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Deciphering the Composition and Bioactivity of Malaysian *Syzygium* Essential Oils: Insights from Multivariate Chemometrics and Molecular Docking Studies

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Abstract: The genus *Syzygium*, an important member of the Myrtaceae family, comprises over 1200 species, primarily found in the tropical regions of Asia. *Syzygium* species are valued throughout their range for their medicinal and economic importance. Characterized by aromatic shrubs and trees, these species are prolific producers of essential oils that are widely used for their natural therapeutic effects in food, medicine, and cosmetics. In recent years, studies have focused on the essential oils of Malaysian *Syzygium* species, many of which have reported interesting pharmacological activities. This review attempts to summarize the information on the essential oils of Malaysian *Syzygium* species in terms of their medicinal uses, chemical composition, and bioactivity. The information on *Syzygium* species was collected through electronic searches (PubMed, SciFinder, Scopus, Google Scholar, and Web of Science) and a library search for articles published in peer-reviewed journals. Our results cover eight *Syzygium* species in Malaysia and highlight eugenol, caryophyllene, *α*-pinene, *α*-humulene, and viridiflorol as the predominant components. Multivariate chemometric analyses, including hierarchical cluster analysis (HCA) and principal component analysis (PCA), were used to discriminate the essential oils based on their chemical profiles. Antibacterial and cytotoxic activities were the most frequently reported bioactive properties. In addition, molecular docking simulations provided insights into the binding interactions of the major components with the active sites of enzymes related to these bioactivities. This review aims to provide comprehensive information on the chemical components and biological properties of the essential oils of Malaysian *Syzygium* species and provide guidance for the selection of accessions or species with optimal chemical profiles.

Keywords: Myrtaceae; *Syzygium*; essential oil; binding affinity; molecular dynamics; multivariate.

1. Introduction

Over millions of years, natural products have evolved a unique chemical diversity that influences their biological activities and drug-like properties, making them a crucial factor in the development of new drugs for the treatment of human diseases [1]. Essential oils, in the form of phytocomplexes, and individual classes of compounds such as polysaccharides, phenols, alkaloids, steroids, lignins, resins, and tannins, are extracted from plants due to their great importance in many sectors such as medicine, agriculture, food, and cosmetics. To date, scientists have identified over 3,000 essential oils from approximately 2,000 different plant species, with around 300 being commercially used for a wide variety of applications [2]. Research has consistently shown that essential oils exhibit a broad spectrum of pharmacological activities, including antioxidant, antimicrobial, antiviral, anti-mutagenic, anti-cancer, anti-inflammatory, and immunomodulatory effects [3].

The genus *Syzygium* (Figure 1) is one of the largest and most important aromatic and medicinal plants of the Myrtaceae family, comprising over 1,200 species distributed across tropical and subtropical regions. *Syzygium* species are the most representative within the Myrtaceae family [4]. Common characteristics of Myrtaceae taxa include glossy green leaves and brightly colored flowers, making them popular ornamental plants. The leaves have oil glands that make them aromatic when crushed. These plants typically have simple, opposite leaves with entire margins and bisexual, actinomorphic flowers with numerous stamens. The flowers have subtended ovaries, and the fruits are usually capsules, berries, or drupes with many seeds [5].

Figure 1. Malaysian Syzygium species: **(a)** *S. aromaticum*; **(b)** *S. polyanthum*; **(c)** *S. dyerianum*; **(d)** *S. malaccense*; **(e)** *S. aqueum*; **(f)** *S. grande*; **(g)** *S. samarangense*.

