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Secondary Metabolites from *Carica papaya,* and its Biological Activities: A Comprehensive Review

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ABSTRACT

Carica papaya L. is the most well-known species of the family Caricaceae. The edible tropical plant was widely used in traditional folk medicine worldwide and is known for possessing high nutritional and medicinal values in all its parts such as fruit, leaf, seed, and latex. This review provides a comprehensive literature survey of the biological activity and the isolated phytochemical compounds reported from *Carica papaya*. The phytochemical survey reported the isolation of several classes of phytochemicals including flavonoids, alkaloids, phenolic acids, fatty acids, sterols, triterpenes, saponins, and isothiocyanates as well as other miscellaneous compounds. The review also focused on the wide range of biological activities reported from the crude extracts and fractions of the different parts of *C. papaya*. This review can contribute to finding alternative therapeutic approaches to combat various health problems and improve the health of the people suffering from those problems. The various biological activities highlight the need for further studies to explore the bioactive compounds responsible for the biological activities and the underlying mechanism of action.

Keywords: *Carica Papaya; Caricaceae; Phytochemical study; Biological activities; Secondary Metabolites; Tropical plants; Edible plants.*

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1. Introduction

Carica papaya L. belongs to the small family Caricaceae which comprises nearly 31 species distributed in six major genera (*Carica*, *Cylicomorpha*, *Jacaratia*, *Jarilla*, *Horovitzia*, and *Vasconcellea*)**[1]**. *Carica papaya* is the only species in the genus *Carica* and is considered the most known and widely used species in the family Caricaceae **[2]**. Papaya is a tropical fruit native to Central America in Mexico and Panama **[3]**. During the Spanish exploration in the 16th century, Papaya was introduced to the south-east Asian Philippines then India followed by further distribution of other tropical areas in central and South Africa and the Pacific **[4]**. The geographical distribution is displayed in **Fig. 1.**

Papaya is a huge source of nutrients. It is rich in vitamin C, vitamin B, and vitamin E which are known for their antioxidant activity. In addition, it contains minerals like iron, magnesium, and potassium. Also, it contains the digestive enzyme papain which is known for its activity in treating injuries and allergies **[5]**. Besides its rich nutritional value, Papaya was used in traditional folk medicine due to its various medicinal uses. In the traditional ayurvedic literature, it was reported that the leaves of papaya were used in the treatment of dengue fever, jaundice, asthma, gonorrhea, urinary complaints, and dressing wounds. The fruit of *Carica papaya was* used as a laxative, diuretic, expectorant, antibacterial, and as a treatment for dysentery and chronic diarrhea. The seeds were used as an antifertility agent in males, as a counter-irritant, and were used as a paste for treatment of ringworm and psoriasis. The roots and stem bark were known for their antifungal and anti-hemolytic activities **[6,7]**. This review aimed to perform a comprehensive literature review on the various medicinal uses and the diverse phytochemical constituents in papaya to study the relationship between the pharmacological activities and the phytochemical constituents isolated from papaya that may be responsible for the reported biological activities through evidence-based information. The present review consists of two sections, the first section includes the information about the phytochemical constituents isolated from different parts of *C. papaya*, and the second section displays the various biological studies reported for *C. papaya*.

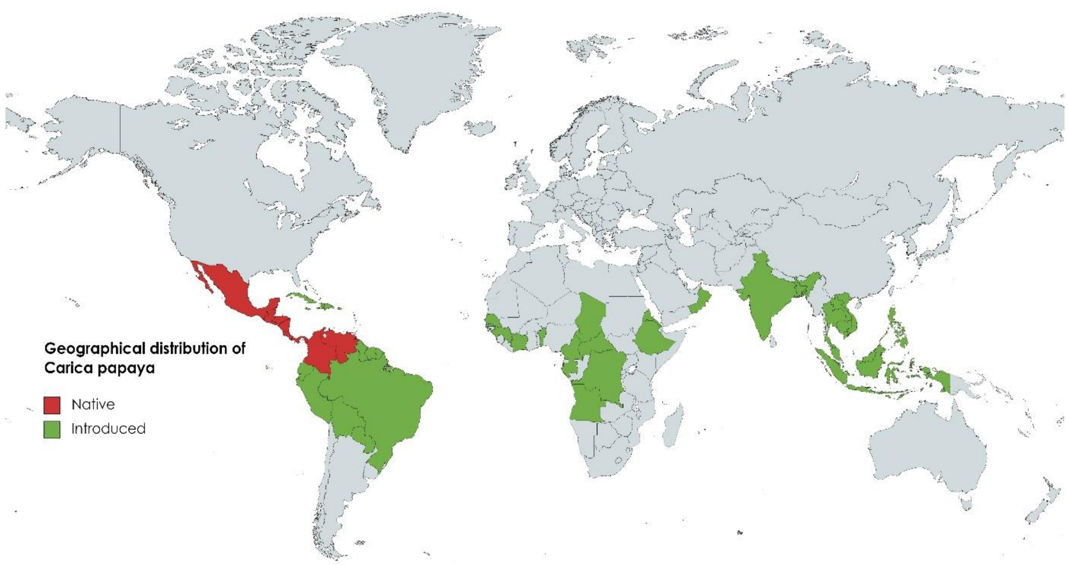


Fig. 1. Geographical distribution of C. papaya worldwide

2. Methods

The process of collecting data and studies search is implemented using different databases including SciFinder, PubMed, Science Direct, Scopus, Web of science and google scholar, Egyptian Knowledge Bank (EKB), and different published articles dealing with *C. papaya*.

2.1. Phytochemical studies

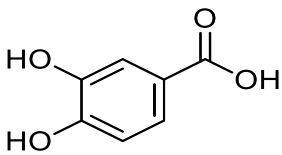
Phytochemical studies performed on *Carica papaya* have demonstrated the presence of several classes of active constituents including phenolic acids **(Table 1 and Fig. 2)**, fatty acids and their esters and amino acids **(Table 2 and Fig. 2)**, flavonoids **(Table 3 and Fig. 3)**, alkaloids **(Table 4 and Fig. 3)**, sterols **(Table 5 and Fig. 3)** and several miscellaneous compounds **(Table 6 and Fig. 4)**.

Table 1. Phenolic acids reported in *C. papaya*

No.	Compound	Extract used	Part used	Reference
1	Protocatechuic acid	Diethyl ether extract	Leaf	**[8]**
2	Caffeic acid	Diethyl ether extract	Leaf	**[8]**
3	Chlorogenic acid	Diethyl ether extract	Leaf	**[8]**
4	*p*-Coumaric acid	Diethyl ether extract	Leaf	**[8]**
		Aqueous extract		**[9]**
5	Ferulic acid	Aqueous extract	Leaf	**[10]**
6	Cinnamic acid	Aqueous extract	Leaf	**[10]**
7	Sinapic acid	Aqueous extract	Leaf	**[10]**

