Valorization 10 (6) (2019) 1755–1766, doi:10.1007/s12649-017-0181-x.

[46] C.A. Obafemi, O.A. Fadare, O.M. Durosinmi, R. Fadare, O.U. Izevbekhai, I.O. Awonyemi, ATR-FTIR AND HPLC spectroscopic studies and evaluation of mineral content of *Carica papaya* leaves and flowers, J. Phytomed. 1 (1) (2015) 1–7 https://ir.oauife.edu.ng/handle/123456789/3732.

[47] B. Joseph, P. Sankarganesh, K. Ichiyama, N. Yamamoto, *In vitro* study on cytotoxic effect and anti-DENV2 activity of *Carica papaya* L. leaf, Front. Life Sci. 8 (1) (2015) 18–22, doi:10.1080/21553769.2014.924080.

[48] J. Senrayan, S. Venkatachalam, Solvent-assisted extraction of oil from papaya (*Carica papaya* L.) seeds: evaluation of its physiochemical properties and fatty-acid composition, Sep. Sci. Technol. 53 (17) (2018) 2852–2859, doi:10.1080/01496395.2018.1480632.

[49] O. Kadiri, C.T. Akanbi, B.T. Olawoye, S.O. Gbadamosi, Characterization and antioxidant evaluation of phenolic compounds extracted from the protein concentrate and protein isolate produced from pawpaw (*Carica papaya* Linn.) seeds, Int. J. Food Prop. 20 (11) (2017) 2423–2436, doi:10.1080/10942912.2016.1230874.

[50] M. Adesola, E. Akande, Effect of extracting solvents on the phyto-chemical properties of fermented pawpaw (*Carica papaya* L.) seed, Asian Food Sci. J. (2019) 1–10, doi:10.9734/afsj/2019/v7i429977.

[51] K. Nilugal, S. Fattepur, V. Veerapandian, F. Asmani, M. Bacayo, I. Abdulah, E. Yusuf, Evaluation of anti-ulcer effect of papaya juice in combination with cumin seed in ethanol induced peptic ulcers in experimental rats, in: Proceedings of the Bromo Conference, Symposium on Natural Products and Biodiversity, 2018, p. 94, doi:10.5220/0008358000940101. 10.

[52] T.A. Okewumi, A.W. Oyeyemi, Gastro-protective activity of aqueous *Carica papaya* seed extract on ethanol induced gastric ulcer in male rats, Afr. J. Biotechnol. 11 (34) (2012) 8612–8615, doi:10.5897/AJB12.034.

[53] L.A. Pinto, K.W. Cordeiro, V. Carrasco, C.A. Carollo, C.A.L. Cardoso, E.J.S. Argadoña, K.D.C. Freitas, Antiulcerogenic activity of *Carica papaya* seed in rats, Naunyn Schmiedeberg's Arch. Pharmacol. 388 (3) (2015) 305–317, doi:10.1007/s00210-014-1069-y.

[54] M. Indran, A.A. Mahmood, U.R. Kuppusamy, Protective effect of *Carica papaya* L leaf extract against alcohol induced acute gastric damage and blood oxidative stress in rats, West Indian Med. J. 57 (4) (2008) 323 6.

[55] H.O.B. Oloyede, M.C. Adaja, T.O. Ajiboye, M.O. Salawu, Anti-ulcerogenic activity of aqueous extract of *Carica papaya* seed on indomethacin-induced peptic ulcer in male albino rats, J. Integr. Med. 13 (2) (2015) 105–114, doi:10.1016/S2095-4964(15)60160-1.

[56] A.C. Ezike, P.A. Akah, C.O. Okoli, N.A. Ezeuchenne, S. Ezeugwu, *Carica papaya* (Paw-Paw) unripe fruit may be beneficial in ulcer, J. Med. Food 12 (6) (2009) 1268–1273, doi:10.1089/jmf.2008.0197.

[57] A. Ologundudu, A.O. Lawal, I.A. Ololade, A.A. Omonkhua, F. Obi, The anti-ulcerogenic activity of aqueous extract of *Carica papaya* fruit on aspirin-induced ulcer in rats, Int. J. Toxicol. 5 (2) (2008) 1–5. https://ispub.com/IJTO/5/2/4180 (Accessed 14 August 2021).

