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An Overview On *Gliricidia Sepium* In The Pharmaceutical Aspect: A Review Article

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Abstract

Medicinal plants have been used in traditional medicine practices since prehistoric times. Humans learned to seek therapy in the barks, leaves, fruits, flowers, and other parts of plants as a result of many years of struggles against illnesses. *Gliricidia sepium* (Jacq.) Kunth. ex. Walp., is one of the most important plants in pharmacognosy and medical fields because it serves as a reservoir for potent bioactive compounds such as saponins, flavonoids, volatile oils, and other bioactive compounds that have been extracted from various parts of it. *Gliricidia sepium* is the topic of much research due to its numerous traditional applications, which include treating coughs, asthma, curing urticaria, rash, burns, scabies, dermatitis, acting as an antipruritic on the skin, and treating bacterial and protozoal infections. Many medicinal uses for *Gliricidia sepium* have been discovered over time, including cytotoxic activity, anti-microbial activity, anti-bacterial activity, anti-inflammatory activity, antioxidant activity, thrombolytic, anti-sickling activity, wound healing, mosquitocidal activity, and anthelmintic activity.

Keywords: *Gliricidia sepium*; Fabaceae; Phytochemical constituents; Biological activities.

1. Introduction

Gliricidia sepium (Jacq.) Kunth. ex. Walp. is a multipurpose legume plant that belongs to Fabaceae family, which is a big commercially and medicinally significant family of flowering plants recognized by its fruit (legume). Fabaceae family contains over 700 genera and roughly 20,000 species, this is the third biggest family after Orchidaceae and Asteraceae[1].

The genus Latin name *Gliricidia* means "mouse killer," in reference to the use of its toxic seeds and bark as rodenticides. Canavanine (2-amino-4-guanidooxy-butyric acid) a thermostable non-protein amino acid toxin, has been reported to be toxic found in *Gliricidia* seeds and barks is responsible for plant toxicity that killed mice within one week of feeding[2].

Gliricidia sepium is also known by other synonym names, including *Galedupa pungam Blanco, Gliricidia lambii Fernald, Gliricidia maculata (Kunth) Walp., Gliricidia maculata var. multijuga Micheli, Gliricidia sepium (Jacq.) Kunth ex Griseb., Lonchocarpus rosea (Mill.) DC., Lonchocarpus sepium (Jacq.) DC., Millettia luzonensis A. Gray, Millettia slendidissima "sensu Naves, non Blume", Robinia maculata Kunth, Robinia rosea Mill., Robinia sepium Jacq., Robinia variegata Schltdl*. It is also known by a variety of other common names such as Gliricidia, Glory Cedar, Mexican Lilac, Mother of Cocoa, Nicaraguan Cacao Shade, Quick Stick, St. Vincent Plum, and Tree of Iron[3].

Gliricidia sepium thrives in an environment with moderate yearly rainfall (900–1,500 mm). It grows best in areas with average temperatures of 20–27 °C, and it can withstand high temperatures of 36–42 °C and cold temperatures of 14 °C.A temperature less than 5°C at night is harmful to the tree. It is evergreen in places with uniformly spread rainfall such as in Kalimantan, Indonesia[3].

It is native to annual dry forest places of Mexico and Central America like Belize, Costa Rica, El Salvador, Guatemala, Honduras, and Nicaragua. It is currently found across the tropical Americas, the Caribbean, Africa, Asia, and the Pacific Islands[4].

Gliricidia sepium is widely applied in a variety of domains such as fodder for cattle and poultry,

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nitrogen- fixing plant, and shade trees for cocoa tree plantations[5].

Saponins, flavonoids, volatile oils, and other chemicals have been regarded as significant phytochemical compounds in *Gliricidia sepium* from various parts of it including leaves, flowers, fruits, stems, seeds and roots. It is known that *Gliricidia sepium* has cytotoxic activity, anti-microbial activity, anti-bacterial activity, anti-inflammatory activity, antioxidant activity, thrombolytic activity, anti-sickling activity, wound healing, larvicidal activity, and anthelmintic activity showing special importance in the medical field[6].

Phytochemical constituents:

There are various essential phytochemical constituents isolated from *Gliricidia sepium* from various parts of it, including saponins, flavonoids, volatile oils, and other miscellaneous compounds.

a) Saponins:

Three saponins(Table 1) hederagenin-3- *O* -(4- *O* -acetyl-*β*-D - xylopyranosyl)-(1 → 3)-*α*-L - hamnopyranosyl-(1 → 2)*α*-L-arabinopyranoside, hederagenin-3- *O* -(3,4-di- *O* -acetyl-*β*- D - xylopyranosyl)-(1 → 3)-*α*-L - rhamnopyranosyl-(1 → 2)-*α*-L - arabinopyranoside and hederagenin-3- *O* -(3,4-di- *O* -acetyl-*α*- L -arabinopyranosyl)-(1 → 3)-*α*-L - rhamnopyranosyl-(1 → 2)-*α*-L - arabinopyranoside were isolated from the fruits[7].

The heartwood of the *Gliricidia sepium* stem yielded stigmastanol glucoside (Table 1), which was isolated from a dichloromethane extract of the stem's heartwood and identified using an infrared spectrum, 1D 1H-NMR (proton nuclear magnetic resonance), and 13C-NMR (C-13nuclear magnetic resonance) technology[8].

From the leaves and roots, two triterpene saponins (gliricidoside A and B) (Table 1) were isolated, each with 3*β*,21*β*,24-trihydroxy- 22-oxoolean-12-ene as an aglycon and oligosaccharide moiety linked to C-3 of the aglycon. They contained two pyranoses (glucuronic acid and xylose), and the glucose residues in 1 and 2 were also linked to C-21. The structure of these compounds was elucidated using 1D and 2D NMR (nuclear magnetic resonance) techniques, which provided detailed information about the sapogenin and saccharide chains, including sugar sequence and glycosylation position[9].

b) Flavonoids:

The insecticidal active hot dichloromethane extract of *Gliricidia sepium* heartwood contained (Table 2) isoflavan (7,4'-dihydroxy-3'-methoxyisoflavan), three additional isoflavonoids (isovestitol, formononetin, and afrormosin), and a pterocarpan (medicarpin) (3-hydroxy-9-methoxy pterocarpan)[10]. Two isoflavones were isolated from *Gliricidia sepium* heartwood (Table 2): 2′,3′,7-trihydroxy-4′-methoxyisoflav-3-ene (sepiol) and 3′,7-dihydroxy-2′,4′-dimethoxyisoflav-3-ene (2′- *O* -methysepiol), a phenolic isoflavan (robinetin) and 7,3′,4′-trihydroxyflavanone[11].

