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***Syzygium cumini* and *Syzygium aromaticum*: A Comprehensive Review of Traditional Uses, *In Vitro* and *In Vivo* Activities, and Advances in Pharmaceutical Formulations**

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Abstract

Syzygium cumini (Java plum) and *Syzygium aromaticum* (clove) are two species of the genus *Syzygium* (Myrtaceae), comprising 1200–1800 species. Both hold significant ethnopharmacological importance in traditional medicine systems across Asia, Africa, and Oceania. This comprehensive review updates the current knowledge on the traditional uses and pharmacological activities of *S. cumini* and *S. aromaticum*, with additional references to other *Syzygium* species (*S. aqueum*, *S. malaccense*, and *S. samarangense*) where relevant data exist. The review integrates information from *in vitro* and *in vivo* experiments, clinical trials, and formulation developments (2013-2026). The identified pharmacological properties are comprehensive, encompassing antioxidant, antibacterial, anti-inflammatory, cytotoxic, antidiabetic, anticholinesterase, and antiparasitic effects. These bioactivities are attributed to a diverse array of phytochemicals, such as flavonoids, phenolic acids, tannins, and essential oil components like eugenol. Recent advances in nanoencapsulation and biopolymer-based formulations have shown promising physicochemical properties and biological activity, supporting further investigation for wound healing and inflammatory conditions; however, enhanced bioavailability remains to be established. This review highlights *S. cumini* and *S. aromaticum* as a vital reservoir of bioactive compounds for evidence-based phytotherapy and underscores the need for further clinical research to translate these findings into effective therapeutic strategies.

Keywords: *Syzygium cumini*; *Syzygium aromaticum*; eugenol; antidiabetic activity; anti-inflammatory activity; antimicrobial activity; nanoencapsulation

1. Introduction

The genus *Syzygium* (Myrtaceae), comprising 1200–1800 species, holds significant ethnopharmacological importance, particularly in Asian traditional medicines of China, India,

and Bangladesh. Among the most extensively studied species are *S. aromaticum* (clove) and *S. cumini* (Java plum), which have been used to treat digestive disorders, diabetes, infections, inflammation, wounds, and respiratory problems ¹. Rich in bioactive phytochemicals such as flavonoids, phenolics, tannins, and volatile oil these plants exhibit validated pharmacological activities including antioxidant, antimicrobial, antidiabetic, anti-inflammatory, and emerging anticancer effects ². Prominent examples include *S. aromaticum*, whose flower buds are used as an aromatic stomachic, analgesic, and antiseptic, and *S. cumini*, where different parts of the plant—fruit, leaves, and bark—are utilized to manage conditions such as diabetes, diarrhea, dysentery, and inflammation. The therapeutic applications of these species are largely attributed to their rich reservoir of bioactive phytochemicals, including flavonoids, phenolic acids, tannins, and volatile terpenes ²⁻⁴.

Modern pharmacological research has begun to validate these traditional uses, revealing a broad spectrum of biological activities for *Syzygium* species. These activities include potent antioxidant, antimicrobial, anti-inflammatory, antidiabetic, and even emerging anticancer effects, as demonstrated in *in vitro* and *in vivo* studies. The growing body of scientific evidence points to the potential of these tropical plants as sources for developing new, evidence-based therapies. This review provides a comprehensive and updated overview of the current knowledge on *S. cumini* and *S. aromaticum*, with selected references to other *Syzygium* species where relevant, integrating information on their ethnopharmacological applications, chemical constituents, and the extensive range of pharmacological studies. This review primarily synthesizes literature published between 2013 and 2026. However, where foundational studies as Teixeira et al., 2006 or recently published cutting-edge research such as El-Fakharany et al., 2026, provide essential findings, they have been included to ensure comprehensive coverage. A literature search was performed in PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Google Scholar. The search criteria included combinations of species names and synonyms with activity and phytochemical keywords (antioxidant, antibacterial, anti-inflammatory, cytotoxic, antidiabetic, anticholinesterase, leishmanicidal, trypanocidal, formulation, nanoencapsulation, clinical trial, eugenol, flavonoid, anthocyanin). Also, reference lists of retrieved papers were hand-searched. Inclusion criteria were original *in vitro*, *in vivo*, formulation or clinical research; quantifiable biological or clinical data; peer-reviewed articles in English language. Exclusion criteria were conference abstracts, theses, non-peer reviewed literature, duplicates and works with insufficient methodological description. Other *Syzygium* species (*S. aqueum*, *S. malaccense*, *S. samarangense*) were included only when they gave comparative or mechanistic insights relevant to the two species.

Although the ethnopharmacology and pharmacological activities of the genus *Syzygium* have been systematically summarized in existing reviews, translational advances in formulation technology have not been adequately integrated, and the influence of plant part, formulation type and degree of standardization on clinical outcomes has not been critically analyzed. In this review, we fill this gap by: (1) comparatively evaluating research on nanoencapsulation and biopolymer carriers based on the type of formulation approach; and (2) analyzing the heterogeneous sources of clinical data for *S. cumini* and *S. aromaticum* according to plant part and level of standardization.

2. Traditional uses and ethnopharmacology

Syzygium species, including prominent ones like *Syzygium aromaticum* (L) Merr. & Perry, commonly known as clove and *Syzygium cumini* (L.) Skeels, commonly known as Java plum, have been integral to traditional medicine across Asia, Africa, and Oceania for treating ailments such as diarrhea, inflammation, diabetes, and infections ¹. *Syzygium aromaticum* utilizes the flower bud as a medicinal part, which serves as an aromatic stomachic, anti-inflammatory agent, deodorant, and disinfectant ⁵, and is traditionally employed to alleviate toothache, gum inflammation, coughs, colds, neuralgic pain, and rheumatism ⁶. Also, *Syzygium cumini* is utilized across multiple parts: the fruit is employed for cough, diabetes, dysentery, inflammation, ringworm, and gastrointestinal complaints; the leaf used in managing diabetes, diarrhea, leucorrhea, and stomach pains; and the stem bark is indicated for bleeding gums, venereal ulcers, dysentery, and fresh wounds ^{2,6}. Another species *S. aqueum*, the leaves are used as an antibiotic and for alleviating childbirth pain ⁷. The therapeutic applications are attributed to bioactive phenolic compounds such as eugenol, flavonoids, and tannins, which support the antimicrobial, antioxidant, and analgesic properties ².

3. *In vitro* activities of selected *Syzygium* species

Plant-based products, such as essential oils, isolated compounds or plant extracts, are reported for a wide range of biological activities, including but not limited to antioxidants, anti-inflammatory, cytotoxic, antimicrobial and antidiabetic activities ^{8–10}. The genus *Syzygium* serves as a vital reservoir of diverse species exhibiting significant biological activities, particularly demonstrated by *S. aromaticum* and *S. cumini* (**Figures 1 & 2**).

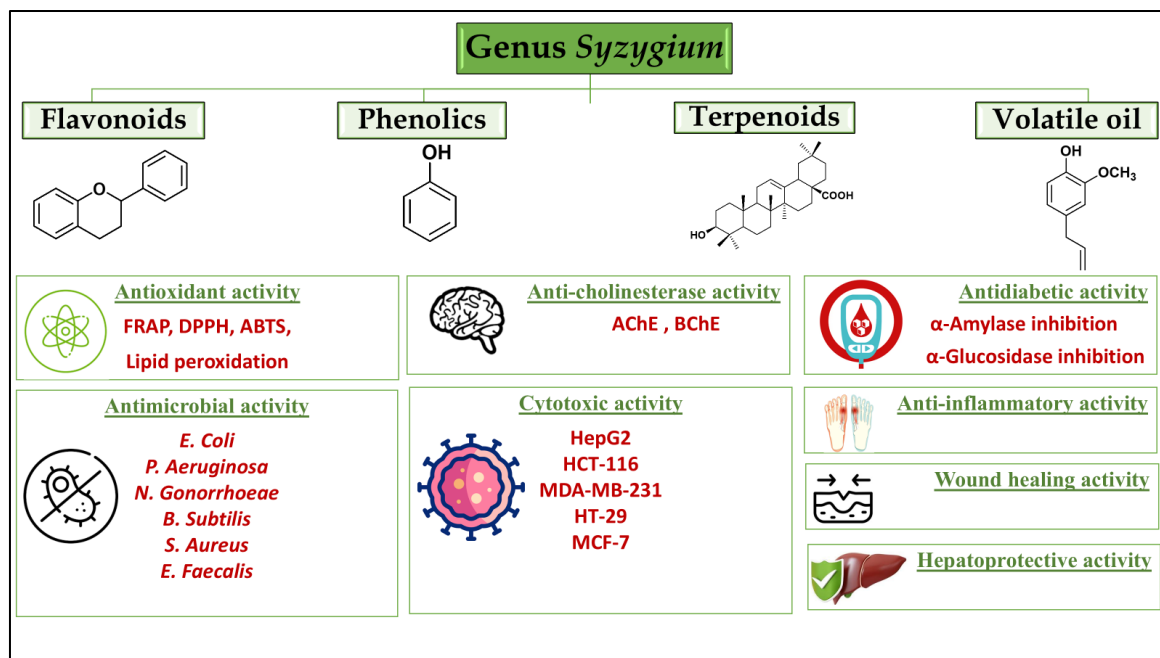


Figure 1. Schematic representation of the various biological activities of the genus *Syzygium*

3.1. Antioxidant activity

Leaves of *Syzygium cumini*, revealed high antioxidant activity with ferric reducing ability (FRAP) equal to $13.14 \pm 0.11 \mu\text{g/g}$ for the methanol extract followed by the methylene chloride extract ($1.22 \pm 0.08 \mu\text{g/g}$) and then the essential oils ($0.47 \pm 0.05 \mu\text{g} / 100 \text{ mg}$ essential oil). Also, the methanol extract showed the highest 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity 70.45% at a concentration of $50 \mu\text{g/mL}$. The promising antioxidant activity of the methanol extract of leaves of *S. cumini* would be attributed to the high total phenolic content $14.03 \pm 0.55 \text{ mg/g}$ and high total flavonoid content $6.22 \pm 0.11 \text{ mg/g}$ as compared to the other extracts ¹¹. Another study on essential oil of leaves of *S. cumini* native to Pakistan revealed its DPPH radical scavenging activity with an IC_{50} value of $1.2 \pm 0.20 \text{ mg/mL}$ as compared to Butylated hydroxyanisole (BHA) as positive control ($\text{IC}_{50} = 0.011 \pm 0.001 \text{ mg/mL}$). Also, the essential oil showed inhibition of linoleic acid peroxidation $72.7 \pm 1.3 \%$ as compared to BHA $91.2 \pm 2.6\%$ ¹². The polyphenols in the ethanol extract of fruits of *S. cumini* (Jambolan) were investigated for the antioxidant activity using DPPH, ABTS and FRAP assays. The results revealed that the jambolan polyphenols showed prominent antioxidant activity with DPPH free radical, ABTS radical scavenging activities and FRAP 6.7 ± 0.2 , 8.2 ± 0.2 and $7.5 \pm 0.4 \text{ mM TE/g}$, respectively as compared to different polyphenol standards as gallic acid, quercetin, caffeic acid, sinapic acid and delphinidin chloride. Where gallic acid and quercetin showed higher antioxidant activities (DPPH and ABTS) than others. Gallic acid showed 210.6 ± 0.4 , 10.3 ± 0.6 and $9.5 \pm 0.2 \text{ mM TE/g}$ for DPPH, ABTS and FRAP assays, respectively. and quercetin 10.4 ± 0.3 , 10.9 ± 0.2 and $7.6 \pm 0.1 \text{ mM TE/g}$ for DPPH, ABTS and FRAP assays, respectively ¹³. Moreover, three anthocyanins di-glucosides from *S. cumini*