[58] K.K. Mak, J.J. Tan, P. Marappan, M.K. Balijepalli, H. Choudhury, S. Ramamurthy, M.R. Pichika, Galangin's potential as a functional food ingredient, J. Funct. Foods 46 (2018) 490–503, doi:10.1016/j.jff.2018.04.054.

[59] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (6) (2018) 394–424, doi:10.3322/caac.21492.

[60] M.S. Copur, State of cancer research around the globe, Oncology 33 (5) (2019) 181–185. http://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=08909091&AN=136403740&h=OsOw49h%2FuEPZ%2B0rCHdVhjI%2FqkvHBDl6EXqJhsQ4XGkCq%2BywO7sQcYv7n4kidr%2Fz%2BgXp3Esq%2FnQLTzbZoEZI9lg%3D%3D&crl=c (Accessed 14 August 2021).

[61] S. Singh, B. Sharma, S.S. Kanwar, A. Kumar, Lead phytochemicals for anticancer drug development, Front. Plant Sci. 7 (2016) 1667, doi:10.3389/fpls.2016.01667.

[62] J. Somanah, E. Bourdon, T. Bahorun, Extracts of mauritian *Carica papaya* (var. solo) protect SW872 and HepG2 cells against hydrogen peroxide induced oxidative stress, J. Food Sci. Technol. 54 (7) (2017) 1917–1927, doi:10.1007/s13197-017-2626-4.

[63] N. Otsuki, N.H. Dang, E. Kumagai, A. Kondo, S. Iwata, C. Morimoto, Aqueous extract of *Carica papaya* leaves exhibits anti-tumor activity and immunomodulatory effects, J. Ethnopharmacol. 127 (3) (2010) 760–767, doi:10.1016/j.jep.2009.11.024.

[64] A. Rahmat, R. Rosli, W. Zain, S. Endrini, H. Sani, Antiproliferative activity of pure lycopene compared to both extracted lycopene and juices from watermelon (*Citrullus vulgaris*) and papaya (*Carica papaya*) on human breast and liver cancer cell lines, J. Med. Sci. 2 (2) (2002) 55–58, doi:10.3923/jms.2002.55.58.

[65] S. Salla, R. Sunkara, S. Ogutu, L.T. Walker, M. Verghese, Antioxidant activity of papaya seed extracts against H_2O_2 induced oxidative stress in HepG2 cells, LWT Food Sci. Technol. 66 (2016) 293–297, doi:10.1016/j.lwt.2015.09.008.

[66] Z.Y. Li, Y. Wang, W.T. Shen, P. Zhou, Content determination of benzyl glucosinolate and anti–cancer activity of its hydrolysis product in *Carica papaya* L, Asian Pac. J. Trop. Med. 5 (3) (2012) 231–233, doi:10.1016/S1995-7645(12)60030-3.

[67] M. Hirose, T. Yamaguchi, N. Kimoto, K. Ogawa, M. Futakuchi, M. Sano, T. Shirai, Strong promoting activity of phenylethyl isothiocyanate and benzyl isothiocyanate on urinary bladder carcinogenesis in F344 male rats, Int. J. Cancer 77 (5) (1998) 773–777, doi:10.1002/(SICI)1097-0215(19980831)77:53C773::AID-IJC173E3.0.CO;2-2.

[68] P. García-Solís, E.M. Yahia, V. Morales-Tlalpan, M. Díaz-Muñoz, Screening of antiproliferative effect of aqueous extracts of plant foods consumed in México on the breast cancer cell line MCF-7, Int. J. Food Sci. Nutr. 60 (sup6) (2009) 32–46, doi:10.1080/09637480802312922.

[69] R. Jayakumar, M.S. Kanthimathi, Inhibitory effects of fruit extracts on nitric oxide-induced proliferation in MCF-7 cells, Food Chem. 126 (3) (2011) 956–960, doi:10.1016/j.foodchem.2010.11.093.

[70] S.A. Hadadi, H. Li, R. Rafie, P. Kaseloo, S.M. Witiak, R.A. Siddiqui, 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. 4 (2018) 1–15, doi:10.20517/2394-4722.2018.22.

[71] G. Oboh, A.A. Olabiyi, A.J. Akinyemi, Inhibitory effect of aqueous extract of different parts of unripe pawpaw (*Carica papaya*) fruit on Fe2+-induced oxidative stress in rat pancreas *in vitro*, Pharm. Biol. 51 (9) (2013) 1165–1174, doi:10.3109/13880209.2013.782321.

