

Review

Gliricidia sepium: Phytochemical Profile, Ethnobotanical Uses, and Emerging Pharmacological Potential in Inflammation and Pain-Related Conditions

Josué Vidal Espinosa-Juárez ¹, Danna Brigith Vera-Carrillo ², Osmar Antonio Jaramillo-Morales ³,
Alfredo Briones Aranda ⁴ and Josselin Carolina Corzo-Gómez ^{1,*}

¹ Escuela de Ciencias Químicas, Universidad Autónoma de Chiapas (UNACH), Ocozacoautla de Espinosa 29140, Mexico; josue.espinosa@unach.mx

² Escuela Superior de Medicina, Instituto Politécnico Nacional, Miguel Hidalgo, Ciudad de México 11340, Mexico; dannavera3010@gmail.com

³ Departamento de Enfermería y Obstetricia, División de Ciencias de la Vida, Campus Irapuato-Salamanca, Universidad de Guanajuato, Irapuato 36500, Mexico; oa.jaramillo@ugto.mx

⁴ Facultad de Medicina Humana, Campus II, Universidad Autónoma de Chiapas (UNACH), Tuxtla Gutiérrez 29090, Mexico; alfredo.briones@unach.mx

* Correspondence: josselin.corzo@unach.mx

Abstract

Gliricidia sepium (*G. sepium*) is a Fabaceae tree native to Mexico and Central America with ethnobotanical relevance in tropical regions. Traditionally, different parts have been used to treat skin disorders, wounds, fever, infections, inflammation, and pain-related conditions. This narrative review summarizes evidence on the ethnobotanical uses, phytochemical profile, biological activities, antinociceptive potential, and safety of *G. sepium*, with an emphasis on inflammation and pain. The literature search used *G. sepium* as the search term combined with keywords related to ethnobotanical uses, traditional medicine, phytochemistry, secondary metabolites, pharmacological activity, toxicity, and safety. Boolean operators, truncation, and searching were applied without publication year restrictions. Articles published in English and Spanish were considered, while superficial or irrelevant mentions were excluded. The literature indicates that *G. sepium* contains diverse constituents, including volatile aromatic compounds, coumarins, flavonoids, phenolic acids, fatty acid derivatives, triterpenoids, and saponins. In vitro and preclinical in vivo studies suggest antioxidant, anti-inflammatory, wound-healing, gastroprotective, and tissue-protective effects. However, evidence of antinociceptive activity remains lacking, and pain-related relevance is mainly inferred from mechanisms involving inflammation, oxidative stress, and tissue repair. Thus, *G. sepium* represents a potential source of bioactive metabolites, although its therapeutic potential requires validation through standardized preparations, validated models, mechanistic studies, and toxicological assessment.



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1. Introduction

Natural products, particularly those derived from medicinal plants, remain a major source of bioactive compounds with significant pharmacological potential. Their remarkable chemical diversity—including alkaloids, flavonoids, terpenoids, phenolic compounds, and other secondary metabolites—underlies a wide range of biological activities, such as

antioxidant, anti-inflammatory, and analgesic effects [1]. In many developing countries, medicinal plants continue to play an essential role in primary healthcare due to their accessibility, affordability, cultural acceptance, and perceived therapeutic benefits. Consequently, a substantial proportion of the population continues to rely on traditional medicine for the prevention and treatment of common health conditions [2–5]. This widespread use is also reflected at the global level. According to a 2019 report by the World Health Organization (WHO), traditional, complementary, and integrative medicine (TCIM) is practiced in 170 countries. Furthermore, a global survey reported that most WHO Member States estimated that between 40% and 99% of their populations use TCIM, highlighting its continued relevance as an important component of healthcare worldwide [6]. Traditional knowledge has facilitated the identification of plant species used to manage pain, inflammation, infections, wounds, gastrointestinal disorders, and other prevalent conditions. Nevertheless, their traditional use requires rigorous scientific validation to characterize their phytochemical composition, confirm their biological and pharmacological activities, and establish their safety. Such evaluation is essential because the therapeutic efficacy and toxicity of medicinal plants depend on factors including the plant part used, extraction method, dosage, route of administration, and chemical standardization [7,8].

Gliricidia sepium is a medicinal plant that has been traditionally used in various regions to manage conditions associated with inflammation, skin disorders, wounds, pain, infections, and gastrointestinal disorders [2,5,7]. Experimental studies have reported a chemically diverse phytochemical profile for this species, including flavonoids, phenolic acids, fatty acid derivatives, aromatic compounds, and triterpenoid saponins [9–11].

Experimental studies have also reported antioxidant activity, modulation of inflammatory responses, wound healing, gastric protection, and tissue repair [11,12]. Nevertheless, the available evidence remains fragmented, and several pharmacological effects attributed to this species are still supported primarily by studies using crude extracts, preliminary in vitro or in vivo assays, or indirect mechanistic interpretations. Moreover, the specific bioactive compounds responsible for these effects, their molecular targets, and the mechanisms underlying their pharmacological activities remain insufficiently characterized. Further research using standardized extracts, bioassay-guided fractionation, well-defined experimental models, and mechanistic approaches is therefore needed to establish robust structure–activity relationships and clarify the therapeutic potential of this species.

Despite its broad ethnobotanical relevance and increasingly documented phytochemical diversity, the pharmacological evidence on *G. sepium* remains dispersed across studies addressing antimicrobial activity, wound healing, gastroprotection, oxidative stress, inflammation, and toxicity. This fragmentation limits a clear interpretation of its therapeutic potential, particularly in pain-related conditions, where direct antinociceptive evidence remains scarce. In addition, many available studies rely on crude extracts, non-standardized preparations, or indirect biological endpoints, making it difficult to identify active constituents, compare findings across studies, or distinguish experimentally demonstrated effects from mechanistic plausibility. Therefore, an integrative and critical synthesis is needed to clarify what is currently supported by evidence, what remains inferential, and which experimental gaps must be addressed before *G. sepium* can be considered for well-defined pharmacological applications.

The objective of this narrative review was to analyze the available scientific evidence on the ethnobotanical uses, phytochemical profile, antioxidant and anti-inflammatory activities, antinociceptive potential, and toxicological aspects of *G. sepium*. This review also aimed to identify the main experimental gaps and safety considerations that should be addressed before proposing more defined therapeutic applications for this species.

