Section A-Systematic review

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The Medicinal Value and the Therapeutic Application of the leaves of *Carica Papaya Linnaeus*

Islam Mazahirul[1]*, Mukul Sharma[4]*,Khatib Ismail Sayeed[1], Ali Kashif Syed[2], Asaduddin Mohammed[1], Alam Afroze[3], and Afraim Koty[5]

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Abstract

Objective

The leaves of the *Carica papaya Linnaeus* (CP) are the least studied portion of the plant since its fruit is well-liked for medical applications. Therefore, finding the literature that exclusively discusses the pharmacological and therapeutic benefits of CP leaves is the primary goal of this research study.

Methods

The medicinal and therapeutic benefits of CP leaves have been identified through research available on electronic databases like Scopus, Web of Science, Google Scholar, Pubmed, ScienceDirect, NIH databases, and grey literature until December 2022.

Results

More than 52 papers in total were searched to determine the medicinal value of the CP leaves. As a result, numerous bioactive substances have been found in the leaves, including alkaloids, glycosides, tannins, saponins, flavonoids, and others which have been intensively examined for their wide range of pharmacological properties.

Conclusion

Numerous studies have demonstrated that papaya leaves have potent antibacterial, antifungal, anti-inflammatory, immune-modulating, hepatoprotective, hypoglycemic, anti-angiogenic, anti- tumor, and antiviral properties. The magical aspect of the leaves also has an antibacterial component. Additionally, it possesses antitoxins functions for the kidneys and liver and hypoglycemic and hypolipidemic properties. Additionally, it has helped treat diabetic heat stroke,sickle cell disease, and diabetic stroke.

Keywords

Antibacterial, Antifungal, Anti-Inflammatory, Immune-Modulating Medical And Therapeutic Advantages, Carica Papaya Leaves, Plant Leaves Extract.

[1]Biology Department, Faculty of Science, Jazan University, Jazan 45142, P.O. Box: 114, SaudiArabia

[2]Chemistry Department, Faculty of Science,Jazan University, Jazan 45142, P.O. Box: 114, SaudiArabia

[3]School of Pharmacy, Al-Karim University, Katihar-854105, Bihar, India

[4]Center for Environmental Research and Studies, Jazan University, Jazan 45142, P. O. Box: 114, Saudi Arabia

[5]Department of Chemistry, College of Science, Mahliya Jazan University, Saudi Arabia

* Corresponding author email: mukulsh77@gmail.com, mazharshahin123@gmail.com

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1. Introduction

***Carica papaya Linn* (CP)** is widely known as papita in Hindi, erandakarkati in Sanskrit, papaya in English, and babaya in Arabic is a gigantic herbaceous plant belonging to the family *Caricaceae* compriing at least six genera and 35 species [1, 2] and biological classified, **Table 1**.Moreover, CP was also the first transgenic fruit tree whose DNA had been sequenced, **Table 2**.It is believedthat papaya evolved in the tropics of the Americas, most probably in southern Mexico and the neighboring Central American nations. However, because it is a polygamous species, it is only possible to identify individuals during the flowering stage [3, 4]. Papaya leaveshave up to 75 cm in diameter, palmately lobes, and long, hollow petioles. The blades include fiveto nine major segments, with pronounced veins and ribs that are yellowish [5], as shown in **Figure 1.** Fresh papaya leaves, like spinach, are cooked and consumed in several Asian countries for health reasons. They may help with liver regeneration and control clotting by increasing white blood cell and platelet counts [6].

1.1. Chemical constituents of *Carica papaya Linn* leaves

Due to the abundance of phenolic compounds, saponins, tannins, terpenoids, alkaloids, flavonoids, glycosides, enzymes, lipids, amino acids, carbohydrates, minerals, and vitaminsfound in the papaya leaves, which is known to have a wide range of health-promoting phytochemicals [7-9]. **Table 3** depicts the biochemical components and medicinal advantages of papaya leaves.

According to the research, papaya leaves contain the maximum total phenolic compounds (TPC),with 424.89 ± 0.22 mg GAE(Gallic acid equivalent)/100 g of dry sample, followed by unripe papaya at 339.91 ± 9.40, mature papaya at 272.66 ± 1.53, and seeds at 30.32 ± 6.90 mgGAE/100 g [10] In variable amounts, papaya leaves contain a variety of ingredients, including phosphoric acid (5.6%), vitamin C (38.6%), carbohydrates (8.3%) and noticeable level of tannin(0.824%) [11]. Additionally, it is stated that the main phytochemicals found in papaya plant leaves are papain, cystatin, tocopherol, chymopapain, Cyanogenic glucosides, phenolic acids, glucosinolates,and vitamin C. [12].

While the variety of phytochemicals, consisting of carpaine, 7-rhamnoside, kaempferol 3- rhamnosyl-(1->2)-galactoside-7-rhamnoside, kaempferol 3-(2″-rhamnosyl-galactoside), kaempferol3-(2G-glucosylrutinoside), orientin 7-O-rhamnoside, 11-hydroperoxy-12,13-epoxy-9-octadecenoic acid, luteolin 7-galactosyl-(1->6)-galactoside, palmiticamide, and 2-hexaprenyl-6-methoxy phenol are also present in the papaya leaves extract [13]. Moreover, seven flavonoids, including quercetin, quercetin 3-rutinoside, kaempferol 3-(2G-rhamnosylrutinoside), kaempferol 3-rutinoside, quercetin3-(2G-rhamnosylrutinoside), and myricetin 3-rhamnoside were discoveredin papaya leaves in another research. While quercetin, 5, 7-dimethyl coumarin, caffeic acid, protocatechuic acid, chlorogenic acid, and p-coumaric acid are some of

the phenolic compounds present in papaya leaves [14].

