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Evergreen trees that heal: Anti-pathogenic properties of *Syzygium Sp*.

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The emergence of antimicrobial, antiviral, and antifungal-resistant pathogens over the past decades has driven the search for potential sources of novel anti-pathogenic compounds. Phytochemicals such as metabolites from *Syzygium* species have been well-reported to possess immense pharmacological potential with their derived bioactive components. Several phytochemicals such as phenolics, flavonoids, triterpenes and tannins have been identified and proven to be associated with antimicrobial potential. A number of inhibitory mechanisms were elucidated through morphological evaluation of bacteria, antibiofilm assays, and analysis of anti-virulence factors, which are strong indications of their therapeutic properties. A vast majority of the *Syzygium* plants are considered safe to use, as verified by numerous *in vitro* and *in vivo* studies. This review explores the scope of proven antibacterial, antiviral, and antifungal effects of *Syzygium* species, which could be utilised as a form of complementary and alternative medicine and provide insight into the current dearth of novel pharmaceuticals to address the challenge of drug resistance.

Keywords: Antibacterial, Antifungal, Antiviral, Bioactive compound, Phytochemicals, *Syzygium* species

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Introduction

Syzygium is the largest genus under the *Myrtaceae* family, with an estimated 1200-1800 species reported to date. It is native to subtropical and tropical regions and is distributed throughout Africa, India, China, Southern Asia, Australia, and New Zealand[1,2] (Fig. 1). The highest level of species diversity is recorded in Southeast Asia. *Syzygium* is morphologically similar to other genera, such as *Eugenia*. In fact, the initial Indochinese species belonged to the genus *Eugenia* and was later revised to *Syzygium*.

The classification of the genus *Syzygium* is as follows: Kingdom: Plantae, Phylum: Streptophyta, Class: Equisetopsida, Subclass: Magnoliidae, Order: Myrtales, Family: Myrtaceae, Genus: *Syzygium*.

The plants are easily identified by the opposite, exstipulate leaves with well-developed secondary and tertiary venation intersecting with intra-marginal vein. The genus mostly consists of medium or large evergreen trees[2,3]. Some of the fruits from the species are edible, and those cultivated for its fruits include *Syzygium jambos* (L.) Alston, *Syzygium cumini* (L.) Skeels, *Syzygium aqueum* (Burm.f.) Alston, *Syzygium samarangense* (Blume) Merr. & L.M.Perry, and *Syzygium malaccense* (L.) Merr. & L.M.Perry. A well-known spice called clove is made of *Syzygium aromaticum* (L.) Merr. & L.M.Perry flower buds. Almost all parts of the tree – the leaves, fruits, bark, young shoots, and roots are commonly used in traditional medicine amongst local communities[4–7]. The fruiting bodies of common *Syzygium* species are morphologically diverse[8] (Fig. 2).

Many species are known to bear flowers, fruit and seeds, which may be edible and contribute to various pharmacological effects. For instance, a comprehensive review by Srivastava S. and Chandra D.[9] reported that *Syzygium cumini* possesses antidiabetic, antihyperlipidaemic, antioxidant, hepatoprotective, antiallergic, antiarthritic, antibacterial, neuroprotective,

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antidiarrhoeal, nephroprotective and anti-inflammatory activities.

This review explores the proven antibacterial, antiviral, and antifungal effects of *Syzygium* species. The common extraction methods and cytotoxicity studies of *Syzygium* extracts are also discussed, providing insight into the potential utilisation of the plant in complementary and alternative medicine to address the current lack of novel pharmaceuticals and counter the challenge of drug resistance.

Methodology

The literature for this study was systematically collected from leading scientific databases, including PubMed/Medline, Scopus, Wiley, ResearchGate and Google Scholar, chosen for their comprehensive coverage of peer-reviewed articles in the fields of plant sciences, pharmacology, and antimicrobial research. Citations on plant taxonomy from reputable websites were also included. The primary data collection was conducted between June and October 2020, with an update conducted in December 2024.

Search terms were designed to capture the scope of the research comprehensively. Key search terms included "*Syzygium*", "antiviral", "antimicrobial", "antifungal", "antibacterial", and "plant-derived bioactive compounds". Boolean operators (e.g., AND, OR) and truncation techniques were applied to optimise search queries and retrieve articles specifically focused on the bioactive compounds and pharmacological properties of the *Syzygium* genus.

The selection process was conducted in two stages. Initially, titles and abstracts were screened for relevance to the study objectives. In the second stage, full-text articles were evaluated against predefined inclusion criteria: Peer-reviewed studies focusing on the *Syzygium* genus, particularly those exploring bioactive compounds, as well as antibacterial, antiviral, antifungal properties, and therapeutic potential. Studies were excluded if they were not peer-reviewed, lacked focus on *Syzygium*

Fig. 1 — Global distribution of *Syzygium* sp., with indications of the plants are indigenous to the area ('Native'), non-indigenous and introduced to the local plantations ('Introduced'), or no longer existing ('Extinct'). The only geographical location where *Syzygium* sp. is considered extinct is Rodrigues Island in the Indian Ocean. Created in https://BioRender.com.

Fig. 2 — Images of well-known *Syzygium* species, depicting variations in the physical characteristics of fruiting bodies. a) *Syzygium aromaticum* (clove), b) *Syzygium jambos* (rose apple), c) *Syzygium cumini* (java plum), d) *Syzygium samarangense* (java apple), e) *Syzygium luehmannii* (riberry).

species, or provided insufficient methodological detail. Articles written in English or with accessible English abstracts were included to ensure accessibility and reliability.

Syzygium sp. bioactive compound extraction methods and antimicrobial assays

Bioactive compounds can be derived from various anatomical parts of the plant, including the leaves, flowers, fruits, seeds, stem and bark. Most studies focus on the phenolic content in higher plants as they are synthesised in all parts of plant and exhibit significant biological effects[10]. Discovery and analysis of useful bioactive components relies on the type of extraction techniques and proper solvent selection to achieve a desirable outcome.

Singh *et al.*[11] investigated several extraction techniques for total phenols and flavonoids from *S. aromaticum*, concluding that the amount of extracted polyphenolic compounds is proportional to the resulting antioxidant activity. The authors evaluated mechanical shaking, refluxing, Soxhlet extraction and centrifugation. Additionally, the solvents chosen were distilled water, acetone and ethyl alcohol. Yet other researchers utilised organic solvents such as methanol, ethyl acetate, ethyl ether, and chloroform, though no ideal solvent could be determined. Kotzé *et al.*[12] suggested that the chemical composition of bioactive compounds showed significant similarity due to the presence of saponin-like components. Factors such as the objectives of extraction, the technique, possible chemical interaction between compound and solvent, duration, temperature, as well as polarity and molecule size must be taken into consideration in order to maximise yield.

Common strategies utilised by researchers to determine the *in vitro* antibacterial potential of *Syzygium* are the *Kirby-Bauer* disc diffusion test, determination of minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC) by broth dilution method[13,14]. Disc diffusion analysis provides useful qualitative information on antibacterial susceptibility, indicating which larger zones of inhibition would indicate stronger antibacterial activity. MIC and MBC are employed to measure the minimum effective dosage of extracts that would either inhibit the growth of or kill bacterial cells. More advanced methodologies have been implemented by some authors to investigate the mode of action of extracts on various bacterial strains. For instance, the use of scanning electron microscopy (SEM) and transmission electron microscopy (TEM) demonstrated the detailed morphology of microbes before and after sample treatment[14]. Famuyide *et al.*[15] employed a method to study the antibiofilm activity of *Eugenia* and *Syzygium* leaf extracts, as they proposed that biofilm formation is a crucial enabling feature for the development of drug resistance.