(SC) were isolated, namely delphinidin 3,5-diglucoside (DDG), petunidin 3,5-diglucoside (PDG), and malvidin 3,5-diglucoside (MDG). The DPPH free radicals scavenging ability of MDG was the most significant as compared to Vitamin C at concentrations of 20 to 60 $\mu\text{g/mL}$. Regarding the ABTS radical scavenging assay, Vitamin C, MDG, DDG and PDG showed ABTS inhibition by 97.57%, 96.63%, 94.68% and 93.87% respectively at concentration of 50 $\mu\text{g/mL}$ ¹⁴. The ethanolic extract of *S. cumini* leaves was investigated for DPPH free radicals scavenging ability and inhibition of the lipid peroxidation. In DPPH assay, the ethanolic extract showed IC_{50} value of 82.8 $\mu\text{g/mL}$ as compared to rutin as positive control at concentration of 25 $\mu\text{g/mL}$ exhibited DPPH scavenging activity of 56.78%. And it showed IC_{50} of 1.27 $\mu\text{g/mL}$ in the lipoperoxidation test ¹⁵. The aqueous extract of the waste *S. cumini* seed kernel's showed DPPH scavenging activity with an IC_{50} value of 12.97 $\mu\text{g/mL}$ as compared to gallic acid IC_{50} value of 5.9 $\mu\text{g/mL}$ ¹⁶.

The 100% methanolic extract, 50% methanolic extract and the 100% DCM (dichloromethane) extracts of *S. cumini* exhibited DPPH scavenging activity with IC_{50} values varied from 220 $\mu\text{g/mL}$ to 81 $\mu\text{g/mL}$. where the 100% methanolic extract showed the most promising activity with an IC_{50} value of 81 $\mu\text{g/mL}$ as compared to ascorbic acid, and quercetin had IC_{50} values of 75 and 68 $\mu\text{g/mL}$, respectively. Also, in the FRAP assay the 100% methanolic extract showed the most promising reducing power (46 mmol Fe/g) ¹⁷. Teles et al. reported that eugenol (53.23%) is the major compound of the essential oil of *S. aromaticum* floral buds. Both the essential oil and eugenol showed a concentration-dependent antioxidant activity by inhibition of the (2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt) (ABTS) radical with IC_{50} values of 78.98 and 12.66 $\mu\text{g/mL}$, respectively ¹⁸. Antioxidant effectiveness of *S. aromaticum* essential oil, eugenol, eugenol benzoate, eugenol acetate were estimated by DPPH and nitric oxide (NO) free radical scavenging assays. The essential oil was the most promising as it showed 91.80 and 91.20 % inhibition at 35 and 60 $\mu\text{g/mL}$, respectively and IC_{50} values of 10.87 and 31.63 $\mu\text{g/mL}$ in DPPH and NO free radical scavenging assays, respectively. Followed by eugenol that exhibited 88.69 and 89.54 % free radical scavenging at the same concentration in DPPH and NO assays, respectively and IC_{50} values of 14.7 and 35.45 $\mu\text{g/mL}$ in DPPH and NO assays, respectively ¹⁹. Another study by Selles et al. investigated the antioxidant activity of the essential oil of the flower buds of *S. aromaticum* using the DPPH radical scavenging assay and reducing power. The results revealed that the oil has an IC_{50} value of $4.82 \pm 0.06 \times 10^{-2} \mu\text{g/mL}$, and the reducing power assay resulted in an EC_{50} value of $3.47 \pm 0.2 \times 10^{-2} \mu\text{g/mL}$, as compared to ascorbic acid as reference drug $\text{IC}_{50} = 6.19 \pm 0.97 \mu\text{g/mL}$ and $\text{EC}_{50} = 13.98 \pm 1.99 \mu\text{g/mL}$. The promising antioxidant activity of the essential oil of flower buds of *S. aromaticum* would be attributed to

the high percentage of eugenol as a major compound (78.72%) followed by β -caryophyllene (8.82%) and eugenyl acetate (8.74%)²⁰ (**Table 1**).

Examination of the antioxidant data among *Syzygium* species reveals several important patterns. First, polar extracts (methanol, ethanol, aqueous) regularly significantly outperform non-polar extracts (DCM, hexane) and essential oils in the FRAP and DPPH assays, except for *S. aromaticum* essential oil, which exhibits remarkable DPPH scavenging owing to its elevated eugenol concentration. This indicates that the antioxidant potential of *Syzygium* species is primarily attributable to polar phenolic compounds rather than terpenoids, with eugenol being a notable exception.

A secondary pattern arises with structure-activity correlations. Eugenol exhibits notable efficacy among isolated compounds ($IC_{50} = 12\text{--}15\ \mu\text{g/mL}$), whilst anthocyanins, particularly malvidin 3,5-diglucoside, have activity comparable to that of Vitamin C. These results indicate that many classes of phytochemicals enhance the total antioxidant potential of *Syzygium* extracts, and that the interaction between compounds may play a crucial role, as crude extracts frequently exhibit activity that is equal to or surpasses that of individual isolated compounds. It is important to recognize that cell-free antioxidant assays do not demonstrate antioxidant effectiveness in biological contexts and must be supplemented by cellular redox, target engagement, and in vivo oxidative stress outcomes.

Table 1. Summary of Antioxidant Activities of *S. cumini* and *S. aromaticum*

Species	Plant Part	Extract/Compound	Assay	Activity Value	Key Finding	Reference
<i>S. cumini</i>	Leaves	Methanol extract	FRAP	13.14 ± 0.11 µg/g	Most promising among tested extracts	11
		DCM extract	FRAP	1.22 ± 0.08 µg/g	Lower activity than methanol extract	
		Essential oil	FRAP	0.47 ± 0.05 µg/100 mg	Weakest reducing ability	
		Methanol extract	DPPH	70.45% at 50 µg/mL	High scavenging activity	12
		Essential oil	DPPH IC ₅₀	1.2 ± 0.20 mg/mL BHA (IC ₅₀ = 0.011 ± 0.001 mg/mL)	Lower activity than BHA	
			Lipid peroxidation	72.7 ± 1.3% inhibition BHA (91.2 ± 2.6%)	Moderate inhibition	13
	Fruit	Ethanol extract (polyphenols)	DPPH	6.7 ± 0.2 mM TE/g Gallic acid (210.6 ± 0.4 mM TE/g)	Lower than individual standards	
			ABTS	8.2 ± 0.2 mM TE/g Gallic acid (10.3 ± 0.6 mM TE/g)	Comparable to gallic acid	
			FRAP	7.5 ± 0.4 mM TE/g Gallic acid (9.5 ± 0.2 mM TE/g)	Moderate reducing power	
	Fruit	Delphinidin 3,5-diglucoside	ABTS	94.68% at 50 µg/mL Vitamin C (97.57%)	Comparable to Vitamin C	14
		Petunidin 3,5-diglucoside	ABTS	93.87% at 50 µg/mL	Slightly lower than Vitamin C	

		Malvidin 3,5-diglucoside	ABTS	96.63% at 50 $\mu\text{g/mL}$	Most promising anthocyanin	
	Leaves	Ethanollic extract	DPPH IC ₅₀	82.8 $\mu\text{g/mL}$ Rutin (56.78% at 25 $\mu\text{g/mL}$)	Moderate activity	15
			Lipid peroxidation IC ₅₀	1.27 $\mu\text{g/mL}$	Promising inhibition	
	Seed	Aqueous extract	DPPH IC ₅₀	12.97 $\mu\text{g/mL}$ Gallic acid (5.9 $\mu\text{g/mL}$)	Promising activity	16
	Fruit	100% Methanol extract	DPPH IC ₅₀	81 $\mu\text{g/mL}$ Ascorbic acid (75 $\mu\text{g/mL}$); Quercetin (68 $\mu\text{g/mL}$)	Comparable to standards	17
			FRAP	46 mmol Fe/g	Most promising reducing power	
	<i>S. aromaticum</i>	Essential oil (53.23% eugenol)	ABTS IC ₅₀	78.98 $\mu\text{g/mL}$	Moderate activity	18
		Eugenol	ABTS IC ₅₀	12.66 $\mu\text{g/mL}$	Superior to essential oil	
		Essential oil	DPPH	91.80% at 35 $\mu\text{g/mL}$	Promising activity	19
			DPPH IC ₅₀	10.87 $\mu\text{g/mL}$	High potency	
			NO scavenging IC ₅₀	31.63 $\mu\text{g/mL}$	Moderate activity	
		Eugenol	DPPH IC ₅₀	14.7 $\mu\text{g/mL}$	Comparable to essential oil	
			NO scavenging IC ₅₀	35.45 $\mu\text{g/mL}$	Comparable to essential oil	
		Essential oil	DPPH IC ₅₀	4.82 $\pm$ 0.06 $\times 10^{-2}$ $\mu\text{g/mL}$ Ascorbic acid (6.19 $\pm$ 0.97 $\mu\text{g/mL}$)	Superior to ascorbic acid	20
		Essential oil	Reducing power EC ₅₀	3.47 $\pm$ 0.2 $\times 10^{-2}$ $\mu\text{g/mL}$	Superior to ascorbic acid	

				Ascorbic acid (13.98 ± 1.99 μg/mL)		
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DCM = Dichloromethane; DPPH = 2,2-diphenyl-1-picrylhydrazyl; ABTS = 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); FRAP = Ferric Reducing Ability; TE = Trolox Equivalents; BHA = Butylated Hydroxyanisole; NO = Nitric Oxide