[72] T. Okoko, D. Ere, Reduction of hydrogen peroxide–induced erythrocyte damage by *Carica papaya* leaf extract, Asian Pac. J. Trop. Biomed. 2 (6) (2012) 449–453, doi:10.1016/S2221-1691(12)60074-4.

[73] E. Panzarini, M. Dwikat, S. Mariano, C. Vergallo, L. Dini, Administration dependent antioxidant effect of Carica papaya seeds water extract, Evid. Based Complement. Altern. Med., 2014 2014, doi:10.1155/2014/281508.

[74] K.S. Alotaibi, H. Li, R. Rafi, R.A. Siddiqui, Papaya black seeds have beneficial anticancer effects on PC-3 prostate cancer cells, J. Cancer Metastasis Treat. 3 (2017) 161–168, doi:10.20517/2394-4722.2017.33.

[75] S. Pandey, C. Walpole, P.J. Cabot, P.N. Shaw, J. Batra, A.K. Hewavitharana, Selective anti-proliferative activities of *Carica papaya* leaf juice extracts against prostate cancer, Biomed. Pharmacother. 89 (2017) 515–523, doi:10.1016/j.biopha.2017.02.050.

[76] S.D. Grosse, I. Odame, H.K. Atrash, D.D. Amendah, F.B. Piel, T.N. Williams, Sickle cell disease in Africa: a neglected cause of early childhood mortality, Am. J. Prev. Med. 41 (6) (2011) S398–S405, doi:10.1016/j.amepre.2011.09.013.

[77] N.O.A. Imaga, The use of phytomedicines as effective therapeutic agents in sickle cell anemia, Sci. Res. Essays 5 (24) (2010) 3803–3807.

[78] N.O.A. Imaga, G.O. Gbenle, V.I. Okochi, S.O. Akanbi, S.O. Edeoghon, V. Oigbochie, M.O. Kehinde, S.B. Bamiro, Antisickling property of *Carica papaya* leaf extract, Afr. J. Biochem. Res. 3 (4) (2009) 102–106.

[79] N.L. Yembeau, P.C.N. Biapa, B. Chetcha, F.L. Nguelewou, C.F. Kengne, P.J.N. Nkwikeu, P. Bruno Telefo, C.A. Pieme, *In vitro* evaluation of antioxidant and anti-sickling properties of theobroma cacao (Sterculiaceae) extracts from east and south regions in Cameroon, Investig. Med. Chem. Pharmacol. 1 (1) (2018) 6.

[80] I.S. Afolabi, I.O. Osikoya, O.D. Fajimi, P.I. Usoro, D.O. Ogunleye, T. Bisi-Adeniyi, A.O. Adeyemi, B.T. Adekeye, Solenostemon monostachyus, ipomoea involucrata and *Carica papaya* seed oil versus glutathione, or vernonia amygdalina: methanolic extracts of novel plants for the management of sickle cell anemia disease, BMC Complement. Altern. Med. 12 (2012), doi:10.1186/1472-6882-12-262.

[81] O.C. Mojisola, E.A. Adebolu, D.M. Alani, Antisickling properties of *Carica papaya* linn, J. Nat. Prod. 1 (2008) 56–66.

[82] E.E.J. Iweala, F.O. Uhegbu, G.N. Ogu, Preliminary *in vitro* antisickilng properties of crude juice, Afr. J. Tradit. Complement. Altern. Med. 7 (2010) 113–117.

[83] I.A.O. Ngozi, S.A. Esther, O. Samson, S.K. Akindele, *In vitro* biochemical investigations of the effects of *Carica papaya* and fagara zanthoxyloides on antioxidant status and sickle erythrocytes, Afr. J. Biochem. Res. 5 (8) (2011) 226–236.

[84] S. Burungale, C. Swati Burungale, Natural remedies to increase platelet count, Pharm. Innov. J. 18 (12) (2016) 18–22.

[85] L.E. Adinolfi, M.G. Giordano, A. Andreana, M.F. Tripodi, R. Utili, G. Cesaro, E. Ragone, E.D. Mangoni, G. Ruggiero, Hepatic fibrosis plays a central role in the pathogenesis of thrombocytopenia in patients with chronic viral hepatitis, Br. J. Haematol. 113 (3) (2001) 590–595, doi:10.1046/j.1365-2141.2001.02824.x.

[86] R. McMillan, The pathogenesis of chronic immune (idiopathic) - thrombocjtopenic purpura, Semin. Hematol. 37 (I) (2000) 5–9, doi:10.1016/S0037-1963(00)90111-2.