Antibacterial activity of *Syzygium Sp.*

Since the 19th century, humanity has been in a constant battle with pathogenic bacteria. The discovery of the first antibiotic 'penicillin' by Sir Alexander Fleming in 1928 revolutionised medicine, leading to the subsequent widespread use of antibiotics due to its accessibility and proven efficacy in treating bacterial infections. However, the overuse of antibiotics resulted in the widespread surge of resistance genes which are necessary for the survival of bacteria[16]. The emergence of antibiotic-resistant bacteria is inevitable, considering that the functional resistance genes in bacteria occur naturally by mutation even in the absence of human intervention[17,18]. Over-prescription and abuse of antibiotics have inadvertently accelerated the phenomenon by offering a competitive advantage for drug-resistant bacteria. Furthermore, the spread of resistance was exacerbated through the unnecessary use of antibiotics in domestic animals and plants for non-therapeutic reasons[19]. Bacteria resistant to first-line antibiotics can have severe consequences for immunocompromised, at-risk patients. Therefore, the paradox of having to treat critically ill patients with potent antibiotics and risk developing resistance likely worsens the outcome of nosocomial infections.

Antibiotic resistance is an urgent topic that needs to be addressed through international efforts. It is responsible for more than 700,000 deaths annually and an estimated 10 million deaths by 2050[20]. The World Health Organization (WHO) released a list of antibiotic-resistant bacteria for new, effective antibiotics to be discovered as they cause extensive burdens in the healthcare and community. These bacteria include the carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*; third-generation cephalosporin-resistant *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp.; methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium*, to name a few[21].

Global efforts to combat antibiotic resistance should focus on exploring novel compounds that trigger less resistance, in addition to exerting minimal side effects on humans. To accomplish this, the discovery of natural products with antibacterial

bioactive molecules has become the mainstay of research. Plant-based natural products are a valid source of therapeutic chemicals, and thus, most drugs approved for the market are often derived from phytochemicals[22]. Most antibacterial compounds derived from medicinal plants are not only well-tolerated and accepted by patients, but they are also sustainable and less costly than synthetic drugs[23]. Some studies reported that certain plant extracts may act in synergy with antibiotics to increase their efficacy, alleviate the risk of side effects and enhance drug bioavailability[24].

In 1985, WHO estimated that most communities depend chiefly on traditional herbal medicines as their primary healthcare resource[25]. The "multi-target/multi-component" approach seen in traditional herbal medicine seems to be more advantageous compared to the conventional "single-targeted" drug method to treat multifaceted diseases[26]. Undiscovered phytochemicals have gained popularity in the research arena to further explore their therapeutic potential. As we are approaching a post-antibiotic era, underrated plants such as *Syzygium* sp. provide researchers with an alternative solution to develop new chemotherapeutic strategies to curb antibiotic resistance.

In this section, the antibacterial properties of several commonly reported species, such as *S. aromaticum*, *S. cumini*, *S. guineense*, *S. jambos* and other species, are discussed and summarised in Table 1.

Table 1 — Summary of antibacterial activities from selected *Syzygium* sp.

Species	Extraction Method/Solvent	Target Bacteria	Key Findings
Syzygium aromaticum	Steam distillation (essential oil)[30]	*Salmonella typhimurium*[30] *Escherichia coli*[30,31,41] *Listeria monocytogenes*[30] *Staphylococcus aureus*[30,38] *Klebsiella pneumoniae*[31,41] *Pseudomonas aeruginosa*[31] *Enterobacter sp.*[31] *Citrobacter sp.*[31] *Acinetobacter baumannii*[31] *Proteus sp.*[31] *Helicobacter pylori*[32] *Porphyromonas gingivalis*[35]	Eugenol disrupts bacterial membranes; significant inhibition of both Gram-positive and Gram-negative bacteria[30,31,42]. Eugenol-rich essential oil also inhibits biofilm formation and disrupts quorum-sensing pathways[35]. *S. aromaticum* bud oil reduced microbial load and improved wound healing in MRSA-infected rats[38]. The essential oil caused cell shrinkage and lysis in extended-spectrum β-lactamase (ESBL) producing bacteria[41].
	Ethanol[14] Ethyl acetate[14] Water[14,34]	*Staphylococcus aureus*[14,34] *Escherichia coli*[14,34] *Salmonella enteritidis*[14] *Listeria monocytogenes*[14] *Serratia marcescens*[14] *Pseudomonas aeruginosa*[34]	Ethanol extracted the highest phenolic content. Morphological deformities of bacterial membranes were observed[14]. Aqueous extract of seed elevates oxidative stress biomarkers and lipid peroxidation in bacteria, causing membrane disruption[34].
Syzygium cumini	Steam distillation (essential oil)[53]	*Escherichia coli* *Pseudomonas aeruginosa* *Staphylococcus aureus*	The major constituent was α-pinene. The oil showed a synergistic effect in combination with antibiotics.
	Ethanol[46] Methanol[46] Petroleum ether[54] Water[56]	*Bacillus amyloliquefaciens*[46] *Staphylococcus aureus*[46,47,52,54,56] *Escherichia coli*[46,47,52,54,56] *Pseudomonas aeruginosa*[46,52] *Salmonella typhimurum*[47] *Salmonella enteric*[47] *Bacillus cereus*[47] *Neisseria gonorrhea*[52] *Bacillus subtilis*[47,52] *Enterococcus faecalis*[52,56] *Klebsiella pneumoniae*[56] *Proteus vulgaris*[56] *Acinetobacter baumannii*[56]	Active phytochemicals isolated from alcoholic solvents inhibit membrane synthesis enzymes; Gram-positive bacteria are generally more susceptible[46,47,52,54]. Gold nanoparticles synthesised from the aqueous leaf extract showed antibacterial activity against several multidrug-resistant urinary tract pathogens[56].
Syzygium guineense	Hydrodistillation (essential oil)[64]	*Pseudomonas aeruginosa*[64] *Klebsiella pneumoniae*[64] *Escherichia coli*[64] *Staphylococcus aureus*[64] *Mycobacterium bovis*[64]	Oxygenated terpenes linked to strong antibacterial activity[64].

(*Contd.*)

Table 1 — Summary of antibacterial activities from selected *Syzygium* sp. — (*Contd.*)

Species	Extraction Method/Solvent	Target Bacteria	Key Findings
	Chloroform (acetone fraction)[65]	*Mycobacterium tuberculosis*[65]	Lipophilic compounds enhance permeation of mycobacterial lipid membranes[65].
Syzygium jambos	Ethanol[72]	*Staphylococcus aureus*[72,74] *Yersinia enterocolitica*[72] *Staphylococcus hominis*[72] *Staphylococcus cohnii*[72] *Staphylococcus warneri*[72] *Propionibacterium acnes*[73] *Alcaligenes faecalis*[74] *Aeromonas hydrophilia*[74] *Bacillus cereus*[74] *Chromobacterium violaceum*[76] *Pseudomonas aeruginosa*[76]	Tannins play a critical role in antibacterial activity; activity diminished upon tannin removal[72]. Other phytochemicals such as phytol and methyl linolenate are implicated in quorum-sensing inhibition[76].
	Methanol[75]	*Staphylococcus aureus*[75]	Synergistic effects observed with chloramphenicol[75].
Syzygium polyanthum	Ethanol[77]	*Escherichia coli*[77] *Klebsiella pneumoniae*[77] *Listeria monocytogenes*[77] *Pseudomonas aeruginosa*[77] *Proteus mirabilis*[77] *Staphylococcus aureus*[77] *Salmonella typhimurium*[77] *Vibrio cholerae*[77] *Vibrio parahaemolyticus*[77]	Wide-spectrum antibacterial activity, particularly sensitive to Gram-positive bacteria. At 4× MIC, complete inhibition within 1–4 hours[77].
	Hydromethanol[78]	*Staphylococcus aureus*[78] *Staphylococcus hyicus*[78] *Staphylococcus intermedius*[78]	Weak growth inhibition against bovine mastitis-causing bacteria[78].
Syzygium legatti; *Syzygium masukuense*	Acetone[79]	Diarrhoeagenic strains of *Escherichia coli*[79]	Reduced adherence of *E. coli* to Caco-2 enterocytes and significant anti-biofilm effects[79].
Syzygium legatti	Acetone[80]	Diarrhoeagenic strains of *Escherichia coli*[80]	Morphological damage to *E. coli* observed *via* electron microscopy[80].
Syzygium caryophyllatum	Water and ethanol[81]	*Staphylococcus aureus*[81] *Escherichia coli*[81] *Salmonella typhi*[81] *Shigella flexneri*[81] *Vibrio cholerae*[81]	Time-kill assay showed bacterial elimination within 2 hours (*S. aureus* and *S. typhi* were particularly sensitive)[81].