3.2. Antimicrobial activity

Leaves of *S. cumini* were investigated for their antimicrobial activity using the disc diffusion method. The methanol extract showed the maximum inhibition zones ranged from 18 to 24 mm towards the different tested bacteria; *Escherichia coli*, *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, *Bacillus subtilis*, *Staphylococcus aureus* and *Enterococcus faecalis* at a concentration of 20 mg/mL, as compared to the Tetracycline reference drug 20 mg/mL with inhibition zones ranging from (30-34 mm) ¹¹. Essential oil of leaves of *S. cumini* native to Pakistan was investigated for its antimicrobial activity using the Disc Diffusion Method and Micro-dilution Broth Susceptibility Assay for MIC determination. The results revealed the highest inhibition zone diameter (IZD) against *Streptococcus pyogenes* and *Bacillus subtilis*, 29.5 ± 1.5 mm and 25.0 ± 1.3 mm, respectively. And MIC values of 1.1 ± 0.6 and 1.3 ± 0.4 mg/mL, respectively. ciprofloxacin used as a reference drug with IZD= 41.5 ± 2.1 and 28.0 ± 1.4 mm and MIC = 12.5 ± 0.6 and 15.7 ± 0.8 μ g/mL, respectively. Regarding the antifungal activity, the essential oil of the leaves of *S. cumini* showed promising activity against *Aspergillus flavus* with IZD= 23.0 mm and MIC = 0.083 mg/mL as compared to Fluconazole as reference drug with IZD= 28.6 ± 1.3 mm and MIC = 80.6 ± 1.2 μ g/mL ¹². Polyphenol extract of Jambolan fruit displayed a broad-spectrum antimicrobial activity against *S. aureus*, MRSA, *E. coli*, *K. pneumoniae*, and *C. albicans* with IZD equal to 23.0 ± 1.2 , 16.0 ± 1.2 , 16.7 ± 0.7 , 15.3 ± 0.6 and 14.3 ± 0.3 mm, respectively. And MIC values in the range of 0.5 to 2.5 mg/ml as compared to standard polyphenols as gallic acid, quercetin, caffeic acid, sinapic acid and delphinidin chloride, that recorded the same MIC range ¹³. By the disk diffusion test, both the *S. aromaticum* essential oil and its major compound eugenol were investigated for their antimicrobial activity against Gram-positive and Gram-negative bacteria (*S. aureus*, *E. coli* and *P. aeruginosa*). The results revealed that the *S. aromaticum* essential oil and eugenol exhibited the highest IZD equals to 25.00 ± 1.000 and 22.33 ± 0.577 mm, respectively against *S. aureus* bacteria, as compared to the gentamycin IZD value 20.33 ± 0.577 mm as a reference drug. The MIC of *S. aromaticum* essential oil 50.0 ± 0.00 μ g/mL against *S. aureus*, indicating a significant antibacterial activity than eugenol (MIC 250 μ g/mL) as compared to gentamycin MIC value 8.00 ± 0.00 μ g/mL ¹⁸. The essential oil of the floral buds of *S. aromaticum* showed concentration-dependent inhibition of growth of vaginal isolates of *Candida albicans* using the agar disc diffusion assay as compared to the positive control, Fluconazole. The MIC and Minimum Fungicidal Concentration (MFC) values were 1.25 μ l/mL and 2.5 μ l/mL, respectively, for all tested isolates ²¹.

Another study by Kaur et al. investigated the antifungal activity of the essential oil of the floral buds of *S. aromaticum*, its major compound eugenol and its derivatives eugenol acetate and eugenol benzoate against three fungi (*Fusarium moniliforme*, *Helminthosporium oryzae* and *Rhizoctonia solani*) using the poison food technique. The results revealed that eugenol benzoate was the most promising against *F. moniliforme* and *H. oryzae* with an EC₅₀ value of 10.17 and 5.3 µg/mL, respectively. Eugenol acetate, eugenol, and clove essential oil showed ED₅₀ values of 10.6, 11.72 and 25.56 µg/mL, respectively, against *F. moniliforme*. Eugenol acetate was most effective against *R. solani* with an ED₅₀ value of 11.76 µg/mL as compared to Bavistin as the reference drug ¹⁹. The antimicrobial activity of the essential oil of flower buds of *S. aromaticum* was investigated by the broth microdilution method towards six enteropathogen bacteria, namely, *Serratia* sp., *Salmonella* sp., *Kluyvera* sp., *Klebsiella* sp., *E. coli* F5 and *E. coli* CS31A isolated from diarrhea of neonatal calves. The results revealed that the essential oil showed MIC values ranging from 1.36 mg/mL to 2.72 mg/mL and MMC values from 5.45 mg/mL to 10.9 mg/mL against all tested bacteria. The efficacy of the essential oil would be attributed to the major compound in the oil, eugenol, which affects bacteria *via* altering the cell membrane, impacting ion and ATP transport, and changing the fatty acid composition of some bacteria ²⁰. Moemenbellah-Fard et al. reported the antibacterial activities of the total essential oil of flower buds of *S. aromaticum* and its major component eugenol (65.41%). The IC₅₀ values of the essential oil were 177.66, 300.53, 362.94, and 248.08 µg/mL against *Staph. aureus*, *E. coli*, *P. aeruginosa*, and *K. pneumoniae*, respectively. Eugenol showed lower activity than oil with IC₅₀ values of 320.80, 692.91, 591.82, and 445.87 µg/mL, respectively ²² (Table 2).

Several observations emerge from the antibacterial data, though direct ranking across studies is limited by differences in assay methods, tested organisms, extraction procedures, and exposure conditions. *S. aromaticum* essential oil and *S. cumini* extracts were tested against different bacterial panels using different methods, preventing direct potency comparison; the high eugenol content of *S. aromaticum* oil (up to 78%) is consistent with its observed activity, but extracts of *S. cumini* also showed meaningful inhibition zones (18–24 mm at 20 mg/mL) against a comparable range of organisms ^{11, 18}. Within studies that tested both Gram-positive and Gram-negative bacteria under identical conditions, Gram-positive organisms (*S. aureus*, *B. subtilis*) tended to show greater susceptibility than Gram-negative organisms (*E. coli*, *P. aeruginosa*) ^{11,12,18}, consistent with the protective outer membrane of Gram-negative species; however, this pattern was not universal across all studies.

Table 2. Summary of Antimicrobial Activities of *S. cumini* and *S. aromaticum*

Species	Plant Part	Extract/Compound	Target Organism	Assay	Activity	Positive Control	Reference
<i>S. cumini</i>	Leaves	Methanol extract	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>N. gonorrhoeae</i> , <i>B. subtilis</i> , <i>S. aureus</i> , <i>E. faecalis</i>	Disc diffusion	IZD= 18–24 mm at 20 mg/mL	Tetracycline (IZD= 30–34 mm at 20 mg/mL)	11
		Essential oil	<i>S. pyogenes</i>	Disc diffusion	IZD= 29.5 ± 1.5 mm	Ciprofloxacin (IZD= 41.5 ± 2.1 mm)	12
			<i>B. subtilis</i>		IZD=25.0 ± 1.3 mm	Ciprofloxacin (IZD= 28.0 ± 1.4 mm)	
			<i>S. pyogenes</i>	MIC	1.1 ± 0.6 mg/mL	Ciprofloxacin (12.5 ± 0.6 µg/mL)	
			<i>B. subtilis</i>		1.3 ± 0.4 mg/mL	Ciprofloxacin (15.7 ± 0.8 µg/mL)	
			<i>A. flavus</i>	Disc diffusion	IZD=23.0 mm	Fluconazole (IZD= 28.6 ± 1.3 mm)	
				MIC	0.083 mg/mL	Fluconazole (80.6 ± 1.2 µg/mL)	
		Fruit	Polyphenol extract	<i>S. aureus</i>	Disc diffusion	IZD= 23.0 ± 1.2 mm	N/A
	Polyphenol extract		MRSA	IZD= 16.0 ± 1.2 mm			
	Polyphenol extract		<i>E. coli</i>	IZD= 16.7 ± 0.7 mm			
	Polyphenol extract		<i>C. albicans</i>	IZD= 14.3 ± 0.3 mm			
	Polyphenol extract		<i>K. pneumoniae</i>	IZD= 15.3 ± 0.6 mm			
	Polyphenol extract		Various bacteria	MIC	0.5–2.5 mg/mL		
	<i>S. aromaticum</i>	Flower buds	Essential oil	<i>S. aureus</i>	Disc diffusion	IZD= 25.00 ± 1.000 mm	Gentamicin (IZD= 20.33 ± 0.577 mm)
Eugenol			IZD= 22.33 ± 0.577 mm				
Essential oil			MIC	50.0 ± 0.00 µg/mL	Gentamicin (8.00 ±		

						0.00 $\mu\text{g/mL}$)	
		Eugenol			250 $\mu\text{g/mL}$	Gentamici n (8.00 $\pm$ 0.00 $\mu\text{g/mL}$)	
		Essential oil	<i>C. albicans</i> (vag inal isolates)	MIC	1.25 $\mu\text{L/mL}$	Fluconazol e	21
		Essential oil		MFC	2.5 $\mu\text{L/mL}$		
		Essential oil			ED ₅₀ : 25.56 $\mu\text{g/mL}$		
		Eugenol	<i>F. moniliforme</i>	Poison food technique	ED ₅₀ : 11.72 $\mu\text{g/mL}$	Bavistin	19
		Eugenol benzoate			ED ₅₀ : 10.17 $\mu\text{g/mL}$		
		Essential oil	Enteropathog ens	Broth microdilut ion	MIC: 1.36–2.72 mg/mL		20
		Essential oil			177.66 $\mu\text{g/mL}$		
		Eugenol	<i>S. aureus</i>		320.80 $\mu\text{g/mL}$		
		Essential oil			300.53 $\mu\text{g/mL}$		
		Eugenol	<i>E. coli</i>		692.91 $\mu\text{g/mL}$	N/A	
		Essential oil		IC ₅₀	362.94 $\mu\text{g/mL}$		
		Eugenol	<i>P. aeruginosa</i>		591.82 $\mu\text{g/mL}$		
		Essential oil			248.08 $\mu\text{g/mL}$		
		Eugenol	<i>K. pneumoniae</i>		445.87 $\mu\text{g/mL}$		22

IZD== Inhibition Zone Diameter; MIC = Minimum Inhibitory Concentration; MFC = Minimum Fungicidal Concentration; MRSA = Methicillin-Resistant *Staphylococcus aureus*

3.3. Anti-inflammatory activity

The anti-inflammatory activities of the 100% methanolic extract, 50% methanolic extract and the 100% DCM of *S. cumini* fruit were evaluated for their anti-inflammatory activities by different assays. In the heat-induced haemolysis assay, the 100% methanolic extract showed 67.3% inhibition and the 50% methanolic extract showed 48.9% inhibition at 300 µg/mL, compared with diclofenac sodium (97.7% inhibition at the same concentration). In the BSA denaturation assay, the 100% methanolic extract showed 82% inhibition at 300 µg/mL, compared with diclofenac sodium (98% inhibition) ¹⁷. The findings indicate that *S. cumini* fruit extracts possess measurable anti-inflammatory activity in these specific assay systems (Table 3).