[87] R. McMillan, The pathogenesis of chronic immune thrombocytopenic purpura, Semin. Hematol. 44 (5) (2007), doi:10.1053/j.seminhematol.2007.11.002.

[88] P.N. Kasture, K.H. Nagabhushan, A. Kumar, A multi-centric, double-blind, placebo-controlled, randomized, prospective study to evaluate the efficacy and safety of *Carica papaya* leaf extract, as empirical therapy for thrombocytopenia associated with dengue fever, J. Assoc. Physicians India 64 (2016) 15–20.

[89] A. Gowda, N. Kumar, P. Kasture, K. Nagabhushan, A pilot study to evaluate the effectiveness of *Carica papaya* leaf extract in increasing the platelet count in cases of dengue with thrombocytopenia, Indian Med. Gaz. (2015) 109–116. https://pesquisa.bvsalud.org/portal/resource/pt/sea-159275 (Accessed 14 August 2021).

[90] S. Subenthiran, T.C. Choon, K.C. Cheong, R. Thayan, M.B. Teck, P.K. Muniandy, A. Afzan, N.R. Abdullah, Z. Ismail, *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. Altern. Med. 2013 (2013) 1–7, doi:10.1155/2013/616737.

[91] W. Abebe, Review of herbal medications with the potential to cause bleeding: dental implications, and risk prediction and prevention avenues, EPMA J. 10 (1) (2019) 51–64, doi:10.1007/s13167-018-0158-2.

[92] P. Meganathan, K.R. Selvaduray, K. Nesaretnam, Blood thinning effects and phytonutrients, Malays. Oil J. 23 (2) (2008) 8–12.

[93] D. Sundarmurthy, C.R. Jayanthi, K.C. Lakshmaiah, Effect of *Carica papaya* leaf extract on platelet count in chemotherapy-induced thrombocytopenic patients: a preliminary study, Natl. J. Physiol. Pharm. Pharmacol. 7 (7) (2017) 685–692, doi:10.5455/njppp.2017.7.0202628022017.

[94] N. Tahir, Z. Zaheer, S. Kausar, S. Chiragh, Prevention of fall in platelet count by *Carica papaya* leaf juice in carboplatin induced thrombocytopaenia in mice, Biomedica 17 (C) (2014) 21–25.

[95] S.L.C.A. Dharmarathna, S. Wickramasinghe, R.N. Waduge, R.P.V.J. Rajapakse, S.A.M. Kularatne, Does *Carica papaya* leaf-extract increase the platelet count? An experimental study in a murine model, Asian Pac. J. Trop. Biomed. 3 (9) (2013) 720–724, doi:10.1016/S2221-1691(13)60145-8.

[96] J. Aziz, N.L. Abu Kassim, N.H. Abu Kasim, N. Haque, M.T. Rahman, *Carica papaya* induces *in vitro* thrombopoietic cytokines secretion by mesenchymal stem cells and haematopoietic cells, BMC Complement. Altern. Med. 15 (1) (2015) 1–8, doi:10.1186/s12906-015-0749-6.

[97] P. Ranasinghe, P. Ranasinghe, W.P. Kaushalya, G.A. Sirimal Premakumara, Y.S. Perera, P. Gurugama, S.B. Gunatilake, *In vitro* erythrocyte membrane stabilization properties of *Carica papaya* L. leaf extracts, Pharmacogn. Res. 4 (4) (2012) 196–202, doi:10.4103/0974-8490.102261.

[98] J.M. Dotto, J.S. Chacha, The potential of pumpkin seeds as a functional food ingredient: a review, Sci. Afr. 10 (2020) e00575, doi:10.1016/j.sciaf.2020.e00575.

[99] M.S. Hounzangbe-Adote, V. Paolini, I. Fouraste, K. Moutairou, H. Hoste, *In vitro* effects of four tropical plants on three life-cycle stages of the parasitic nematode, haemonchus contortus, Res. Vet. Sci. 78 (2) (2005) 155–160, doi:10.1016/j.rvsc.2004.05.009.

[100] S. Hounzangbe-Adote, I. Fouraste, K. Moutairou, H. Hoste, *In vitro* effects of four tropical plants on the activity and development of the parasitic nematode, trichostrongylus colubriformis, J. Helminthol. 79 (1) (2005) 29–33, doi:10.1079/joh2004265.