Table 2. Fatty acids, fatty acid esters, and amino acids reported in *C. papaya*

No.	Compound	Extract used	Part used	Reference
8	Linoleic acid	Aqueous extract	Leaf	**[10]**
		Hydroalcoholic extract	Fruit peel	**[11]**
9	*trans*-Oleic acid	Aqueous extract	Leaf	**[10]**
10	3-Octadecylenic acid	Aqueous extract	Leaf	**[10]**
11	4-Octadecylenic acid	Aqueous extract	Leaf	**[10]**
12	3-Keto-*n*-caproic acid	Aqueous extract	Leaf	**[10]**
13	2-Keto-hexanoic acid	Aqueous extract	Leaf	**[10]**
14	Hexadecanoic acid; methyl ester	Ethanolic extract	Seed	**[12]**
15	Heptadecanoic acid; ethyl ester	Ethanolic extract	Seed	**[12]**
16	Hexadecanoic acid; phenylmethyl ester	Ethanolic extract	Seed	**[12]**
17	*cis*-11-Eicosenoic acid; methyl ester	Ethanolic extract	Seed	**[12]**
18	Cyclopentaneundecanoic acid; methyl ester	Isopropanol extract	Leaf	**[13]**
19	Hexadecanoic acid; ethyl ester	Ethanolic extract	Seed	**[12]**
20	Dodecanoic acid; ethyl ester	Ethanolic extract	Seed	**[12]**
21	iso-Propyl 9-octadecenoate	Ethanolic extract	Seed	**[12]**
22	9-Octadecenoic acid (Z)-; methyl ester	Ethanolic extract	Seed	**[12]**
24	Ethyl tetracosanoate	Ethanolic extract	Seed	[12]
25	Ethyl linoleolate	Ethanolic extract	Seed	[12]
26	Coumaroyl quinic acid	Aqueous extract	Leaf	[14]
27	Cystine	Aqueous extract	Leaf	[14]
28	Homocystiene	Aqueous extract	Leaf	[14]
29	L-Glutamic acid	Aqueous extract	Leaf	[14]
30	Phenylalanine	Aqueous extract	Leaf	[14]



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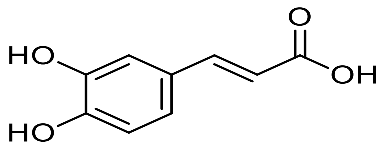

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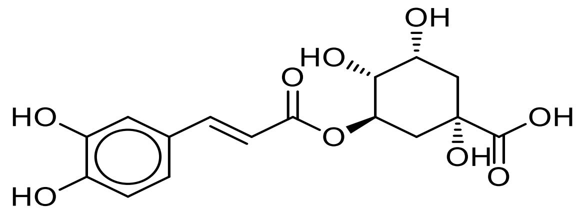

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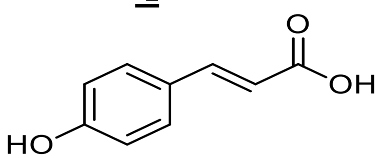

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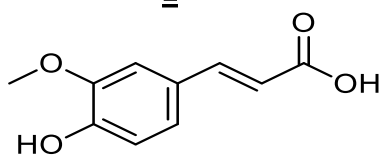

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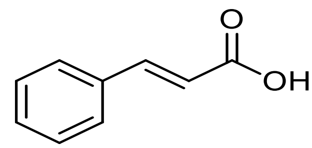

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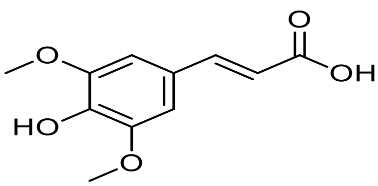

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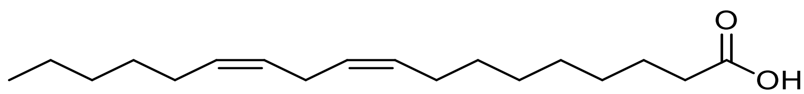

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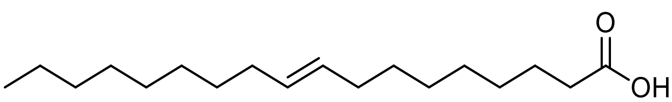

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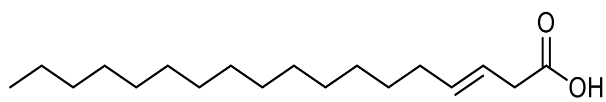

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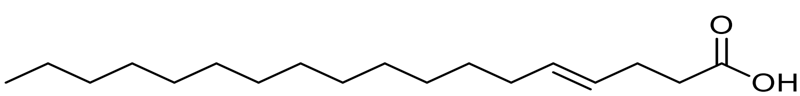

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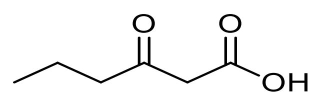

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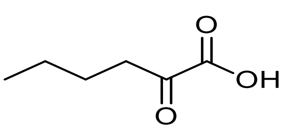

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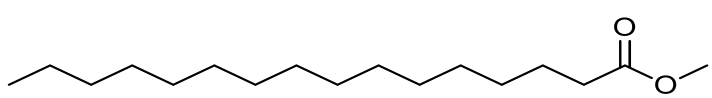

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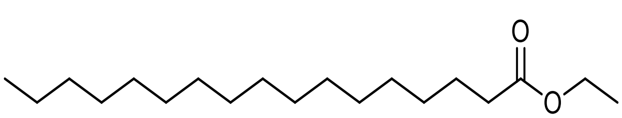

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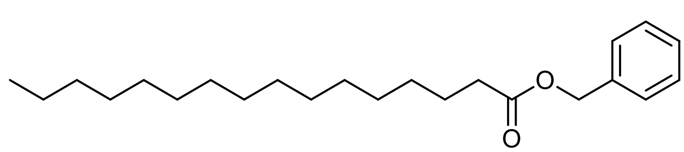

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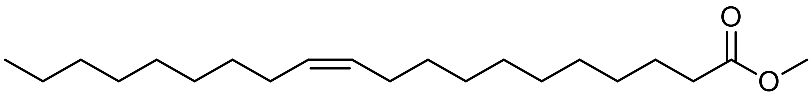

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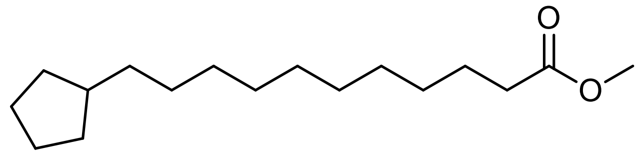

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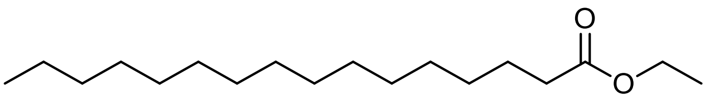

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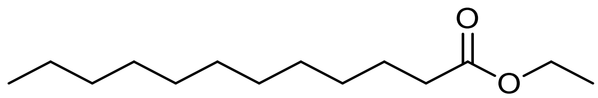

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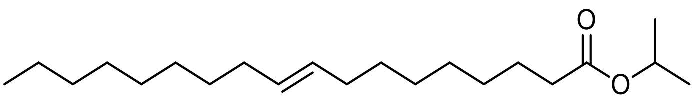

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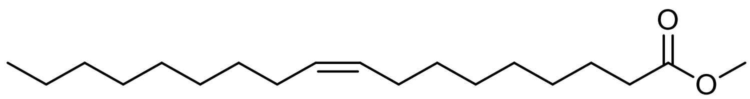

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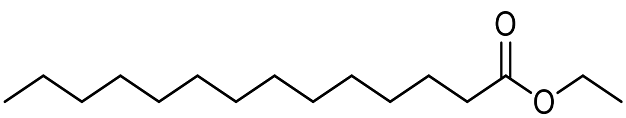

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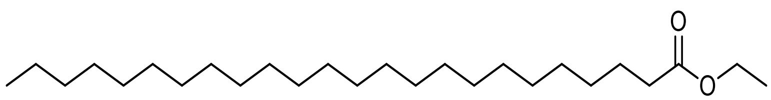