Table 3. Summary of Anti-inflammatory Activities of *S. cumini* and *S. aqueum*

Species	Plant Part	Extract/Compound	Assay	Activity	Positive Control	Key Finding	Reference
<i>S. cumini</i>	Fruit	100% Methanol extract	Heat-induced hemolysis	67.3% inhibition at 300 µg/mL	Diclofenac sodium (97.7%)	Moderate activity	17
		50% Methanol extract		48.9% inhibition at 300 µg/mL		Lower activity	
		100% Methanol extract	BSA denaturation	82% inhibition at 300 µg/mL	Diclofenac sodium (98%)	Promising activity	

BSA = Bovine Serum Albumin

3.4. Cytotoxic activity

Essential oil isolated from leaves of *S. cumini* exhibited a moderate cytotoxic activity towards human liver cancer cells (HepG2) with an IC₅₀ value of 38.15 ± 2.09 µg/mL as compared to a reference drug, staurosporine, with an IC₅₀ value of 8.637 ± 0.47 µg/mL. ²³. Elhawary et al. reported the cytotoxicity of different parts extracts of *S. cumini* (Leaf, seed, fruit, flower) against human breast cancer cell line (MDA-MB-231) and the colon cancer cell line (HCT -116), compared to the reference drug doxorubicin. The results revealed that seed and leaf extracts showed the most promising cytotoxicity towards HCT -116 with an IC₅₀ value of 1.24 ± 0.09 µg/mL and 1.42 ± 0.34 µg/mL, respectively, as compared to doxorubicin an IC₅₀ value of 1.14 ± 0.12 µg/mL. The leaf and flower extracts showed moderate cytotoxicity towards the MDA-MB-231 cell line with IC₅₀ of 5.86 ± 0.63 µg/mL and 6.97 ± 0.68 µg/mL,

respectively, as compared to doxorubicin, with an IC_{50} value of $2.04 \pm 0.22 \mu\text{g/mL}$. It was noticed that the fruit extracts showed weak cytotoxicity towards the tested cell ²⁴.

The cytotoxicity of biosynthesised silver nanoparticles (AgNPs) using the aqueous extract of *S. aromaticum* was investigated against Breast (MCF-7) and Lung (A549) cancer cell lines using the MTT assay. The results revealed the potency of AgNPs with *S. aromaticum* extract as it showed an IC_{50} of 60 and 50 $\mu\text{g/mL}$ against MCF7 and A549 cells, respectively. The *S. aromaticum* extract only recorded an IC_{50} of 70 $\mu\text{g/mL}$ against both MCF7 and A549 cells. Also, the apoptotic effects of AgNPs with *S. aromaticum* extract on MCF7 cells were investigated through morphological evaluation of the MCF7 treated cells by Acridine orange (AO), Ethidium Bromide (EtBr) staining and DAPI. From the AO / EtBr staining, the mechanism of cell death by the AgNPs is through apoptosis by the nuclear changes, such as chromatin condensation and nuclear fragmentation in the cells ²⁵.

Kumar et al. reported the cytotoxic potential of water, ethanol extract, and essential oil of *S. aromaticum* against MCF-7 cell lines using a brine shrimp lethality test (BSLT) and an MTT assay. In the BSLT assay, the essential oil showed significant activity after 24 h with LD_{50} of 37 $\mu\text{g/mL}$, followed by the ethanol extract LD_{50} of 103 $\mu\text{g/mL}$, and the water extract didn't record any LD_{50} concentration even at the highest concentration used. In the MTT assay, the essential oil showed the most significant IC_{50} values, 36.43 and 17.6 $\mu\text{g/mL}$ in the 24 h and 48 h, respectively ²⁶.

The dried peel powder (DP) and freeze-dried (FD) extracts of *S. cumini* were investigated for their antiproliferative effects on human colon adenocarcinoma cells (HT-29 cells) using the MTT assay. Both the DP and FD extracts of *S. cumini* exhibited a reduction in cell viability of HT-29 cells by 30% and 24.17%, respectively, at a concentration of 1000 $\mu\text{g/mL}$ as compared to the control ²⁷ (**Table 4**).

The cytotoxicity results indicate that extracts from *S. cumini* seeds and leaves have significant efficacy against HCT-116 colon cancer cells ($IC_{50} = 1.24\text{--}1.42 \mu\text{g/mL}$), similar to doxorubicin (1.14 $\mu\text{g/mL}$). This is a promising finding that warrants further investigation. Nonetheless, the identical extracts demonstrate very moderate efficacy against MDA-MB-231 breast cancer cells ($IC_{50} = 5.86\text{--}6.97 \mu\text{g/mL}$), indicating selectivity for cell type.

The enhanced activity of AgNPs synthesized using *S. aromaticum* extract ($IC_{50} = 50\text{--}60 \mu\text{g/mL}$) in contrast to the extract by itself ($IC_{50} = 70 \mu\text{g/mL}$) implies that the nanoparticle formulation exhibit additive/synergistic properties. Subsequent cytotoxic investigations must incorporate suitable controls to differentiate the impacts of the plant extract, the nanoparticle carrier, and their combination.

Table 4. Summary of Cytotoxic Activities of *S. cumini* and *S. aromaticum*

Species	Plant Part	Extract/Compound	Cell Line	Assay	Activity	Key Finding	Reference
<i>S. cumini</i>	Leaves	Essential oil	HepG 2	MTT	IC ₅₀ = 38.15 ± 2.09 µg/mL Staurosporine (8.637 ± 0.47 µg/mL)	Moderate activity	23
	Seed	Extract	HCT-116		IC ₅₀ = 1.24 ± 0.09 µg/mL Doxorubicin (1.14 ± 0.12 µg/mL)	Promising activity	24
	Leaf				IC ₅₀ = 1.42 ± 0.34 µg/mL Doxorubicin (1.14 ± 0.12 µg/mL)	Promising activity	
	Leaf				MDA-MB-231	IC ₅₀ = 5.86 ± 0.63 µg/mL Doxorubicin (2.04 ± 0.22 µg/mL)	
	Flower		IC ₅₀ = 6.97 ± 0.68 µg/mL Doxorubicin (2.04 ± 0.22 µg/mL)			Moderate activity	
	Fruit	Extract	HT-29	30% reduction at 1000 µg/mL	Weak activity	27	
<i>S. aromaticum</i>	Flower buds	AgNPs + extract	MCF-7	MTT	IC ₅₀ = 60 µg/mL	Enhanced activity	25
		AgNPs + extract	A549		IC ₅₀ = 50 µg/mL	Enhanced activity	
		Extract only	MCF-7		IC ₅₀ = 70 µg/mL	Moderate activity	
		Extract only	A549		IC ₅₀ = 70 µg/mL	Moderate activity	
		Essential oil	MCF-7 (24 h)	BSLT	IC ₅₀ = 36.43 µg/mL	Promising activity	26
			MCF-7 (48 h)		IC ₅₀ = 17.6 µg/mL	Time-dependent increase	
			Brine shrimp		LD ₅₀ = 37 µg/mL	Significant activity	

AgNPs = Silver Nanoparticles; BSLT = Brine Shrimp Lethality Test; MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

3.5. Antidiabetic activity

Essential oil isolated from leaves of *S. cumini* exhibited a hypoglycaemic effect by inhibition of α -amylase with an IC_{50} value of $57.80 \pm 3.30 \mu\text{g/mL}$ as compared to acarbose reference drug with an IC_{50} value of $34.71 \pm 2.30 \mu\text{g/mL}$ and α -glucosidase inhibitory activity with an IC_{50} value of $274.03 \pm 12.37 \mu\text{g/mL}$ as compared to acarbose reference drug ($IC_{50} = 138.76 \pm 7.59 \mu\text{g/mL}$)²³.

Moreover, a bioassay-guided fractionation of the leaf extract of *S. cumini* was conducted based on α -amylase inhibitory activity. Methanol and water extracts showed the highest α -amylase inhibitory activity, 98.3 ± 2.3 and $98.6 \pm 1.6\%$, respectively, at a concentration of 1 mg/mL extracts. The ethyl acetate extract showed $72.6 \pm 3.75\%$ inhibitory activity, while the hexane fraction didn't show any inhibitory activity. The ethyl acetate extract was subjected to further purification to isolate ursolic acid and oleanolic acid that showed significant α -amylase inhibitory activity with an IC_{50} value of 6.7 and $57.4 \mu\text{g/mL}$, respectively and 3.1 and $44.1 \mu\text{g/mL}$, respectively, against α -glucosidase²⁸.

Another study on different fractions of fruits of *S. cumini* reported their α -glucosidase inhibitory effects. Where the methanol extract, ethyl acetate, chloroform, and *n*-butanol fractions showed promising α -glucosidase inhibitory activity with an IC_{50} value of 129.98 ± 1.23 , 702.74 ± 1.65 , 430.21 ± 1.98 , and $650.11 \pm 1.00 \mu\text{g}$, respectively, as compared to the reference drug acarbose with an IC_{50} value of $879.99 \pm 1.021 \mu\text{M}$. It was noticed that the methanol extract showed the highest α -glucosidase inhibitory activity²⁹.

Mahindrakar and Rathod evaluated the efficacy of the waste *S. cumini* seed kernel towards α -amylase and α -glucosidase. The aqueous extract showed IC_{50} values of 9.03 and $7.13 \mu\text{g/mL}$, respectively, as compared to Acarbose with an IC_{50} value of $23.95 \mu\text{g/mL}$ against α -amylase and an IC_{50} value of $58.22 \mu\text{g/mL}$ against α -glucosidase¹⁶.

The essential oil of *S. aromaticum* showed α -amylase inhibitory activity with an IC_{50} value of $74.53 \mu\text{g/mL}$ as compared to acarbose reference drug ($IC_{50} = 14.79 \mu\text{g/mL}$). A prepared emulsion of *S. aromaticum* essential oil and a mixture of tween-80, ethanol, and water showed the highest percent of inhibition of α -amylase, $95.30 \pm 0.01 \%$ ³⁰ (Table 5).