The conceptual framework of this review is summarized in Figure 1, which integrates the ethnobotanical relevance of *G. sepium*, its phytochemical diversity, the main experimental and mechanistic evidence, and the translational gaps that currently limit its therapeutic interpretation. The arrows connecting *G. sepium* with these modules represent conceptual relationships rather than causal or sequential pathways. Ethnobotanical information provides the historical and empirical context for the traditional uses of the species, whereas phytochemical evidence defines the diversity of constituents that may underlie its reported biological properties. Experimental and mechanistic studies subsequently provide varying degrees of support for antioxidant, anti-inflammatory, tissue-protective, and pain-related effects and help identify the molecular pathways potentially involved. In parallel, the limitations of the available evidence—including the heterogeneity of extracts and experimental models, limited bioassay-guided isolation of active compounds, and insufficient toxicological and herb–drug interaction data—define the translational gaps and research priorities that must be addressed before stronger therapeutic conclusions can be drawn. Thus, Figure 1 should be interpreted as an integrative framework linking traditional knowledge and phytochemical composition with experimental validation and the remaining requirements for pharmacological translation.

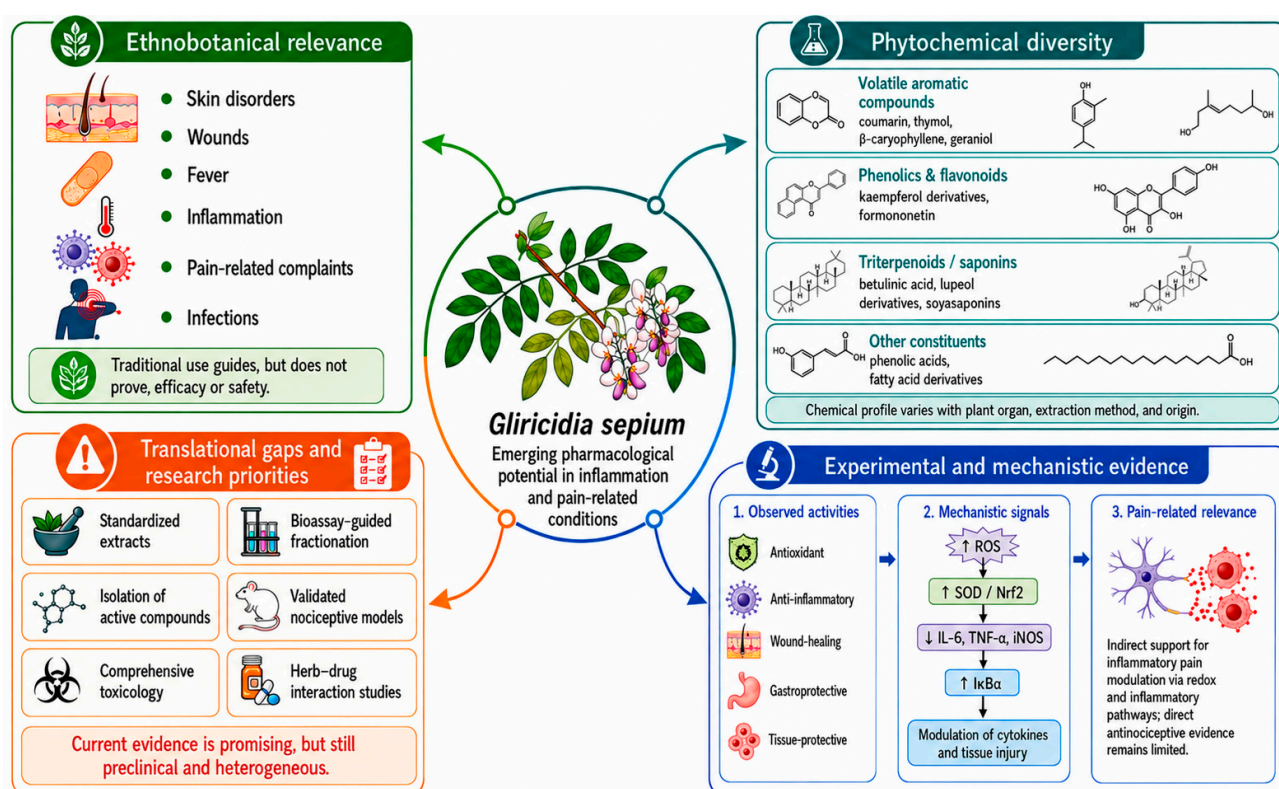


Figure 1. Integrative framework of the ethnobotanical relevance, phytochemical diversity, mechanistic plausibility, and translational gaps of *Gliricidia sepium*.

2. Materials and Methods

This narrative review included publications identified through a comprehensive literature search conducted up to August 2026. The literature reviewed comprised both early foundational studies and recent advances in the field, with a few notable exceptions for older publications that provided particularly relevant or significant data.

A comprehensive literature search was conducted using major academic databases, including Scopus, Web of Science, PubMed, ScienceDirect, and Google Scholar. These databases were selected because of their extensive coverage of ethnobotanical, phyto-

chemical, pharmacological, and biomedical research. The search focused primarily on the traditional and ethnobotanical uses of *G. sepium*, its reported phytochemical constituents, biological activities, and potential pharmacological applications.

The scientific name "*Gliricidia sepium*" was used as the primary search term, both independently and in combination with keywords related to ethnobotanical uses, traditional medicine, phytochemistry, secondary metabolites, bioactive compounds, antioxidant activity, anti-inflammatory activity, antinociceptive activity, analgesic activity, wound healing, toxicity, and safety. An additional targeted search was conducted using *Gliricidia sepium* in combination with toxicity-related terms, including toxicity, toxicology, safety, acute toxicity, LD₅₀, and mortality. Boolean operators, truncation, and phrase searching were employed to broaden and refine the search strategy and to capture relevant variations in terminology and spelling. No restrictions were imposed on publication year.

Articles published in English and Spanish were considered if they provided relevant information on the botanical, ethnobotanical, phytochemical, pharmacological, or toxicological characteristics of the species. Studies were excluded if they only briefly mentioned *G. sepium* or did not provide information directly relevant to the scope and objectives of this review.

A two-stage screening process was subsequently implemented. In the first stage, titles and abstracts were screened to identify potentially relevant studies. In the second stage, the full texts of the selected articles were assessed according to the predefined eligibility criteria. Peer-reviewed studies were prioritized when evaluating phytochemical, pharmacological, and toxicological evidence. Authoritative institutional documents and foundational botanical or ethnobotanical sources were also considered when directly relevant to the scope of the review.

Finally, an information extraction matrix was developed to systematically organize and compare the available evidence, assess methodological and reporting inconsistencies, and identify gaps in the current body of knowledge.

3. Botanical Description, Geographical Distribution, and Ethnobotanical Relevance

Gliricidia sepium (Jacq.) Kunth is a small- to medium-sized deciduous tree belonging to the family Fabaceae, one of the largest families of flowering plants and an important source of species with ethnobotanical and pharmacological relevance. Members of this family are known to produce a diverse array of secondary metabolites, including phenolic compounds, flavonoids, alkaloids, terpenoids, and saponins, which may contribute to their reported traditional medicinal properties [13–16].