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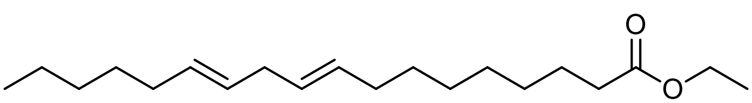

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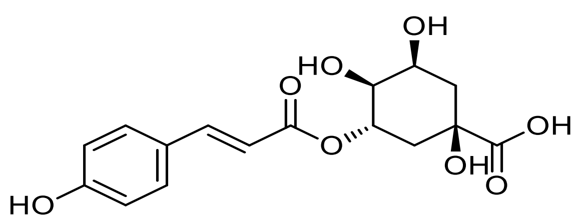

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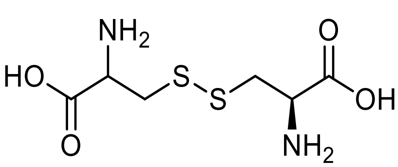

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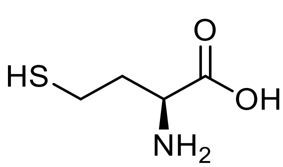

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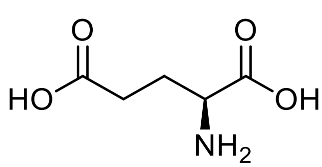

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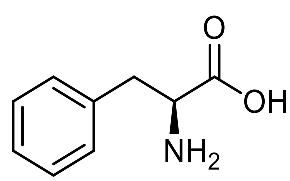

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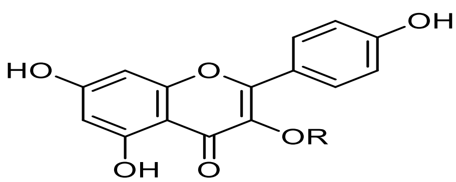
Fig. 2. Chemical structures of phenolic acids, amino acids, fatty acids and fatty acid esters isolated from *C. papaya*

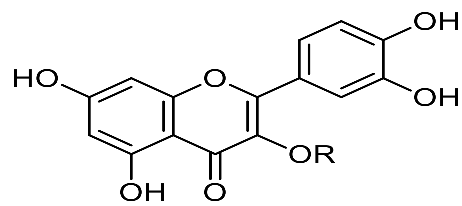
Table 3. Flavonoids reported in *C. papaya*

No.	Compound	Extract used	Part used	Reference
31	Kaempferol	Aqueous extract	**Leaf**	**[10,14]**
		Butanol fraction		**[15]**
32	Quercetin	Aqueous extract	**Leaf**	**[10,14]**
		Butanol fraction		**[15]**
33	Myricetin	Aqueous extract	**Leaf**	**[10]**
		Ethanol extract		**[16]**
		Butanol fraction		**[15]**
34	Rutin	Ethyl acetate fraction	**Leaf**	**[17]**
		Aqueous extract	**Leaf**	**[9]**
		Chloroform extract	**Flower**	**[18]**
35	Manghaslin	Ethyl acetate fraction	**Leaf**	**[17]**
36	Clitorin	Ethyl acetate fraction	**Leaf**	**[17]**
37	Nictoflorin	Ethyl acetate fraction	**Leaf**	**[17]**

Table 4. Alkaloids reported in *C. papaya*

No.	Compound	Extract used	Part used	Reference
38	Carpaine	Alkaloid fraction (acid-base extraction)	**Leaf**	**[19,20]**
		Butanol fraction		**[15]**
39	Pseudocarpaine	Ether fraction	**Leaf**	**[22]**
		(acid-base extraction)	**Leaf and heartwood**	
		Ether fraction		**[23]**
40	13,26-Dimethyl-2,15-dioxa-12,25-diazatricyclo[22.2.2.211,14] triacontane-3,16-dione	Alkaloid fraction (acid base extraction)	**Leaf**	**[17]**
41	6-(8-Methoxy-8-oxooctyl)-2-methylpiperidin-3-yl 8-(5-hydroxy- 6-methylpiperidin-2-yl)octanoate	Alkaloid fraction (acid base extraction)	**Leaf**	**[17]**





31: R= H

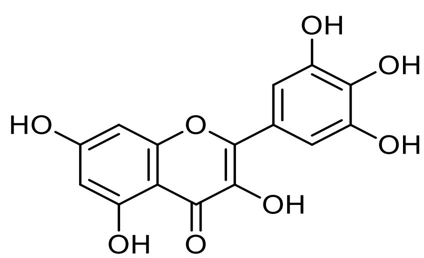
36: R= α-L-Rha-(1→2)- α-L-Rha-(1→6)-β-D-Glc

37: R= α-L-Rha-(1→6)-β-D-Glc

32: R= H

34: R= α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranose

35: R= (2′′,6′′-di-Rha*p*)-Glc*p*



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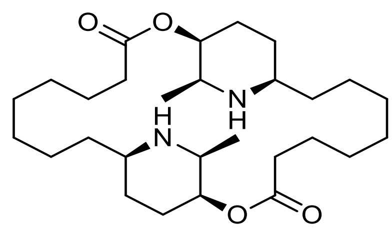

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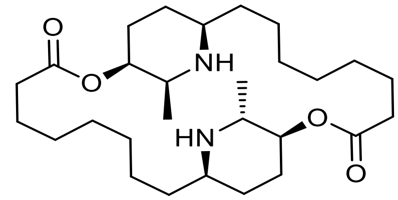

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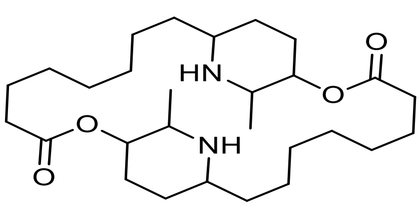

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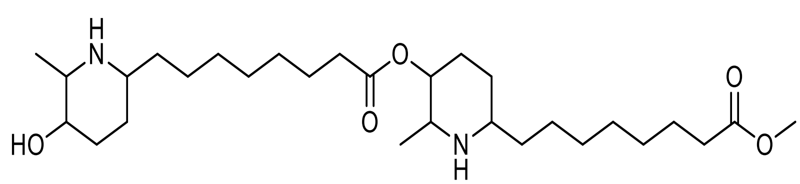

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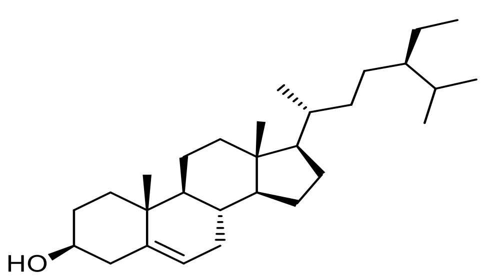

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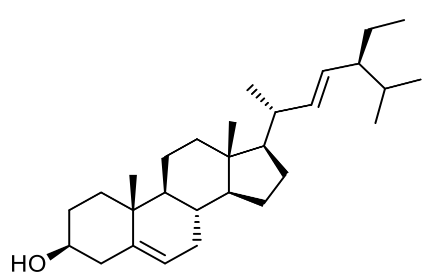

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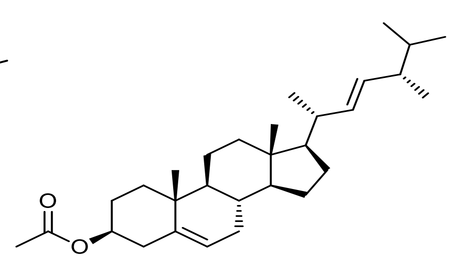