The most significant health-promising and key bioactive components found in CP leaves are carpaine, together with dehydrocarpaine I and II. Organic papaya leaves are utilized in Ayurvedicmedicine to cure several physical maladies and viral fevers, including chikungunya and dengue [15]. Furthermore, powerful anti-helminthic and anti-cancerous properties of carpaine have beenidentified [16]. Carpaine content is highest in ripe papaya leaves (9.30 mg/g),fruit pulp (4.90 mg/100 g), fruit peel (1.99 mg/100 g), and seeds (0.65 mg/g) [17]. In addition, papaya leaves are rich in biological enzymes including papain and chymopapain. Papain concentrations in papaya leaf extract range from 0.054 to 0.002 mg/mL [18]. Additionally, papaya leaves included significant amounts of calcium and magnesium, as well as other minerals including zinc, iron, chromium, manganese, and copper. Whereas papaya leaves have the highest amount of Vitamin Cconcentration than ripe papaya, unripe papaya, and seeds [10].

Table 1: Biological classification of Papaya **[2]**

Domain	Flowering plant
Kingdom	Plantae
Sub Kingdom	Tracheobionta
Class	Magnoliopsida
Subclass	Dilleniidae
Superdivision	Spermatophyta
Phylum	Steptophyta
Magnoliopsida	Magnoliopsida
order	Brassicales
family	Caricaceae
Genus	Carica
Botanical Name	Carica papaya Linn

Table 2: Genomic information about papaya **[1]**

NCBI genome id	513
Ploidy	Diploid
Genome size	372 million bp
number of chromosomes	36
year of completion	2014

Table 3: Phytochemical components in *Carica papaya* leaves along with their therapeutic benefits

Class	Components	Therapeutic effect	Ref
Flavonoids	Myricetin, Protocatechuic acid, Kaempferol, Deoxykaempferol, Deoxyquercetin, Rutin	Anti-oxidant, Anti-bacterial, Anti-dengue, Anti-viral, Anti-allergic, Anti-inflammatory, Anti-cancerous	**[14]**
Phenols	2,6-methoxyphenyl, Caffeic acid, protocatechuic acid, quercetin, 5,7-dimethyl coumarin, P-coumaric acid, and Chlorogenic acid		
Cyanogen glycosides	Coumarins, O-Coumaric acid, 5,7-dimethoxycoumarin, P-coumaric acid, P-coumaric alcohol	Anti-cancerous	**[12]**
Vita pigment and minerals	Non provitamin A carotenoid as Lycopene, Lutein, Zeaxanthin Vitamin A, B, C, E and K Minerals such as P, Fe, K, Ca, and Mg	Anti-oxidant, Anti-angiogenic, Anti-cancerous, Anti-microbial, Immuno-modulator	**[7, 10]**
Alkaloids	Carpaine, Pseudocarpaine, Dehydro-carpaine I& II, Emetine, Carposide	Anti-malarial, Anti-viral, Anti-bacterial, Anti-inflammatory, Anti-hypertensive	**[13]**

Fig. 1 (A): Fresh leaves gathered in Ar Rawdah Jizan, KSA **(B):** Ripened fruits from the vegetable market of Jizan, KSA.

2. Methodology

2.1. Research strategy

This systematic review investigated the medicinal value and therapeutic application of the Carica papaya Linn. (CP) plant leaves. The data were collected according to set inclusion and exclusion criteriaand are represented by following the Prisma guidelines for systematic reviews as illustrated in Figure 2 [19].