Syzygium species have long been used in traditional medicine to treat diseases, demonstrating this genus's economic importance in herbal medicines. For example, the leaves

of *S. aqueum* are traditionally used to treat stomach ache, the roots of *S. cordatum* are used to treat colds, and the fruits of *S. caryophyllum* are used to treat diabetes [6]. In Malaysia, *Syzygium* species, commonly known as "jambu" and "kelat", are extensively utilized. The fruits of *Syzygium samarangense* (wax apple) and *Syzygium malaccense* (Malay apple) are often eaten raw by the local population. "Jambu" is widespread in Malaysia, where these plants are often found in residential areas, indicating their integration into daily life and traditional practices. Additionally, the fruit holds value in local markets with increasing consumer demand for high-quality fruits [7]. Beyond human treatment, *Syzygium* is also used in the food industry. *S. aromaticum* has been found to act as a disinfectant to improve the freshness of fruit for export [8]. Furthermore, *S. cumini* has the potential to be used as one of the alternative treatments for the current COVID-19 outbreak [9].

Extensive research on *Syzygium* species has led to the identification of numerous pharmacologically active compounds, including flavonoids, tannins, anthocyanins, and triterpenoids. They have been extensively investigated as sources of new natural products with potential antioxidant, antimicrobial, antifungal, anticholinesterase, anti-inflammatory, anti-tyrosinase, and insecticidal activities [6,10,11]. Recently, interest in essential oils and other aromatic compounds extracted from plants and used in alternative medicine has increased. Therefore, a comprehensive review of *Syzygium* essential oils is needed to consolidate and summarise the available information. The data for this review were collected through electronic searches in databases such as Scopus, PubMed, ScienceDirect, SciFinder, and Google Scholar. This review aims to provide an overview of the chemical composition, biological activities, and medicinal applications of Malaysian *Syzygium* essential oils based on all published reports.

Recently, chromatographic fingerprint analysis has become established for quality control in herbal medicine. It can effectively address problems related to the identification and authentication of multicomponent substances such as herbal extracts and essential oils. Combining chromatographic fingerprint data with multivariate analyses enables a comprehensive understanding of the overall chemical composition [12]. Multivariate analysis, a statistical technique for analysing complex data sets with multiple variables simultaneously, has been used extensively in this field to investigate the interactions between different chemical constituents due to the inherent complexity and diversity of natural products [13]. Principal component analysis (PCA) is a tool for multivariate exploratory data analysis that helps to identify similarities and differences between samples, group them together, and examine the correlations between variables. In contrast, hierarchical clustering analysis (HCA) groups items based on their similarities using certain characteristic variables. HCA is becoming increasingly popular in the quality control of plant materials. The combination of PCA and HCA helps to determine the variation of chemical components in individual Malaysian *Syzygium* essential oils and to reveal the relationships between species from different regions and their chemical compositions. These methods also help researchers to develop ideas about the possible activities of the chemical clusters of the phytocomplex. PCA and HCA are therefore recognised as valuable tools for the quality control of herbal medicine [14].

Molecular docking, a well-known biomolecular simulation technique, is used to predict the binding values of ligand-target complexes with high accuracy. This calculation method evaluates various energy profiles, including binding energy, binding length, binding strength, and binding constants. By calculating the interaction strengths and quality between micromolecular ligands and macromolecular protein targets, molecular docking defines preliminary interaction parameters [15]. In addition, these techniques facilitate the prediction

of binding modes and affinities at the molecular or atomic level, which promotes drug discovery and the identification of new bioactive compounds. Molecular docking, widely used in drug discovery and virtual screening, helps in the discovery of new active biomolecules, such as bioactive peptides [16]. Starting from the bioactivities, we perform molecular docking of the main components in Malaysian *Syzygium* essential oils to the active sites of the enzymes related to these bioactivities. The molecular docking simulations were performed using the AutoDock Vina program integrated in PyRx.

2. Search Strategy

The protocol for conducting this study was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. First, duplicate articles were excluded. The titles and abstracts were screened based on the inclusion and exclusion criteria. Next, the full texts of the remaining articles were screened, applying the criteria again. Figure 2 illustrates the flowchart of the article identification and selection process, which resulted in the final selection of articles for the study.