Aromatic compounds extracted from the leaves of *Gliricidia sepium* have been identified (Table 2) as pterocarpan (3-hydroxy-9-methoxy pterocarpan), two isoflavans (isovestitol and 7,4′-dihydroxy-3′-methoxy-isoflavan), and four favonol glycosides (Kampeferol -*O*-glycosides), and these compounds structures were elucidated using a variety of 1D and 2D NMR (nuclear magnetic resonance) techniques[9]. In addition to vestitol and 2′-*O*–methylvestitol, 12a-hydroxyrotenoids, gliricidol,2-methoxygliricidol, and gliricidin were isolated from *Gliricidia sepium* bark methanol extract (Table 2), and their structures were determined using 1D and 2D NMR (nuclear magnetic resonance) methods[12].

The flavonol glycoside (Table 2) was discovered in the fresh pale pinkish flowers of *Gliricidia sepium* (isoquercitrin). Modern physical methods such as UV (ultraviolet), 1H-NMR (proton nuclear magnetic resonance),13C-NMR (C-13 nuclear magnetic resonance), chemical reactions, chromatographic examinations, and hydrolytic studies were used to determine the structure of the isolated polyphenolic compounds[13].

The methanolic extract of *Gliricidia sepium* leaves contains amounts of flavonoids such as isorhamnetin (Table 2) by using MALDI MS (matrix-assisted laser desorption ionization mass spectrometry) [14].

c) Volatile oils:

The essential oil isolated from the leaves of *Gliricidia sepium* (Jacq.) Kunth ex Steud. cultivated in Colombia was analyzed using GC-FID (gas chromatography-flame ionization detector) and GC-MS. A total of 80 volatile chemicals were discovered (Table 3), with safrole (12.3%) being the most prevalent and 2'-hydroxy-acetophenone (12.1%)[15].

The chemical composition of hydro distilled essential oils of *Gliricidia sepium*, which grows wild on Costa Rica's Central Pacific coast, was analyzed using capillary gas chromatography-flame ionization detector (GC-FID) and capillary GC-MS. There was a total of 96 and 109 chemicals in the leaf and flower oils, respectively. The leaf oil (Table 3) was primarily composed of aliphatics (54.9%), terpenoids (28.1%),pentadecanal (18.7 %), (Z)-phytol (7.8%), methyl linoleate (6.0 %), and nonanal (5.1%)were the most abundant compounds in the leaf oil. The flower oil (Table 3) was primarily composed of aliphatics (58.9 %), terpenoids (25.8 %), hexadecanoic acid (19.7 %), myrtenol (7.7 %), and (E)-nerolidol (5.9%) were the main components of the flower oil[16].

Gliricidia sepium's leaves and flowers have been found to contain 42 known compounds. Sixteen of them were discovered and quantified using GC (gas chromatography) analysis from the leaf essential oil, while twenty-six were identified and quantified using GC-MS analysis from the flower essential oil. The major compounds found in the leaf oil (Table 3) are propylene glycol (25.1%), coumarin (18.2 %), (Z)-3-hexenol (17.7 %), *β*-farnesene (14.2 %), and (E)-2-hexenol (6.5 %), while the flower oil contains coumarin (43.1%), hydroquinone (21.6 %), and myrtenol (12.7%) [17].

The bark oil of *Gliricidia sepium* was analyzed using GC-MS to identify and quantify nineteen components. The major components are (Table 3) methyl- 3(E)- pentenyl ether (11.55%), 3- methyl- 2- butanol (10.65%), 3- methoxy hexane (10.14%), 1- (1- ethoxy ethoxy) - 2- hexene (9.72%), 2- decanol (8.97%), coumarin (8.07%) and hexadecanoic acid (5.16%)[18].

The chemical content of the essential oil of the flower has been described(Table 3), with the fundamental components being coumarin (43.07 %), hydroquinone (21.64 %), myrtenol (12.73 %), maltol (4.42 %), p -mentha-1,8-dien- 1-ol (1.83 %), γ-nonalactone (1.31 %) and 2-butyl-2-hexanol (1.03 %) and also reported the chemical composition of the leaf essential oil(Table 3), the chief components of which are propylene glycol (25.1 %), coumarin (18.2 %), (Z)-2-hexenol (17.7 %), *β*-farnesene (14.2 %), (E)-2-hexenol (6.5 %), thymol (3.6 %), benzyl alcohol (3.5 %), caryophyllene (2.3 %) and *α*-farnesene(2.0%)[19].