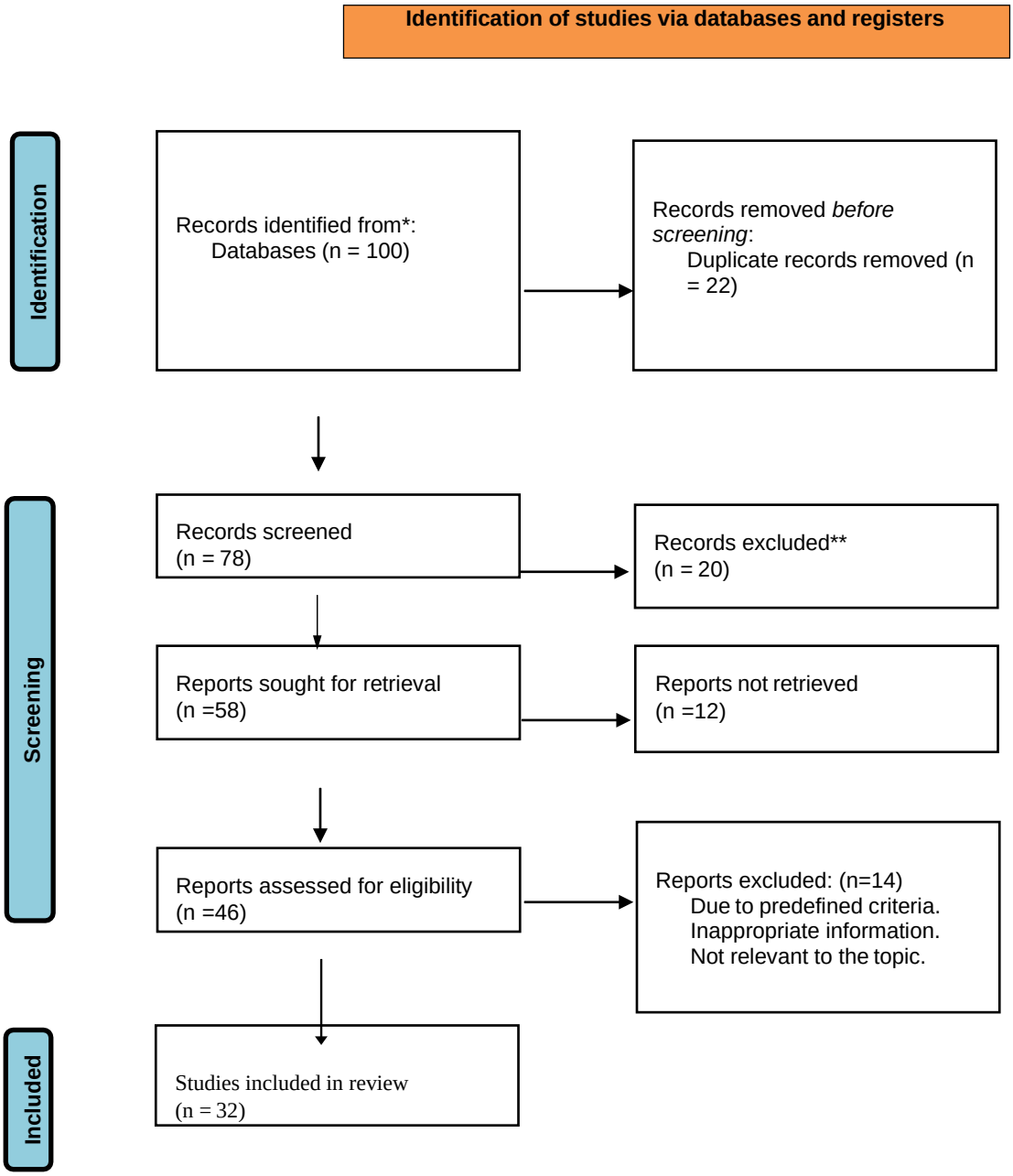

Fig. 2: PRISMA flow chart for a selection of studies in the systematic review.

2.2 Data collection

The data was collected through searches of various journal articles, review articles, and internet sources through databases, such as Google Scholar, Scopus, Science Direct, Web of Science, NIHdatabase, Pubmed, and grey literature from the Google search engine. A manual search of web- based materials was also conducted using the Google search engine. The databases were searchedfor literature published until 2022 using the following web terms: *Carica papaya Linn*, Antibacterial, antifungal, anti-inflammatory, medical treatment, immune-modulating therapeutic advantages, dengue, malaria, papaya leaves, and papaya leaf extract.

2.3 Selection criteria

Available articles in the English language were selected for the literature review. Literature that gives information other than the *CP Linn* plant was excluded. Likewise, literature that was not available in full length were excluded from the study.

Literature review on papaya therapeutic medical advantages

2.4 Antimicrobial property

Through the well and disc diffusion procedures, it was discovered that papaya leaf extracts in various organic solvents have antibacterial characteristics. In literature, it is reported that an in-vitro agar well diffusion method performed with five plants, including the papaya leaf extract in an aqueous medium, in comparison to chloroform, showed pronounced inhibition against *Bacillus subtilis* (*B. subtilis*), *Staphylococcus aureus* (*S. aureus*), *Klebsiella pneumonia* (*K. pneumonia*), *Escherichia coli* (*E. coli*), and *Pseudomonas aeruginosa* [20]. A related investigation (well diffusion) showed papaya leaf extracts in various solvents, including ethyl acetate, ethanol, methanol, chloroform, acetone, hexane, petroleum ether, and hot water have remarkable antimicrobial activity against twelve microorganisms, including human pathogenic bacteria and fungus. The author reports that in comparison to other solvents, the acetone extract ofpapaya leaves exhibited more activity against *Candida albicans* (C. *albicans*), showing an Inhibition zone (IZ) of 11.23 ± 0.25mm, while the chloroform extract showed greateractivity against *Micrococcus luteus* (IZ = 15.17 ± 0.29mm) [21]. Another comprehensive study determinedthe antimicrobial and antioxidant properties of five plants (cashew, papaya, coconut, sweet orange, lemon) leaves extracted in ethanol, hexane, and water against eight microorganisms using agar diffusion techniques. Among all plants, cashew and papaya leaf extracts were the most active and showed broad-spectrum antimicrobial and antioxidant properties [22].

In a comparative investigation, the disc diffusion technique was used to examine the antifungal and antibacterial effects of dried and fresh papaya leaf extracts on isolates of bacteria and fungi at doses of 25, 50, and 100 mg/mL. It was shown that organic CP leaf extracts were more effectivethan aqueous medium extracts. In addition, the results showed that dried CP leaf was more efficacious against Gram-negative and positive bacteria, while fresh CP leaf was more beneficial against Gram-negative bacteria. Additionally, the research found that several

microorganisms resistant to conventional antibiotics were susceptible to the dried leaf extract [23].