Syzygium aromaticum

S. aromaticum is an evergreen tree native to the Moluccas Islands. The tree is glabrous throughout and may grow up to 20 m tall. The leaves are opposite, slightly leathery and pale greenish in appearance, with black spots on the underside[27]. The flower is the source of clove, which is made up of four unopened petals surrounded by four spreading sepals[3].

Clove is a staple spice in various cuisines all around the world. Many communities plant this tree for its commercial value in spice, particularly in Indonesia, Pakistan, India, Sri Lanka, Madagascar, and Tanzania. Although the medicinal usage of clove has not been approved by the FDA, clove essential oil has been used as an alternative medicine or supplement to treat dental plaque, burns, wounds, vomiting, diarrhoea, flatulence and inhibition of microbial growth[28]. Many of its biological effects, including antibacterial activity, have been explored extensively due to its ubiquity and accessibility in various regions of the world. Numerous studies detailed the compositions of clove, which are associated with its strong antibacterial ability, including eugenol, eugenol acetate, beta-caryophyllene, acetyl-eugenol, alpha-humulene, and other trace compounds[14,29].

The antibacterial properties of *S. aromaticum* were illustrated by Radünz *et al.*[30] on standard strains of *Salmonella typhimurium*, *Escherichia coli* O157:H7, *Listeria monocytogenes* and *Staphylococcus aureus*. Clove essential oil was extracted by steam distillation. The authors assessed its antibacterial activity via disc diffusion analysis, MIC as well as MBC determination – all of which showed significant antibacterial activity. The authors speculated that the zone of inhibition (ZOI) seen in disc diffusion was

due to the alteration of bacterial cell membrane permeability by lipophilic interaction with clove essential oil, whereas the higher degree of antibacterial activity seen in MIC and MBC were attributable to the effect of eugenol that facilitated disruption of the cytoplasmic membrane, resulting in non-specific permeability.

Radünz *et al.* subsequently discovered that clove essential oil inhibited the growth of *S. aureus* better than conventional nitrite preservatives in the span of seven days. A study with similar methodology uncovered *S. aromaticum*'s wide spectrum of antibacterial properties against several beta lactamase-producing strains of Gram-negative uropathogens, including *E. coli*, *Klebsiella pneumoniae*, *P. aeruginosa*, *Enterobacter* sp., *Citrobacter* sp., *Acinetobacter baumannii* and *Proteus* sp.[31]. The overall result suggested that all strains were sensitive to ethanolic extracts of clove, with *E. coli* and *Proteus* sp. responding exceptionally well against the extracts. *S. aromaticum* extract also exerted significant antibacterial activities against the Pan-Drug Resistant strain of *Helicobacter pylori* with a maximum inhibition diameter of 25±0.57 mm[32]. The non-selective antibacterial actions of *S. aromaticum* can be seen evidently in the effectiveness of clove extracts against both Gram-positive and Gram-negative bacteria.

El-Maati's group demonstrated the antibacterial action of clove using a similar repertoire of pathogenic bacteria, including *S. aureus, E. coli, L. monocytogenes, Salmonella enteritidis* and *Serratia marcescens*[14]. Unlike the aforementioned studies, extraction of bioactive compounds was achieved separately by individual solvents, namely ethyl acetate, ethanol (80%) and water, and their ability to inhibit bacterial growth was evaluated. Ethanol was found to be superior in extracting phenolic content from clove, while water was better at extracting flavonoids. In the disc diffusion assay, ethanol extract outperformed the rest of the solvent extracts - the ZOI was 10-17 mm on all tested bacteria, with no discernable difference between Gram-positive and Gram-negative strains. Broth dilution assay using clove ethanol extract indicated strong antibacterial activities (MIC: 50-100 µg/mL, MBC: 100-150 µg/mL) on *E. coli*, and *S. aureus* in particular.

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) were utilised to evaluate the morphological changes of *S. aureus, E. coli* and *S. enteritidis* after exposure to clove extract. The results revealed visible structural deformity on the outer surface, cell wall and cell membrane segregation, irregular size, loss of cellular shapes and presence of aggregated cellular debris[14]. Similarly, morphological changes of eugenol-treated *S. typhi* were extensively studied *via* atomic force microscopy, which revealed irregular cell surfaces with shrunken cell size. The results are in accordance with SEM images, which clearly depicted membrane deformities and loss of normal cell structure. Further evidence was illustrated by crystal violet assay and SDS-PAGE, which indicated enhanced membrane permeability and intracellular protein leakage, respectively after eugenol treatment. In addition, molecular analysis of membrane macromolecules by Fourier transform infrared (FT-IR) spectroscopy revealed significant modifications of ester functional groups in lipids, proteins, and nucleic acids with notable membrane deformity[33]. The above-mentioned features collectively established that the antibacterial mechanism of *S. aromaticum* may be associated with compromised cellular membranes.

Ajiboye *et al*.[34] investigated the potential mode of the plant's antibacterial activity by examining the level of oxidative stress and membrane perturbations in bacterial cells induced by aqueous extracts of S. *aromaticum* seeds. In the study, *E. coli*, *P. aeruginosa* and *S. aureus* showed prominent increases in oxidative stress through the overproduction of superoxide anion radicals, enhanced superoxide dismutase and catalase activities, and elevated glutathione disulfide (GSSH)-to-glutathione reduced (GSH) ratio. Membrane disruption and functional disturbance were depicted by the increased level of malondialdehyde, a marker of lipid bilayer peroxidation that is released concomitantly with nucleotide and protein leakage.

However, the induction of superoxide radicals by *S. aromaticum* seeds seems to contradict other sources detailing the antioxidant properties of *S. aromaticum*[14,30]. The origin of reactive oxygen species (ROS) remains uncertain. A possible justification is that intracellular ROS formation is accelerated in response to exogenous stressors, namely the compounds found in *Syzygium* extracts. Therefore, more oxidative markers should be developed and incorporated into the research to validate the mechanism of antibacterial activity by means of inducing oxidative stress.

Zhang *et al.*[35] highlighted the antibiofilm effect of clove leaf essential oil against *Porphyromonas gingivalis*, a biofilm-forming oral pathogen that elicits periodontitis. They confirmed that eugenol, a major constituent in essential oil, can inhibit biofilm formation even in sub-inhibitory concentrations, whilst complete removal of pre-formed biofilm was observed under higher doses. Downregulation of biofilm-associated genes (*fimA, hagA, hagB, rpgA, rpgB* and *kgp*) by eugenol further proved that the antibiofilm effect was not the established consequence of growth inhibition. A more comprehensive description can be found in a study which used *S. aromaticum* as a potential quorum-sensing inhibitor in biofilm-associated clinical isolates of *P. aeruginosa*[36]. Not only did the authors illustrate the effectiveness of clove bioactive fraction in suppressing biofilm masses at sub-inhibitory levels, but they also depicted the notable downregulation of several genes associated with quorum-regulated virulence factors (*lasA, rhlB, lasB* and *pvdA*).