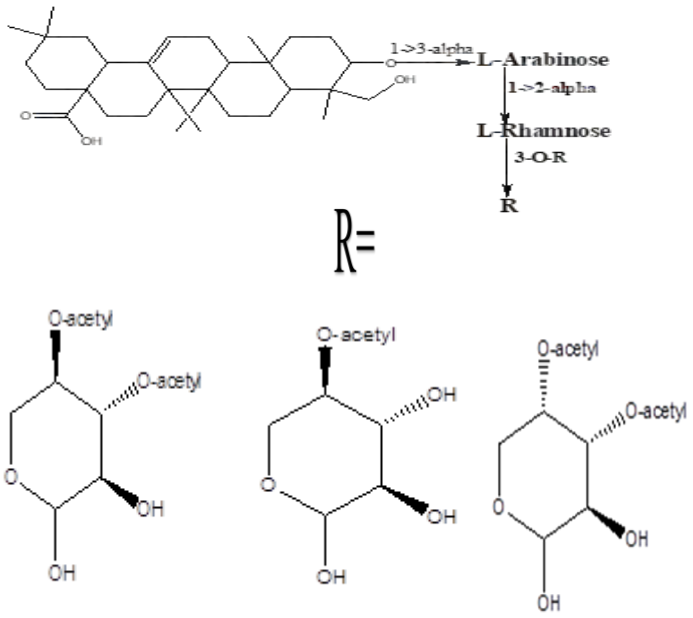
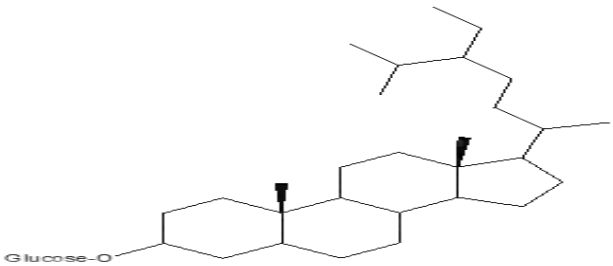
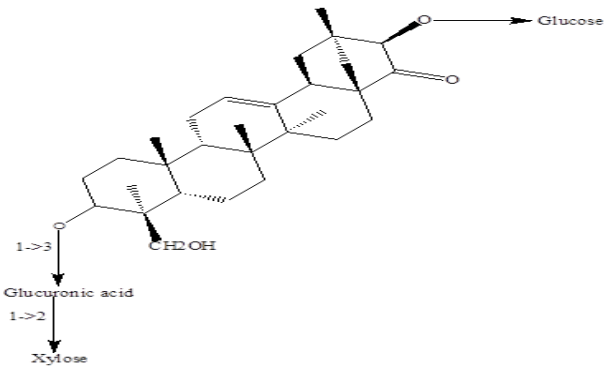
The chemical composition of volatile oils produced by hydrodistillation from the leaf and stem of *Gliricidia sepium* (Jacq.) Walp. was examined. There were 43 and 44 components in the leaf (Table 3) and stem oils(Table 3), respectively. The main components found in the leaf oil were (E)-hexadecatrienal (16.9%) and pentadecanal (16.0%), whereas the stem oil was dominated by humulene epoxide II (17.5%) and caryophyllene oxide (10.6%)[20].

d) Miscellaneous:

Gliricidia sepium stem heartwood yielded 3,4 -dihydroxy-trans-cinnamic acid octacosylester(Table 4), which was isolated from dichloromethane extract of the stem heartwood and identified using IR (infrared) spectrum, 1D 1H-NMR (proton nuclear magnetic resonance), and 13C-NMR(C-13 nuclear magnetic resonance) technology[8].

Pinoresinol and lariciresinol (Table 4) are two lignans isolated from the leaves of *Gliricidia sepium* and structurally elucidated using 1D and 2D –NMR (nuclear magnetic resonance) spectroscopy and mass spectrometry[21]. 4-hydroxy-3-methoxycinnamaldehyde (Table 4), which was isolated from a hot dichloromethane extract of the heartwood of *Gliricidia sepium*, and its structure was elucidated using IR (infrared), NMR (nuclear magnetic resonance), and MS(mass spectrometry) spectral techniques[10].

Table 1: enumerating *Gliricidia sepium* saponins content

Compound name	Structure	Part used	Reference
Three saponins Hederagenin-3-*O*-glycoside		Fruit	[7]
Stigmastanol glucoside		The heartwood of the stem	[8]
two-triterpene saponin(gliricidoside Aand B)	gliricidoside A  gliricidoside B	Leaves Roots	[9]