[101] S. Bi, P.K. Goya, Anthelmintic effect of natural plant (*Carica papaya*) extract against the gastrointestinal nematode, ancylostoma caninum in mice, ISCA J. Biol. Sci. 1 (1) (2012) 2 2.

[102] G. Stepek, D.J. Buttle, I. Duce, A. Lowe, J.M. Behnke, Assessment of the anthelmintic effect of natural plant cysteine proteinases against the gastrointestinal nematode, heligmosomoides polygyrus, *in vitro*, Parasitology 130 (2) (2005) 203–211, doi:10.1017/S0031182004006225.
[103] R. Kermanshai, B.E. McCarry, J. Rosenfeld, P.S. Summers, E.A. Weretilnyk, G.J. Sorger, Benzyl isothiocyanate is the chief or sole anthelmintic in papaya seed extracts, Phytochemistry 57 (3) (2001) 427–435, doi:10.1016/S0031-9422(01)00077-2.
[104] S.T. Mohammed, S.A. Al-Sharqi, N. Mohammed, Antiparasitic activity of natural plant *Carica papaya* seed extract against gastrointestinal parasite *entamoeba histolytica*, Int. J. Innov. Appl. Stud. 7 (1) (2014) 58.
[105] S.K. Sarker, N. Begum, D. Mondal, M.A. Siddique, M.A. Rashid, *In vitro* study of antiamoebic effect of methanol extract of mature seeds of *Carica papaya* on trophozoites of *entamoeba histolytica*, Bangladesh J. Pharmacol. 5 (1) (2010) 45–47, doi:10.3329/bjp.v5i1.5003.
[106] J.A.O. Okeniyi, T.A. Ogunlesi, O.A. Oyelami, L.A. Adeyemi, Effectiveness of dried *Carica papaya* seeds against human intestinal parasitosis: a pilot study, J. Med. Food 10 (1) (2007) 194–196, doi:10.1089/jmf.2005.065.
[107] T. Zhang, W. Chen, The candida albicans inhibitory activity of the extract from papaya (*Carica papaya* L.) seed relates to mitochondria dysfunction, Int. J. Mol. Sci. 18 (9) (2017), doi:10.3390/ijms18091858.
[108] P.X.M. Bastiaensen, The use of indigeneous papaya (*Carica papaya*) as an anthelmintic for the treatment of gastro-intestinal nematodes in naturally infected calves in suriname, Bastiaensen 2 (4) (1995) 1–5.
[109] L. Tona, K. Kambu, N. Ngimbi, K. Mesia, O. Penge, M. Lusakibanza, K. Cimanga, T. De Bruyne, S. Apers, J. Totte, L. Pieters, A.J. Vlietinck, Antiamoebic and spasmolytic activities of extracts from some antidiarrhoeal traditional preparations used in Kinshasa, Congo, Phytomedicine 7 (1) (2000) 31–38, doi:10.1016/S0944-7113(00)80019-7.
[110] I.I. Anibijuwon, A.O. Udeze, Antimicrobial activity of *Carica papaya* (Pawpaw Leaf) on some pathogenic organisms of clinical origin from South-Western Nigeria, Ethnobot. Leafl. 13 (Mic) (2009) 850–864.
[111] J.H. Doughari, A.M. Elmahmood, S. Manzara, Studies on the antibacterial activity of root extracts of *Carica papaya* L, Afr. J. Microbiol. Res. 1 (3) (2007) 37–41.
[112] J. Lohidas, S. Manjusha, G. Glory Gnana Jothi, Antimicrobial activities of *Carica papaya* L, Plant Arch. 15 (2) (2015) 1179–1186.
[113] N. Nirosha, R. Mangalanayaki, Antibacterial activity of leaves and stem extract of *Carica papaya* L, Int. J. Adv. Pharm. Biol. Chem. 2 (3) (2013) 473–476.