The antibacterial properties of *S. aromaticum* essential oil have garnered a strong interest in recent years[37], particularly in multidrug-resistant (MDR) microorganisms such as *E. coli*, *P. aeruginosa*, *S. aureus*, and *S. typhi*[38–40]. Among the compelling evidence contributed by researchers, Ginting *et al.* showed that extended-spectrum β-lactamase (ESBL) producing bacteria such as *E. coli* and *K. pneumoniae* were susceptible to cell shrinkage and lysis from clove oil exposure[41]. In a study by Alanazi *et al*., clove bud oil analysis through gas chromatography-mass spectrometry (GC-MS) unveiled 16 volatile compounds. Combined with imipenem, more rapid wound healing and a reduction in microbial load were observed in methicillin-resistant *S. aureus* (MRSA)--infected rats[38]. Moreover, with its principal compound, eugenol, clove essential oil was not only found to inhibit the growth of both Gram-positive and Gram-negative bacterial strains but also demonstrated strong antioxidant and promising anticancer capacity[42]. These findings emphasise the superiority of the 'essential oil' formulation compared to other solvent extraction methods.

Syzygium cumini

S. cumini is generally known as the Black plum tree, Malabar plum, Indian blackberry, Portuguese plum, Java plum, jamun or jambolan. The tree has been recorded to grow up to 30 m tall. This species is endemic to India, Sri Lanka and Myanmar but also distributed throughout South America, Oceania, and North Australia as an invasive species. It was also introduced in Nepal, Malaysia, Java, Indonesia, China, Philippines, Queensland and various tropical regions during pre-historical times. The distinctive features of *S. cumini* can be found in the leaves - coriaceous, slender, and elliptical oblong with a turpentine aroma. Young leaves are pinkish, turning dark green above, lighter below and yellowish midribs when mature. The rough and cracked dark-grey bark at the base becomes smooth and lighter-grey on the higher branches.

The fruits are round or ovoid and appear in clusters, and unripe green fruits turn to magenta or dark purple as they mature with purple or white pulp within. The mature fruits taste sweet, fairly sour and usually astringent[2,43]. *S. cumini* is a multipurpose plant of great importance. From an economic standpoint, its edible fruits, lumber and ornamental properties highlight the plant's versatility. Furthermore, *S. cumini* is one of the most widely recognised medicinal plants in developing countries. Different plant parts of *S. cumini*, including leaves, stem bark, flowers, roots and fruits, have been reported to harbour antidiabetic[44,45], antihyperlipidaemic[45], neuroprotective[46], antibacterial[47], antioxidant[46,47], anti-inflammatory[48], antidiarrhoeal[49] and antifungal[50] activities. The above-described pharmacological effects are attributed to a variety of bioactive compounds highlighted by Ayyanar and Subash-Babu[51], including phenolic acids (e.g. ellagic acid and gallic acid), flavonoids (e.g. anthocynanins, kaemferol, rutin, myricetin, and quercetin), tannins, terpenoids and alkaloids.

In vitro studies showed that the stem[46], seeds[47], and leaves[52,53] of *S. cumini* exhibited a broad spectrum of antibacterial properties against Gram-positive and -negative bacteria. An investigation of *S. cumini* stem on different extracts; aqueous, ethanol and methanol revealed varying antibacterial activities against *Bacillus amyloliquefaciens*, *S. aureus, E. coli* and *P. aeruginosa*[46]. Ethanolic extract of *S. cumini* stem was the most potent, followed by methanolic extract, with *B. amyloliquefaciens* reported to be the most susceptible. Interestingly, the aqueous extract did not exert any inhibitory activity against all tested bacteria. Preliminary phytochemical study showed that phenol was absent in the aqueous extract but present in both alcoholic extracts. Similar studies emphasised the superiority of alcoholic extraction. Maximum ZOI was observed in methanol extracts of *S. cumini* leaves

against *E. coli*, *S. aureus*, *P. aeruginosa*, *Neisseria gonorrhea*, *Bacillus subtilis* and *Enterococcus faecalis* as compared to methylene chloride extracts and essential oil treatment[52]. However, the distillation method should not be overlooked as de Sousa *et al.* found that *S. cumini* essential oil, with its major component α-pinene, exerted significant antibacterial effects on multidrug-resistant clinical isolates of *E. coli*, *P. aeruginosa* and *S. aureus*[53].

Methanol extract of *S. cumini* seeds was also proven to outperform acetone and aqueous extractions against strains of *B. subtilis*, *S. typhimurum*, *Salmonella enteric*, *S. aureus*, *E. coli* and *Bacillus cereus*[47]. A considerable synergistic effect of the antibiotic Ampicillin with *S. cumini* leaf petroleum ether extract was also observed against multidrug-resistant strains of *S. aureus* and *E. coli*[54]. In general, Gram-positive bacteria have a greater susceptibility against all reported *S. cumini* extracts, possibly attributable to the composition of the bacterial cell wall.

To elucidate the antibacterial property of *S. cumini*, Yadav *et al.* tested the effect of *S. cumini* seed methanolic extract on *B. subtilis* by determining the cell viability and membrane permeability over 72 hours. The uptake of propidium iodide (PI) was increased in tested bacteria in comparison with the control. Field emission scanning electron microscopy revealed a shrunken and cracked surface on *B. subtilis* in a time-dependent manner. Furthermore, the degree of DNA fragmentation was notable in at least 48 hours of extract treatment, in addition to RNA degradation - which showed possible inhibition of pathogenic protein synthesis. Interestingly, *in silico* molecular docking analysis revealed that lupeol and stigmasterol from *S. cumini* seed extract possess the ability to inhibit enzymes associated with plasma membrane synthesis (PDB ID-1W5D, 4OX3, 3MFD and 5E2F)[55].

In the advent of nano-drug delivery formulations, Diksha and team developed gold nanoparticles (NPs) derived from *S. cumini* leaf extract against urinary tract microbes. After characterisation of the nanoparticles using UV-vis spectroscopy, Transmission electron microscopy (TEM), Fourier-transform infrared spectroscopy (FTIR), and X-ray diffraction, which revealed the presence of phenolic and aromatic compounds, the biosynthesised NPs significantly reduced bacterial density *via* the disk diffusion and MIC assays. The multidrug-resistant strains tested included *S. aureus*, *A. baumannii*, *E. coli*, and *P. aeruginosa*[56].

Syzygium guineense

A leafy forest tree found abundantly in tropical Africa, *Syzygium guineense* is commonly used as herbal medicine among the local communities. The plant is called Malmo (Hausa) in northern Nigeria and Adere (Yoruba) in the southern region. Internationally, it is known as bi-coloured waterberry, forest waterberry, mountain waterberry, and snake bean tree. Its flower has an inflorescence of the densely branched compact head, a result of the gall insect attack[57]. The tree can grow up to 15-20 m high, and young trees have an overall smooth, greyish-white or grey-brown bark. The bark of older trees is flaky, cracked and darker in appearance. The elliptical to lanceolate leaves are 50-175 mm long and 15-75 mm wide, and glossy dark green above and pale green beneath. The mature fruits are generally dark purple with a rounded seed within.

S. guineense often thrives in moist conditions near swampy areas but will also grow in woodlands[58]. Traditionally, the plant extract is taken as a remedy for intestinal parasites, stomachache, diarrhoea, dysentery and ophthalmia[57]. The medicinal values of *S. guineense* plant were subject to scientific evaluation, which, apart from antimicrobial activity, revealed antidiabetic[59], antihypertensive[60], anthelmintic[61] and antimalarial[62] effects.