Morphologically, *G. sepium* is generally described as a small- to medium-sized tree, typically reaching 2–12 m in height [17]. It is often branched from the base and develops an irregular, spreading crown with relatively sparse foliage. The leaves are alternate and pinnately compound, usually comprising 7–17 leaflets. The flowers are borne in axillary racemes and are typically pinkish-white to pale purple [18]. The fruits are flattened pods that range from yellowish-green when immature to brown or nearly black at maturity. Upon maturation, the pods dehisce to release several dark reddish-brown seeds [17].

Gliricidia sepium is native to Mexico and Central America and is widely distributed across tropical and subtropical Mesoamerica, with additional cultivation in the Caribbean, Africa, Asia, and Australia [19,20]. In Mexico, it is particularly common in tropical states such as Chiapas, Veracruz, Guerrero, and Yucatán [21].

The species is known by numerous vernacular names, including matarratón, madero negro, madre de cacao, cacahuananche, and cocuite, as well as the indigenous names

Cuchunuc (Zoque) and Ujcum (Tzeltal), reflecting its strong cultural and traditional importance [21].

3.1. Ethnobotanical Uses of *Gliricidia sepium*

The traditional use of *G. sepium* is closely associated with its cultural acceptance among rural communities, as well as with its widespread availability in local environments. Ethnobotanical information on this species has been documented using various methodological approaches, including semi-structured interviews, surveys, social mapping, and guided ethnobotanical walks [22–24]. These studies indicate that the leaves are among the most frequently used plant parts and are commonly collected from wild or cultivated trees by local informants, farmers, and traditional healers [24,25].

Traditional preparations of *G. sepium* are primarily associated with the management of skin conditions, fever, infections, and localized inflammatory processes. In some communities, fresh leaves are prepared as decoctions or macerated in water and subsequently applied externally during bathing to alleviate pruritic skin conditions and fever [24]. Similar topical practices have been reported for fever associated with COVID-19, in which crushed leaves were mixed with water, filtered, and used as a cooling bath preparation [23]. Although these practices do not provide evidence of clinical efficacy, they constitute relevant ethnobotanical evidence supporting the traditional external use of *G. sepium* for conditions associated with heat, discomfort, inflammation, and skin irritation.

The antimicrobial use of *G. sepium* has also been investigated experimentally based on ethnomedicinal reports. In one study, traditional knowledge guided the in vitro evaluation of plant extracts against bacterial strains, including *Staphylococcus aureus*, β -hemolytic *Streptococcus* spp., *Bacillus cereus*, *Pseudomonas aeruginosa*, and *Escherichia coli*, as well as the yeast *Candida albicans* [25]. These findings provide preliminary experimental support for some of the traditional antimicrobial uses of *G. sepium*; however, they should be interpreted as in vitro evidence rather than as evidence of clinical effectiveness.

Additional ethnobotanical reports have described the use of *G. sepium* leaves and other plant parts for wound healing, skin infections, inflammatory disorders, and related conditions [26]. Collectively, these reports underscore the ethnomedical relevance of *G. sepium* while highlighting the need to distinguish traditional use from demonstrated therapeutic efficacy.

3.2. Phytochemical Profile of *Gliricidia sepium*

Phytochemical studies of *G. sepium* have reported a broad spectrum of secondary metabolites, although the chemical profile varies according to plant organ, solvent system, geographic origin, and analytical approach. Preliminary screenings of leaf extracts from Indian specimens detected alkaloids, saponins, phenolic compounds, flavonoids, and tannins [27], in addition to steroids from the leaves of trees in Nigeria [28]. In contrast, a study conducted with ethanolic leaf extracts from specimens collected in the Philippines did not detect alkaloids but reported abundant steroids, highlighting the variability of qualitative phytochemical profiles across studies and extraction conditions [29]. The differences reported among samples collected in India, Nigeria, and the Philippines may reflect not only methodological variation but also underlying geographic and biological variability. Genetic studies have demonstrated substantial differentiation among populations of *G. sepium*, suggesting that provenance may contribute to phenotypic heterogeneity within the species [30]. In addition, the biosynthesis and accumulation of plant secondary metabolites are known to be influenced by environmental conditions, including light, temperature, water availability, soil fertility, and salinity [31]. Thus, differences in local growing conditions, together with genetic background, could potentially contribute to the contrasting

phytochemical profiles reported for *G. sepium* from different geographic regions. However, the available studies were not designed as standardized comparisons among populations and differ in plant material, extraction procedures, and analytical methods. Consequently, these geographic differences should not currently be interpreted as evidence of distinct chemotypes of *G. sepium*. Establishing chemotypic variation would require comparative phytochemical profiling of multiple populations using standardized sampling, extraction, and analytical procedures. Additionally, diethyl ether extracts and essential oil analyses of leaves and flowers have identified volatile and semi-volatile constituents, including coumarin, (Z)-3-hexenol, (E)-2-hexenol, β -farnesene, α -farnesene, thymol, benzyl alcohol, β -caryophyllene, caryophyllene oxide, myrtenol, hydroquinone, maltol, and geraniol. Among these, coumarin appears repeatedly in leaf and floral fractions and is therefore one of the most consistently reported volatile aromatic constituents of *G. sepium* [32]. Hydroquinone has also been reported, particularly in floral and ethyl acetate leaf extracts, but its toxicological relevance requires caution when discussing the biological potential of this species [33].

Non-volatile metabolites reported in *G. sepium* include flavonoids, phenolic acids, triterpenoids, and related compounds. Previous studies have identified compounds such as formononetin in heartwood, o-coumaric acid in leaf extracts, and triterpenoid-related metabolites such as betulinol, betulinic acid, lupeol acetate, and saponins [33]. Another study reported flavonoids such as astragalin, robinin, and trifolin [34]. The metabolites reported across the different plant organs, extraction systems, and analytical approaches are summarized in Table 1.

Table 1. Compounds reported in *G. sepium*.

Main Compound Identified	Plant Part	Extract	Country	Tentative Identification *	Reference
Coumarin	Leaves	diethyl ether	India	GC-MS	[32]
	Flowers			GC-FID	
		Ethyl acetate		GC-MS	[33]
	Leaves	Acid-hydrolyzed extract	Singapore	TLC	[35]
(Z)-3-Hexenol	Leaves	Diethyl ether	India	GC-MS	[32]
(E)-2-Hexenol				GC-FID	
β -Farnesene	Leaves	Diethyl ether	India	GC-MS	[32]
α -Farnesene				GC-FID	
Thymol	Leaves	Diethyl ether	India	GC-MS GC-FID	[32]
Benzyl alcohol	Leaves	Diethyl ether	India	GC-MS	[32]
	Flowers			GC-FID	
β -Caryophyllene	Leaves	Diethyl ether	India	GC-MS GC-FID	[32]
	Stem	Hydrodistillation	Nigeria	GC-MS	[36]
Caryophyllene oxide	Stem	Hydrodistillation	Nigeria	GC-MS	[36]
Myrtenol	Flowers	Diethyl ether	India	GC-MS GC-FID	[32]

Table 1. Cont.