The antidiabetic data reveal substantial variation in potency depending on the species and extract type. *S. cumini* seed aqueous extract ($IC_{50} = 9.03$ and $7.13 \mu\text{g/mL}$ for α -amylase and α -glucosidase, respectively) and isolated ursolic acid ($IC_{50} = 6.7$ and $3.1 \mu\text{g/mL}$) exhibit potential efficacy that surpasses that of acarbose in certain instances. Conversely, the essential oil of *S. aromaticum* exhibits merely moderate efficacy ($IC_{50} = 74.53 \mu\text{g/mL}$ for α -amylase). This indicates that *S. cumini* seeds, especially their phenolic and triterpenoid components, provide the most viable source of natural α -glucosidase and α -amylase inhibitors. Future

studies should prioritize *in vivo* pharmacokinetic studies and identify which specific compounds are responsible for the observed *in vitro* activity.

Table 5. Summary of Antidiabetic Activities of *S. cumini* and *S. aromaticum*

Species	Plant Part	Extract/Compound	Assay	Activity	Reference
<i>S. cumini</i>	Leaves	Essential oil	α -Amylase inhibition	IC ₅₀ = 57.80 $\pm$ 3.30 μ g/mL Acarbose (IC ₅₀ = 34.71 $\pm$ 2.30 μ g/mL)	23
		Essential oil	α -Glucosidase inhibition	IC ₅₀ = 274.03 $\pm$ 12.37 μ g/mL Acarbose (IC ₅₀ = 138.76 $\pm$ 7.59 μ g/mL)	
		Methanol extract	α -Amylase inhibition	98.3 $\pm$ 2.3% at 1 mg/mL	28
		Water extract		98.6 $\pm$ 1.6% at 1 mg/mL	
		Ursolic acid		IC ₅₀ = 6.7 μ g/mL	
		Oleanolic acid		IC ₅₀ = 57.4 μ g/mL	
		Ursolic acid	α -Glucosidase inhibition	IC ₅₀ = 3.1 μ g/mL	
		Oleanolic acid		IC ₅₀ = 44.1 μ g/mL	
	Fruit	Methanol extract	α -Glucosidase inhibition	IC ₅₀ = 129.98 $\pm$ 1.23 μ g Acarbose (879.99 $\pm$ 1.021 μ M)	29
	Seed	Aqueous extract	α -Amylase inhibition	IC ₅₀ = 9.03 μ g/mL Acarbose (23.95 μ g/mL)	16
	Seed	Aqueous extract	α -Glucosidase inhibition	IC ₅₀ = 7.13 μ g/mL Acarbose (58.22 μ g/mL)	
<i>S. aromaticum</i>	Flower buds	Essential oil	α -Amylase inhibition	IC ₅₀ = 74.53 μ g/mL Acarbose (14.79 μ g/mL)	30
		Essential oil emulsion		95.30 $\pm$ 0.01% inhibition	

3.6. Anti-cholinesterase activity

Essential oil isolated from leaves of *S. cumini* inhibited acetylcholinesterase effectively with an IC_{50} value of $32.9 \pm 2.1 \mu\text{g/mL}$ as compared to a reference drug donepezil ($IC_{50} = 7.89 \pm 1.30 \mu\text{g/mL}$)²³. The methanol extract of flower buds of *S. aromaticum*, the oil and eugenol were investigated for their inhibitory activity against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). The results revealed that the methanol extract the oil possesses inhibition of the AChE with IC_{50} values of 61.5 ± 1.88 , 49.73 ± 1.33 and $42.44 \pm 1.33 \mu\text{g/mL}$, respectively, as compared to the reference drug galantamine IC_{50} value $10.14 \pm 0.71 \mu\text{g/mL}$. Also, the methanol extract of the oil and eugenol possess inhibition of the BChE with an IC_{50} values of 103.53 ± 1.47 , 88.14 ± 1.74 , and $63.51 \pm 1.88 \mu\text{g/mL}$, respectively, as compared to the reference drug galantamine IC_{50} value $21.15 \pm 0.18 \mu\text{g/mL}$ ³¹.

The ethanolic extract of *S. cumini* leaves was investigated for inhibition of acetylcholinesterase and monoamine oxidase activities, the key targets for different drugs acting on the central nervous system. The ethanol extract showed IC_{50} values of 44.54 and 432.7 $\mu\text{g/mL}$, respectively. Rivastigmine (10 $\mu\text{g/mL}$), used as a positive control, inhibited the AChE in 65.66%¹⁵.

3.7. Leishmanicidal and Trypanocidal activity

Rodrigues et al. evaluated the anti-Leishmania activity of the essential oil of *S. cumini* leaves and its major component α -pinene using MTT assay. The α -pinene showed activity against *Leishmania amazonensis* promastigote forms with an IC_{50} value of 19.7 $\mu\text{g/mL}$. α -Pinene showed promising activity against axenic and intracellular amastigotes with an IC_{50} value of 16.1 and 15.6 $\mu\text{g/mL}$, respectively. And the essential oil exhibited lower activity towards axenic and intracellular amastigotes with an IC_{50} value of 43.9 and 38.1 $\mu\text{g/mL}$, respectively³².

The essential oil *S. aromaticum* and eugenol showed a *Trypanosoma cruzi* inhibitory activity, with an IC_{50} value of 28.68 ± 1.073 and $31.97 \pm 1.061 \mu\text{g/mL}$, respectively, against epimastigotes as compared to the reference drug Benznidazole IC_{50} value = $1.950 \pm 1.066 \mu\text{g/mL}$. Besides, they showed IC_{50} of 64.51 ± 1.658 and $45.73 \pm 1.252 \mu\text{g/mL}$, respectively, against intracellular amastigotes. The *S. aromaticum* essential oil exhibited a greater selectivity for the parasite than the cells, with an SI of more than 15.5. Regarding the nitrite levels in *T. cruzi* stimulated cells were reduced when treated with the essential oil and eugenol by 47.01% and 48.05%¹⁸.

The essential oil of flower buds of *S. aromaticum* and its major component eugenol showed promising leishmanicidal activity on promastigotes of *Leishmania tropica* with IC_{50}

values of 180.24 and 233.52 $\mu\text{g/mL}$, respectively and *Leishmania major* with IC_{50} values of 654.76 and 517.14 $\mu\text{g/mL}$, respectively ²².

3.8. Miscellaneous activity

Different extracts of fruits of *S. cumini* were investigated for their phosphodiesterase inhibitory activity, and the most promising fractions were the ethyl acetate and *n*-butanol fractions with an IC_{50} value of 270.77 ± 1.98 and 139.09 ± 1.09 μg , respectively, as compared to EDTA ($\text{IC}_{50} = 265.09 \pm 1.09$ μM). Also, the methanol extract showed moderate activity with an IC_{50} value of 128.00 ± 1.45 μg . Moreover, the different fractions were tested for their urease inhibitory activity, where the IC_{50} values were equal to 10.17 ± 1.00 , 7.09 ± 2.00 , 8.32 ± 1.76 , and 12.23 ± 1.09 μg for the methanol, ethyl acetate, *n*-butanol, and chloroform fractions, respectively. Due to the inhibition of the urease enzyme, *S. cumini* would be a good candidate for the treatment of peptic ulcer as an anti-*H. pylori* infection, and hepatic-associated problems as hepatoprotective. Also, inhibition of phosphodiesterase would be useful in the management of diabetes associated problems as erectile dysfunction ²⁹.

Anti-haem biocrystallisation activity of leaves of *S. cumini* native to Pakistan exhibited 66.33% inhibition (IC_{50} 15.25 mg/mL) at the concentration of 20 mg/mL, as compared to the reference drug chloroquine diphosphate, 91.4% inhibition at 5 mg/mL ($\text{IC}_{50} = 0.394$ mg/mL) ¹².

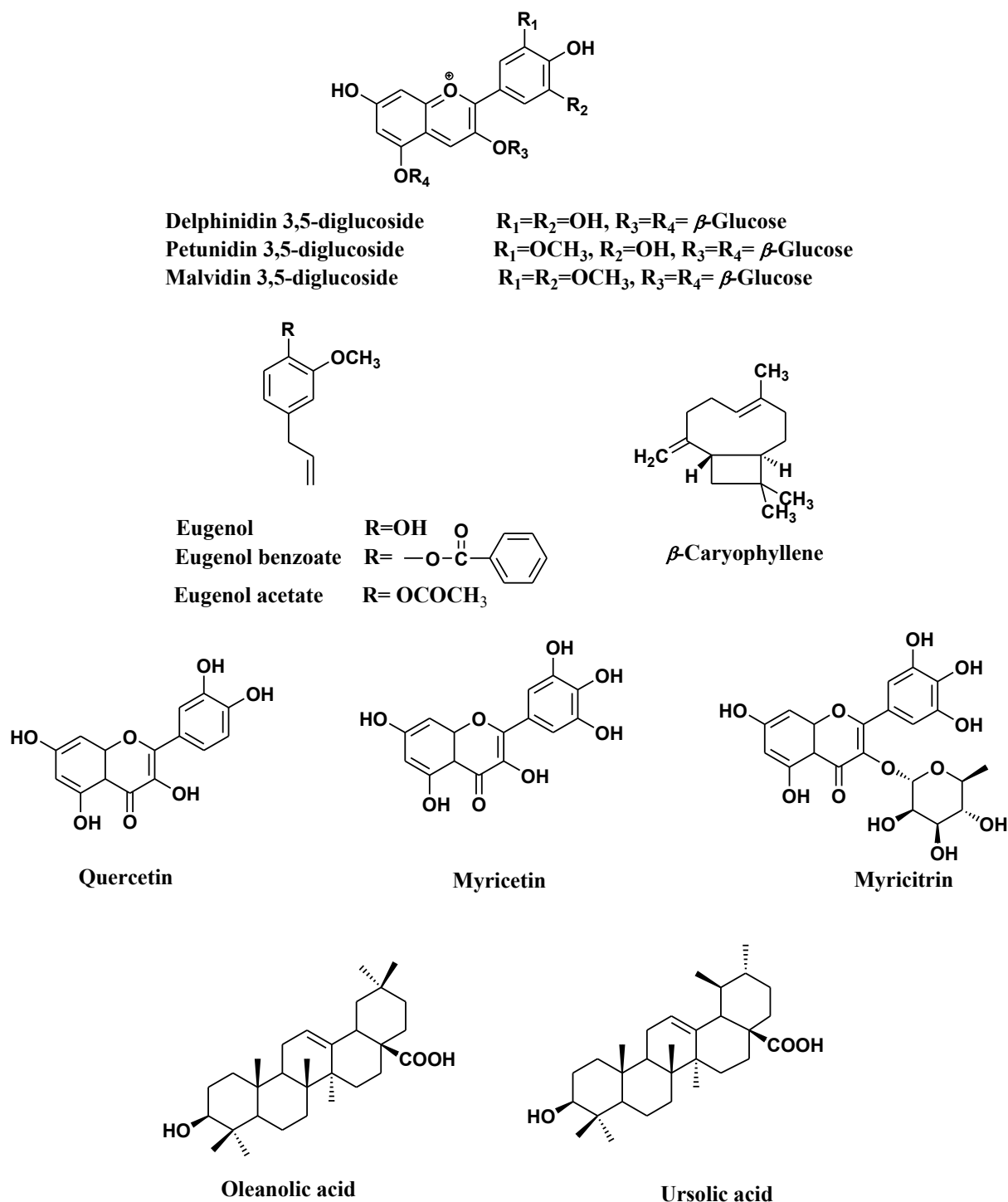


Figure 2. Chemical structures of various compounds from the genus *Syzygium* with potential biological properties

3.9.Shared Molecular Mechanisms Underlying the Reported Biological Activities of selected *Syzygium* species

The pharmacological actions exhibited by *Syzygium* species such as antioxidant, antibacterial, anti-inflammatory, antidiabetic, cytotoxic and neuroprotective actions are not independent effects but rather a network of molecular pathways controlled by a common group of bioactive

phytochemicals. The understanding of these common processes gives a cohesive framework to explain the broad spectrum of activity exhibited by a single plant extract and supports the holistic therapeutic potential of these species.