On the other hand, Tewari et al. (2014) extracted the bioactive component of papaya leaves and roots in organic solvents and an aqueous medium. The extract was evaluated against clinical isolates from Nigeria using the agar diffusion method. While the aqueous extract of the roots hadlittle effect, the methanol extracts showed the most significant efficacy against the tested isolates.The aqueous leaf extract demonstrated more potent inhibition and activity against the studied microorganisms than the organic solvents. The root extracts showed greater activity against all gram-positive bacteria than the gram-negative bacteria, with the greatest activity against Pseudomonas aeruginosa (P. aeruginosa), IZ = 14 mm. In addition, the extracts were more effective than the gram-negative test organisms against all gram-positive bacteria, with P. aeruginosa havingthe highest activity (IZ = 4.2 mm). Papaya extracts' activity was decreased by an alkaline pH but boosted by a temperature rise [24]. Similarly, the methanolic extract of papaya leaf extracts exhibited more antimicrobial activity against *E. coli* and, *C. albicans*, *S.aureus* [25].

Using cup-plate agar, hot and cold ethanol extracts of air-dried Pterocarpus soyauxii, Carica papaya, and Vernonia amygdalina leaves were tested for antibacterial activity against *E. coli*, *S. aureus*, *K. pneumonia*, and *B. subtilis* by Nirosha and Mangalanayaki, 2013 group. All plant extracts tested on clinical isolates were adequate, but the IZ of the examined plant extracts (cold and hot ethanol) was not significantly different from all test isolates. All leaf samples possess anthraquinones, flavonoids, alkaloids, saponins, steroids, terpenoids, tannins, and glycosides. Theresults imply that leaf extracts of selected plants might be used to generate new herbal antimicrobials [26]. In a different research, ethanol and ethyl acetate were the types of solvents used to extract papaya leaves using the maceration method. Using the diffusion method, papaya leaf and stem extracts were evaluated for their ability to combat *S. aureus*, *S. pneumonia*, *Bacilluscereus*, *E. coli*, *P. aeroginosa*, and *Salmonella typhi (S. typhi)*. The extract showed the maximum activity against *S. typhi* (IZ = 16 mm), which showed higher activity against all tested bacteria. The activity of the extracts was improved by a rise in temperature, inhibited by an increase in alkaline pH and the exttact minimum inhibitory concentration (MIC) varied from 50 to 200 mg/mL, respectively [27].

Papaya leaves were extracted using the maceration procedure and three different solvent types; ethanol, ethyl acetate, and hexane. Using the agar diffusion method, papaya leaf extracts were examined for their ability to combat *B. stearothermophilus*, *Pseudomonas sp*., *E. coli*, and *Listeria monocytogenes*. Moreover, papaya extract ability was also observed under the set conditions; pH, NaCl, and heat. Data indicated that ethyl acetate extract could inhibit all examinedmicroorganisms. While pH had an impact on the activity of the extract, and a low pH made the extract more potent. Whereas NaCl impacts the extract's anti-*B.* stearothermophillus and anti-*E. coli* activities but did not affect *Listeria monocytogenes* and *Pseudomonas sp*. Althoughthe heating method had an impact on the extract activity against all of the tested microorganisms [28].

Through an agar well diffusion experiment, the study examined the antibacterial effects of an aqueous chloroform extract of the leaves and an aqueous methanolic extract of the seeds of the CPon *S. aureus*, *P. aeruginosa*, *E. coli*, and *S. typhi*. It was discovered that seeds' aqueous and methanolic extracts successfully inhibited bacterial pathogens. However, the chloroform extract

of the leaves of papaya did not exhibit any antibacterial activity, but the aqueous leaf extract was highly effective [29]. In summary, most methods used to conduct the study appear to be primary,which calls for more studies into the molecular changes linked to its antibacterial action.

2.5 Anti-inflammatory and anti-oxidant properties

Gammulle et al. (2012) and their co-workers were the first to justify the claims of traditional medicine and proved that CP leaf is orally active, non-toxic, and efficiently increases platelet, RBC, and WBC counts in normal thrombocytopenic and non-thrombocytopenic rats, as well as possess potent anti-inflammatory activity. In summary, their research demonstrates that CP leavescan be used as an herbal medicinal agent for thrombocytopenia and related inflammatory disease states, which are present in illnesses like dengue, chikungunya, leptospirosis, and sepsis.[30]. Gupta et al., 2017 used the Nanodrop technique to extract the protein content of CP aqueous leaves.Using CP aqueous leaf extract, ELISA experiments were conducted to ascertain the antibody production against ovalbumin. Additionally, the group also conducted the MTT (3- (4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide test to detect CP leave extract antigen-specific proliferation in human blood samples which was virally infected. Results demonstrate that CP aqueous leaf extract increased protein production and antibodies against ovalbumin. Furthermore,a decrease in bacterial population and proliferation rate was also seen in the aqueous extract at higher dosages when compared to the control group. In contrast, greater dosages of the aqueous extract had antibacterial and anti inflammatory effects [31]. In a related study, rats were used to test the anti-inflammatory effects of an ethanolic extract of CP leaves, utilizing models of arthritiscaused by formaldehyde, carrageenan-induced paw edema, and cotton pellet granuloma. The reference group received 5 mg/Kg of indomethacin, whereas the treated mice received oral doses of 25–200 mg/Kg of the extracts or saline (control). Investigations were done on the extract's ulcerogenic potential. The carrageenan test findings demonstrate that the extracts considerably ($p= 0.05$) decreased paw edema. The amount of granuloma generated was significantly reduced by the extract from 0.58 ± 0.07 to 0.22 ± 0.03 g. The extracts significantly reduced chronic edema inthe formaldehyde arthritis model from the fourth to the tenth day of the trial. At high dosages, theextracts also caused minor mucosal irritation. The research confirms that CP leaves have anti- inflammatory properties [32].