Main Compound Identified	Plant Part	Extract	Country	Tentative Identification *	Reference
Hydroquinone	Leaves	Ethyl acetate	India	GC-MS	[33]
	Flowers	Diethyl ether		GC-MS GC-FID	[32]
Maltol	Flowers	Diethyl ether	India	GC-MS GC-FID	[32]
Phytol	Leaves	Ethanollic	Philippines	GC-MS	[29]
Heneicosane	Leaves	Ethanollic	Philippines	GC-MS	[29]
Lupeol acetate	Leaves	Ethanollic	Philippines	GC-MS	[29]
Neophytadiene	Leaves	Ethanollic	Philippines	GC-MS	[29]
Formononetin	Heartwood	Dichloromethane	Sri Lanka	HR-MS	[37]
o-Coumaric acid	Leaves	Ethyl acetate	Mexico	HPLC	[38]
	Leaves	Acid-hydrolyzed extract	Singapore	TLC	[35]
Betulinol	Leaves	Ethyl acetate	Mexico	NMR	[39]
Betulinic acid	Leaves	Ethyl acetate	Mexico	NMR	[39]
Geraniol	Flowers	Diethyl ether	India	GC-MS GC-FID	[32]
Astragalin (kaempferol 3-glucoside) Robinin (kaempferol-3-robinobioside-7-rhamnoside) Trifolin (kaempferol-3-galactoside)	Flowers	Alcohol	India	UV, acetate NMR, permethylation studies and direct comparison with respective authentic samples (co-TLC, m.m.p. and superimposable IR)	[34]

* GC-MS (Gas Chromatography coupled to Mass Spectrometry), GC-FID (Gas Chromatography with Flame Ionization Detection), TLC (Thin-Layer Chromatography), HPLC (High-Performance Liquid Chromatography), HR-MS (High-Resolution Mass Spectrometry), NMR (Nuclear Magnetic Resonance).

Importantly, the level of confidence associated with compound identification differs among the analytical approaches used in these studies. Preliminary phytochemical screening provides evidence for broad classes of metabolites rather than unequivocal identification of individual compounds. Likewise, TLC and HPLC provide useful chromatographic evidence, but when used alone they do not necessarily establish an unequivocal structural identification; confidence depends on factors such as comparison with authentic standards and the availability of complementary spectroscopic information. In GC-MS analyses, spectral-library matching is useful for compound annotation, but assignments are more robust when supported by additional criteria such as retention indices and comparison with authentic standards. In contrast, compounds isolated and characterized using complementary spectroscopic approaches, including NMR and mass spectrometry, or directly compared with authentic samples, generally have stronger structural support. This distinction is consistent with established reporting standards for chemical analysis, which emphasize the use of multiple independent and orthogonal analytical criteria for confident metabolite identification [40]. Accordingly, the compounds summarized in Table 1 should be regarded as reported constituents whose level of structural confirmation depends on the analytical evidence provided in each original study.

Overall, the phytochemical evidence is heterogeneous in both analytical confidence and cross-study comparability. Compounds isolated and characterized using complemen-

tary spectroscopic approaches, such as NMR and mass spectrometry, or directly compared with authentic standards have stronger structural support than metabolites inferred from preliminary phytochemical screening or chromatographic annotation alone. Moreover, differences in plant organ, geographic origin, extraction procedure, and analytical workflow make it difficult to determine whether contrasting chemical profiles reflect true biological variation or methodological effects. Therefore, Table 1 should be interpreted as a compilation of reported constituents with different levels of structural confirmation rather than as a directly comparable chemical profile of the species.

4. Experimental Pharmacological Evidence and Its Relevance to Inflammation and Pain

The experimental evidence relevant to the central focus of this review is derived primarily from models of oxidative stress, wound healing, and gastric inflammatory injury. Although these models were not specifically designed to investigate pain, they provide evidence of modulation of inflammatory and redox pathways that may influence nociceptive sensitization. Accordingly, the following sections first examine the antioxidant and anti-inflammatory evidence across these experimental models and subsequently distinguish these findings from the current absence of direct evidence of antinociceptive activity. The main experimental models, extracts, doses, identified compounds, and reported biological effects are summarized in Table 2.

Table 2. Experimental evidence of biological activities reported for *G. sepium*.

Plant Part	Extract	Experimental Model	Dose/Concentration	Route	Main Compounds Identified	Main Results	Reference
Leaves	Ointment	Wound healing (rat)	Daily topical	Topical	Flavonoids, saponins, tannins, and alkaloids	Reduced inflammatory infiltration; decreased IL-1 β and IL-6 expression	[12]
Leaves	Methanolic	antioxidant, antimicrobial, and cytotoxicity assays	100 mg/mL	In vitro	Polyphenols, tannins, kaempferol, isorhamnetin, and fatty acids	Antioxidant or antimicrobial activity and no detectable cytotoxicity under tested conditions	[10]
Stem	Zinc oxide nanoparticles synthesized using ethanolic stem extract	Ethanol-induced gastritis in rats	200 mg/kg	oral	Vanillic acid, apigenin-7-O-glucoside, syringic acid, and p-coumaric acid	Reduced gastric lesions and mucosal injury	[41]
Stem	Ethanolic extract	Pyloric ligation-induced gastritis in rats	200 and 400 mg/kg	oral	Flavonoids, phenolic acids, fatty acid derivatives, and triterpenoid saponins; including kaempferol	Mitigated pyloric ligation-induced gastric tissue injury; reduced ROS, IL-6, TNF- α , and iNOS; increased SOD and I κ B α mechanisms	[11]
Leaves	Ethanolic leaf extract-derived zinc oxide nanoparticles incorporated into PVA hydrogel	STZ-induced diabetic wound-healing model in rats	5% and 10% GSL ZnONPs hydrogel; daily dressing changes for 21 days	Topical	Apigenin-7-O-glucoside, kaempferol, and protocatechuic acid as major compounds; other phenolics/flavonoids also detected	Accelerated diabetic wound healing; enhanced tissue regeneration; reduced apoptosis; modulated inflammation; decreased VCAM-1 and AGE	[11]

For the purposes of this review, the available evidence was interpreted according to its proximity to the biological effect attributed to *G. sepium*. Direct evidence refers to studies

in which *G. sepium* extracts or preparations were themselves evaluated in experimental assays, with in vivo findings considered separately from in vitro activity. Indirect evidence includes effects observed with *G. sepium*-derived formulations, such as nanoparticle systems, or mechanistic endpoints measured in models not specifically designed to assess the claimed pharmacological effect. Circumstantial or inferential evidence refers to pharmacological activities reported for individual metabolites identified in *G. sepium* but investigated independently of this species. This hierarchy is used throughout the following sections to distinguish experimentally demonstrated effects from mechanistic plausibility and to avoid attributing compound- or formulation-specific effects directly to *G. sepium*.