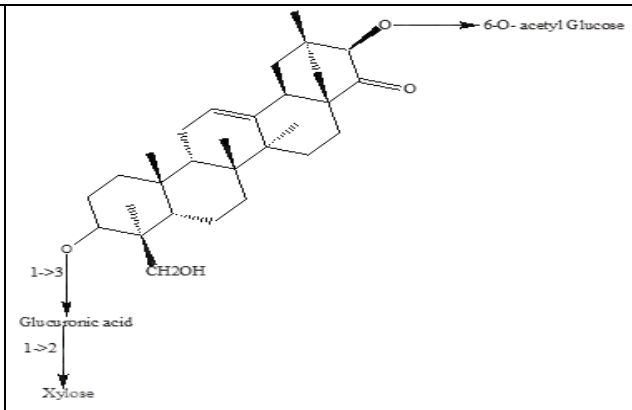
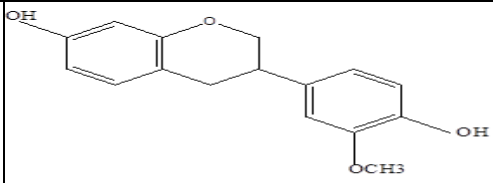
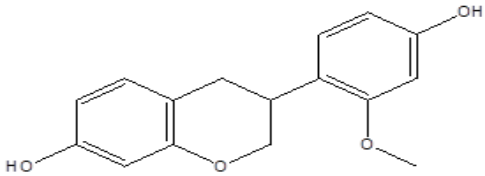
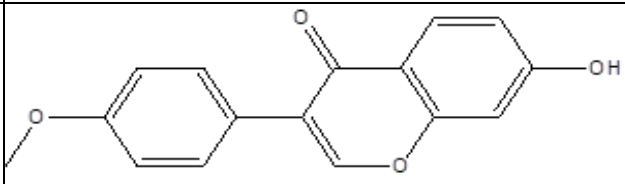
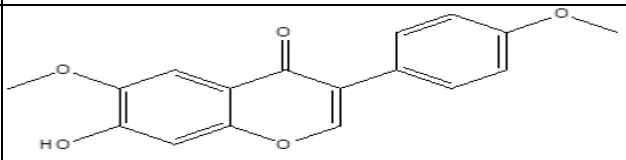
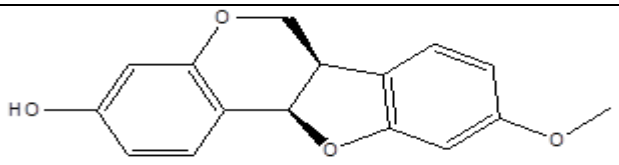
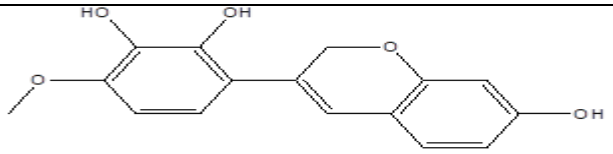
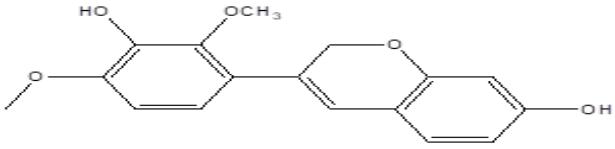
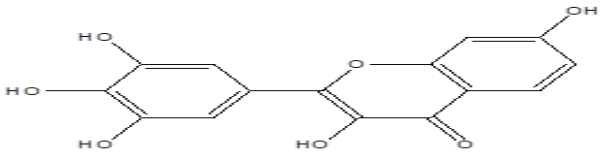
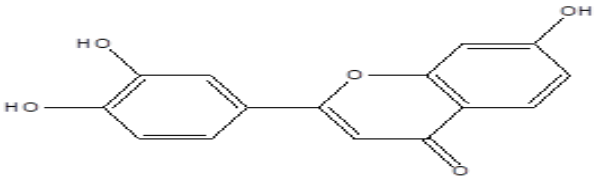
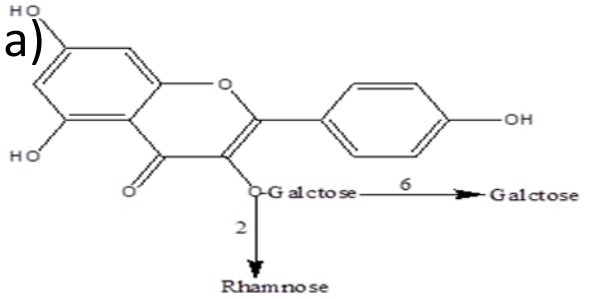
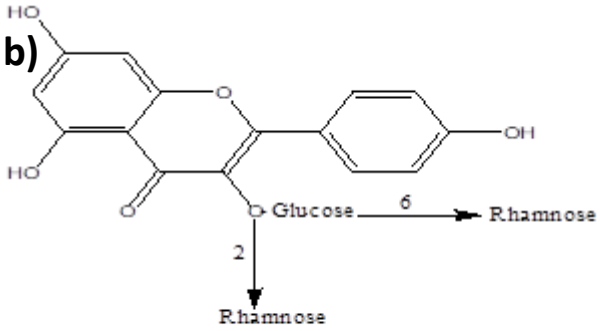
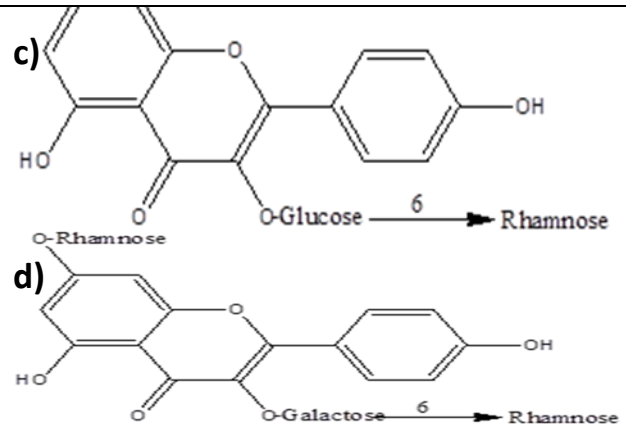
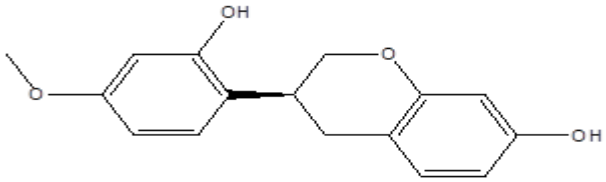
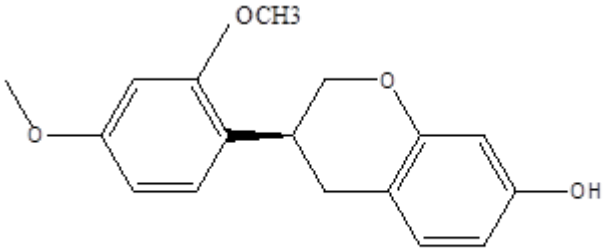
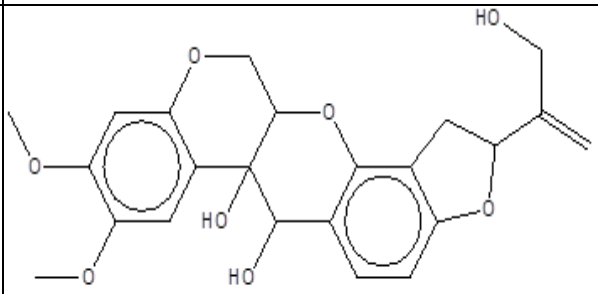
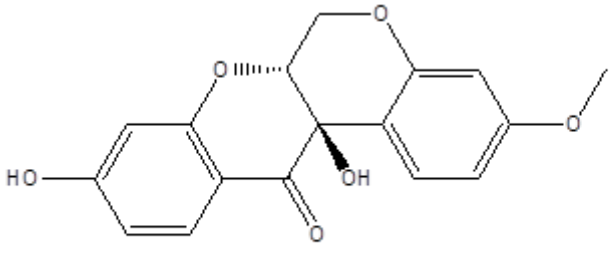
			

Table 2: enumerating *Gliricidia sepium* flavonoids content

compound name	Structure	Part used	Reference
7,4'-dihydroxy-3'-methoxyisoflavan		leaves	[9]
Isovestitol		Leaves	[9]
Formononetin		The heartwood of the stem	[10]
Afrormosin		The heartwood of the stem	[10]
3-hydroxy-9-methoxy pterocarpan		The heartwood of the stem and leaves	[3,4]

Sepiol		The heartwood of the stem	[11]
2′-*O* -methysepiol		The heartwood of the stem	[11]
Robinetin		The heartwood of the stem	[11]
7,3′,4′trihydroxyflavanone		The heartwood of the stem	[11]
Kampeferol-*O*-glycosides (Four favonol glycosides)	 	Leaves	[9]