[114] K. Suresh, P. Deepa, R. Harisaranraj, A.V. Vaira, Antimicrobial and phytochemical investigation of the leaves of *Carica papaya* L., cynodon dactylon (L.) Pers., Euphorbia hirta *L., and* Psidium guajava *L*, Ethnobot. Leafl. 12 (2008) 1184–1191.
[115] C. Baskaran, S. Velu, K. Kumaran, The efficacy of *Carica papaya* leaf extract on some bacterial and a fungal strain by well diffusion method, Asian Pac. J. Trop. Dis. 2 (2012) S658–S662.
[116] B. Tewari, G. Subramanian, R. Gomathinayagm, Antimicrobial properties of *Carica papaya* (Papaya) different leaf extract against *E. coli, S. aureus* and *C. albicans*, Am. J. Pharmacol. Pharmacother. 1 (1) (2014) 025–039.
[117] A.C. Emeruwa, Antibacterial substance from *Carica papaya* fruit extract, J. Nat. Prod. 45 (2) (1982) 123–127, doi:10.1021/np50020a002.
[118] X. He, Y. Ma, G. Yi, J. Wu, L. Zhou, H. Guo, Chemical composition and antifungal activity of *Carica papaya* lin*n. seed essential oil against* candida *spp*, Lett. Appl. Microbiol. 64 (5) (2017) 350–354, doi:10.1111/lam.12711.
[119] G. Morace, F. Perdoni, E. Borghi, Antifungal drug resistance in candida species, J. Glob. Antimicrob. Resist. 2 (4) (2014) 254–259, doi:10.1016/j.jgar.2014.09.002.
[120] R. Wirth, J. Bauer, C. Sieber, Necrotizing *candida* infection after percutaneous endoscopic gastrostomy: a fatal and rare complication, J. Parenter. Enter. Nutr. 32 (3) (2008) 285–287, doi:10.1177/0148607108316190.
[121] N. Sheikh, V. Jahagirdar, S. Kothadia, B. Nagoba, Antifungal drug resistance in *candida* species, Electron. J. Gen. Med. 10 (4) (2018) 254–258, doi:10.29333/ejgm/82217.
[122] R. Laniado-Laborín, M.N. Cabrales-Vargas, Amphotericin B: side effects and toxicity, Rev. Iberoam. Micol. 26 (4) (2009) 223–227, doi:10.1016/j.riam.2009.06.003.
[123] D. Barrett, From natural products to clinically useful antifungals, Biochim. Biophys. Acta 1587 (2) (2002) 224–233, doi:10.1016/S0925-4439(02)00085-6.
[124] A.L. Demain, Antibiotics: natural products essential to human health, Med. Res. Rev. 29 (6) (2009) 821–842, doi:10.1002/med.20154.
[125] A.H. Rahmani, Y.H. Aldebasi, Potential role of *Carica papaya* and their active constituents in the prevention and treatment of diseases, Int. J. Pharm. Pharm. Sci. 8 (1) (2016) 11–15.
[126] O. Singh, M. Ali, Phytochemical and antifungal profiles of the seeds of *Carica papaya* L, Indian J. Pharm. Sci. 73 (4) (2011) 447–451, doi:10.4103/0250-474X.95648.
[127] T. Zhang, W. Chen, The candida albicans inhibitory activity of the extract from papaya (*Carica papaya* L.) seed relates to mitochondria dysfunction, Int. J. Mol. Sci. 18 (9) (2017), doi:10.3390/ijms18091858.
[128] P. Chávez-Quintal, T. González-Flores, I. Rodríguez-Buenfil, S. Gallegos-Tintoré, Antifungal activity in ethanolic extracts of *Carica papaya* L. cv. Maradol leaves and seeds, Indian J. Microbiol. 51 (1) (2011) 54–60, doi:10.1007/s12088-011-0086-5.