4.1. Antioxidant Activity

Oxidative stress plays a central role in inflammation, tissue injury, and pain sensitization; therefore, antioxidant activity is an important pharmacological dimension when evaluating the therapeutic potential of medicinal plants [42–44]. In *G. sepium*, the antioxidant profile is supported by both phytochemical and functional evidence, particularly the presence of phenolic acids and flavonoids together with measurable effects on redox-related endpoints, including reduced reactive oxygen species levels and increased superoxide dismutase activity in experimental gastric injury [11]. A phytochemical and mass spectrometry imaging study of *G. sepium* leaves showed that methanolic extracts contain polyphenols and tannins, with higher flavonoid content than other tested extracts. Using MALDI-MS and MALDI-MSI approaches, kaempferol, isorhamnetin, and fatty acids were detected on the leaf surface, whereas biological assays indicated antioxidant activity without detectable cytotoxicity under the experimental conditions evaluated. These findings are relevant because flavonoids and polyphenols are widely associated with free-radical scavenging, metal-chelating capacity, and modulation of endogenous antioxidant defense systems [10]. Additional evidence comes from an ethanolic stem extract analyzed by UHPLC-QTOF-MS/MS, in which 23 compounds were dereplicated, including flavonoids, phenolic acids, fatty acid derivatives, and triterpenoid saponins. Among the identified constituents were kaempferol derivatives, isoquercitrin, apigenin derivatives, luteolin, apigenin, liquiritigenin, 4-hydroxycinnamic acid, 2-hydroxyhydrocinnamic acid, soyasaponins, and kaikasaponin III. In a pyloric ligation-induced gastritis model in rats, the extract reduced reactive oxygen species levels and increased superoxide dismutase activity, indicating modulation of oxidative stress in vivo. These findings suggest that *G. sepium* may not only contain antioxidant constituents but may also influence endogenous redox homeostasis under pathological conditions characterized by oxidative injury [11].

Quantitative in vitro studies further support the radical-scavenging capacity of *G. sepium*, although the magnitude of the effect varies according to the plant material and extraction procedure. An ethanolic leaf extract from Philippine specimens showed a DPPH radical-scavenging IC_{50} of 144 $\mu\text{g/mL}$, with inhibition increasing to 81.52% at 300 $\mu\text{g/mL}$ [29]. In a separate study using volatile oils obtained by hydrodistillation from Nigerian specimens, the leaf and stem oils displayed DPPH IC_{50} values of 84.26 and 142.15 $\mu\text{g/mL}$, respectively. For comparison, the positive controls butylated hydroxyanisole (BHA) and α -tocopherol showed IC_{50} values of 45.11 and 81.58 $\mu\text{g/mL}$, respectively [36]. Thus, the leaf volatile oil showed radical-scavenging activity close to, although slightly weaker than, α -tocopherol, whereas both volatile oils were less potent than BHA. These quantitative differences also emphasize that antioxidant activity cannot be generalized across *G. sepium* preparations, because extraction method, plant organ, and chemical composition substantially influence the observed response.

The antioxidant potential of *G. sepium* has also been explored through green synthesis approaches. Zinc oxide nanoparticles synthesized using ethanolic stem extract showed

gastroprotective effects in an ethanol-induced gastritis model, accompanied by histopathological improvement and increased expression of nuclear factor erythroid 2-related factor 2, a key transcriptional regulator of antioxidant responses. Because this model involves nanoparticle-assisted delivery, the findings should not be interpreted as evidence of the crude extract alone. Nevertheless, they suggest that phytochemicals present in *G. sepium*, including vanillic acid, apigenin-7-O-glucoside, syringic acid, and p-coumaric acid, may participate in redox-modulating biological responses [41].

4.2. Anti-Inflammatory Evidence Across Experimental Models

Among the biological effects reported for *G. sepium*, anti-inflammatory activity is one of the most pharmacologically relevant, particularly because several traditional uses of this species involve conditions associated with tissue injury, skin disorders, swelling, and local inflammation. Current evidence indicates that extracts and formulations obtained from leaves and stems can modulate inflammatory cell infiltration, cytokine expression, nitric oxide-related pathways, and histopathological features of tissue damage.

In a rat excisional wound model, topical treatment with ointments containing *G. sepium* leaves collected from Indonesia and the Philippines promoted wound healing and reduced inflammatory parameters. The study reported decreased inflammatory cell infiltration, together with modulation of interleukin-1 β and interleukin-6 expression, two cytokines involved in local inflammatory amplification. Although this study was conducted in a wound-healing model rather than a classical inflammation assay, its findings are relevant because inflammation is a central phase of tissue repair and excessive cytokine production can delay healing. The reported presence of flavonoids, saponins, and tannins in the leaves provides additional pharmacological plausibility for these effects [12].

Further mechanistic support comes from the ethanolic stem extract evaluated in a pyloric ligation-induced gastritis model. In this study, *G. sepium* extract reduced inflammatory cytokines, including IL-6 and TNF- α , decreased inducible nitric oxide synthase expression, and increased I κ B α levels. These effects are relevant because I κ B α negatively regulates NF- κ B activation, a central pathway involved in cytokine production, inflammatory cell recruitment, COX-2 expression, and nitric oxide signaling. The same study also reported histopathological improvement in gastric tissue, with reduced inflammatory infiltration and tissue injury in treated groups. These data suggest that *G. sepium* may attenuate inflammation through coordinated modulation of oxidative stress, cytokine signaling, and NF- κ B-related pathways [11].

Nanotechnology-based formulations provide additional, although indirect, support. Zinc oxide nanoparticles synthesized with ethanolic stem extract showed gastroprotective effects against ethanol-induced gastric injury in rats, accompanied by histopathological improvement and modulation of Nrf2 expression. Because the observed response may reflect the combined contribution of zinc oxide nanoparticles and plant-derived reducing or stabilizing compounds, this evidence should be interpreted as nanoparticle-assisted bioactivity rather than as a direct effect of the crude extract. Even so, the study supports the capacity of *G. sepium*-derived phytochemicals to participate in tissue-protective and inflammation-related responses in vivo [41].