			
Vestitol		Bark	[12]
2′-*O*–methylvestitol		Bark	[12]
12a-hydroxyrotenoids		Bark	[12]
Gliricidol		Bark	[12]

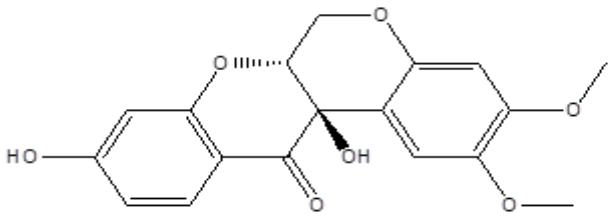
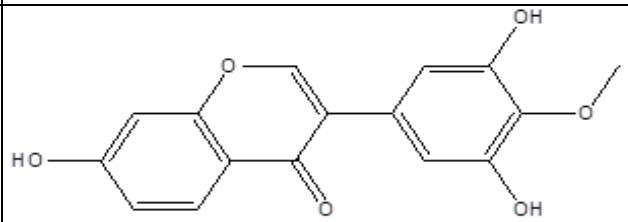
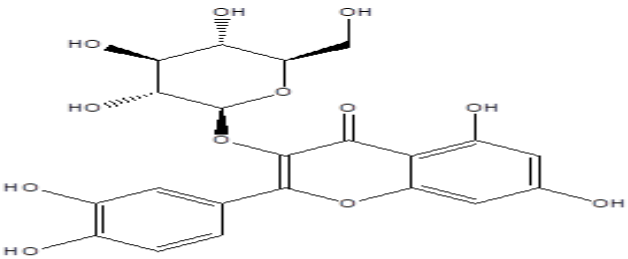
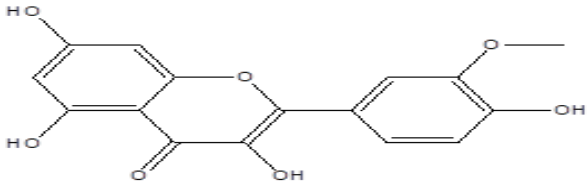
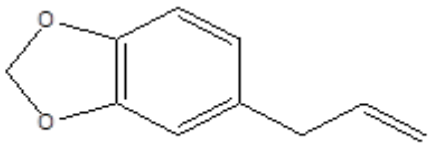
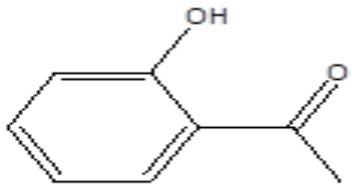
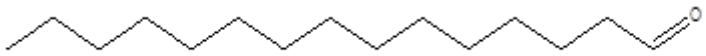
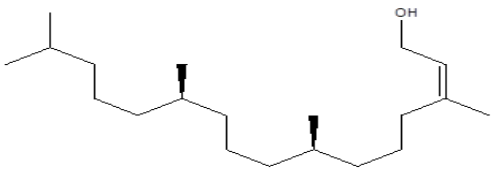
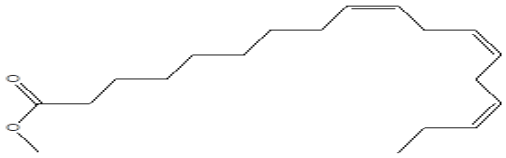
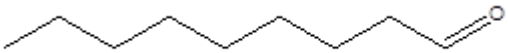
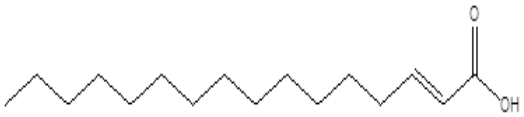
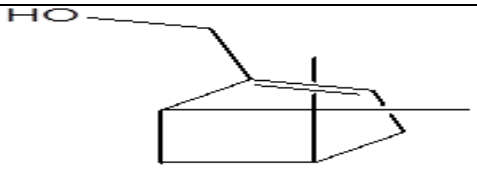
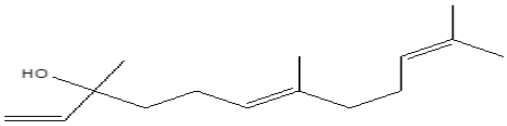
2-methoxygliricidol		Bark	[12]
Gliricidin		Bark	[12]
Isoquercitrin		Flower	[13]
Isorhamnetin		Leaves	[14]

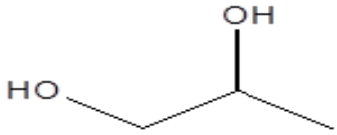
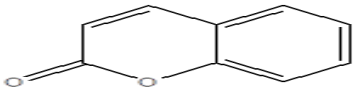
Table 3: enumerating *Gliricidia sepium* volatile oils content

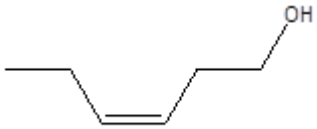
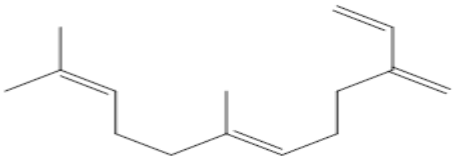
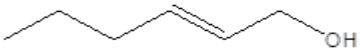
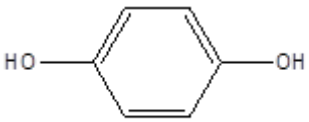
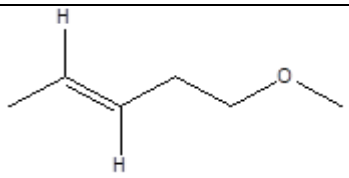
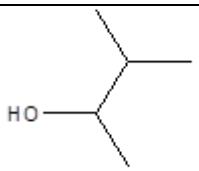
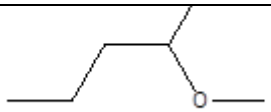
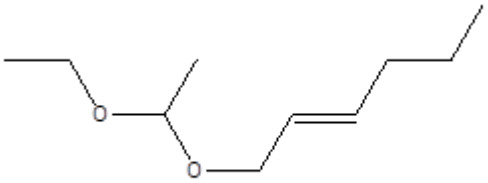
Compound name	Structure	Part used	Reference
Safrole		Leaves	[15]
2'-hydroxy-acetophenone		Leaves	[15]