Maisarah et al. (2013) study determined the total antioxidant activity (TAA), total flavonoid content (TFC), and total phenolic content (TPC) of papaya tree components, including their youngleaves, mature and unripe fruit, and seed. The TAA asses by β-carotene bleaching and DPPH radical scavenging activity assays, while the Folin-Ciocalteu technique and $AlCl_3$ were employedto determine the TPC and TFC, respectively. The β-carotene bleaching assay findings revealed that unripe fruit had more antioxidant activity than young leaves, mature fruit, and seeds. The dose needed to reduce the absorbance of the DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) control solution by 50% (EC50) was determined at 1.0 ± 0.08 mg/ml for young leaves, incontrast, showing a much more decisive scavenging action than the others. Young leaves also possessed the greatest antioxidant content, as demonstrated by TPC (424.89 ± 0.22mg GAE (Gallicacid equivalent)/100 g dry weight) and TFC (333.14 ± 1.03mg rutin equivalent/100 g dry weight).According to the statistical analysis, TPC ($r=0.846$) and TFC ($r=0.873$) had positive associations with the antioxidant activity measured by the DPPH radical scavenging experiment. However, TPC and TFC did not correlate with the bleaching activity of β -carotene. In summary,the author explains that antioxidants properties were highest in young leaves > unripe fruit > mature fruit > seed [33]. Similarly, CP leaf extracts' phytochemical and

antioxidant qualities were investigated by assessing TFC using the AlCl3 technique, TPC by the Folin-Ciocalteu method, and antioxidantsusing the 2,2,1-diphenyl-1-picrylhydrazyl method by Palanisamy and Basalingappa (2020). The results of phytochemical screening showed that bioactive substances like alkaloids, amino acids, and carbohydrates, as well as TFC and TPC concentrations, varied concerning solvents. Since methanolic CP leaf extracts demonstrated the highest amount of phytochemical extraction, therefore, it possesses noticeable antioxidant property [12]. Different conditions were applied in another research to improve the extraction process and ascertain how CP leaf polyphenol output will be affected by aqueous extraction. The results demonstrated that the extracted polyphenol production, scavenging, and overall antioxidant activity were significantly influenced by temperature (70°C), extraction duration (20 min), and water-to-leaf ratio (100:7.5 mL/g). Moreover, water extraction yielded higher quantities of polyphenols than the organic solvents (acetone, methanol, and ethanol), but ethanol extraction yielded the greatest levels of saponins. Using a straightforward and scalable process, one kg of dried papaya leaves was converted into around 190 g of powder. Vitamins E and C and epigallocatechin gallate showed lower scavengingand overall antioxidant activity in the crude powder, which included 6.3% polyphenols comparedto butylated hydroxytoluene [34]. Studies on CP leaf drying in hot air (60, 70, and 80 °C), shade, and freeze drying have been also done to study the extraction process more deeply for medical applications observed that the highest amount of total polyphenols was present in the freeze-driedsamples of CP leaves, which also had the greatest levels of 2,2'-azino-bis(3-ethyl benzothiazoline-6-sulfonic acid (571 mg TE 100 g DW^{-1}) and 2,2'-diphenyl-1-picrylhydrazyl (215 micro gm/mg) antioxidant activity.

Contrarily, hot air and shade drying of CP leaves do not favor the preservation of antioxidants dueto the potential for thermal destruction at high temperatures and the occurrence of oxidation under extended drying conditions. On the other hand, Nugroho, agung et al. conducted a comprehensiveinvestigation by extracting seven flavonoids, including kaempferol 3-rutinoside, kaempferol 3- (2G-rhamnosylrutinoside), kaempferol, quercetin, quercetin 3-(2G-rhamnosylrutinoside), and myricetin 3-rhamnoside from the CP leaves. Compared to the positivecontrol, l-penicillamine (6.90 mol/L), all compounds showed robust peroxynitrite scavenging capability (IC50 4.15 mol/L). Compared to other discovered chemicals, kaempferol 3-(2G- rhamnosylrutinoside) had a substantially greater concentration (123.18 mg/g BuOH (Butyl alcohol fraction and 7.23 mg/g MeOH (Methyl alcohol extract)). The current study's findings show that the CP leaf contains strongantioxidant flavonoids, with kaempferol 3-(2G-rhamnosylrutinoside) being the main one [36].