Ten triterpene derivatives isolated from the leaf of *S. guineense* have been reported by Djoukeng *et al.*[63], namely betulinic acid, oleanolic acid, 2-hydroxyoleanolic acid, 2-hydroxyursolic acid, arjunolic acid, asiatic acid, terminolic acid, 6-hydroxyasiatic acid, arjunolic acid 28-β-glucopyranosyl ester and asiatic acid 28-β-glucopyranosyl ester. Arjunolic acid and asiatic acid showed promising antibacterial activities against *E. coli*, *B. subtilis* and *Shigella sonnei*.

On the other hand, *S. guineense* essential oils obtained by hydrodistillation showed strong antibacterial activities against *P. aeruginosa*, *K. pneumonia*, *E. coli*, *S. aureus* and *Mycobacterium bovis*, with *P. aeruginosa* being the most susceptible (MIC: 50 µg/mL) followed by other tested bacteria (MIC: 100 µg/mL)[64]. The authors suggested the observed antibacterial property may be attributable to the oxygenated terpenes and aromadendrene, which are characterised by gas chromatography coupled with mass spectrometry.

Reports also outlined the phytochemical analysis of *S. guineense* stem bark in an attempt to elucidate its anti-tuberculosis potential[65]. The acetone fraction of

chloroform extract was determined to have significant bactericidal activity against tested clinical strains of *Mycobacterium tuberculosis*, with betulinic acid methylenediol ester (MIC: 0.15 mg/mL) seemingly more potent than betulinic acid (MIC: 0.6 mg/mL). The lipophilic nature of isolated compounds was believed to be responsible for the increased permeation of lipoidal mycolic acid membrane found on the outer surfaces of *Mycobacterium*. Therefore, *S. guineense* may serve as a possible candidate for novel drug development to curb multidrug-resistant strains of *M. tuberculosis*.

Syzygium jambos

S. jambos (rose apple) has been well-documented in many regions, reflecting its widespread potential as a tropical botanical fruit tree or as an invasive species. Geographically, *S. jambos* is distributed in humid tropic countries like Southeast Asia, Indonesia, Philippines and Malaysia. The plant is an evergreen tree which can reach up to 7-12 m in height and 50 cm in diameter. The leathery opposite and narrowly lanceolate leaves are dark green superiorly and lighter green underneath. Small pellucid glands are present on both leaf surfaces. *S. jambos* fruit is a drupe and physically resembles guava but has a rose-scented sweet taste; hence the name "rose apple". The large, rounded and rough-coated seeds are situated loosely in the centre of the fruit cavity when ripe[66]. Different parts of the plant, such as the fruit and root bark, have been used as a traditional medicine in Chinese culture to promote health and well-being. Scientific studies on the phytochemical constituents of *S. jambos* revealed a multitude of pharmacological effects, including antioxidant[67], anti-inflammatory[68], analgesic[69], hepatoprotective[67] and anticancer[70,71] activities.

In vitro antibacterial studies of *S. jambos* bark extracts have shown a strong indication of inhibitory activities against strains of *S. aureus*, *Yersinia enterocolitica*, *Staphylococcus hominis*, *Staphylococcus cohnii* and *Staphylococcus warneri*[72]. The extracts were particularly active against two strains of *S. hominis* and one resistant strain of *S. warneri*, with the lowest MIC obtained at 15.5 µg/mL. The observed antibacterial activities of *S. jambos* are correlated with a high tannin content found in aqueous (77%) and acetone (83%) bark extracts. Total elimination of tannins from the extracts resulted in repressed antibacterial activities, which proved that tannins played a crucial role.

Sharma *et al.*[73] provided evidence that the leaf ethanol extracts and one of its isolated compounds, anacardic acid analogue, exhibited a significant antibacterial effect against *Propionibacterium acnes*, the bacteria responsible for acne vulgaris. Microscopy studies revealed cell wall breakage and intracellular content perturbance on treated *P. acnes* in a dose-dependent manner. Furthermore, a leaf methanolic extract was also reported to be active against *Alcaligenes faecalis* (ZOI: 12.6±0.5 mm), *Aeromonas hydrophilia* (ZOI: 9.7±0.8 mm), *B. cereus* (ZOI: 10.2±0.5 mm) and *S. aureus* (ZOI: 9.0±0 mm)[74].

Similarly, crude methanol extracts of bark and leaves were evaluated against resistant strains of *S. aureus* and several Gram-negative bacteria, wherein significant inhibitory activities were observed at concentration ranges of 32-512 µg/mL in leaf extracts[75]. A preliminary study on the antibiotic-modulating effect of *S. jambos* by the same authors revealed increased antibacterial effects on more than 70% of strains of *S. aureus* tested when the leaf extract was used in combination with chloramphenicol. The authors proposed that the leaf extract of *S. jambos* may serve as potential efflux pump inhibitors, working synergistically with existing antibiotics to enhance antibacterial activity. Furthermore, a preliminary screening of various Myrtaceae plant species showed that ethanolic leaf extracts of *S. jambos* have prominent anti-virulence potential wherein quorum-sensing associated virulence factors, violacein pigment production and pyoverdin were seen inhibited in *Chromobacterium violaceum* and *P. aeruginosa*, respectively[76]. Molecular docking studies revealed significant activity of three phytochemicals isolated from *S. jambos* and *Syzygium antisepticum*, namely phytol, ethyl linoleate and methyl linolenate, on the quorum-sensing receptor system of *P. aeruginosa*.

Other *Syzygium* species

Syzygium polyanthum (*Salam*) has been reported to possess potent antibacterial activity. An article reported that a wide spectrum of foodborne pathogens, including *E. coli*, *K. pneumoniae*, *L. monocytogenes*, *P. aeruginosa*, *Proteus mirabilis*, *S. aureus*, *S. typhimurium*, *Vibrio cholerae* and *Vibrio parahaemolyticus* were sensitive to leaf ethanolic extract of *S. polyanthum*[77]. Gram-positive bacteria such as *L. monocytogenes* and *S. aureus* were found to be particularly sensitive to the extract. At a concentration of 4x MIC, the leaf extract completely

inhibited the growth of most bacterial species within 1 to 4 hours. On the other hand, hydromethanolic extract of the *S. polyanthum* leaves treated against the causative agents of bovine mastitis: *S. aureus*, *Staphylococcus hyicus* and *Staphylococcus intermedius* revealed weak growth inhibition[78].

Famuyide *et al.*[79] evaluated the antibacterial activity of acetone leaf extracts of various plant species from the Myrtaceae family. Results showed that *Syzygium legatti* extract was very effective against diarrhoeagenic strains of *E. coli* (MIC: 0.05 mg/mL) followed by *Syzygium masukuense* (MIC: 0.06 mg/mL). In addition, *S. masukuense* also showed significant reduction in the number of adhered *E. coli* to the Caco-2 enterocytes in an anti-adhesion assay. A separate study done by the same authors looked further into the morphological damage of pathogenic *E. coli* when exposed to the MIC of *S. legatti* extracts[80]. Electron microscopy showed alteration and disfigurement of *E. coli* cellular morphology, which provided clear evidence of its effectiveness in inhibiting the growth of bacteria. Likewise, *S. legatti*, *S. masukuense* and an unidentified *Syzygium* sp. exhibited significant antibacterial effect against Gram-positive and Gram-negative bacteria, with MIC varying from 0.04 to 0.08 mg/mL[15]. Anti-biofilm properties of *S. legatti* were also seen after extract treatment.

Additionally, MIC and time-kill assay were utilised for the determination of antibacterial activities of *Syzygium caryophyllatum* against *S. aureus*, *E. coli*, *S. typhi*, *Shigella flexneri* and *V. cholerae*[81]. Results showed that the bacterial samples were sensitive to aqueous and, more potently, ethanolic leaf extracts. In the time-kill assay, all tested bacteria were killed by the extracts of *S. caryophyllatum* within 2 hours of treatment. *S. aureus* and *S. typhi* were seen particularly sensitive to the extracts with 1-hour kill time. The lowest MIC values (0.075 mg/mL) were recorded against *S. typhi* and *V. cholerae* when treated with ethanolic extracts.