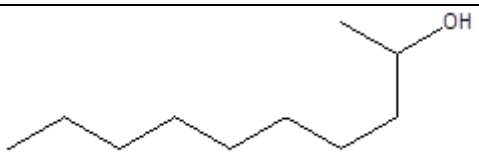
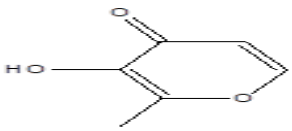
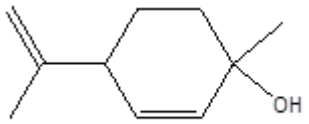
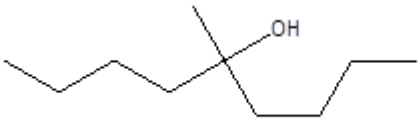
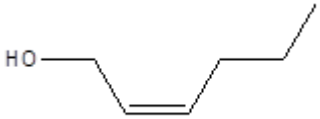
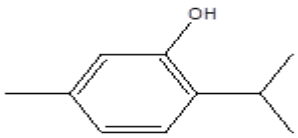
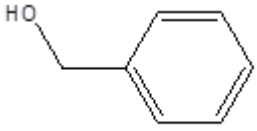
Pentadecanal		Leaves	[9,13]

Z-phytol		Leaves	[16]
methyl linoleate		Leaves	[16]
Nonanal		Leaves	[16]
hexadecanoic acid		Flower Bark	[9,11]

Myrtenol		Flower	[9,10,12]
(E)-nerolidol		Flower	[16]

propylene glycol		Leaves	[10,12]
Coumarin		Leaves Flower Bark	[10,11, 12,[22]16]

(Z)-3-hexenol		Leaves	[17]
β-farnesene		Leaves	[10,12]
(E)-2-hexenol		Flower Leaves	[10,12]
Hydroquinone		Flower	[10,12]
methyl-3(E)-pentenyl ether		Bark	[18]
3-methyl-2-butanol		Bark	[18]
3-methoxy hexane		Bark	[18]
1-(1-ethoxy ethoxy)-2-hexene		Bark	[18]

2-decanol		Bark	[18]
Maltol		Flower	[19]
p-mentha-1,8-dien-1-ol		Flower	[19]
γ-nonalactone		Flower	[19]
2-butyl-2-hexanol		Flower	[19]
(Z)-2- hexenol		Leaves	[19]
Thymol		Leaves	[19]
Benzyl alcohol		Leaves	[19]

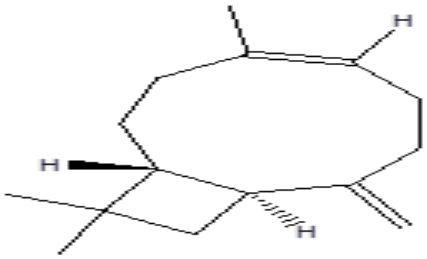
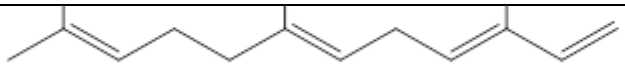
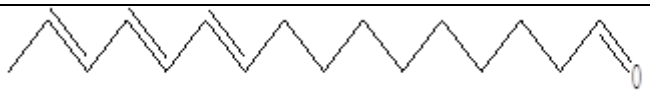
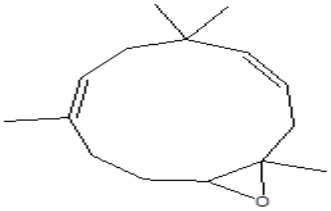
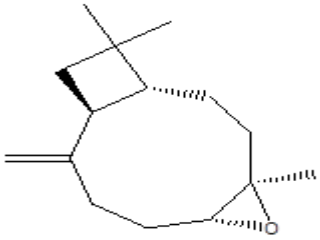
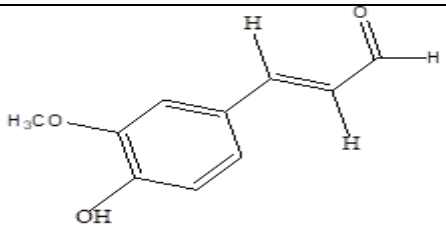
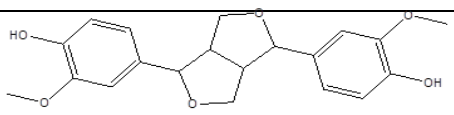
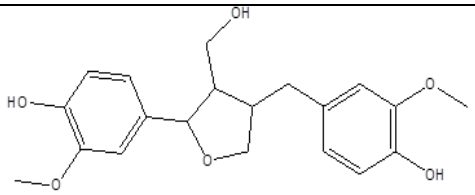
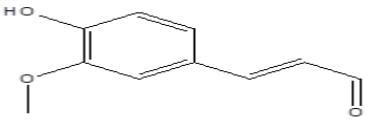
Caryophyllene		Leaves	[19]
α-farnesene		Leaves	[19]
(E)-hexadecatrienal		Leaves	[20]
humulene epoxide II		Stem	[20]
caryophyllene oxide		Stem	[20]

Table 4: enumerating *Gliricidia sepium* miscellaneous content

Compound name	Structure	Part used	Reference
3,4 -dihydroxy-trans-cinnamic acid octacosylester		The heartwood of the stem	[8]
Pinoresinol		Leaves	[21]

Lariciresinol		Leaves	[21]
4-hydroxy-3-methoxycinnamaldehyde		The heartwood of the stem	[10]

Traditional uses:

Herbal medicine has long been used in ancient societies and civilizations. Ancient people prepared remedies to cure certain ailments using native plants. *Gliricidia sepium*, as it is generally known, is one of these plants with several folkloric uses. For example, in Saint Lucia, the leaves are brewed as tea, sweetened, and drank to treat coughs and asthma; the leaves are also beneficial for skin infections. In Mexico, crushed fresh leaves are used as a poultice. A decoction of the leaves is used to cure urticaria, rash, and burns in Panama. In the Philippines, leaf juice or decoctions and bark decoctions are used for scabies and dermatitis and an antipruritic on the skin; fresh leaves are applied to the skin as an insect repellent, crushed leaves are used for rheumatic pains, sprains, and closed fractures. In Guatemala and Costa Rica, the bark decoction is used to treat bacterial and protozoal infections[6].