Among the available studies, the ethanolic stem extract provides comparatively stronger direct in vivo evidence because inflammatory cytokines, iNOS, I κ B α , oxidative-stress markers, and histopathological outcomes were evaluated within the same gastric injury model at 200 and 400 mg/kg [11]. However, the evaluation of only two doses limits interpretation of the dose–response relationship. The wound-healing study provides supportive in vivo evidence after topical administration, but it was not designed as a classical inflammation model [12]. In contrast, the nanoparticle-based study provides more indirect

evidence because the contribution of the zinc oxide formulation cannot be separated from that of the plant-derived constituents [41]. Thus, differences in experimental model, route of administration, preparation, dose range, and measured endpoints currently prevent direct quantitative comparisons across studies and limit the ability to define a consistent anti-inflammatory effect or mechanism for *G. sepium*.

4.3. Antinociceptive Potential and Current Evidence Gaps

In contrast to the antioxidant and anti-inflammatory evidence described above, there is currently no direct experimental evidence demonstrating an antinociceptive effect of *G. sepium* in validated behavioral pain assays. Specifically, no studies identified in the literature reviewed here have evaluated *G. sepium* using commonly employed nociceptive tests such as acetic acid-induced writhing, hot plate, tail-flick, or formalin. This distinction is important because anti-inflammatory activity may reduce inflammatory pain when peripheral mediators sensitize nociceptors, but it does not by itself demonstrate intrinsic analgesic or antinociceptive activity. Dedicated behavioral assays are therefore required to determine whether *G. sepium* extracts reduce pain-like responses and to clarify the mechanisms involved.

The available evidence nevertheless provides a rationale for such studies. In experimental injury models, *G. sepium* preparations have been associated with reduced inflammatory infiltration and modulation of cytokine, nitric oxide, and oxidative stress-related endpoints, all of which are relevant to peripheral sensitization. However, because pain-like behavior has not been directly evaluated, these findings should be interpreted only as indirect support for future antinociceptive studies rather than as evidence of analgesic activity [11,12].

Future studies should evaluate *G. sepium* in validated nociceptive models, including the acetic acid-induced writhing test, hot plate, tail-flick, and formalin assays. The formalin test would be particularly informative because it distinguishes between neurogenic and inflammatory phases, allowing assessment of whether the plant preferentially affects inflammatory nociception.

5. Hypothesis-Generating Interpretation of Selected Metabolites Reported in *Gliricidia sepium*

This section is intended as a hypothesis-generating synthesis of selected metabolites reported in *G. sepium*. The biological activities discussed below derive from studies in which these metabolites were evaluated in experimental systems independently of *G. sepium*. Importantly, their detection in this species does not establish that they occur at pharmacologically relevant concentrations, are retained during extraction or preparation, are bioavailable, or contribute meaningfully to the biological activity of the complete extract. Accordingly, these metabolites are discussed only as candidates that may help prioritize future pharmacological and mechanistic investigation, rather than as constituents demonstrated to mediate the biological effects of *G. sepium*.

A causal relationship between the chemical composition of *G. sepium* and its reported pharmacological effects cannot currently be established. A chemical-pharmacological correlation would require the chemical composition and biological activity to be evaluated in the same extracts or fractions, ideally using quantitative profiling to determine whether changes in metabolite abundance are associated with changes in pharmacological response. Subsequent bioassay-guided fractionation and testing of isolated constituents would be necessary to identify compounds directly contributing to the observed effects. Moreover, because plant extracts contain multiple potentially bioactive constituents, their activity may reflect additive, synergistic, or antagonistic interactions rather than the action

of a single metabolite. Such multicomponent effects remain hypothetical for *G. sepium*, however, because systematic fraction-recombination or compound-interaction studies have not yet been reported. Therefore, the metabolite-based discussion below should be interpreted as a hypothesis-generating framework for candidate prioritization and future mechanistic testing, rather than as evidence of causal attribution or species-specific pharmacological activity.

5.1. Volatile Metabolites as Candidates for Pharmacological Investigation

Within the volatile fraction, coumarin is one of the most noteworthy constituents reported in *G. sepium*. This is relevant because coumarins, as a chemical class, have been associated with anti-inflammatory and antioxidant effects. Experimental and mechanistic studies indicate that coumarin derivatives can attenuate inflammatory signaling, including NF- κ B-related pathways, while also supporting antioxidant responses through free-radical scavenging and modulation of redox-sensitive mechanisms [45–47]. Coumarin has been quantitatively detected in the leaf essential oil of Colombian *G. sepium* specimens, where it represented 5.2% of the relative composition [48]. However, coumarin also has a dose- and exposure-dependent toxicological profile, with hepatotoxicity representing its principal safety concern and marked interindividual and interspecies differences in susceptibility [49]. Importantly, coumarin itself should not be conflated with anticoagulant 4-hydroxycoumarin derivatives, such as warfarin, acenocoumarol, and phenprocoumon, whose anticoagulant activity results from vitamin K antagonism [50]. Therefore, the relatively high abundance of coumarin reported in some *G. sepium* volatile preparations reinforces the need for quantitative exposure and safety assessment before pharmacological relevance can be inferred.

Other volatile constituents reported in *G. sepium* can likewise be considered as candidates for future pharmacological evaluation. Thymol was reported at a relative abundance of 3.6% in the leaf essential oil analyzed from Indian specimens [32]. Independent experimental evidence supports its anti-inflammatory and antioxidant activity, with some studies also suggesting analgesic potential [51]. β -Caryophyllene has also been quantitatively reported in *G. sepium* volatile oils, accounting for 1.8% of the stem oil in Nigerian specimens [36]. This relatively low abundance should be considered when interpreting its possible pharmacological relevance. Independently, preclinical studies have shown that β -caryophyllene exerts antinociceptive effects in inflammatory and neuropathic pain models, at least in part through activation of the cannabinoid CB2 receptor [52]. Geraniol was reported at a relative abundance of 0.72% in the flower essential oil [30]. Independently, geraniol has demonstrated anti-inflammatory and antioxidant activity in vivo, including reductions in oxidative injury and inflammatory cytokine levels [53].

A more cautious interpretation is warranted for hydroquinone, which represented 21.64% of the relative composition of the flower essential oil reported by Kaniampady et al. [32]. Although hydroquinone is a phenolic compound and may appear relevant to redox biology, the available literature more strongly associates it with oxidative stress, genotoxicity, cytotoxicity, and tissue injury than with a favorable analgesic or anti-inflammatory profile. For this reason, hydroquinone should not be emphasized as a beneficial bioactive constituent in the same way as coumarin, thymol, β -caryophyllene, or geraniol. Its presence is more appropriately discussed in the toxicological context of the species, or as an example of the fact that medicinal plants may contain both potentially beneficial and potentially harmful metabolites [54,55].