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Fig. 3. Chemical structures of flavonoids, alkaloids and sterols isolated form *C. papaya*

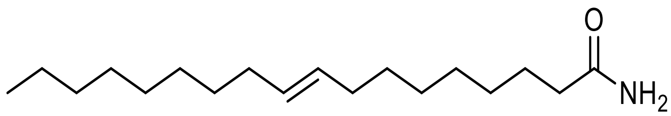
Table 5. Sterols reported in *C. papaya*

No.	Compound	Extract used	Part used	Reference
42	β-Sitosterol	Aqueous	**Leaf**	**[10]**
		Petroleum ether extract		**[24]**
		Petroleum ether extract	**Aerial parts**	**[25]**
		Ethanolic extract	**Leaf**	**[26]**
43	Stigmasterol	Petroleum ether extract	**Aerial parts**	**[25]**
		Ethanolic extract	**Leaf**	**[26]**
44	Ergosta-5,22-dien-3-ol acetate (3β, 22E)	Aqueous extract	**Root**	**[27]**

` **Table 6. Miscellaneous compounds reported in *C. papaya***

No.	Compound	Extract used	Part used	Reference
45	9-octadecenamide	Isopropanolic extract	**Leaf**	**[13]**
		Ethanolic extract	**Seed**	**[12]**
46	3,7,11,15-tetramethyl-2- hexadecen-1-ol	Isopropanolic extract	**Leaf**	**[13]**
47	3- methyl-4-(phenylthio)-2-enyl-2,5-dihydrothiophene-1,1-dioxide	Isopropanolic extract	**Leaf**	**[13]**
48	3,7-dimethyloct-7-en-1-ol	Isopropanolic extract	**Leaf**	**[13]**
49	hexahydro-1-aH-naphtho[1,8a-b]oxiren-2(3H)-one	Isopropanolic extract	**Leaf**	**[13]**
50	Tocopherol	Aqueous extract	**Leaf**	**[14]**
		Ethanolic extract	**Leaf**	**[26]**
51	Ascorbic acid	Aqueous extract	**Leaf**	**[14]**
52	Dicoumarol	Aqueous extract	**Leaf**	**[14]**
53	Folic acid	Aqueous extract	**Leaf**	**[14]**
54	*p*-coumaroyl alcohol	Aqueous extract	**Leaf**	**[14]**
55	Caffeoyl alcohol	Aqueous extract	**Leaf**	**[14]**
56	Umbelliferone	Aqueous extract	**Leaf**	**[14]**
57	Methyl nonyl ketone	Aqueous extract	**Leaf**	**[14]**
58	Benzyl isothiocyanate	Methanol /Aqueous extract	**Seed and pulp**	**[28]**
		Hydroalcoholic extract	**Fruit peel**	**[11]**
59	Allyl isothiocyanate	Methanol /Aqueous extract	**Seed and pulp**	**[28]**
60	4-(Methylthio)-3-butenyl isothiocyanate	Methanol /Aqueous extract	**Seed and pulp**	**[28]**
61	Benzyl glucosinolate	Methanol /Aqueous extract	**Seed and pulp**	**[28]**
62	Sinigrin	Methanol /Aqueous extract	**Seed and pulp**	**[28]**

63	4-methylthio-3-butenyl glucosinolate	Methanol /Aqueous extract	**Seed and pulp**	**[28]**
64	1-(2'-Methoxy-5- nitrophenyl) ethanone	Ethanolic extract	**Seed**	**[12]**
65	Phenol, 2-methyl-5- (1,2,2- trimethylcyclopentyl)-, (S)	Ethanolic extract	**Seed**	**[12]**
66	Tributyl acetylcitrate	Ethanolic extract	**Seed**	**[12]**
67	2-Propenoic acid, 3-(4- methoxyphenyl)-; 2-ethylhexylester	Ethanolic extract	**Seed**	**[12]**
68	(11R)-(-)-11- Carbomethoxy-11-[(-)- methoxyacetyl]-9,10- dihydroxy-9,10- ethanoanthracene	Ethanolic extract	**Seed**	**[12]**
69	2-Methyl-5H- dibenz[b,f]azepine	Ethanolic extract	**Seed**	**[12]**
70	3-Methyl-5- trifluoromethyl-3,4- diazatetracyclo[7.3.1.1(7, 11).0(2,6)]tetradeca- 2(6),4-diene	Ethanolic extract	**Seed**	**[12]**
71	(2S,3R)-2-tert-Butylthio- 1-phenylbutan-2-ol	Ethanolic extract	**Seed**	**[12]**
72	Supraene	Ethanolic extract	**Seed**	**[12]**
73	6-Methyl-3-Methylimino- 4-Oxo-3,4-Dihydro-2h- 1- Benzothiopyran-N-Oxide	Ethanolic extract	**Seed**	**[12]**
74	Tetramethyl Dibenzotetraaza-18- Crown-6	Ethanolic extract	**Seed**	**[12]**
75	2-Heptyl-6,7-dihydro-3- methyl-4H-pyrrolo[2,1- b][1,3]oxazine-4,8(8aH)- dione 8-oxime	Ethanolic extract	**Seed**	**[12]**
76	Danielone	Ethyl acetate extract	**Fruit**	**[29]**
77	Dianhydromannitol	Aqueous extract	**Root**	**[27]**
78	1,1,3,3,5,5,7,7,9,9,11,11- Dodecamethylhexasiloxane	Aqueous extract	**Root**	**[27]**
79	Carpamic acid	Alkaloidal fraction (acid- base extraction)	**Leaf**	**[17]**
80	Methyl carpamate	Alkaloidal fraction (acid- base extraction)	**Leaf**	**[17]**



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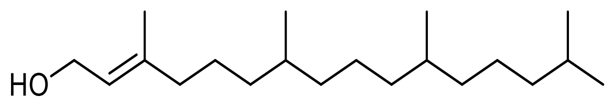

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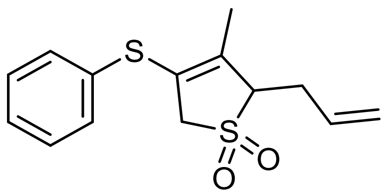

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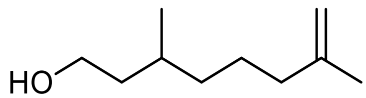

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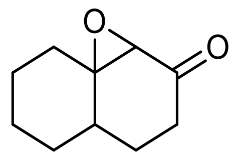

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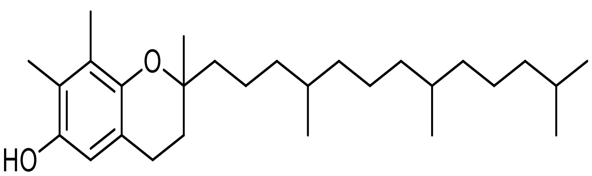

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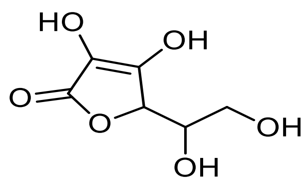

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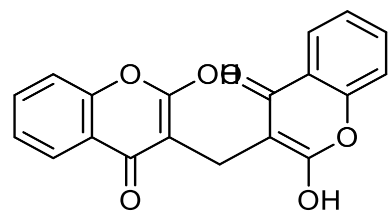