Biological activities:

a) Cytotoxic activity:

Gliricidia sepium leaves methanolic extract has a potential anti-proliferative action against gastric adenocarcinoma cells owing to its phytochemical constituents [24]. The reported correlation between the antioxidant effect and antitumor action was discussed before[25]. The scavenging power of stem bark methanol extract and other fractions (aqueous, chloroform, and ethyl acetate) of *Gliricidia sepium* had been demonstrated by recent research work which gives spot on its promising tumor growth inhibitory effects especially aqueous fraction that is more potent and rich in phenols and flavonoids [26]. Pereira et al recently displayed the phytochemical composition of *Gliricidia sepium* using MALDI Mass Spectrometry Imaging to identify the relation between the potent antioxidant and antimicrobial activity as well as Kaempferol, isorhamnetin content that potentiates it in the cosmetic industry[14].

b) Anthelmintic activity:

The ethanolic extract of *Gliricidia sepium* leaves was used to test its efficacy against parasitic nematodes. The extract exhibited nematocidal activity against Meloidogyne incognita nematodes at various concentrations, with 60 % mortality[27].

The anthelmintic activity of *Gliricidia sepium* was determined from an acetonic extract using the egg hatch assay (EHA). The final fraction was tested with EHA at decreasing concentrations of 1.100; 0.500, 0.250, 0.125, 0.060, 0.001and 0.00001 mg /ml[22].

The anthelmintic activity (AA) of ethanolic extracts of *Gliricidia sepium*, *Leucaena leucocephala*, and Pithecellobium dulce against Haemonchus contortus was evaluated using the third-stage-larval (L3) exsheathment inhibition test (LEIT) and egg hatch test (EHT). *Gliricidia sepium* revealed a larger diversity of chemicals possibly efficacious against gastrointestinal nematode control, which was related to the findings obtained in the tests[28].

Three acetonic extracts from the leaves of three forage legumes were investigated in vitro for ovicidal activity against *Haemonchus contortus: Calliandra calotyrsus (C. calotyrsus), Gliricidia sepium (G. sepium), and Leucaena diversifolia (L. diversifolia) (H. contortus). The acetonic extract of G. sepium was shown to be more active for embryonation and egg hatching than extracts of C. calothyrsus and L. diversifolia*[29].

Gliricidol, 2-methoxygliricidol, and gliricidin isolated from *Gliricidia sepium* bark exhibited cytotoxic activity against the brine shrimp Artemia salina larvae[12].

c)Larvicidal activity:

Gliricidia sepium leaf extracts were tested for their efficacy against Aedes aegypti, mortality rates were compared by utilizing different solvent leaves extracts to identify the highest rate of larval death using several solvents. The data showed that the ethanolic extract of *Gliricidia sepium* leaves was more efficient than other solvent extracts in inhibiting the larval growth [30]. Another report affirmed that various concentrations of ethyl acetate leaf extracts of *Gliricidia sepium* could reveal the larvicidal activity gainst Aedes aegypti larvae (I-IV) and pupae after a 24-hour exposure period [31]. The larvicidal activity of *Gliricidia*

sepium leaves on Anopheles mosquitos was observed using aqueous and methanolic plant extracts and shows a high mortality rate 48 hours after the plant extracts exposure. [32]. The promising larvicidal activity on Aedes aegypti larvae (II, III, and IV instars) was also reported for the methanolic and hexane extracts of *Gliricidia sepium* flowers with different doses and showed LC50 values at very little concentration (50-250 ppm) after 24 h exposure [33].

d)Anti-inflammatory:

The scientific report revealed that *Gliricidia sepium* (Fabaceae) flower aqueous extract has a strong anti-inflammatory properties either in vitro through HRBC (human red blood cell) membrane stabilization assay [34]or in vivo models via carrageenan-induced paw edema model in albino Wistar rats against diclofenac sodium [35]. It is characterized by long-acting anti-inflammatory activity achieving 80% activity until 5.5hr[36].

f) Wound healing:

The wound healing properties is tightly linked with the anti-inflammatory effect of any agent used for treatment [37]so the synthesized ointment containing *Gliricidia sepium* leaves from Indonesia and the Philippines has a potent wound healing activity through decreasing the levels of inflammatory cells and decreasing the expression of interleukin-6(IL-6) and IL-1(interleukin-1) [38]. The other topical formulation that disclosed the promising wound healing activities of *Gliricidia sepium* water extract is gel-based formulation prepared from lyophilized *Gliricidia sepium* sap[39]. The gel formulation is characterized by low-cost, safe, pH, heat and light exposure stability [40].

e) Anti-oxidant:

The antioxidant capacity of crude and fraction extracts of *Gliricidia sepium* and Spathodea campanulata leaf in methanol, ethanol, and petroleum ether was examined. Spathodea campanulata demonstrated greater levels of ferric reducing antioxidant capabilities and free radical scavenging activities than *Gliricidia sepium* in the antioxidant DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) free radical test[41]. *Gliricidia sepium* ethanolic leaf extract contains anti-oxidant phytochemicals such as flavonoids, saponins, tannins and steroids which reflect its antioxidant activity. After examining the bioactive components in the extract using Gas Chromatography-Mass Spectrometry, eight molecules were recognized as known antioxidants based on published literature[42]. The biological activity of volatile oils produced by hydrodistillation from *Gliricidia sepium* (Jacq.) Walp. leaf and stem were examined using the DPPH(2,2-diphenyl-1-picryl-hydrazyl-hydrate) radical-scavenging technique[20].

g) Anti-microbial activity and anti-bacterial activity:

Gliricidia sepium ethanolic extract was evaluated for antibacterial efficacy against gram-positive and gram-negtive bacteria, as well as certain fungi, at varying doses[43][44]. Essential oils from the leaf and flower of *Gliricidia sepium* were tested for antibacterial activity against ten bacterial strains using the agar well diffusion method, including Bacillus cereus, Enterobacter faecalis, Salmonella paratyphi, Staphylococcus aureus, Escherichia coli, Streptococcus faecalis, Proteus Vulgaris, Klebsiella pneumonia, Pseudomonas aeruginosa and Serratia marcescens[19]. Using the 'agar well diffusion method,' the essential oil of the bark was tested for antibacterial activity against Bacillus cereus, Enterobacter faecalis, Salmonella paratyphi, Staphylococcus aureus, Escherichia coli, Streptococcus faecalis, Proteus Vulgaris, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Serratia marcescens[18].