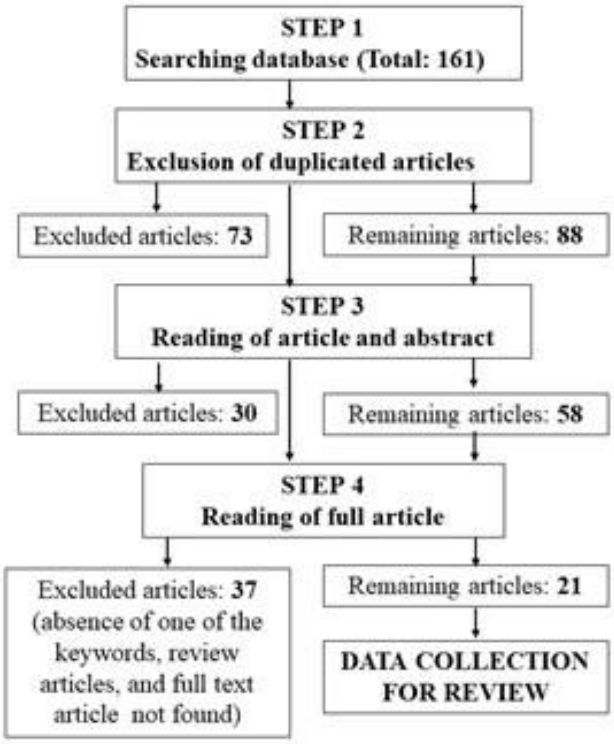

Figure 2. PRISMA flow diagram of included studies.

The systematic review included searches in Scopus, PubMed, ScienceDirect, SciFinder, and Google Scholar using the keywords 'Syzygium', 'essential oil', and 'biological activity', covering the period from the start of the respective database to 2025. In addition, a manual search of the reference lists from included studies was performed as a secondary strategy. The review included studies on the genus *Syzygium* reported from Malaysia, focusing on traditional uses, essential oils, and bioactivities. The inclusion criteria were: (1) original research articles, (2) articles in English, (3) articles presenting the chemical composition of Malaysian *Syzygium* essential oils, and (4) articles discussing the bioactivity of these oils. The exclusion criteria were: (1) articles without search terms in the title or abstract, (2) review articles, (3) inaccessible full-text articles, (4) articles in which one of the keywords was missing, and (5) articles that did not provide information on the composition of the essential oils. Values are

presented as mean ± SEM, and statistical significance was determined using one-way ANOVA. Differences were considered significant at $p < 0.05$. To evaluate variations in essential oil profiles according to geographic origin, multivariate analyses were applied, specifically principal component analysis (PCA) and hierarchical cluster analysis (HCA). Both PCA and HCA were conducted using MINITAB Version 16.2.3 statistical software (Minitab Incorporated, State College, PA, USA).

3. Medicinal Uses

Syzygium species have long been recognised for their medicinal properties. Essential oils are extracted from various parts of the plant, including leaves, cloves, fruits, roots, stems, and bark, and are used for different purposes: (i) in medicine, (ii) for direct consumption, and (iii) in therapeutic applications. These essential oils are traditionally consumed as daily remedies to treat ailments and promote overall physical and mental health. They are also widely used in perfumes, cosmetics, health, medicine, flavoring, and food industries [18]. Table 1 shows the medicinal uses of Malaysian *Syzygium* species.

Table 1. Medicinal uses of several Malaysian *Syzygium* species.