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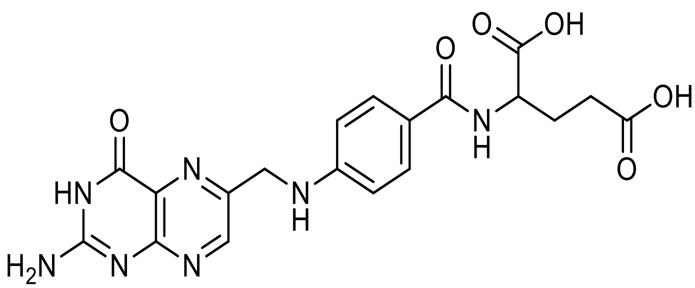

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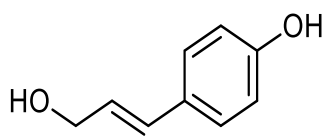

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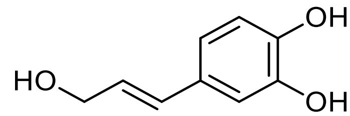

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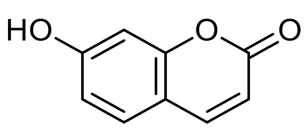

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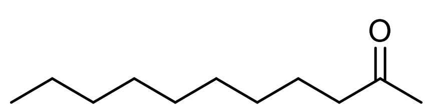

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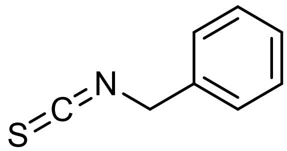

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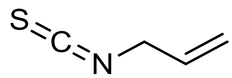

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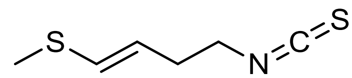

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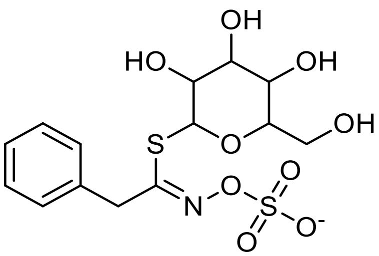

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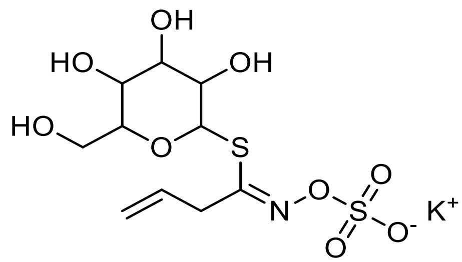

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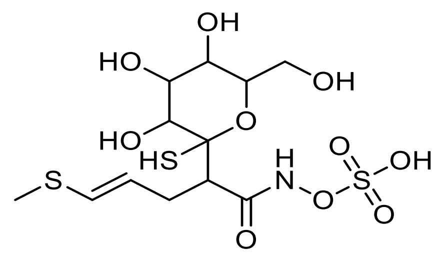

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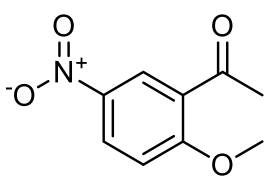

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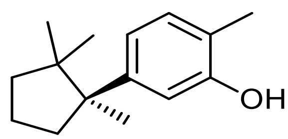

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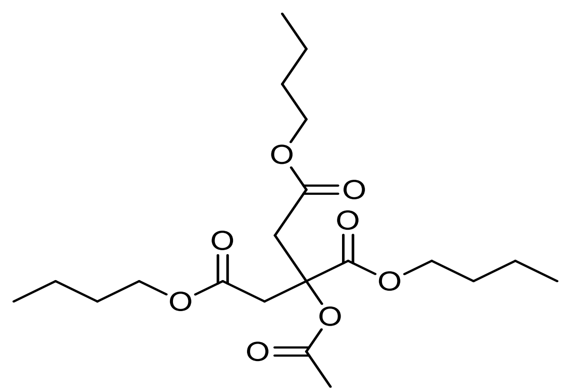

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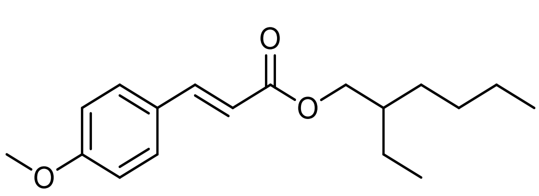

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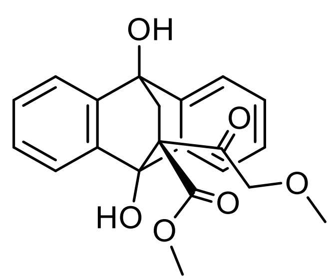

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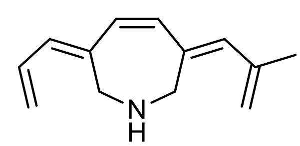

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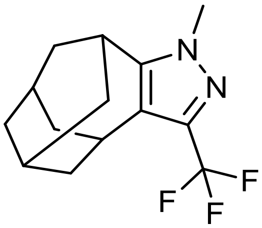

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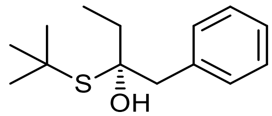

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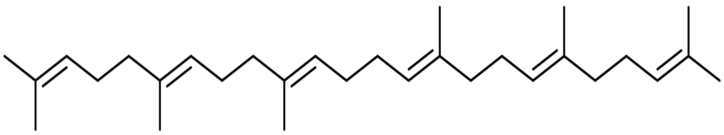

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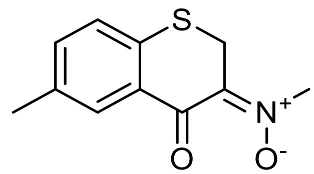

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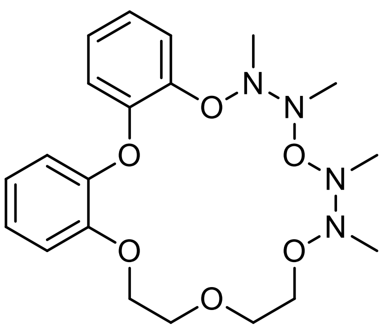

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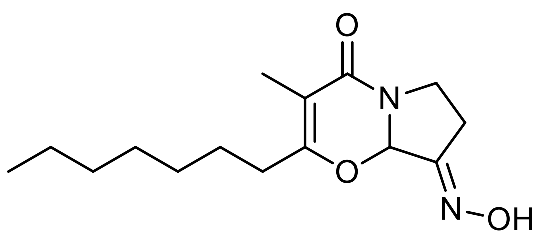

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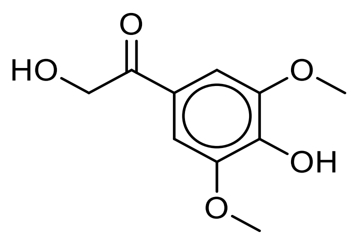

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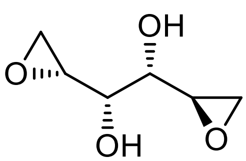

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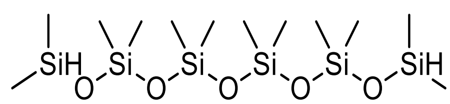

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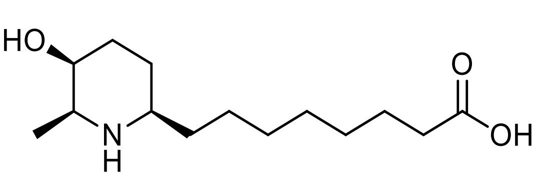

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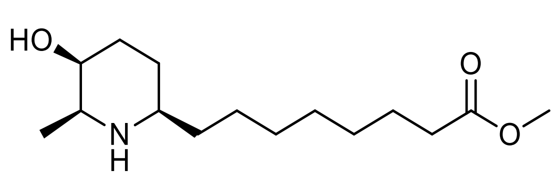

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Fig. 4. Chemical structures of miscellaneous compounds isolated form *C. papaya*

2.2. Biological studies

The screening of the available literature on *Carica papaya* revealed many significant biological activities in various *in-vivo* and *in-vitro* models. Biological activities comprised anti-inflammatory, anti-cancer, anti-protozoal, anti-microbial, anti-oxidant, anti-cancer, anti-diabetic, anti-fungal, anti-hyperlipidemic, anti-thrombocytopenic, anti-viral, anti-gout, anti-hypertensive, analgesic, and hepato-protective activities. The major reported biological activities are summarized and displayed as shown in **Fig. 5**.