2.6 Anticancer property

The papaya plant is well known for its medicinal advantages in the world worldwide because of its exceptional chemical constituents. In this regard, Fauziya and Krishnamurthy,2013 reported that the cancer-fighting papain enzyme in papaya could break down the fibrin cancer cell wall intoamino acids. The author also includes lycopene and isothiocyanate in the anticancer group, as it was found that lycopene is highly reactive toward oxygen and free radicals. In contrast, isothiocyanate is helpful against lung, breast, colon, pancreatic, and prostate cancer. [37].

Gurudatta et al. (2015), in contrast, assessed the anticancer properties of aqueous CP leaf extract anticancer properties in rat mammary cancer generated by 7,12 Dimethyl Benz(A)anthracene

Among the different cancer markers, lactate dehydrogenase and antigen 15 (CA15-3) are significant biochemical indicators that provide a comprehensive knowledge of the development and proliferation of cancer cells. It was discovered that the administration of an aqueous CP leaf extract at a concentration of 200 mg/kg bodyweight, reduced the levels of CA15-3 and lactate dehydrogenase, and stopped the growth of tumor [38]

Otsuki et al. (2010) repotted human peripheral blood mononuclear cells (PBMC) and tumor cell lines' proliferative responses to Carica Papaya Plant (C.P.P.) leaves extract, and their cytotoxic effects were evaluated by [3H]-thymidine incorporation. To confirm that tumor cells' triggering ofapoptosis has occurred, flow cytometric analysis and caspase-3/7 activity were carried out. PBMCcytokine production was assessed using an ELISA. Microarray analysis and real-time RT-PCR were used to undertake gene profiling of the impact of Carica Papaya Plant (C.P.P) leaf extract treatment was observed that Carica Papaya Plant (C.P.P) leaf extract has a sizable growth inhibitory effect on tumor cell lines. Following the addition of Carica Papaya Plant (C.P.P.) leavesextract, the production of IL-2 and IL-4 in PBMC decreased, but the production of IL-12p40, IL-12p70, I.F.N., and TNF increased without inhibiting growth. In addition, the inclusion of Carica Papaya Plant (C.P.P) leaf extract increased the cytotoxicity of activated PBMC against K562.Furthermore, microarray investigations demonstrated that the addition of Carica Papaya Plant (C.P.P) extract improved the expression of 23 immunomodulatory genes that were categorized by gene ontology analysis. These elevated genes included chemokine ligands2, CCL7,CCL8, and Serpin family B2 tripeptidyl peptidase 2 (SERPINB2), which may act as indicators ofthe immunomodulatory effects of Carica Papaya Plant (C.P.P) leaves extract. Additionally, it wasalso reported that in C.P.Pleaf extract, the fraction with M.W.less than 1000 was recognized as theactive component that can inhibit tumor cell development and increase antitumor action. [39].

In their study, Nguyen et al. (2016) reported the in vitro cytotoxicity of CP leaf decoction and juice/brewing on human squamous cell carcinoma cells. Results from the MTT assay revealed thatthe leaf juice had a more potent cytotoxic impact on malignant squamous cell carcinoma (SCC25) cells than the decoction and that studies on non-cancerous human keratinocyte HaCaT cells also revealed a substantial cancer-selective effect. Additionally, the results revealed that the brewing procedure significantly diminished the CP leaf's selective action on squamous cell carcinoma (SCC25) cells. Using an untargeted metabolomic approach that combined multivariatedata analysis with UHPLC quadrupole MS, it was possible to infer the compounds responsible forthe leaf juice's distinct selective anticancer activity. From the chemical profile of leaf juice, around 90 and 104 peaks in the positive and negative modes were chosen as discriminating characteristics,and more than 1500 potential compound IDs were discovered by database searching. PheophorbideA was validated to match its indicated authentic standard using tandem mass spectral data with existing reference compounds and direct chromatographic comparison. Although pheophorbide A had cytotoxic effects on squamous cell carcinoma (SCC25) cells, it was not the molecule primarilyin charge of the selective action of CP leaf juice. Further research on CP leaf juice constituents isrequired to examine the selectives action on various cancer cell lines, particularly those that are impacted by the prolonged heating methodused to prepare the traditional Aboriginal remedy [40].

2.7 Anti-angiogenic properties

Cancer is the world's most prominent cause of death, and angiogenesis is critical to its progression.Angiogenesis is crucial for developing new blood vessels and providing nutrients to tumor cells, and several "on" and "off" switches the control the procedure. Recently, a study was done to examine the CP leaf's potential antiangiogenic properties. The Swiss Dock Web server (In silico)was used to know the CP leaf bioactive compounds with angiogenic receptors VEGFR(vascular endothelial growth factor receptor (1 and 2) and their putative binding sites. CP leaf aqueous extract was utilized to create a model for chorioallantois membrane egg yolk angiogenesis based on the docking results (in vivo). According to docking studies and binding free energy estimation,it was found that lycopene, quercetin, and riboflavin have the highest freeenergies when comparedto other examined ligands among the known bioactive components of leaves, i.e., Vitamin C. Comparatively to an untreated egg yolk, chorioallantois membrane test also demonstrated the inhibitory impact of the CP length, leaf on the size, and connections of blood capillaries. Accordingto the findings, leaf components such as Vitamin C, riboflavin, quercetin, and lycopene can reduceangiogenesis in pathological situations and have significant medicinal and drug-discovery potential [41].