[129] J. Khanja, Y. Srivastava, P.K. Pal, *In vitro* evaluation of antimicrobial properties of *Carica papaya*, Int. J. Biol. Pharm. Allied Sci. 1 (7) (2012) 933–945.
[130] P.C. Collignon, J.M. Conly, A. Andremont, S.A. McEwen, A. Aidara-Kane, P.M. Griffin, Y. Agerso, T. Dang Ninh, P. Donado-Godoy, P. Fedorka-Cray, H. Fernandez, M. Galas, R. Irwin, B. Karp, G. Matar, P. McDermott, E. Mitema, R. Reid-Smith, H.M. Scott, R. Singh, C.S. Dewaal, J. Stelling, M. Toleman, H. Watanabe, G.J. Woo, World health organization ranking of antimicrobials according to their importance in human medicine: a critical step for developing risk management strategies to control antimicrobial resistance from food animal production, Clin. Infect. Dis. 63 (8) (2016) 1087–1093, doi:10.1093/cid/ciw475.
[131] G. Roglic, WHO global report on diabetes: a summary, Int. J. Non Commun. Dis. 1 (2016) 3–8.
[132] J.E. Shaw, R.A. Sicree, P.Z. Zimmet, Global estimates of the prevalence of diabetes for 2010 and 2030, Diabetes Res. Clin. Pract. 87 (1) (2010) 4–14, doi:10.1016/j.diabres.2009.10.007.
[133] WHO, Diabetes Action Now Booklet. Geneva, Switzerland: World Health Organization. 49 (2) 2004. Available from: https://www.who.int/diabetes/actionnow/en/DANbooklet.pdf [Accessed on August 14, 2021].
[134] R. Hillson, in: Herbs and Diabetes, 36, John Wiley & Sons, 2019, pp. 159–160, doi:10.1186/s13098-017-0254-9.
[135] I.E. Juárez-Rojop, C.A. Tovilla-Zárate, D.E. Aguilar-Domínguez, L.F.R.d.L. Fuente, C.E. Lobato-García, J.L. Blé-Castillo, L. López-Meraz, J.C. Díaz-Zagoya, D.Y. Bermúdez-Ocaña, Phytochemical screening and hypoglycemic activity of *Carica papaya* leaf in streptozotocin-induced diabetic rats, Braz. J. Pharm. 24 (3) (2014) 341–347, doi:10.1016/j.bjp.2014.07.012.
[136] A. Olubodun, A. Olayemi, B. Shade, S. Abidat, D. Odunayo, Anti-diabetic effect of ethanol extract of *Carica papaya* leaf in alloxan induced diabetic mice, Mediterr. J. Basic Appl. Sci. 2 (3) (2018) 46–56.
[137] R. Agada, W.A. Usman, S. Shehu, D. Thagariki, *In vitro* and *in vivo* inhibitory effects of *Carica papaya* seed on α-amylase and α-glucosidase enzymes, Heliyon 6 (3) (2020) e03618 e03618, doi:10.1016/j.heliyon.2020.e03618.
[138] O.I. Aruoma, J. Somanah, E. Bourdon, P. Rondeau, T. Bahorun, 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. 768 (C) (2014) 60–68 Fundamental and Molecular Mechanisms of Mutagenesis, doi:10.1016/j.mrfmmm.2014.04.007.
[139] M. Sadeque, Z. Begum, B. Umar, A. Ferdous, S. Sultana, M. Uddin, Comparative efficacy of dried fruits of *Carica papaya* Linn. and vitamin-E on preventing hepatotoxicity in rats, Faridpur Med. Coll. J. 7 (1) (2012) 29–32, doi:10.3329/fmcj.v7i1.10295.
[140] B. Rajkapoor, B. Jayakar, S. Kavimani, N. Murugesh, Effect of dried fruits of *Carica papaya* L INN on hepatotoxicity, Biol. Pharm. Bull. 25 (12) (2002) 1645–1646, doi:10.1248/bpb.25.1645.