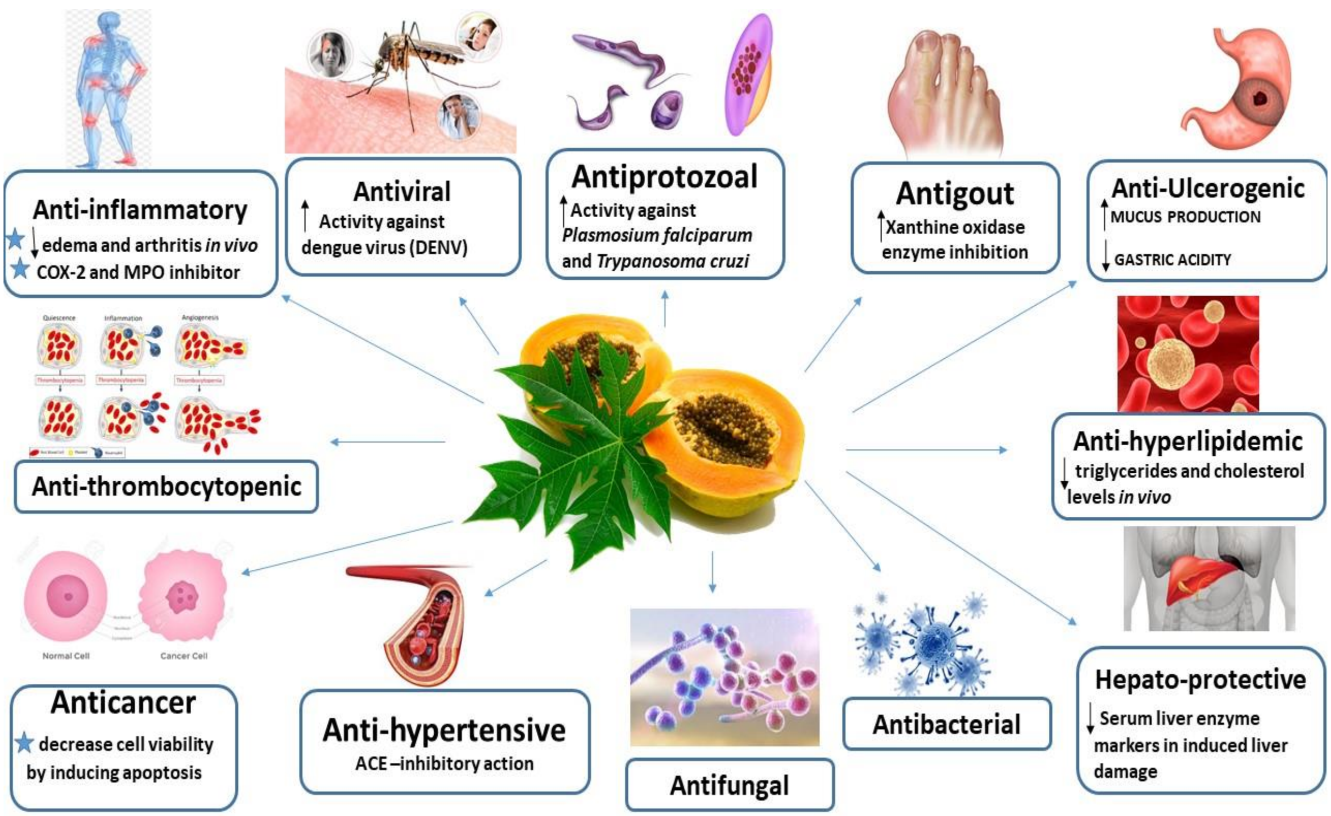

Fig. 5. Major reported biological activities of *Carica papaya*

2.2.1. Anti-inflammatory activity

The anti-inflammatory activity of ethanolic extract of *C. papaya* leaves was investigated using carrageenan-induced paw edema, cotton pellet granuloma, and formaldehyde-induced arthritis models in rats. Oral administration of the ethanolic extracts at a dose range of 25–200 mg/Kg triggered a significant reduction of edema in the carrageenan test and formaldehyde arthritis model, also a significant reduction in the amount of induced granuloma was observed **[30]**. In addition, intraperitoneal administration of the methanolic extracts of *C. papaya* seeds at a dose range of 50-200 mg/kg showed a dose and time-dependent inhibition of the induced paw edema in adult white Wistar rats **[31]**. Another study revealed that the phosphate-buffered saline (PBS) extract of *C. papaya* unripe fruit with a concentration of 5 mg/mL and the selenium-added PBS papaya extract possessed anti-inflammatory activity by significant inhibition of the pro-inflammatory enzymes cyclooxygenase-2 (COX-2) and myeloperoxidase enzyme (MPO) activity in cutaneous wounds of adult female Sprague–Dawley rats **[32]**.

2.2.2. Anticancer activity

Numerous studies discussed the efficacy of *C. papaya* extracts against different types of cancers and suggested that some specific bioactive molecules are responsible for that high efficacy. At a concentration of 100 μgmL^{-1}, a saponin-enriched ethanolic papaya leaf extract exerted an anti-pancreatic cancer activity via decreasing the viability of MiaPaCa-2 and ASPC-1 pancreatic cancer cell lines by 81 and 54% respectively. Compared with gemcitabine, the extract possessed equal cytotoxicity against MiaPaCa-2 cell lines and higher cytotoxicity against ASPC-1 cell lines **[33]**. The aqueous papaya leaf extract was also tested for its activity against breast cancer. Using MTT assay, the extract induced inhibition to the proliferation of breast cancer cell lines MCF-7 more than quercetin and doxorubicin with IC_{50} of 1319.25 $\mu g\ mL^{-1}$ and induced the apoptosis of MCF-7 cell lines (by 22.54%) via Annexin V assay at a concentration of 659.63 $\mu g\ mL^{-1}$ which is considered a lower apoptotic activity than quercetin and doxorubicin **[34]**.

Bioassay-guided fractionation of the ethyl acetate extract obtained from the juice of papaya leaf leaves resulted in an active sub-fraction that showed selective anti-proliferative activities against PCa cells and was superior to those of Paclitaxel. Furthermore, the active sub-fraction exerted a synergistic growth-inhibitory action when combined with Paclitaxel **[35]**. In addition, pectin extracted from the papaya pulp during the intermediate ripening phase decreased cell viability and induced apoptosis in three types of cancer lines including PC3 prostate cancer cell line and HCT116 and HT29 colon cancer cell lines **[36]**. Another study implied that the high content of phenolic and flavonoid compounds in the acidic ethanol and acidic aqueous papaya leaf extracts may be responsible for decreasing the cell viability and the cytotoxicity of human oral squamous cell carcinoma (SCC25) and non-cancerous human keratinocyte (HaCaT) cell lines **[37]**. Previously known for its cytotoxicity, benzyl isothiocyanate in papaya seed extract was believed to contribute to inhibiting the cell viability of acute promyelocytic leukemia (HL-60) cells with an IC_{50} of 20 μg/mL **[28]**.