Using the agar well and disc diffusion methods, the antibacterial activity of methanol, ethanol, and petroleum ether soluble crude and fraction extracts of *Gliricidia sepium* and Spathodea campanulata leaf were studied[41].

An ethanolic extract of the leaves of *Gliricidia sepium* was tested for antibacterial activity against E. coli, S.aureus, Pseudomonas spp., S.typhi, Klebsiella spp., using the well diffusion technique[27]. Isoquercitrin, a flavonol glycoside found in *Gliricidia sepium* flowers, was revealed to be antibacterial. This characteristic has been comparable to conventional medications[13].

The agar cup technique was used to investigate the antibacterial activity of dried leaf extracts of *Gliricidia sepium* against two gram-negative bacterial strains, Escherichia coli, and Pseudomonas aeruginosa[45]. The leaves of the plant were extracted using petroleum ether, ethyl acetate, and ethanol. These extracts were tested for antibacterial activity using the disc diffusion technique. The extract was evaluated against four pathogenic gram-positive and gram-negative bacterial strains. *Gliricidia sepium* ethyl acetate extract possesses potent antibacterial properties[46]. The agar well diffusion method was used to evaluate the antimicrobial properties of *Gliricidia sepium* ethanolic leaf extract, which showed inhibition against the bacterial organism Bacillus subtilis and the fungus Candida albicans[42].

Crude extracts of Panamian plants (153 representing 28 species from 21 groups) were evaluated for antifungal activity against Candida albicans and Cladosporium cucumerinum. The semiquantitative activity was assessed using

bioautography on TLC plates. When tested at 100 pg, 15% of the extracts showed action against one of the fungi and 9% of the extracts showed activity against both test species. Traditional medicinal plants such as Eursera simaruba (Burseraceae), *Gliricidia sepium* (Leguminosae), and Piper auritum (Piperaceae) provide the most promising extracts[47]. Chloroform, methanol, and aqueous extracts of the bark of Gymnanthes lucida, *Gliricidia sepium*, Lysiloma divaricata, Lysiloma tergemina, and Coccolaba cozumelensis were tested against S. lutea, E. coli, S. epidermidis, L. monocytogenes, S. choleraesuis, S. aureus, P. aeruginosa, B.pumillus, S. typhimurium, P. vulgaris, V. cholerae, and C. albicans[48].

Aqueous extracts from 22 Guatemalan plants, including *Gliricidia sepium*, inhibited the dermatophytes. Epidermophyton floccosum (43.2 %), Trichophyton rubrum (36.0 %), and Trichophyton mentagrophytes (31.8 %) were the most often inhibited dermatophytes and Microsporum canis (22.7 %) and Microsporum gypseum (24.0 %) were the least inhibited[49]. A randomized, double-blind, controlled clinical trial comparing the efficacy and safety of *Gliricidia sepium* poultice versus sulfur lotion as an anti-scabies agent[50].

Gliricidia sepium and seven other American plants were examined for their resistance to four harmful fungi (Aspergillus flavus, Epidermophyton floccosum, Microsporum gypseum, and Trichophyton rubrum). The most active solvent for the bark and leaves of these American plants was ethanol[51]. From the 46 plants studied, Plants commonly used in Guatemala to treat Neisseria gonorrhoeae. Nine of these plants were found to be effective against five strains of N. gonorrhoea., including *Gliricidia sepium*[52].

Coumarin isolated from *Gliricidia sepium* water leaf extract inhibited Trichophyton mentagrophytes growth in vitro with an average antimicrobial index (AI) of 1.45, while standard clotrimazole inhibited AI at 2.0[23]. The antimicrobial activity of volatile oils obtained by hydrodistillation from *Gliricidia sepium* (Jacq.) Walp. leaf and stem were tested using brine shrimp lethality assays and the agar diffusion method[20].

h)Anti-viral activities:

Gliricidia sepium leaves extract has been observed as an antiviral agent against dengue fever virus, this result was reported in a clinical study on 30 patients with dengue fever virus and concluded that *Gliricidia sepium* leaves extract not only showed antiviral activity but also relieve accompanied symptoms[53].

Another reported antiviral activity was shown in a recent Colombian traditional medicine study where an aqueous extract of *Gliricidia sepium* leaves showed anti-SARS-COV-2 by in-vitro study at different concentrations[54]. Also, the incorporation of *Gliricidia sepium* leaves in several pharmaceutical preparations with other Colombian medicinal plants showed a very promising antiviral effect against COVID-19 and accompanied respiratory symptoms[55].

Miscellaneous biological activities:

i)- Thrombolytic activity:

The promising thrombolytic activity of *Gliricidia sepium* was achieved by using aqueous two-phase systems containing polyethylene glycol and sodium phosphate to extract a cysteine protease which has fibrinolytic and fibrinogenolytic activity [56]. Gliricidia sepium is reported as an alternative source of the fibrinolytic enzymes [57].

ii) Anti-sickling activity:

Gliricidia sepium aqueous leaf extract revealed in vitro anti-sickling effects utilizing varient doses (5mg, 10mg, 15mg, 20mg, 25mg, 30mg, 35mg, 40mg, 45mg, and 50mg) but 20mg is the best dose giving 100% activity. [58].

Another report confirms that *Gliricidia sepium* aqueous leaf extract seems to be an anti-sickling agent without inducing any oxidative stress [59].

Conclusion:

Gliricidia sepium plant is crucial in a variety of fields as it includes a wide group of phytochemical constituents that have been used in a variety of sectors, including medicine. It performs well in many biological activity studies, including cytotoxic activity, anti-microbial activity, anti-inflammatory activity, anthelmintic activity, larvicidal activity, and antioxidant activity. Finally, more research on *Gliricidia sepium* is needed to discover its other secrets.

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