Syzygium extracts modulate cellular redox balance through complementary direct and indirect antioxidant mechanisms. Their phenolic constituents, including flavonoids, anthocyanins, phenolic acids, and tannins, scavenge reactive oxygen species and chelate transition metals in cell-free assays, as demonstrated by DPPH, ABTS, FRAP, and lipid peroxidation assays ^{11,13,14}. In addition, compounds such as myricetin derivatives ³³ and eugenol ³⁴ may activate the Nrf2/HO-1 pathway and enhance endogenous antioxidant defenses, including SOD, CAT, GPx, GST, and HO-1, protecting cellular membranes and tissues from oxidative injury ^{12,15}. This redox-modulating activity provides a mechanistic basis for the extracts' anti-inflammatory, antidiabetic, hepatoprotective, cardioprotective, and neuroprotective effects, while concentration-dependent pro-oxidant activity may also contribute to cancer-cell apoptosis.

Syzygium phytochemicals demonstrate a multitarget enzyme-inhibition profile that may underlie their therapeutic versatility. Ursolic acid, oleanolic acid, and tannins inhibit α -amylase and α -glucosidase, potentially slowing carbohydrate digestion and reducing postprandial hyperglycemia, while their antioxidant effects may additionally protect pancreatic β -cells ^{16,28}. Phenolic compounds such as eugenol inhibit acetylcholinesterase and butyrylcholinesterase, which could increase synaptic acetylcholine and support neuroprotective effects relevant to neurodegenerative disorders ^{23,31}. Other activities, including phosphodiesterase inhibition, may contribute to vasodilation, whereas urease inhibition suggests possible anti-*H. pylori* potential, collectively demonstrating the broad disease relevance of *Syzygium* enzyme modulation ²⁹.

Moreover, essential oils of *Syzygium* species rich in eugenol, exhibit antimicrobial activity through multiple complementary mechanisms. Eugenol and other terpenes integrate into bacterial membranes, increasing permeability, disturbing ion gradients, and causing leakage of ATP and intracellular contents. They may also inhibit ATP synthesis, alter fatty-acid composition, and interfere with quorum sensing, thereby disrupting bacterial metabolism and communication ²⁰. This combination of membrane and intracellular effects contributes to broad-spectrum antimicrobial activity and may reduce the likelihood of resistance development.

Additionally, *Syzygium* compounds, including eugenol, quercetin, and anthocyanins, may exert anticancer effects by inducing mitochondrial apoptosis and arresting cell-cycle progression. They promote Bax expression, suppress Bcl-2, disrupt mitochondrial membrane

potential, release cytochrome c, and activate caspase-9 and caspase-3, while also modulating cyclins and cyclin-dependent kinases to induce G1 or G2/M ²⁵. Their potential selectivity toward cancer cells may reflect the higher basal ROS levels, differential uptake or metabolism, and preferential disruption of cancer-associated signaling pathways in malignant cells.

The elucidation of prevalent pathways of *Syzygium* extracts supports the promise of *Syzygium* extracts as multitarget therapies for complicated disorders. *Syzygium* extracts could have potential benefits over single-target treatments and chances for synergistic combinations with conventional therapy. Their integrated antioxidant, anti-inflammatory and enzyme-inhibitory actions may also be relevant for disease prevention, and mechanistic insights can guide formulation development and clinical-trial design. However, translation is impeded by ambiguities about the compounds responsible for various effects, the molecular basis for selectivity, pharmacokinetic behaviour, interactions between constituents and unknown molecular targets. Future research should include target identification techniques, molecular docking, thermal-stability experiments, and structure-activity relationship analyses to explain these pathways and provide a solid basis for therapeutic development. It is recommended to perform particular subsequent experiments, encompassing target identification, molecular docking corroborated by biochemical validation, transcriptomic/proteomic profiling, and structure–activity relationship investigations.

4. *In vivo* studies of selected *Syzygium* species

A study evaluated the anti-inflammatory and antioxidant effects of aqueous *S. aromaticum* (clove) extract (AEC) in an ovalbumin (OVA)-induced asthma model in Wistar rats, using four groups: control, OVA-sensitized, AEC-treated (15 mg/kg body weight/day by gavage), and OVA/AEC-treated. AEC significantly reduced lung malondialdehyde (MDA) levels while elevating glutathione peroxidase (GPx) and catalase (CAT) activities, though GSH levels showed no significant change; erythrocyte parameters remained unaffected across groups. Anti-inflammatory effects were evident through normalised total protein and interleukin-4 (IL-4) levels in serum, lung, and bronchoalveolar lavage fluid (BALF), corroborated by improved lung histology with reduced inflammation, positioning AEC as a promising natural agent for asthma management ³⁵.

Oldoni et al. ³⁶ reported that a hydroalcoholic extract of *S. malaccense* leaves (400 mg/kg) demonstrated promising antihyperglycemic effects in diabetic rats, restoring kidney catalase activity, maintaining non-protein sulfhydryl (NPSH) levels, enhancing glutathione S-transferase (GST) activity, and reducing MDA to mitigate lipid peroxidation across tissues.

Bioguided fractionation isolated phenolic compounds from the bioactive acetone fraction, quercetin, myricetin and myricitrin that likely correlate with its therapeutic profile against hyperglycaemia and oxidative stress³⁶. Nallappan et al.³³ reported that a myricetin derivative-rich fraction from *S. malaccense* leaves effectively prevents high-fat diet (HFD)-induced obesity, glucose intolerance, and oxidative stress in C57BL/6J mice by reducing body weight gain, adiposity, and fasting glucose levels while improving insulin sensitivity and glucose tolerance compared to HFD controls. The fraction upregulated antioxidant enzymes (SOD, CAT, GPx) and Nrf2/HO-1 pathway markers in liver and adipose tissues, lowered lipid peroxidation (MDA), and modulated inflammatory cytokines (decreased TNF- α , IL-6; increased IL-10), with histopathological evidence of reduced hepatic steatosis and adipose hypertrophy, highlighting its therapeutic potential against metabolic syndrome via myricetin-mediated redox modulation³³.

A recent study investigates the anti-fibrotic potential of *S. aromaticum* (clove) ethanolic extract (CEE), alone and combined with Silymarin®, against carbon tetrachloride (CCl₄)-induced liver fibrosis in animal models, demonstrating significant amelioration of hepatic damage through robust antioxidant effects (elevated GSH, SOD, CAT; reduced MDA and NO), anti-inflammatory activity (downregulated TNF- α , IL-1 β , IL-6 via NF- κ B inhibition), and antibacterial properties against fibrosis-associated pathogens. CEE+Silymarin® synergistically outperformed individual treatments in reducing fibrotic markers (Collagen-I, α -SMA, TGF- β 1), histopathological scores, and serum ALT/AST levels, while preserving liver architecture, positioning this combination as a promising hepatoprotective strategy for advancing clinical management of liver cirrhosis and its progression to hepatocellular carcinoma³⁷.

Aljarari³⁸ reported that a combination of *Boswellia papyrifera* and *S. aromaticum* methanolic extracts (200 mg/kg each, orally for 8 weeks) provided superior neuroprotection against AlCl₃-induced Alzheimer's disease in male albino rats compared to individual treatments, significantly improving cognitive function in the Y-maze test (increased arm entries and spontaneous alternation percentage), elevating AChE levels, boosting antioxidant enzymes (SOD, GSH), and reducing MDA in cerebral cortex and hippocampus homogenates. Histopathological analysis confirmed reduced neuronal vacuolation, inflammation, and damage in cortex and hippocampus, with the dual therapy outperforming monotherapy by modulating oxidative stress and cholinergic deficits more effectively, offering preliminary evidence for its potential in managing AlCl₃-associated cognitive impairment³⁸.

Syzygium samarangense fruit extract (SSE) effectively attenuates hyperglycemia in type 2 diabetic rats by preserving pancreatic β -cell function and modulating oxidative stress and inflammation. Oral administration over 28 days moderately reduced fasting blood glucose while significantly elevating serum and pancreatic insulin levels, alongside decreased MDA and enhanced activities of antioxidant enzymes CAT and superoxide dismutase (SOD) in pancreatic tissue. SSE also lowered pro-inflammatory TNF- α , suppressed hepatic gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK), and improved liver enzyme profiles, demonstrating hepatoprotection and anti-inflammatory benefits that collectively support SSE's potential as a complementary therapy for type 2 diabetes management ³⁹.

Syzygium cumini fruit extract (SCFE) and quercetin (QU) effectively ameliorate cadmium (CdCl₂)-induced ovarian toxicity and apoptosis in female rats over 35 days, particularly at SCFE 400 mg/kg. Cd exposure disrupted estrus cycles induced oxidative stress (elevated MDA, reduced SOD/CAT/GSH), hormonal imbalances (decreased FSH/LH/AMH/estrogen/progesterone), and apoptosis via miRNA-204-5p upregulation, which downregulated Bcl-2 while upregulating Bax/Caspase-9/Caspase-3. Both treatments, especially high-dose SCFE (400 mg/kg), restored antioxidant status, hormone levels, ovarian/uterine histoarchitecture, and modulated the miRNA-204-5p/Bcl-2 intrinsic pathway, confirming their protective potential against heavy metal reproductive toxicity ⁴⁰.