5.2. Non-Volatile Phenolics and Flavonoids

The non-volatile fraction of *G. sepium* includes several phenolic and flavonoid constituents that may be considered as candidates for hypothesis-generating investigation of

inflammation, oxidative stress, and pain-related mechanisms. These include kaempferol derivatives, formononetin, and other phenolic constituents reported in this species. Independent experimental studies have shown that flavonoids can modulate oxidative stress and inflammatory signaling through pathways involving NF- κ B, MAPKs, and endogenous antioxidant defense systems. However, these class-level properties should not be directly attributed to *G. sepium* preparations without experimental validation.

Kaempferol-type compounds are especially relevant because experimental evidence supports their anti-inflammatory and antinociceptive effects in preclinical models, along with antioxidant actions mediated by reactive oxygen species scavenging and enhancement of cellular defense mechanisms. Accordingly, the reported occurrence of kaempferol-related metabolites in *G. sepium* supports their prioritization as candidates for direct testing in chemically characterized extracts, fractions, or isolated-compound studies, but does not establish that they contribute to the biological effects of this species [56,57].

Formononetin represents another candidate metabolite for future investigation. Although formononetin was isolated from the dichloromethane extract of *G. sepium* heartwood, its quantitative abundance was not reported [37]. Independent experimental studies have associated this isoflavone with anti-inflammatory and antioxidant effects, including modulation of cytokine production, attenuation of oxidative injury, and regulation of stress-responsive signaling pathways. However, its occurrence in *G. sepium* should not be taken as evidence that it contributes to the pharmacological activity of *G. sepium* preparations, since its quantitative abundance, retention during extraction, bioavailability, and biological contribution have not been established in this species [58,59].

5.3. Triterpenoids and Diterpenoid-Related Metabolites

Triterpenoids and diterpenoid-related metabolites represent another group of candidates for hypothesis-generating pharmacological investigation. Studies on *G. sepium* have reported triterpene saponins and related constituents, as well as metabolites such as betulinic acid, lupeol derivatives, and phytol. Independent experimental studies have shown that betulinic acid and related triterpenoids can reduce inflammatory mediators, modulate oxidative stress, and exert antinociceptive effects in preclinical models [60]. Similarly, lupeol and lupeol acetate have demonstrated anti-inflammatory activity in both in vivo and in vitro systems, whereas analgesic effects have also been reported for lupeol. These independent observations justify prioritizing these metabolites for future investigation but do not demonstrate their contribution to *G. sepium* activity. It also remains methodologically important not to assume that different lupeol derivatives exert identical biological effects unless they have been directly evaluated [61,62].

Phytol may also be considered a candidate for future investigation. It was reported at a relative abundance of 0.9% in the leaf volatile oil of Nigerian *G. sepium* specimens [36]. Independent preclinical studies have reported antinociceptive, anti-inflammatory, and antioxidant effects of phytol [63]. These activities are potentially relevant to inflammatory pain, in which oxidative and nitrosative stress can contribute to nociceptor sensitization and tissue injury. However, its relatively low abundance in the analyzed volatile oil, together with the absence of quantitative exposure and bioavailability data, precludes attributing any meaningful contribution of phytol to the biological activity of *G. sepium* preparations. A summary of selected metabolites reported in *G. sepium* and their reported biological effects is presented in Table 3.

Table 3. Selected metabolites reported in *Gliricidia sepium* and their independently reported biological activities.

Metabolite	Chemical Class	Reported Abundance in <i>G. sepium</i>	Independently Reported Biological Effects	References
Coumarin	Phenolic (coumarin)	18.2% of leaf essential oil and 43.07% of flower essential oil	Anti-inflammatory, antioxidant	[45–47]
Thymol	Monoterpene	3.6% of leaf essential oil	Anti-inflammatory, antioxidant, potential analgesic	[51]
β -Caryophyllene	Sesquiterpene	1.8% of stem volatile oil	Antinociceptive, anti-inflammatory	[52]
Geraniol	Monoterpene	0.72% of flower essential oil	Antinociceptive, anti-inflammatory, antioxidant	[53]
Hydroquinone	Phenolic compound	21.64% of flower essential oil	Pro-oxidant, cytotoxic	[54,55]
Kaempferol derivatives	Flavonoids	Not reported	Antinociceptive, anti-inflammatory, antioxidant	[56,57]
Formononetin	Isoflavone	Not reported	Anti-inflammatory, antioxidant	[58,59]
Betulinic acid	Triterpene	Not reported	Anti-inflammatory, antinociceptive	[60]
Lupeol/lupeol acetate	Triterpene	Not reported	Anti-inflammatory, analgesic	[61,62]
Phytol	Diterpene	0.9% of leaf volatile oil	Antinociceptive, anti-inflammatory, antioxidant	[63,64]

Note: Quantitative data for individual metabolites were available predominantly from volatile-oil studies and represent relative chromatographic composition rather than absolute concentrations in plant material. For non-volatile metabolites, the cited studies primarily reported identification or isolation without directly comparable quantitative abundance data. NR, quantitative abundance was not reported in the *G. sepium* study cited in this review. The biological activities summarized here were reported for the individual metabolites in experimental systems independent of *G. sepium* and therefore do not establish their contribution to the biological activity of *G. sepium* preparations.

The quantitative evidence also differs substantially among the selected metabolites. Coumarin represented 18.2% and 43.07% of the relative composition of leaf and flower essential oils, respectively, whereas hydroquinone accounted for 21.64% of the flower oil [32]. In contrast, β -caryophyllene (1.8%), geraniol (0.72%), and phytol (0.9%) were reported at comparatively low relative abundances in the specific preparations analyzed [32,36]. For several non-volatile candidates, including kaempferol derivatives, formononetin, betulinic acid, and lupeol derivatives, comparable quantitative abundance data are unavailable. This uneven quantitative evidence indicates that candidate prioritization should not rely on chemical detection alone, but should integrate abundance in the same bioactive preparation, bioavailability, and activity-guided fractionation.

6. Safety Considerations and Toxicological Aspects

Despite increasing interest in the anti-inflammatory, wound-healing, gastroprotective, and pain-related pharmacological potential of *G. sepium*, its safety profile remains insufficiently characterized. This limitation is particularly relevant because *G. sepium* has a documented history of traditional medicinal use, while experimental evidence has also reported larvicidal, ovicidal, and pupicidal activity against mosquito vectors. These findings

indicate that the species contains bioactive constituents with biological effects beyond its ethnomedicinal applications. Therefore, safety should not be assumed solely on the basis of traditional use, and toxicological outcomes may depend on the plant organ, extraction method, preparation, dose, target organism, and route of administration [65].