2.2.3. Anti-protozoal activity

The *in vitro* testing of the antiprotozoal activity revealed that the ethyl acetate fraction of *C. papaya* leaves showed high anti-plasmodial activity against *Plasmodium falciparum* with an IC_{50} of 2.96 μg/mL **[38]**. Moreover, the campaign isolated from the alkaloidal fraction of *C. papaya* exhibited remarkable activity against *Plasmodium falciparum* with an IC_{50} of 0.2 μM and a selectivity index of 107 **[39]**. The crude chloroform extract of *Carica papaya* seeds at doses of 50 and 75 mg/Kg also showed activity against *Trypanosoma cruzi* in mice with a significant reduction in parasite count compared with the positive control allopurinol (8.5 mg/kg) **[40]**. Aqueous and ethanolic extracts of *C. papaya* seeds showed an *in vitro* larvicidal and ovicidal activity against the eggs of the parasite *Heligmosomoides bakeri* (obtained from *Mus musculus*) at a concentration of 2.75 mg/mL **[41]**.

2.2.4. Antiviral activity

Aqueous extract of *C. papaya* leaf at a 200 µg/mL concentration showed anti-dengue activity and was examined via immunoblotting and flow cytometry. The aqueous extract significantly decreased the envelope and non-structural (NS1) proteins expression in dengue virus (DENV)-infected THP-1 cells **[42]**. Another study displayed the activity of aqueous *C. papaya* extracts against the dengue virus. The antiviral effects of extracts were evaluated *In vitro* in Vero cells using foci forming unit reduction assay (FFURA) and demonstrated a significant reduction in foci formation, in addition, the MTT cytotoxicity assay confirmed the cytotoxic activity of papaya aqueous extracts against virus-infected Vero cells with an IC_{50} value of 137.6 µgmL-1 and selective index value of 75.85 **[43]**. Another recent study revealed that papaya fruit pulp has been recently reported to exert antiviral activity against Zika virus *in vitro* with IC_{50} of 0.3 mg/mL**[44]**.

2.2.5. Anti-ulcerogenic activity

Methanolic extract of *Carica papaya* seeds showed a high gastroprotective activity in rat models with gastric ulcers induced by ethanol and indomethacin and chronic ulcer induced by acetic acid. A dose of 500 mg/kg showed the most significant reduction of the gastric lesion. Moreover, the methanolic extract showed systemic action, increasing mucus production and depleting gastric acidity **[45]**. Another study revealed that the aqueous extract of *C. papaya* unripe fruits significantly reduced gastric mucosa lesions in rat modes. A dose of 4.5 mL/kg of the decoction reduced the ulcer score significantly in both HCl/ethanol and indomethacin-induced gastric lesions **[46]**.

2.2.6. Anti-hypertensive activity

The methanolic extract of *Carica papaya* leaves at a dose of 100 mg/kg twice daily elicited an inhibitory action on the angiotensin-converting enzyme. The antihypertensive activity was evaluated *in vivo* on hypertensive rats in comparison with enalapril. Polyphenolic compounds such as caffeic acid, ferulic acid, gallic acid, and flavonoid compounds like quercetin, rutin, nicotiflorin, clitorin, and manghaslin were identified in the extract and the study believed that the identified compounds may contribute to the extract's antihypertensive activity **[47]**.

2.2.7. Hypoglycemic activity

A study reported that oral administration of *C. papaya* leaves chloroformic extract at doses of 31 and 62 mg/kg induced a decrease in the blood glucose levels in streptozotocin-induced diabetic rats **[48]**. After administration of *C. papaya* leaves ethanolic extract at doses of 50,150 and 300 mg/kg to streptozotocin-induced diabetic mice, a significant decline in blood glucose level (101. 48) was observed as compared to the hyperglycemic level in diabetic animals (197.84 mg/dL) and standard drug Glucophage (101.34 mg/dL) which proved the hypoglycemic effect of the extract **[49]**. The aqueous extracts of the leaves and the roots of *C. papaya* have remarkable hypoglycemic activity. At a dose of 400 mg/kg body weight, aqueous extract of *C. papaya* leaves decreased the blood glucose levels in alloxan-induced diabetic rats as compared with glibenclamide as a control **[50, 51]**. In addition, The yield of the concentrated aqueous extract of *C. papaya* roots was further suspended in ethyl acetate and analyzed via GC-MS and the analysis revealed the presence of phytoconstituents, namely, hexadecanoic acid; methyl ester, 10-octadecenoic acid; methyl ester, ergosta-5,22-dien-3-ol acetate (3β, 22E), dianhydromannitol, methyl-11- hexadecanoic, 1,1,3,3,5,5,7,7,9,9,11,11 dodecamethylhexasiloxane and octadecanoic acid; methyl ester. Those phytoconstituents in the aqueous extract ameliorated hyperglycemia by decreasing the fasting blood glucose concentration in alloxan-induced diabetic rats by 30.95% **[27, 52]**.

2.2.8. Anti-gout activity

Aqueous extract of *C. papaya* leaves had inhibitory activity against xanthine oxidase enzyme which catalyzes the metabolism of hypoxanthine and xanthine into uric acid leading to a medical condition known as gout. The inhibitory effect on xanthine oxidase was measured spectrophotometrically at 295 nm under the aerobic condition and showed that the aqueous extract of *C. papaya* exhibited inhibitory activity against xanthine oxidase compared with allopurinol as a control **[53]**.

2.2.9. Analgesic activity

The analgesic activity of papaya leaves extracts (*n*-Hexane, ethyl acetate, and ethanol) was investigated via an acetic acid-induced pain technique on experimental mice. All extracts at the doses of 0.175, 0.35, and 0.70 mg/kg body weight induced a notable analgesic activity in mice, and the ethanolic extract showed the best activity at a dose of 0.70 mg/kg body weight compared to aspirin as a control **[54]**.

2.2.10. Diuretic activity

At an oral dose of 10 mg/kg, an aqueous root extract of *C. papaya* showed a diuretic activity via increasing the urinary output in adult male Sprague–Dawley rats. The extract's activity was 74% of the activity of the equivalent dose of hydrochlorothiazide which was used as a control **[55]**.

2.2.11. Anti-thrombocytopenic activity

The bioactive compound campaign was isolated from the alkaloidal fraction of *C. papaya* leaves and administered at a dose of 2 mg/kg for 20 days to busulfan-induced thrombocytopenic Wistar rats.

The anti-thrombocytopenic activity was assessed by monitoring the blood platelet count and the findings showed that the campaign exhibited potent activity in sustaining the platelet counts up to 555.50 ± 85.17 ×109 /L with no acute toxicity **[56]**. Another study detected the presence of myricetin, caffeic acid, trans-ferulic acid, and kaempferol via UPLC-qTOF/MS in the aqueous papaya leaves extract which exhibited a significant increase in the thrombocytic count through oral administration to thrombocytic rats **[10]**.