The *in vivo* studies reviewed here represent a diverse range of disease models and administration protocols, making direct comparison challenging. However, several patterns emerge. First, oral administration of extracts (typically 15–400 mg/kg) shows consistent efficacy in reducing oxidative stress markers across multiple disease models (asthma, diabetes, obesity, fibrosis). Second, the anti-inflammatory effects of clove and other *Syzygium* extracts appear to be mediated through NF- κ B pathway modulation, with downstream effects on TNF- α , IL-1 β , and IL-6. Third, the combination of clove with other botanicals (e.g., *Boswellia papyrifera*) shows synergistic effects, suggesting potential for polyherbal formulations.

Several limitations are notable across the *in vivo* studies. Most use relatively short treatment durations (14–35 days), limiting assessment of long-term safety and efficacy. The use of healthy animals or acute disease models does not fully capture the complexity of chronic human diseases. Additionally, the lack of dose-response studies in most investigations prevents identification of optimal therapeutic doses. Large-scale, long-term studies in disease-relevant animal models are urgently needed (**Table 6**).

Table 6. Summary of *In Vivo* Studies of Selected *Syzygium* Species

Plant extract/compound	Species / Model	Dose	Route	Comparator	Major outcomes	References
Aqueous extract of <i>S. aromaticum</i>	Wistar rats / OVA-induced asthma 28 Wistar albino male rats	15 mg/kg/day for 16 days	Gavage	OVA-sensitized control	↓ Lung MDA; ↑ GPx, CAT; normalized IL-4 and total protein; improved lung histology	35
Hydroalcoholic extract of <i>S. malaccense</i>	Diabetic rats / hyperglycaemia 24 male Wistar rat	400 mg/kg for 45 days	Oral	Diabetic control	Restored kidney CAT; maintained NPSH; ↑ GST; ↓ MDA; isolated quercetin, myricetin, myricitrin	36
Myricetin derivative-rich fraction from <i>S. malaccense</i> extract	C57BL/6J mice / HFD-induced obesity C57BL/6J male mice	50 mg/kg, 100 mg/kg, and 150 mg/kg for 16 weeks	Oral	HFD control	↓ Body weight gain, adiposity, fasting glucose; ↑ insulin sensitivity; ↑ SOD, CAT, GPx, Nrf2/HO-1; ↓ MDA, TNF- α , IL-6; ↑ IL-10; ↓ hepatic steatosis	33
Ethanol extract of <i>S. aromaticum</i>	Animal model / CCl ₄ -induced liver fibrosis 60 male adult albino rats	40 mg/kg for six week	Oral	CCl ₄ control; Silymarin®	↑ GSH, SOD, CAT; ↓ MDA, NO; ↓ TNF- α , IL-1 β , IL-6 via NF- κ B; ↓ Collagen-I, α -SMA, TGF- β 1; ↓ ALT/AST; synergistic with Silymarin®	37
Methanolic extract of <i>S. aromaticum</i>	Male albino rats / AlCl ₃ -induced Alzheimer's 40 male albino Wistar rats	200 mg/kg for eight weeks	Oral	AlCl ₃ control; individual extracts	↑ Y-maze arm entries and alternation; ↑ AChE; ↑ SOD, GSH; ↓ MDA; reduced neuronal vacuolation, inflammation	38

<i>Hydroethanolic extract of S. samarangense</i> fruit	Type 2 diabetic rats (Streptozotocin induced) 20 adult male Wistar rats	400 mg/kg for 4 weeks	Oral	Glibenclamide control	↓ Fasting glucose; ↑ serum and pancreatic insulin; ↓ MDA; ↑ CAT, SOD; ↓ TNF- α ; ↓ PEPCK; improved liver enzymes	39
<i>Hydroethanolic extract of S. cumini</i> fruit	Female rats / CdCl ₂ -induced ovarian toxicity 55 adult Wistar albino female rats	200 and 400 mg/kg for 35 days	Oral	Cd control; quercetin	Restored estrus cycles; ↓ MDA; ↑ SOD, CAT, GSH; restored FSH, LH, AMH, estrogen, progesterone; ↑ Bcl-2; ↓ Bax, caspase-9, caspase-3; restored ovarian/uterine histology	40

5. Formulations incorporating selected *Syzygium* species

A study by Abdelazim et al., demonstrates that electrospun nanofibers incorporating *S. cumini* leaf extract (SCLE) with PLGA, PMMA, collagen, and glycine exhibit optimised nanosized, uniform morphology with smooth surfaces and favourable swelling properties, as confirmed by *in vitro* assessments. The SCLE-loaded nanofibers (at 0.5% and 1% w/v) displayed superior antibacterial efficacy against multidrug-resistant Gram-positive (*Staphylococcus aureus*, *Bacillus cereus*) and Gram-negative (*Escherichia coli*, *Salmonella paratyphi*) and fungal strains (*Candida albicans*, *Candida glabrata*) compared to equivalent plain extract concentrations via agar-well diffusion. *In vivo* evaluation in Wistar rats over 14 days revealed that SCLE-collagen nanofiber mats significantly accelerated topical wound closure relative to untreated controls, highlighting their promising role as advanced wound dressings for acute wound management ⁴¹.

Dos Santos et al. ⁴² reported that nanoencapsulation of phenolic-rich jambolan (*S. cumini* (L.) Skeels) extract using whey protein and pectin biopolymers via nanoprecipitation markedly enhances the stability and bioactivity of anthocyanins and other phenolics, overcoming limitations posed by their low stability and food matrix interactions. Nanoparticles exhibited spherical morphology, smooth surfaces, diameters of 82–116 nm, high encapsulation efficiency for phenolics (73.81–84.65%), and superior anthocyanin retention (up to 56.89%) in acetone-based antisolvents, with FTIR confirming molecular interactions. Antioxidant activity was potentiated by up to 110% compared to crude extract, positioning these biopolymer nanoparticles as promising carriers for food additives and health products ⁴².

A recent study reports the green synthesis of gelatin/PLA-loaded gold nanocomposites using *S. cumini* fruit extract as a reducing agent, yielding stable nanoparticles with an average particle size 21 nm, and strong plasmonic absorbance at 534 nm, confirmed by UV-Vis, FTIR, XRD, TEM, and DLS analyses. The nanocomposites exhibited promising antioxidant activity (DPPH scavenging up to 92%), broad-spectrum antibacterial effects against *E. coli*, *S. aureus*, and *P. aeruginosa* with IZD ranging from 16 to 22 mm, significant anti-inflammatory potential with 60% inhibition in protein denaturation assay, and antidiabetic efficacy via α -amylase and α -glucosidase inhibition 82.56 and 80.27%, respectively. Moreover, neuroprotective anti-Alzheimer's properties through AChE, BChE inhibition 76.37 and 85.94%, respectively.

In vivo investigations of zebrafish embryos demonstrated that Ge/PLA/AuNCs exhibit exceptional biocompatibility and non-toxicity. The research of the SH-SY5Y cell line revealed increased cell viability (95.27%) and augmented neuronal cell proliferation after Ge/PLA/AuNCs therapy ⁴³.

Elshopakey et al.³⁴ reported that nanoencapsulated *S. aromaticum* essential oil significantly alleviates acetic acid-induced ulcerative colitis in rats compared to free oil and sulfasalazine, by restoring colonic architecture, reducing macroscopic/microscopic damage scores, and suppressing pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) through NF- κ B/iNOS pathway inhibition. Nanoencapsulated clove oil enhanced antioxidant defenses, with changes involving Keap1/Nrf2/HO-1 signaling, reduced MDA and NO levels, and increased GSH, SOD, and CAT levels. These outcomes do not establish enhanced bioavailability, and the contribution of altered pharmacokinetic behavior remains to be determined. These findings position nanoencapsulated clove oil as a promising natural therapeutic candidate for inflammatory bowel diseases³⁴.

Jayasankar et al., successfully formulated a biocompatible herbal antifungal gel incorporating *Origanum vulgare* (oregano) and *S. aromaticum* (clove) essential oils at an optimised concentration of 0.6 μ l/ml each, leveraging their synergistic antifungal effects against oral *Candida albicans*. The combination exhibited a markedly lower minimum inhibitory concentration (MIC) of 0.19 μ l/mL and minimum fungicidal concentration (MFC) of 0.39 μ l/mL compared to individual oils, with the gel achieving a zone of inhibition (~19 mm) comparable to standard fluconazole discs via agar diffusion assays. MTT cytotoxicity assays confirmed the gel's safety for topical use, positioning it as a promising natural alternative to conventional antifungals for managing oral candidiasis⁴⁴.

The following study reveals that a soap formulated with clove (*Syzygium aromaticum*) and oregano essential oils exhibits promising broad-spectrum antimicrobial activity against multidrug-resistant bacteria (*E. coli* EW222/EW239, *P. aeruginosa*) and fungi (*A. fumigatus*, *T. rubrum*), with MIC values as low as 1.56–3.12 μ L/mL for clove oil and synergistic reductions when combined with oregano and thyme oils. Clove oil particularly excelled against fungal strains (MIC 1.56 μ L/mL), while all tested oils inhibited ATCC strains (*S. aureus*, *E. coli*) at 1.56–50 μ L/mL, matching or surpassing synthetic antiseptics in vivo hand hygiene assays. GC-MS analysis confirmed key bioactive components like eugenol and carvacrol, positioning this essential oil-based soap as a safe, natural alternative for combating antimicrobial resistance in healthcare settings⁴⁵.

Ayyanar et al.⁴⁶ reported that *S. cumini* leaf extract-loaded carboxymethylcellulose films accelerated wound closure in rats via solution casting, with phytochemical analysis confirming quercetin as a key bioactive and FT-IR/XRD verifying uniform nanosized morphology (14.58 nm crystallite size) and functional group compatibility. In vitro assays on L929 fibroblasts achieved 83% scratch closure at 100 μ l concentration, while controlled drug

release kinetics supported sustained activity; in vivo excision wounds in rats healed completely within 7 days versus no recovery in controls after 14 days, highlighting SCLE-CMC films' promising antimicrobial, antioxidant, and proliferative effects for advanced topical wound management ⁴⁶.

The formulation studies reviewed here represent an exciting frontier in *Syzygium* research (**Table 7**), demonstrating that encapsulation and carrier-based delivery are feasible strategies for improving the handling, stability, and *in vitro* activity of *Syzygium* bioactives. Whey protein–pectin nanoparticles achieved high phenolic encapsulation efficiency (73–85%) and preserved anthocyanin integrity ⁴²; electrospun PLGA/PMMA/collagen nanofibers supported wound healing in a rat model ⁴¹; and nanoencapsulated clove oil reduced colitis severity in rats with associated modulation of NF- κ B and Nrf2 pathways ³⁴.