2.8 Immunomodulatory activity

In a recent investigation by Mohd Abd Razak et al. (2021), AG 129 mice (IFN alpha /beta stimulation) infected with a clinical DENV-2 (DMOF015)dimethyl oxalate isolate were used as atest subject to determine the immunomodulatory effects of freeze-dried CP leaf juice. The CP leafjuice was administered orally to the infected AG129 mice for three days (500 and 1000 mg/kg/day). The numbers of platelets, leukocytes, lymphocytes, and neutrophils were assessed microscopically. Using a multiplex immunoassay, the amount of plasma pro inflammatory cytokines was determined. RT-qPCR was used to measure the amounts of viral RNA and intracellular cytokines. The findings demonstrated that the CP leaf juice therapy raised the neutrophil and total WBC counts in the infected mice. In the plasma of infected mice, CP leaf juicetherapy reduced the levels of GRO-alpha (Growth Regulatory), GM, CSF (granulocyte macrophage colony-stimulating factor), IL-6, IL-1 beta, MIP-1 beta (macrophage inflammatory protein), and MCP-1 (monocyte chemoattractant protein1). CP leaf juice therapy reduced the intracellular IL-6 and viral RNA levels in the liver of infected mice. According to the findings, theCP leaf juice may have an immunomodulatory function in a non-lethal, symptomatic dengue mouse model. The author recommends doing more research on the mechanism of action of CP leafjuice and its potential application in adjuvant dengue immunotherapy [42].

3. Active ingredients in papaya for illness prevention and treatment

3.1 Sickle cell anemia

Red blood cell (RBC) form and movements in blood arteries are affected by the hereditary blood condition sickle cell disease (SCD), which can cause several clinical issues. Numerous medications available to treat the condition are either poisonous, prohibitively costly, or only partially successful. Thus, there is an urgent need for safe, efficient, and affordable medicinal agents from local plants that utilize traditional medicines. In this context,Imaga et al. (2009) used5 g/ml p-hydroxybenzoic acid and normal saline as controls for anti sickling studies and osmotic fragility test on Hb ss red blood cells derived from non-crisis stage sickle cell patients to investigate the possibility in vitro anti sickling and membrane-stabilizing properties of methanolicleaf extractsof CP. Fragiliograms demonstrated that the plant extract reduced

hemolysis and retained the integrity of the erythrocyte membrane under osmotic stress conditions. Pretreating SS cell suspensions with CP leaf extract under intense hypoxia inhibited the development of sickle cells, in contrast to untreated SS cell suspensions, which had more than 60% sickle cells at 40 minutes. These results indicate that CP is a potential biotherapeutic option for SCD and that itis feasible and acceptable [43]. In another study, Nurain et al. (2017) used sodium metabisulfite (2%) for sickling induction. Results conclude that the aqueous extracts of CP leaves, *Zanthoxylum zanthoxyloides* leaves, and *Cajanus cajan* leaves and seeds had promising for treating SCD. Theresults showed that the presence of hydroxyurea, *Cajanus cajan* leaves, *Cajanus cajan* seed, *Zanthoxylum zanthoxyloides* leaf, and CP leaf extracts, respectively, the percentage of sickled cells, which was initially 91.6% in the control, was reduced to 37.92 % (mean). Additionally, it was discovered that the presence of the tested medicines strengthened the RBC resistance to hemolysis, as evidenced by the drop in theproportion of hemolyzed cells from 100%to 0%. Moreover, a GC-MS investigation revealed that the plants contained significant secondarymetabolites. These findings imply that plant extracts may one day replace hydroxyurea as a primary antisickling medication in the treatment of SCD [44].

In a recent work by Olasunkanmi and Bankole (2019), unripe fruits and leaf extracts of CP were compared in terms of their in vitro antisickling abilities. Blood samples from sickle cell disease patients were used in in-vitro antisickling experiments, along with para-hydroxybenzoic acid and normal saline as negative and positive controls, respectively. It was found that the antisickling effectiveness of both plant materials was dose-dependent. In comparison to the leaf extract and fractions (methanol (3%), ethylacetate (6%), and aqueous (9%) the unripe fruit fraction methanol((2%), ethyl acetate (3%), and aqueous (4%)) was found to be more potent against sickling. In conclusion, the unripe fruit of the CP possesses more substantial antisickling properties than the leaves [45].

3.2 Dengue

CP extracts have long been used in traditional medicine to treat dengue fever, dengue shock syndrome, and dengue hemorrhagic fever[46].Recently, in a comprehensive examination, seven compounds were extracted from CP leaf extract to see whether they can act as NS(Non-structural)3 and NS5 inhibitors, proteins essential for viral RNA replication. The authors used computational methods, including classical molecular docking, molecular dynamics simulations, and Swiss ADM, to calculate the binding free energy, binding affinity, absorption, metabolism, distribution, and excretion (ADME) as properties that are similar to those of drugs. As a result, Kaempferol, Chlorogenic acid, and Quercetin were identified as potential candidates, with Quercetin and Kaempferol scoring the highest. To measure the Quercetin-NS and Kaempferol- NSH-bonding, hybrid quantum mechanical/molecular mechanical (QM/MM) geometry and frequency calculations were carried out for the Kaempferol and Quercetin complexes. Based on the results, the papaya extract containing kaempferol and quercetin as active compounds was recommended as a potent NS3 and NS5 inhibitor to be further studied in vitro [47].Many public health systems continue to struggle with dengue hemorrhagic fever, an illness causedby the dengue virus. Using chemical larvicides to control Aedes aegypti has caused populations ofmosquitoes to become resistant. As a result, higher larvicide quantities are required, which are hazardous to humans, animals, and the environment. Therefore, Dhenge