Antiviral activity of *Syzygium Sp.*

Viruses reproduce by infecting a susceptible cell and hijacking the cell's machinery to generate more copies of itself. The genetic material of the virus is either DNA (double-stranded) or RNA (single-stranded)[82]. Generally, viruses cause a broad range of pathological effects ranging from a self-resolving acute condition to chronic fatal disease. Various emergent strains of viruses that have caused pathological disease include the COVID-19 coronavirus, Ebola virus, Nipah virus, Marburg virus, and enterovirus. Some viruses are highly associated with carcinogenesis, such as human papillomavirus (HPV), which confers a high risk of developing cervical cancer, and hepatitis B virus, which will induce hepatocellular carcinoma[83].

To this day, a range of antiviral drugs have been approved for the treatment of viral infections, such as ribavirin for hepatitis C, which targets the viral protein NS5A, NS5B polymerase, and NS3/4 protease[84]. On the other hand, genital ulcers mainly caused by the herpes simplex virus (HSV) are highly prevalent worldwide, with 10 to 60% of the general population affected by HSV type 2[85]. The antiviral drug against this virus, acyclovir, had been a cornerstone for HSV infection therapy as it showed an exceptional safety record. Acyclovir has since given rise to its prodrugs valacyclovir, penciclovir, and famciclovir[86].

Currently, available drugs used in the management of viral infections often exert undesirable adverse effects. For instance, the bone mineral density of patients with human immunodeficiency virus (HIV) infection may be reduced with prolonged use of the antiviral drug tenofovir[87]. Akin to drug-resistant bacteria, the advent of drug-resistant viral strains has become a primary concern and threat to society[88].

To address this issue, researchers have shifted their focus towards plant-based antiviral compounds. *Sambucus nigra* L., also known as the black elder, is a commonly used plant-based medicine for viral infection treatment, particularly for influenza. The United States Food and Drug Administration (USFDA) recognised that this plant was generally safe to be used as treatment[89]. Another example is silvestrol, a metabolite of *Aglaia foveolate*, which was discovered to exert a potent antiviral effect on the Ebola virus, Picornavirus, and Coronavirus. The antiviral activity of this compound was *via* the inhibition factor to the DEAD-box RNA helicase eukaryotic initiation factor-4A (eIF4A) that perturbs the viral translation process[90].

In this section, the antiviral properties of *S. cumini*, *S. aromaticum*, and *S. alternifolium* are explored – although the literature is not as comprehensive as the antibacterial effects of *Syzygium*. The key findings are summarised in Table 2.

Syzygium cumini

As mentioned, *S. cumini* fruits contain pharmacologically active phytochemicals that exert a wide range of therapeutic effects, including antiviral,

Table 2 — Summary of antiviral activities from selected *Syzygium* sp.

Species	Preparation Method	Target Virus	Key Findings
Syzygium cumini	Tannic acid incorporated with silver nanoparticles (TA-AgNPs)[93]	Herpes Simplex Virus-2 (HSV-2)[93]	TA-AgNPs showed antiviral activity by interfering with viral adsorption; reduced virus titer in vaginal tissues and improved clinical outcomes in mice[93].
Syzyzium aromaticum	Clove extract rich in eugeniin[28]	Hepatitis C virus[28] Herpes simplex virus (HSV-1)[28] Varicella zoster virus[95]	Eugeniin inhibited viral DNA polymerase activity; inhibited viral adhesion, penetration, and transcription[28,94,95].
Syzygium alternifolium	Copper oxide nanoparticles (CuO NPs) derived from fruit extract[100]	Newcastle Disease Virus (NDV)[100]	CuO NPs demonstrated growth inhibition of NDV. Nanoparticles were characterised as spherical (2–69 nm) and confirmed to stabilise viral inhibition[100].

antifungal, anti-inflammatory, antioxidant, and antidiabetic effects[91]. Phytochemical screening of the leaf extract revealed a composition of tannins, steroids, flavonoids, alkaloids, phenols and saponins[92].

A study on tannic acid, a polyphenolic compound from tannins, demonstrated antiviral properties by interfering with the adsorption of the virus. In the study, tannic acid was incorporated with silver nanoparticles (TA-AgNPs) to treat genital herpes infection. Herpes simplex virus 2 (HSV-2)-infected mice were treated with TA-AgNPs intravaginally, and the findings showed a low virus titer in the vaginal tissues as well as a good clinical score[93].

Syzygium aromaticum

Clove extracts are rich in phytochemicals such as eugenol (which makes up about 95% of the phytochemical composition), methyl salicylate, acetyl eugenol, β-caryophyllene, and pinene[28]. Eugeniin from *S. aromaticum* possesses antiviral properties *via* the inhibition of the viral DNA polymerase enzyme. Its antiviral efficacy can be seen in its effect on the hepatitis C virus and various strains of herpes virus[28].

From a study on wild type 1 HSV (HSV-1) – infected Vero cells, the effective concentration of eugeniin was 5 μg/mL. The study also showed that eugeniin can inhibit late viral protein and DNA synthesis in the infected Vero cells[94]. Another *in vitro* study on eugeniin revealed an antiviral mechanism against the varicella-zoster virus in a reporter cell line (MV9G cells) – the inhibition of adhesion or penetration of cell-free viruses to MV9G cells. The compound also caused a direct inactivation of the virus and transcription inhibition of the virus immediate-early gene 62 (IE62)[95].

Syzygium alternifolium

S. alternifolium is locally known as adavineredu or mogi, and native to the Indian districts of Chittor, Cuddaph, Kurnool, and Nagari hills[96,97]. It is a flowering, semi-evergreen tree that inhabits a dry forest in the South-Eastern Ghats. *S. alternifolium* can grow at elevations of 600 – 1000 meters in dry, slate and rocky environments[98] and is documented by the International Union for Conservation of Nature's - The Conservation Assessment and Management Plan (IUCN-CAMP) as a globally endangered species[99].

To evaluate antiviral activity against Newcastle Disease Virus (NDV), Yugandhar *et al.* utilised *S. alternifolium* fruit extract to synthesise copper oxide nanoparticles (CuO NPs)[100]. The study employed different microscopic and spectroscopic tools to characterise the synthesised CuO NPs. To confirm the synthesis of CuO NPs, analysis using UV–Vis showed a peak at 285 nm. Spectroscopic analysis was done using FTIR, which confirmed that the nanoparticles were involved in stabilising the capping of nanoparticles. Microscopic analysis using TEM, SEM, and AFM revealed that the CuO NPs were spherical particles of 2 – 69 nm in size. Based on the study, nanoparticles extracted from *S. alternifolium* exhibited a growth inhibition effect on the NDV virus[100]. Copper oxide nanoparticles, on their own, have been proven to inhibit viral growth – underlining their potential in the development of new antivirals[101].

Antifungal activity of *Syzygium Sp.*

Fungi are eukaryotic organisms with a large biodiversity of species. From mushrooms to mould, they are known for their heterotrophic characteristics to absorb nutrition since the chlorophyll pigment is absent[102]. They may cause serious health issues to humans as fungal infections are notoriously challenging to treat. Fungal infections usually occur in immunocompromised individuals and rarely infect a healthy person with a functioning immune system[103].

Some of the clinically significant fungi include *Aspergillus* sp., *Cryptococcus* sp., *Candida* sp., and *Pneumocystis*[104]. The isolation and identification of these fungi are helpful in determining the most suitable treatment regime as they have an almost indistinguishable appearance on tissue[105].