2.2.12. Anti-fungal activity

Aqueous extract of crushed *C. papaya* leaves showed an *in vitro* antifungal activity against different types of saprophytic fungi, dermatophytes fungi, and yeast. The antifungal activity was observed in four saprophytic fungi namely; *Penicillium sp, Aspergillus flavus, Aspergillus niger, and Rhizopus* with an inhibition zone range of 15-20 mm and a minimum inhibitory concentration (MIC) range of 120-160 mg/mL. For dermatophytes fungi, the activity was observed against two fungi namely; *Microsporum canis and Trichophyton mentagrophytes* with an inhibition zone range of 16-20 mm and MIC range of 180-320 mg/mL. In the case of yeast, the activity was observed against all Candida species including *Candida albicans, Candida albicans ATCC 0383, Candida galbrata, Candida tropicalis, and Candida kruzei* with an inhibition zone range of 12-20 mm and MIC range of 80-200 mg/mL. All activities were compared with the antifungal drug Greseiofulvin as control which gave an inhibition zone around >20 mm in almost all tested fungi **[57]**. In another study, silver nanoparticles containing an aqueous extract of *C. papaya* leaves showed antifungal activity against *Candida albicans* and *Aspergillus fumigatus* with zones of inhibition of 13 mm and 11 mm respectively **[58]**. Furthermore, danielone is a phytoalexin compound isolated from papaya fruit and was reported to exhibit high antifungal activity against *Colletotrichum gloesporioides* pathogenic fungus **[29]**.

2.2.13. Hepatoprotective activity

Aqueous extract of *C. papaya* leaves was tested *in vivo* for its hepatoprotective activity on rats via CCl_4-induced liver damage and was administered subcutaneously with 75mg/kg CCl_4 after 48 h. At a dose of 400 mg/kg/day, *C. papaya* aqueous extract showed a maximum hepatoprotective activity by decreasing the elevation of serum liver enzyme markers of acute hepatocellular injury (ALT, AST, ALP, serum MDA, and bilirubin) and the results were confirmed histologically **[59]**. Furthermore, the aqueous extract of unripe *C. papaya* fruits induced a decline in the elevated serum levels of liver enzyme markers in CCl_4 and acetaminophen-induced liver toxicity in rats at doses of 100 and 300 mg/kg respectively **[60]**. In addition, aqueous extracts of *C. papaya* seeds at a dose of 400 mg/kg also decreased the serum levels of enzyme biomarkers of acute hepatocellular injury induced by CCl_4 in rats and the improvement result were confirmed via monitoring the hepatic histological changes **[61]**.

2.2.14. Anti-hyperlipidemic activity

At a dose of 400 mg/kg, an aqueous extract of *C. papaya* leaves reduced the elevated triglycerides and cholesterol levels in alloxan-induced diabetic rats **[51]**. In addition, *C. papaya* methanolic seeds extract at a dose of 200 mg/kg decreased the serum levels of cholesterol, triglycerides, and HDL showing an anti-hyperlipidemic activity against *in vivo* Triton X100 and atherogenic diet-induced hyperlipidemia Albino Wistar rats **[62]**. Additionally, the aqueous ethanol extract of papaya leaves was assayed quantitatively for its polyphenolic content after being extracted by different methods. Microwave-assisted extraction (MAE) possessed the highest polyphenols content (29.99 mg/g) and showed an anti-hyperlipidemic activity in hyperlipidemic rats **[63]**.

2.2.15. Antibacterial activity

At a dose of 200 µg/mL, silver nanoparticles of aqueous extract of *C. papaya* leaves showed a substantial antibacterial activity against *Staphylococcus aureus* via the agar cup plate method with an inhibition rate of 2.9 cm, in addition, it showed a moderate activity at the same dose against *Bacillus subtilis*, *Proteus vulgaris* and least against *Escherichia coli* with inhibition rates of 2.7, 2.5 and 1.9 cm respectively in comparison with streptomycin as a control **[64]**. In another study, *n*-hexane fraction of *C. papaya* leaves at a dose of 400 mg/mL showed a more significant antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) than ethyl acetate fractions and *n*-butanol fractions with a zone of inhibition of 18.23±1.12 mm **[65]**.

2.2.16. Antioxidant activity

The free radical scavenging activity was tested *in-vitro* via the DPPH assay technique. Ethanolic extract of *C. papaya* leaves (wild species) showed a scavenging activity with an IC_{50} of 53.68 µg/ ml compared with ascorbic acid as a standard which possessed an IC_{50} of 40.24

µg/ mL **[66]**. Another study tested the antioxidant activity of the methanolic, aqueous, and petroleum ether extracts of *C.papaya* leaf and it was found that all three extracts showed a good scavenging activity. The IC50 values of C. papaya were 247, 262.18 µg/mL, and 171.52 µg/mL for aqueous, methanol, and petroleum ether respectively **[67]**. Methanol extract of *C.papaya* seeds at a concentration of 1 mg/mL concentration inhibited at least 50% of DPPH radical. The study believed that the activity was due to the high polyphenol and flavonoid content in the methanolic extract compared to the hexane one **[68]**. The total phenolic and flavonoid contents were assessed in another study on different papaya leave extracts and the methanolic extract showed the highest phenolic and flavonoid content with a reported phenolic content of 13.7 mg/g as gallic acid equivalent and 21.60 mg/g as quercetin equivalent for the flavonoid content. The methanolic extract exhibited a free radical scavenging activity with an IC_{50} of 80 µg/mL using the DPPH assay **[69]**.

2.2.17. Contraceptive activity

The aqueous extract of *C. papaya* seeds was assessed for its contraceptive activity *in vivo* on female Albino rats. The rats were treated with 200 mg/kg of the aqueous extract and the activity was daily monitored. The results showed that the aqueous extract exhibited a significant decrease in progesterone level and a disruption in the pattern of the oestrus cycle. In addition, the histological analysis of the utero-ovarian tissue showed marked alterations. All these findings prove that the aqueous extract of papaya affects fertility and implantation and confirms its contraceptive potential **[70]**.

2.2.18. Immunomodulatory activity

Aqueous extract of C. papaya leaf was found to have an immunity-enhancing activity via *in vitro* screening. The aqueous extracts significantly increased the levels of prostaglandin E_2 (PGE_2) and nitric oxide (NO) by adjusting the activity of nitric oxide synthase and cyclo-oxygenase-2 enzymes. The aqueous extract also activated the extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) pathways in macrophages. This led to an increase in the production of pro-inflammatory cytokines which illustrates the immunity-enhancing potential of the extract **[9]**.

Conclusion

A substantial literature review on *Carica papaya* has revealed the presence of a variety of chemical constituents. Phenolic acids, fatty acids, flavonoids, alkaloids, isothiocyanates, and sterols were the major compounds found in different parts of *Carica papaya*. In addition, the current literature review displayed the biological studies performed on the different extracts and the isolated compounds from different parts of *Carica papaya* that proved a high biological activity against different types of diseases as the studies focused on assessing anti-inflammatory, anti-cancer, anti-protozoal, anti-microbial, anti-oxidant, anti-cancer, anti-diabetic, anti-fungal, anti-hyperlipidemic, anti-thrombocytopenic, anti-viral, anti-gout, anti-hypertensive, analgesic and hepato-protective activities, contraceptive and immunomodulatory activities. This review provides an extensive perception of the phytochemistry and the biology of *Carica papaya*, which may open the door for developing new studies on isolating other compounds from this species and understanding their mechanism for the various previously reported biological activities and serve in discovering alternative medication for different health problems.

Declarations

Ethics approval and consent to participate

Not Available.

Availability of data and materials

Not available

Competing interests

The authors declare that they have no competing interests.

Consent to publish

Not available.

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Authors' contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis. The first draft of the manuscript was written by Amr Adel and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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