etal. (2021) examined the efficiency of CP leaf extract in preventing the death of Aedes aegypti mosquito larvae in theirthird instar. With a post-test-only control group design, this study is an actual experiment. The Aedes aegypti mosquito larvae instar III/IV, papaya leaf ethanol extract, abate as a positive controlgroup, and aqua dest as a negative control group were then used to conduct the investigation. Theresults showed that there were zero (0) larvae in the negative control group, 25 larvae in the positive control group, 9.5 larvae in the 5% concentration group,11.75 larvae in the 10% concentration group, 12.75 larvae in the 15% concentration group, 14.75larvae in the 20% concentration group, and 25 larvae in the 25% concentration group (19.5 larvae)[48].

3.3 Malaria

Malaria is a severe feverish sickness brought on by *Plasmodium* parasites that can infect people when they are bitten by female Anopheles mosquitoes carrying the disease [49]. Papaya leaves aretraditionally used as medicine for the treatment of malaria.Recently, Babangida et al. (2022) usedthe fresh CP leaves extraction in ethanolic solvent to experiment with albino mice of both sexes To conduct this, an infected blood solution containing about $1x10^{-6}$ parasitemia of *P. berghei* was administered intraperitoneally to the animals via injection. For comparative analysis,the animals were separated into groups and given doses of normal saline, chloroquine diphosphate,and ethanolic leaf extract. It was observed that the packed cell volume (PCV), RBC, and WBC levels varied significantly (P = 0.05) between the groups that received ethanolic leaf extract treatment.
Moreover, with the rise in concentration, the extracts increased animal production of neutrophils,lymphocytes, eosinophils, monocytes, and basophils.

Additionally, the number of parasitized erythrocytes decreased considerably (P = 0.05) in infectedmice treated with CP, which also showed the maximum (75.04%) suppression. The extracts' active components were alkaloids, flavonoids, anthraquinones, saponins, tannins, diterpenoids,terpenoids, steroids, and cardiac glycosides, which may be responsible for their antiplasmodial effect. The author also advises 400 mg/kg of CP extract for treating malaria [50].

On the other hand, Babangida et al. (2022) examined the impact of CP leaf extract in methanolon hepato-renal toxicity and the anti-malarial effectiveness of artesunate in *Plasmodium berghei*- infected mice. Artesunate, CP extract, and their combination were used to treat sick mice. The findings showed that concomitant treatment of CP and artesunate considerably decreased daily parasitemia load and significantly attenuated a sharp decline in packed cell volume, RBC, and hemoglobin levels. However, the combination did not negatively affect WBC, differential WBC, and hepato-renal indicators, significantly decreasing oxidative stress. The report suggested that theco-administration of CP and artesunate is a successful drug-herb combination and should be usedto treat malaria in people after being properly clinically investigated [51].

3.4 Chikungunya

Kovendan et al. (2012) determined the effects of bacterial pesticide spinosad and CP leaf extract on larvicidal and pupicidal against the chikungunya virus Aedes aegypti. After being exposed for24 hours, the CP plant extract exhibited larvicidal and pupicidal effects; however, the leaf extractof methanol CP was found to have the highest levels of larval and pupal mortality against first- tofourth-instar larvae and pupae. According to preliminary research, A. aegypti, the vector of the chikungunya virus, is susceptible to the larvicidal and pupicidal effects of CP leaf extract

and the bacterial pesticide Spinosad. This is the best environmentally friendly strategy for managing the A. aegypti vector, which is the main objective of the vector management initiative [52].

4. Limitation of study

Despite the scope of our search and the inclusion of several medical libraries, conference abstractsand other unpublished works of literature may have been missed, limiting the scope of our results.Due to the significant methodologic discrepancies between the studies, a meta-analysis study would not have been appropriate since it limits the comprehension of shared conclusions. The quality of the available literature constrains a systematics review, and our results may have been impacted by selection bias or patient-specific treatment differences.

5. Conclusion

In summary, papaya leaf extract has been studied for antimicrobial, anti-cancer, anti- oxidant, anti-fungal, anti-parasitic, anti-angiogenic, and hepato-protective properties. Existing evidence suggests that papaya leaves hold promising potential as a medical agent. In the meantime, severalstudy holes in the scientific literature on papaya leaf bioactive components have been found, and they should be investigated further in terms of organicprocesses. There is a dearth of research on the discovery, characterization, and pharmacokinetics of papaya leaf bioactive and metabolites. Research is still needed to linkthe pharmacodynamics and pharmacokinetics of papaya's bioactive and metabolites. Theprotection and effectiveness of papaya leave without the dosage, duration, and mode of administration that may increase phytochemical strength need to be validated despite thesignificant advancements made in papaya bioactive studies over the centuries in terms ofboth animal and human scientific trials. This evaluation highlights the numerous medicinal healing benefits of researchers should look into the ability of papaya, which hasmany bioactive that could be beneficial. In addition, we have to look at more informationandthe ability of papaya leaves.

Conflict of Interest Statement

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