Antifungal medication may be categorised into three major groups - polyenes, echinocandins, and azole[106]. The polyenes family mainly consists of amphotericin B and nystatin. Amphotericin B is known as a gold-standard fungicidal drug, highly practical for the treatment of systemic fungal infections[107]. On the other hand, a membrane-active polyene macrolide, nystatin, is generally used for the prevention of systemic or oral candidiasis in immunocompromised patients and infants with immature immune systems[108]. Caspofungin, from the family of echinocandins, is an alternative drug for paediatric prophylaxis and treatment from invasive *Candida albicans* infections[109,110].

The emergence of single- and multiple-drug resistance in some fungal species is an alarming development. Among the *Candida* and *Aspergillus* species, some strains developed resistance to the drug Azole. As such, continuous development of antifungal drug discovery initiatives is essential as it will conserve the availability of effective treatment options for fungal infections[111].

In a study of selected Malaysian medicinal plants to discover potential antifungal compounds, a hexane extract from *Cissus quadrangularis* demonstrated strong antifungal activity. In addition, ethanol, chloroform, ethanol, and hexane extracts from *Pereskia bleo* similarly showed fungicidal activity[112], underscoring the need to unearth the wealth of antifungal phytochemicals from nature.

In the following section, the antifungal properties of *S. aqueum*, *S. samarangense*, and *S. polyanthum* are discussed (Table 3).

Syzygium aqueum

S. aqueum, also known as the water apple or watery-rose apple, bears distinctly shaped broadly campanulate fruit with incurved and persistent calyx lobes. The leaves have numerous oil dots on the surface with grooved midribs on the upper surface of the leaves. *S. aqueum* can be found throughout Southeast Asian regions, such as Malaysia, Myanmar, Indonesia, New Guinea, and Australia. The edible fruit can be eaten raw, with a crispy and juicy texture[113].

Many parts of the tree are used in traditional medicine; for instance, the leaf infusion can aid in the treatment of dysentery and stomachaches[114]. In a study to identify phenolic compounds from *Syzygium* sp., the presence of flavonoids, tyrosols, phenolic acids, lignans, stilbenes, and alkylphenols was recorded. *S. aqueum* was reported to contain the highest concentrations of phenolic compounds, cumulatively amounting to 266.4 mg/g in dry matter[115].

Consistent with this finding, Aboody *et al.* investigated a class of naturally occurring phenolics, flavonoids, which possess significant antifungal activity. This phenolic compound is a secondary

Table 3 — Summary of antifungal activities from selected *Syzygium* sp.

Species	Active Compounds/Extract	Target Fungi	Key Findings
Syzygium aqueum	Quercetin-3-O-rutinoside (flavonoid)[116] Phenolic acids[117]	*Candida albicans*[116,117]	Quercetin-3-O-rutinoside demonstrated significant activity; phenolic acids found to disrupt virulence factors such as hyphae formation and biofilm synthesis[116,117,119].
Syzygium samarangense	Chalcone derivatives (e.g., 6-quinolinyl N-oxide chalcone 4c)[122] Tannins (e.g., Tellimagrandin II)[125]	*Paracoccidioides spp.*[122] *Candida parapsilosis*[125]	Chalcone derivative 4c reduced colony-forming units in murine lungs similar to itraconazole[122]. Tellimagrandin II inhibited growth of *Candida parapsilosis*. Scanning electron microscopy (SEM) confirmed antifungal activity[125].
	Leaf extract[126]	*Candida albicans, C. krusei, C. parapsilosis, C. glabrata, C. auris, C. tropicalis*[126]	*Syzygium samarangense* leaf extracts (SSLE) showed fungicidal activity in disc diffusion assays and SEM, *ex vivo* assays on porcine and *D. melanogaster* models[126].
Syzygium polyanthum	Saponins (Holothurin A, Echinoside A) Steroidal saponins[132]	*Candida albicans*[132]	Saponins inhibited fungal growth across Candida albicans isolates; structural variations of steroidal saponins influence antifungal activity[132]. Emphasis on structure-activity relationships for future studies[133].

metabolite found abundantly in plants such as *S. aqueum*. The group screened for antifungal activity using agar wells, disc diffusion, broth dilution, and spore germination. Quercetin-3-O-rutinoside, a plant-derived flavonoid, was found to exert a significant effect on *C. albicans* (MIC: 16 μg/mL)[116].

Aside from flavonoids, other studies suggest that naturally derived phenolic acids demonstrated antifungal properties against the *Candida* species[117]. The composition of phenolic acids in the extract should be clearly defined for novel antifungal agents to be elucidated[118]. Zhang *et al.* showed that other phenolic molecules can be seen to affect the virulent factors of *Candida*, including bisbibenzyl, which was found to stimulate the synthesis of farnesol. By upregulating the Dpp3 gene, farnesol can inhibit *C. albicans* hyphae formation, which in turn stunts biofilm formation[119].

Syzygium samarangense

Java apples or wax apples (*S. samarangense*) are cultivated in Asian regions such as Malaysia, Indonesia, Taiwan, and Thailand[120]. The wax apple is an evergreen tree that can grow up to 5 - 15 meters tall[61]. The fruit is usually light red or pink with a refreshing and juicy texture, as it contains up to 90% water.

S. samarangense has been reported to harbour medical benefits, as the plant is rich in flavonol glycosides, proanthocyanidins, tannins, triterpenoids, volatile terpenoids, and chalcones[121]. Studies showed that chalcones, along with its derivatives, exert antifungal, antibacterial, anti-inflammatory, and antinociceptive activity[122]. A study using a murine model treated with chalcone derivatives, 6-quinolinyl N-oxide chalcone 4c, exerted antifungal activity against *Paracoccidioides* spp. Compound 4c showed similar activity to itraconazole, a known antifungal drug. The number of colony-forming units (CFU) of *Paracoccidioides* spp. recovered from mice's lungs were effectively reduced. These findings suggested that chalcones may be a potential antifungal compound for the treatment of paracoccidioidomycosis[123].

Another derivative from the Java apple plant is tannins, a group of phenolic metabolites ubiquitous to most vegetation. The two major groups of tannins are hydrolysable tannins and proanthocyanidins[124]. One of the hydrolysable tannins, tellimagrandin II, showed promising antifungal activity. This compound was found to inhibit the growth of *Candida parapsilosis* strain ATCC 22019 (MIC: 1.6 μM), with confirmatory studies using SEM[125]. The antifungal activity of *S. samarangense* leaf extracts has also been proven to be effective against six different *Candida* species, including C. *albicans*. This was revealed in SEM-visualised cell wall degradation as well as decreased fungal counts in porcine and *Drosophila melanogaster* (fruit fly) *ex vivo* models[126].

Syzygium polyanthum

Commonly known as the Indian bay leaf, *S. polyanthum* is a medium-sized evergreen tree that could grow up to 30 meters in height. Among Malaysians, this plant is usually recognised as "serai kayu", "samal kelat "or "salam". *S. polyanthum* can be found abundantly in the Southeast Asian region, including Malaysia, Indonesia, Thailand, and Singapore. The plants thrive in forests or hilly areas and are usually seen planted in gardens near residential areas[127]. Several parts of the plant – its leaves, fruits, and bark are traditionally used for many remedies. The fruits and the roots are consumed to alleviate hangovers from alcohol consumption, and the leaves may counter various illnesses such as skin disease, ulcers, diabetes, hypertension, and infections[128,129].

Current literature shows that phytochemical composition differs between the leaves and unripe or ripe fruit. The unripe fruit and leaves of *S. polyanthum* contain tannins, steroids, alkaloids, triterpenoids, and flavonoids, while the ripe fruit contains all of these, and in addition, saponins[130]. This unique compound found in ripened fruit possesses diverse pharmacological, biological as well as physicochemical activities[131]. In a study to determine the antifungal properties of saponins against isolates of *C. albicans*, the parent compounds were separated into two fractions, namely Holothurin A and Echinoside A, by reverse-phase semi-preparative HPLC. Both compounds were screened against different *Candida* strains - *Candida* 580(1), *Candida* 581(2) and *Candida* MEO47228. The study revealed positive antifungal activity, and thus, saponins may be considered in the treatment of fungal infections[132]. Steroidal saponins exert a different biological activity, depending on their aglycone moieties and the structure and number of monosaccharide sugar chains. A slight difference in structural conformation can affect their cytotoxic and antifungal properties[133], underlining the need for further work on structure-activity associations in novel drug discovery.