Existing systems can be classified according to the context in which they are delivered. The *S. cumini* leaf extract-loaded electrospun PLGA/PMMA/collagen nanofibers and carboxymethylcellulose films are topical wound-healing systems for local retention and prolonged interaction with the wound bed, not systemic administration. Therefore, the most significant evidence is local antibacterial action, fibroblast migration or proliferation, regulated release and acceleration of wound closure in animal models. These systems show promising preclinical activity, but their evaluation remains incomplete because studies have not consistently quantified local extract exposure, assessed dose–response relationships, or evaluated long-term tissue compatibility.

Conversely, the biopolymer nanoparticles obtained from *S. cumini* phenolic-rich extract are mainly aimed at protecting labile phenolics and anthocyanins and improving their handling in food or nutraceutical settings. The remarkable encapsulation efficiency, retention of anthocyanins and increased *in vitro* antioxidant activity revealed here, demonstrate the potential for the creation of whey protein–pectin nanoparticles. However, these results did not provide any evidence of enhanced gastrointestinal stability, absorption, systemic exposure or biological activity *in vivo*. Therefore, the next step should be not just further antioxidant testing but comparative stability and release investigations under gastrointestinal conditions, followed by pharmacokinetic examination of free versus encapsulated phenolics.

The most advanced formulation studied was nanoencapsulated *S. aromaticum* essential oil, which was tested in a disease-relevant in vivo model. Encapsulation may promote local retention, preserve eugenol from breakdown, or modulate release at the inflamed colonic mucosa since it protects better than free oil in acetic acid-induced colitis. However, the study did not directly assess eugenol amounts in plasma, colon tissue, or inflammatory cells,

therefore the superior effect mechanism remains unknown. This encourages further development but does not prove better bioavailability.

Based on the formulation data, physicochemical characterisation has led to biological proof-of-concept but not translational validation. The top research priority is to match formulation to clinical indication and delivery route. Topical systems should prioritize local retention, release kinetics, antibacterial activity, wound-bed compatibility, and compare efficacy to regular dressings. Oral or systemic systems should focus safety, gastrointestinal stability, regulated release, permeability, plasma and tissue exposure. Standardized phytochemical profiling, batch reproducibility, blank-carrier controls, physiologically relevant release testing, pharmacokinetic comparison with the free extract, and biodistribution studies are required for all systems to claim improved bioavailability or targeted delivery.

Table 7. Summary of different Formulation Studies incorporating *Syzygium* species

Plant extract used	Carrier / Synthesis Type	Dimensions (nm)	Physicochemical characterization	Key efficacy findings and experimental model	Reference
Jambolan phenolic-rich extract (7.33%)	Whey protein–pectin nanoparticles (nanoprecipitation)	82–116 nm (DLS)	Spherical, smooth surface (SEM); FTIR confirmed molecular interactions	<i>In vitro</i> characterization + antioxidant assay Enhanced <i>in vitro</i> antioxidant activity, with potentiation of up to 110% compared with crude extract	42
<i>S. cumini</i> leaf extract (0.5–1% w/v)	PLGA/PMMA/collagen electrospun nanofibers	0.48 μ m thickness	Uniform morphology; favorable swelling	<i>In vitro</i> antimicrobial + <i>in vivo</i> wound healing (rat), acceleration of wound closure in Wistar rats over 14 days	41
Clove essential oil	Nanoencapsulated <i>S. aromaticum</i> oil	261.1 $\pm$ 0.53 nm (DLS)	Homogeneous size distribution	<i>In vivo</i> colitis model (rat); reduced colonic damage and inflammatory cytokines; modulation of NF- κ B/iNOS and Keap1/Nrf2/HO-1 signaling	34

<i>S. cumini</i> leaf extract	CMC film (solution casting)	Crystallite size 14.58 nm (XRD)	FTIR, XRD, FESEM characterization	<i>In vitro</i> L929 fibroblast scratch closure (83% at 100 μ L); controlled release kinetics; complete wound closure within 7 days in an <i>in vivo</i> rat excision-wound model	⁴⁶
<i>S. cumini</i> fruit extract as reducing agent	Gelatin/PLA gold nanocomposite (green synthesis)	21 nm (TEM)	Stable plasmonic absorbance at 534 nm	<i>In vitro</i> bioassays + zebrafish biocompatibility ; increased SH-SY5Y viability and neuronal proliferation <i>in vitro</i>	⁴³

6. Evidence-based clinical trials

Many species of *Syzygium* were not only subjected to *in vitro* or *in vivo* pharmacological studies, but also clinical trials on extracts or essential oils were conducted. Interestingly, certain pharmaceutical products approved and available in the market are formulated with herbal ingredients from the genus *Syzygium*. For example, a randomised controlled, double-blinded clinical trial was conducted to study the efficacy of a clove-containing toothpaste. A total of 79 participants were randomised of whom 75 completed follow-up and divided into two groups: a control group receiving a fluoridated dentifrice, and the test group received non-fluorinated herbal dentifrice with clove extract. Volunteers were asked to brush with the dentifrices twice daily for a month. Although reductions in mean plaque, gingival, and halitosis scores were observed within both the test and control groups from baseline to follow-up, between-group analysis revealed no statistically significant differences for any outcome ⁴⁷.

In a randomized, double-blind clinical trial, 90 patients with lower-limb venous stasis ulcers received either standard hydrocolloid gel dressing (n = 46) or hydrocolloid gel dressing containing *S. cumini* extract (n = 44). No statistically significant difference in healing rate was observed between the two dressing groups at the 14-day follow-up. The original study reported that *Pseudomonas aeruginosa*-positive wound cultures substantially reduced the odds of healing by 88% reduction ($p < 0.0001$). The available evidence supports absence of a statistically significant treatment effect in this trial ($p = 0.15$), but does not establish equivalence, non-inferiority, or superiority of the extract-containing dressing ⁴⁸.

In a randomized, double-dummy controlled trial, 27 patients with type 2 diabetes received *S. cumini* leaf tea (2 g/L as a water substitute), glyburide 5 mg twice daily, or placebo for 28 days. Fasting blood glucose did not change significantly in the *S. cumini* tea group, whereas glyburide produced a significant reduction from baseline. ($P>0.05$). No alterations occurred in BMI, lipids, renal function, or liver enzymes across groups, indicating that while folk medicine attributes antidiabetic potential to *S. cumini*, this preparation lacks clinical efficacy in managing type 2 diabetes ⁴⁹.

The clinical evidence for *Syzygium* species is limited and mixed, highlighting the gap between preclinical promise and clinical translation. The positive results of clove-containing toothpaste are encouraging and consistent with the well-established antimicrobial properties of clove ⁴⁷. However, the negative results of *S. cumini* leaf tea for diabetes management underscore the importance of preparation standardization and the possibility that traditional use may be limited to specific plant parts (seeds rather than leaves) ⁴⁹.

The negative results of *S. cumini* extract dressings for venous ulcers highlight an important point: *in vitro* activity does not guarantee clinical efficacy, particularly in complex wounds where infection control and wound bed preparation are critical ⁴⁸. This emphasizes the need for mechanistic clinical studies that can identify which patients may benefit from *Syzygium*-based interventions.

7. Conclusions

The genus *Syzygium*, particularly the well-studied species *S. cumini* and *S. aromaticum*, represents a valuable source of bioactive compounds with significant therapeutic potential. This comprehensive review integrates the extensive body of evidence supporting the traditional uses of these plants through modern pharmacological investigations. The documented *in vitro* and *in vivo* studies validate their efficacy as promising antioxidants, antimicrobials, anti-inflammatory agents, and antidiabetic remedies. Key bioactive constituents, including eugenol, anthocyanins, and various flavonoids like quercetin and myricetin, have been identified as the primary drivers of these activities, acting through well-defined mechanisms such as free radical scavenging, enzyme inhibition, and modulation of critical inflammatory pathways such as NF- κ B, COX-2. Recent advances in formulation science, particularly nanoencapsulation and biocompatible scaffolds, provide promising approaches for improving the stability and delivery of *Syzygium* bioactives. These innovations have shown promising results in preclinical models for applications ranging from wound healing and antimicrobial therapy to the management of metabolic syndrome and inflammatory bowel disease. However, the translation of these promising preclinical findings into clinical

practice remains limited. We need to underscore for standardised extracts and mechanistic studies to fully elucidate their pharmacokinetic and pharmacodynamic profiles. Future studies must include toxicity assessment, synergistic formulations, and clinical use to maximise *Syzygium*'s potential in current pharmacotherapy.

List of Abbreviations:

AChE= Acetylcholinesterase
 ABTS = 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt
 AO= Acridine Orange
 AEC= Aqueous Extract of Clove
 BALF= Bronchoalveolar Lavage Fluid
 BChE = Butyrylcholinesterase
 BHA = Butylated hydroxyanisole
 CMC= carboxymethylcellulose
 COX-2= Cyclooxygenase-2
 CAT= Catalase
 DAPI= 4',6-diamidino-2-phenylindole
 DCM=dichloromethane
 DLS= Dynamic Light Scattering
 DPPH = 2,2-diphenyl-1-picrylhydrazyl
 EtBr=Ethidium Bromide
 FTIR= Fourier Transform Infrared Spectroscopy
 FRAP = Ferric reducing antioxidant power.
 GST= glutathione S-transferase
 GSH = Glutathione
 GPx= Glutathione peroxidase
 HFD= high-fat diet
 HO-1= Heme oxygenase-1
 iNOS= Inducible Nitric oxide synthase
 IZD = Inhibition Zone Diameter
 MTT= 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
 MIC = Minimum inhibitory concentration
 MMC = Minimum Microbicidal Concentration
 MDA= Malondialdehyde
 MFC = Minimum Fungicidal Concentration
 NF-KB=Nuclear factor kappa-light-chain-enhancer of activated B cells
 NO= Nitric oxide
 Nrf2= Nuclear factor erythroid 2-related factor 2
 NPSH= Non-protein sulfhydryl
 OVA= ovalbumin
 PEPCK= Phosphoenolpyruvate Carboxykinase
 PLA= Polylactic Acid
 PLGA= Poly(lactic-co-glycolide)
 PMMA= Poly(Methyl Methacrylate)
 SI= Selectivity Index
 SOD= Superoxide Dismutase
 TEM= Transmission Electron Microscopy
 XRD= X-ray Diffraction

SCLE= *Syzygium cumini* Leaf Extract
CEE= Clove Ethanolic Extract
SCFE= *Syzygium cumini* fruit extract
SSE= *Syzygium samarangense* fruit extract

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