[141] Y. Jiang, C. Wang, Y.Y. Li, X.C. Wang, J.D. An, Y.J. Wang, X.J. Wang, Mistletoe alkaloid fractions alleviates carbon tetrachloride-induced liver fibrosis through inhibition of hepatic stellate cell activation via TGF-β/Smad interference, J. Ethnopharmacol. 158 (2014) 230–238, doi:10.1016/j.jep.2014.10.028.
[142] A. Pandit, T. Sachdeva, P. Bafna, Ameliorative effect of leaves of *Carica papaya* in ethanol and antitubercular drug induced hepatotoxicity, J. Pharm. Res. Int. (2013) 648–661, doi:10.9734/BJPR/2013/4517.
[143] M. Kanadi, A. Wudil, A. Alhassan, A. Ngwen, A. Yaradua, A. Nasir, Dose-dependent chemopreventive effect of methanol extract of *Carica papaya* seed on potassium bromate-induced nephrotoxicity in rats, Asian J. Biochem. Genet. Mol. Biol. (2019) 1–12, doi:10.9734/ajbgmb/2019/v2i130051.
[144] N. Madinah, M. Nozmo, I. Ezekiel, The protective effects of aqueous extract of *Carica papaya* seeds in paracetamol induced nephrotoxicity in male wistar rats, Afr. Health Sci. 15 (2) (2015) 598–605, doi:10.4314/ahs.v15i2.37.
[145] I. Gheith, A. El-Mahmoudy, Novel and classical renal biomarkers as evidence for the nephroprotective effect of *Carica papaya* leaf extract, Biosci. Rep. 38 (5) (2018), doi:10.1042/BSR20181187.
[146] J. Olagunju, A. Adeneye, B. Fagbohunka, N. Bisuga, A. Ketiku, A. Benebo, O. Olufowobi, A. Adeoye, M. Alimi, A. Adeleke, Nephroprotective activities of the aqueous seed extract of *Carica papaya* Linn. in carbon tetrachloride induced renal injured wistar rats: a dose-and time-dependent study, Biol. Med. 1 (1) (2009) 11–19.
[147] A.E. Memudu, T.J. Oluwole, The contraceptive potential of *Carica papaya* seed on oestrus cycle, progesterone, and histomorphology of the Utero-ovarian tissue of adult wistar rats, JBRA Assist. Reprod. (2021) 34–43, doi:10.5935/1518-0557.20200023.
[148] S. Nita, A. Setiawan, R. Inggarsih, U. Tantri, M. Herdiana, Papaya (*Carica papaya* L.) seed extract as male contraception via decreasing the quality of Rat's (*Rattus Norvegicus*) sperm, Biosci. Med. 4 (1) (2019) 19–28, doi:10.32539/bsm.v4i1.110.
[149] L. Chola, S. McGee, A. Tugendhaft, E. Buchmann, K. Hofman, Scaling up family planning to reduce maternal and child mortality: the potential costs and benefits of modern contraceptive use in South Africa, PLoS One 10 (6) (2015) e0130077, doi:10.1371/journal.pone.0130077.
[150] A.M. Albsoul-Younes, F. Saleh, W. El-Khateeb, Perception of efficacy and safety as determinants for use and discontinuation of birth control methods in Muslim Jordanian women, Eur. J. Contracept. Reprod. Health Care 8 (3) (2003) 156–161, doi:10.1080/ejc.8.3.156.161.
[151] J.A. Rosenfeld, P.M. Zahorik, W. Saint, G. Murphy, Women's satisfaction with birth control, J. Fam. Pract. 36 (2) (1993) 169–173.
[152] M. Sinha, K. Balamurgan, N. Ganesh, Pharmacological evaluation of nanoemulsion of the seed extract of *Carica papaya* for male oral contraceptive action in mice, Panacea J. Pharm. Pharm. Sci. 3 (4) (2014) 57–61.
[153] E. Julaeha, Y. Permatasari, T. Mayanti, A. Diantini, Antifertility compound from the seeds of *Carica papaya*, Procedia Chem. 17 (2015) 66–69, doi:10.1016/j.proche.2015.12.135.
[154] R. Verma, N. Chinoy, Effect of papaya seed extract on contractile response of cauda epididymal tubules, Asian J. Androl. 4 (1) (2002) 77–78.
[155] S. Goyal, B. Manivannan, A.S. Ansari, S.C. Jain, N.K. Lohiya, Safety evaluation of long term oral treatment of methanol sub-fraction of the seeds of *Carica papaya* as a male contraceptive in albino rats, J. Ethnopharmacol. 127 (2) (2010) 286–291, doi:10.1016/j.jep.2009.11.007.
[156] A. Airaodion, E. Airaodion, J. Ekenjoku, E. Ogbuagu, U. Ogbuagu, Antiplasmodial potency of ethanolic leaf extract of *Carica papaya* against plasmodium berghei in infected swiss albino mice, Asian J. Med. Princ. Clin. Pract. 2 (2) (2019) 1–8.
[157] R.A. Wiryawan, S. Purwaningsih, M. Doctor, S. Program, U. Airlangga, Papaya seed extract lowers sperm concentrations, motility and viability in male mice, Folia Med. Indones. 51 (4) (2015) 252–256.
[158] F. Udoh, P. Udoh, E. Umoh, Activity of alkaloid extract of *Carica papaya*. Seeds on reproductive functions in male wistar rats, Pharm. Biol. 43 (6) (2005) 563–567, doi:10.1080/13880200500220961.
[159] Y. Raji, Impact of the chloroform extract of *Carica papaya* seed on oestrous cycle and fertility. In female albino rats, J. Med. Sci. 5 (4) (2005) 337–343.
[160] J.M. Dotto, J.S. Chacha, The potential of pumpkin seeds as a functional food ingredient: a review, Sci. Afr. 10 (2020) e00575, doi:10.1016/j.sciaf.2020.e00575.

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