Evaluating the cytotoxicity of *Syzygium* extracts

The plant extracts from *Syzygium* species must be evaluated through toxicity studies before they can be

developed as a safe pharmaceutical product. When clove essential oil was screened against human fibroblasts and dermal endothelial cells to simulate topical application, the data showed clove essential oil was highly toxic at concentrations as low as 0.03% (v/v). Of the bioactive components within the oil, 54-73% of cytotoxic activity was attributable to eugenol[134]. The brine shrimp lethality assay revealed that clove essential oils exhibit the most potent toxicity (LD_{50}: 37 µg/mL), followed by ethanol (LD_{50}: 103 µg/mL) over a 24-hour course. The aqueous extract caused zero mortality even up to the highest test concentration[135].

On the other hand, methanolic extracts of clove were recorded to be safe even up to a concentration of 100 mg/mL when tested on peripheral blood mononuclear cells[32]. In contrast, another cytotoxicity study on a human hepatoma cell line revealed that methanolic clove extract was the most toxic (IC_{50}: 24.17 µg/mL) when compared to extracts from other solvents. Clove extract of diethyl ether was reported to be the safest, with a relatively high IC_{50} of 62.43 µg/mL. The proportion of eugenol present in diethyl ether extract (66.48%) was recorded as slightly higher than the methanolic extract (55.58%)[136]. Therefore, the proportion of eugenol may not be a viable parameter in predicting the cytotoxic potential of clove extracts. In short, the data on clove extract toxicity are inconsistent, prompting the need for further studies to elucidate the underlying cytotoxic mechanisms of eugenol and other compounds isolated from the clove.

In a study depicting the anti-Leishmania activity of *S. cumini*, a negligible toxic effect was observed from the exposure of murine peritoneal macrophages and human red blood cells to *S. cumini* essential oil. The extracts exhibited high selectivity for *Leishmania amazonensis* compared to mammalian cells, with a selectivity index (SI) of 10.2 - 16.1 (macrophages) and 14.5 - 22.9 (erythrocytes). Remarkably, the first-line drug Glucantime® used clinically to treat leishmaniasis showed stronger cytotoxicity against these cells than Leishmania, with SI values lower than 1[137]. An *in vivo* study showed that *S. cumini* leaves had a good safety profile when administered orally at doses up to 2 g/kg in rats and 6 g/kg in mice. However, a 100% mortality rate was observed when using a dose of 1 g/kg *via* intraperitoneal administration. The LD_{50} value was reported as 0.489 g/kg in mice. On the other hand, a 67% death rate was observed in rats at the highest dose of 2 g/kg of extract[138].

The crude ethanolic leaf extract of *S. guineense* was shown to be relatively toxic towards LLC-MK2 monkey kidney epithelial cells in an *in vitro* cytotoxicity study. The 50% cytotoxic concentration (CC_{50}) of the extracts was 77.9±0.71 µg/mL, with minimal selectivity against *Plasmodium falciparium*. In an acute toxicity study, the LD_{50} value of the extract was determined to be over 5000 mg/mL since it had caused death in 20% of mice[139].

As for *S. jambos*, its ethanolic leaf extract was observed to be toxic to B16-F10 mouse melanocytes (EC_{50}: 60.0 µg/mL) but not to U937 human macrophage cells (EC_{50}: 440.0 µg/mL). The compounds myricetin and gallic acid isolated from *S. jambos* were reported as 'moderately toxic' to both cell lines[73]. Likewise, *S. jambos* leaf extract was observed to be relatively toxic against *Artemia franciscana nauplii* with 48 and 72 hour LD_{50} values of 387.9±38.8 and 87.0±11.3 µg/mL, respectively[74].

On the other hand, the *S. polyanthum* extract had been proven to be weakly toxic against 4T1 and MCF-7 mammary carcinoma cells with IC_{50} values of 672.57±59.42 and 126.05±50.89 µg/mL, respectively[78]. Mild cytotoxicity effects were also seen in other species, such as *S. legatti*, *S. masukuense* and an unidentified *Syzygium* species against the Vero African green monkey kidney cells. Generally, the SI values were greater than 1, which clearly indicated that the extracts were more potent against the tested pathogen than mammalian cells[15].

To assess the toxicity of the modified tannic acid with silver nanoparticles (TA-AgNPs) for antiviral effect, a study used human-derived keratinocytes (HaCaT) in the form of spheroids and stationary cultures. After exposure to the complexes, the cell line showed activation of ERK kinase and reduced production of reactive oxygen species (ROS). A Comet assay showed that the size of TA-AgNPs above 30 nm did not cause DNA breakdown. The *in vitro* toxicity testing of TA-AgNPs presented a good toxicological profile with a size above 30 nm[140]. In a toxicity assessment of the *S. samarangense* extract, researchers showed that there was not only minimal cytotoxicity in Vero cells but also no mutagenicity in mice[125].

Based on these cytotoxicity studies, most *Syzygium* extracts were found to be minimally toxic at low concentrations, although these were preliminary *in vitro* or *in vivo* experiments. To date, there is yet to

be a clinical trial on the toxicological profiles and safety assessments of patients treated with these phytochemicals for antimicrobial indications.

Discussion and Conclusion

The *Syzygium* genus emerges as a remarkable source of bioactive compounds with diverse and potent anti-pathogenic properties. This review has underscored its potential, particularly in combating bacterial pathogens, where multiple species have demonstrated robust efficacy against both Gram-positive and Gram-negative bacteria. Phytochemicals such as phenolics, flavonoids, triterpenes, and tannins have been identified as key contributors to these effects, functioning through mechanisms like disrupting microbial cell membranes, inhibiting biofilm formation, and downregulating quorum-sensing pathways. These findings not only highlight *Syzygium*'s pharmacological promise but also suggest its suitability as a complementary or alternative treatment, especially in the face of escalating antimicrobial resistance.

However, our exploration reveals that antiviral and antifungal activities within the genus remain under investigated. While preliminary studies indicate promising results - for example, eugenol-rich extracts targeting viral adhesion or tannin derivatives disrupting fungal virulence-these findings need further validation through more extensive research. Equally important is the refinement of extraction techniques to enhance yield and purity, enabling a deeper understanding of the specific compounds responsible for these effects.

From a translational perspective, *Syzygium* extracts appear to have a favourable safety profile in preliminary studies on mammalian cells and animal models. Yet, the potential for side effects, such as disruptions to normal microbiota or cytotoxicity at higher concentrations, must be thoroughly assessed before advancing to clinical applications. Looking ahead, the road to harnessing *Syzygium*'s full potential lies in several key areas. Future work should prioritise the isolation of individual compounds and rigorous testing to ascertain their therapeutic viability. The unexplored diversity of *Syzygium* species also offers untapped opportunities for discovering novel bioactive molecules. Moreover, standardised protocols for antimicrobial assays and toxicity studies are crucial to facilitate comparisons across studies and ensure the reliability of findings.

In conclusion, *Syzygium* species hold immense promise as a source of novel, sustainable, and cost-effective antimicrobial agents. As we stand on the brink of a post-antibiotic era, these evergreen trees symbolise hope - offering a natural and holistic solution to some of the most pressing challenges in modern medicine. By investing in the detailed exploration of their therapeutic properties, we may yet unlock their full healing potential and contribute to a healthier, more resilient future.

Conflict of interest

The authors declare that they have no conflict of interest.

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