Available toxicological evidence for *G. sepium* remains limited. In an acute oral toxicity assessment, an ethanolic stem extract did not produce mortality or evident toxicity at 2000 mg/kg in rats, suggesting an oral LD₅₀ greater than 2000 mg/kg [11]. These findings indicate relatively low acute oral toxicity under the specific experimental conditions evaluated, but they do not establish the safety of repeated, prolonged, or systemic exposure.

Additional toxicity-related evidence has been reported using different plant preparations and experimental systems. An early study specifically investigated the reported toxicity of *G. sepium* in rats [66]. Beyond mammalian models, ethanolic leaf extracts showed concentration-dependent toxicity toward *Tetranychus cinnabarinus*, reaching 100% mortality at the highest concentration tested [67]. Toxicologically relevant activity has also been reported for other plant parts and extraction systems; rotenoids isolated from a methanolic bark extract showed toxicity toward *Artemia salina* larvae [68]. In addition, the previously reported larvicidal, ovicidal, and pupicidal effects of *G. sepium* further indicate that some preparations contain constituents capable of producing biological toxicity in non-mammalian organisms [65]. These findings should be interpreted according to the experimental model, since acaricidal, larvicidal, or *Artemia salina* lethality does not constitute evidence of systemic or clinical toxicity. Collectively, the available literature indicates that toxicological outcomes may vary according to the plant part, extraction method, chemical composition, dose, and experimental system.

Topical studies also suggest that preparations containing *G. sepium* leaves may be well tolerated in experimental wound models. In rats, ointments prepared from *G. sepium* leaves improved wound-related parameters and reduced inflammatory cell infiltration and pro-inflammatory marker expression. Nevertheless, these studies were designed primarily to evaluate wound-healing activity rather than formal dermal safety, irritation, sensitization, or systemic absorption. Thus, dedicated dermatological toxicity studies are still required before assuming the safety of topical preparations [12].

The chemical variability of *G. sepium* preparations also has important safety implications. Toxicological findings obtained with one plant organ, solvent system, or extract type cannot necessarily be extrapolated to other preparations. Therefore, future safety studies should include chemical characterization of the tested material to allow a clearer interpretation of toxicological outcomes and to improve reproducibility across studies [9,11,37]. Potential herb–drug interactions also remain unexplored. Although no robust evidence currently demonstrates clinically relevant interactions between *G. sepium* preparations and conventional drugs, the presence of polyphenols, flavonoids, and other bioactive metabolites justifies further investigation. This is particularly important for possible concomitant use with nonsteroidal anti-inflammatory drugs, corticosteroids, antidiabetic agents, anticoagulants, or other medications whose pharmacokinetics or pharmacodynamics may be altered by plant-derived constituents [69–71]. From a translational and regulatory perspective, the absence of standardized extract composition is a major limitation. Variability related to geographic origin, plant organ, harvesting conditions, extraction solvent, and processing method may influence both efficacy and safety. Therefore, future studies should include chemical standardization, batch-to-batch quality control, and toxicological assessment using internationally accepted protocols.

7. Future Directions and Strategic Priorities

Ethnobotanical knowledge provides a valuable starting point for pharmacological research on *G. sepium*, particularly for conditions involving inflammation, skin disorders, tissue injury, and pain-related complaints. However, the transition from traditional use to therapeutic application requires a structured research agenda focused on chemical standardization, direct pharmacological validation, mechanistic clarification, and toxicological assessment. This approach is consistent with the 2023 World Health Organization technical brief on traditional and complementary medicine, which emphasizes evidence-informed, safe, regulated, and context-sensitive integration into health systems [72].

Although *G. sepium* has relevant ethnobotanical support and an increasingly documented phytochemical profile, its pharmacological development still requires more rigorous and targeted studies. Future research should prioritize the chemical standardization of extracts and fractions, since differences in plant organ, geographic origin, harvest conditions, extraction solvent, and analytical method may substantially influence both biological activity and safety. A key gap is the current absence of direct evidence of antinociceptive activity. Most current interpretations related to pain are based on anti-inflammatory, antioxidant, wound-healing, or tissue-protective effects rather than on validated pain models. Therefore, future studies should evaluate *G. sepium* preparations in established nociceptive assays, particularly the formalin test, which would allow differentiation between neurogenic and inflammatory pain components. These studies should be complemented with mechanistic endpoints related to inflammatory mediators, oxidative stress, and nociceptive sensitization.

Another priority is the identification of the metabolites or fractions responsible for the reported biological effects. Most available studies have used crude extracts, making it difficult to establish clear relationships between specific compounds and pharmacological activity. Bioassay-guided fractionation, isolation of active constituents, and evaluation of standardized preparations would provide stronger evidence for the therapeutic relevance of this species. Future studies should also integrate quantitative chemical profiling with pharmacological assays performed on the same extracts and fractions to establish chemical–pharmacological correlations. Once active constituents are identified, fraction-recombination and compound-combination experiments could determine whether the observed activity results from individual compounds or from additive, synergistic, or antagonistic interactions among multiple constituents. Finally, safety assessment remains essential. Current toxicological information is still insufficient to support prolonged, repeated, systemic, or clinical use. Future studies should include subacute and subchronic toxicity, dermal safety for topical preparations, genotoxicity when appropriate, and potential herb–drug interactions. These approaches would help determine whether *G. sepium* can progress from traditional use and preliminary experimental evidence toward safer and more clearly defined therapeutic applications.

8. Conclusions

Gliricidia sepium is an ethnobotanically relevant species with a diverse phytochemical profile and experimental evidence supporting antioxidant, anti-inflammatory, wound-healing, gastroprotective, and tissue-protective effects. These findings provide a plausible biological basis for some of its traditional uses, particularly those related to inflammation, skin disorders, and tissue injury. However, because direct evidence of antinociceptive activity is currently lacking, its role in pain-related conditions should be considered mechanistically plausible but not yet demonstrated. Although *G. sepium* represents a potentially valuable source of bioactive metabolites for pharmacological research, the current evidence is limited by the small number of standardized in vivo studies and the absence of direct

clinical and antinociceptive evidence. Further investigation is therefore required to establish its efficacy, mechanisms of action, safety, and reproducibility. Practical translation will also require addressing challenges related to the standardization and scalable production of chemically consistent preparations. Variability in phytochemical composition among plant organs, geographic origins, and extraction procedures may affect extraction yield, the abundance of potentially active constituents, and batch-to-batch reproducibility. Moreover, the feasibility of large-scale extraction and purification, solvent and processing requirements, raw-material supply, and quality-control procedures should be evaluated before the development of standardized pharmaceutical or phytopharmaceutical products can be considered.

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