Species	Local Name	Part	Medicinal uses
S. dyerianum	'Haji Samat', 'Lebai Samat', 'Ubai Samak'	Leaf, stem, roots	Enhancing sexual desire [4].
S. aromaticum	'Pokok Halau Nyamuk'	Clove	Treating asthma, digestive system and respiratory disorders, headaches, sore throat, toothache, sore gums, and oral ulcers, and are also employed in dentistry, as natural repellents, and as herbs and spices [19-22].
S. polyanthum	Bay leaves, 'Serai Kayu', 'Daun Salam', 'Kelat'	Leaf	Treating gastritis, hypercholesterolemia, skin diseases, diabetes mellitus, malaria, postpartum, hypertension, diarrhea, endometriosis, and as herbs and spices [22-24].
S. malaccense	'Jambu Bol', 'Jambu Merah', Malay Apple	Fruit, Root, Leaf	Used in dermatological, digestive, head and throat, and endocrine remedies [25].
S. aqueum	Watery Rose Apple, Water Apple	Leaf, Root	Treating a cracked tongue, relieving itching, and reducing swelling [26].
S. grande	Sea Apple, 'Jambu Ayer Laut', 'Jambu Laut', 'Jemba'	Fruit	Treating cough, piles, tooth diseases, dysentery, bronchitis, and diabetes [27].
S. samarangense	Wax Apple, 'Wax Jambu', 'Jambu Air', Bell Fruit	Fruit, Leaf, Flower, Root, Stem, Bark	Treating edema, skin itching, menstrual pain, asthma, bronchitis, fever, waist pain, mouth ulcers, sore throat, and high blood pressure. They also act as stimulants to increase urine levels, improve blood circulation in the pelvis and uterus, serve as astringents for treating diarrhea, relieve thirst, treat a cracked tongue, reduce swelling, and relieve itching [28,29].

4. Chemical Composition of Essential Oils

In earlier studies, we have analysed the composition of the essential oils from eight *Syzygium* species. These species include *S. aromaticum*, *S. polyanthum*, *S. pyrifolium*, *S. cerinum*, *S. dyerianum*, *S. fliforme*, *S. malaccense*, and *S. variolosum*. They were mainly found in Pahang, as well as in Selangor, Terengganu, and Kuala Lumpur. One species, namely, *S. aromaticum*, was purchased from a local market in Malaysia [30]. The essential oils were mainly extracted from the leaves, cloves, stems, and fruit of these plants. The essential oil of *S. aromaticum* has been extensively studied in Malaysia, especially its clove part. This oil contains significant amounts of eugenol, ranging from 24.3% to 74.0%, and caryophyllene, ranging from 7.5% to 19.4%. Remarkably, the clove essential oil of *S. aromaticum* from Selangor contains the highest number of components, with fifty-two identified constituents. Due to its versatility and numerous benefits, *S. aromaticum* was considered the most

remarkable species within the genus *Syzygium*. Meanwhile, *S. dyerianum* has the highest percentage of total oils with thirty-one identified constituents, accounting for about 99.5% of the total oils [4]. The chemical analysis of the essential oils of *Syzygium* shows that the oil is mainly composed of oxygenated monoterpenes, sesquiterpene hydrocarbons, oxygenated sesquiterpenes, phenylpropanoids, ketones, fatty acids, and alcohols. Table 2 shows the major constituents identified in the essential oils of *Syzygium* from different states in Malaysia.

Table 2. Major components identified from the essential oils of Malaysian *Syzygium* species.

Species	Locality (Label)	Part	Total No. (%)	Method (Yield)	Major components
S. dyerianum	Pahang (**SDL**)	Leaf	31 (99.5%)	Hydrodistillation (0.2%)	*β*-Pinene (15.6 %), *α*-terpineol (13.3%), *α*-pinene (11.1%) [4].
S. aromaticum	Terengganu (**SAC1**)	Flower bud (Clove)	9 (71.0%)	Steam distillation (3.0%)	Eugenol (49.0%), caryophyllene (7.5%), 2-propanone (4.2%), methylhydrazone (5.6%) [19].
	Selangor (**SAC3**)	Clove	42 (71.3%)	NS	Isobornyl propanoate (53.2 %), (*E*)-isoeugenol (11.4 %), *γ*-muurolene (1.3%) [20].
	Pahang (**SAC4**)	Clove	30 (88.7%)	Hydrodistillation (NS)	Eugenol (48.9%), *β*-caryophyllene (19.4%), eugenol acetate (11.8%) [21].
	Local market (**SAL**)	Leaf	10 (98.5%)	NS	Eugenol (65.8%), eugenol acetate (19.2%), caryophyllene (8.6%) [30].
	Local market (**SAF**)	Floral bud	12 (98.1%)	NS	Eugenol (74.0%), caryophyllene (12.2%), *α*-humulene (4.5%) [30].
	Kuala Lumpur (**SAC2**)	Clove	10 (56.0%)	Hydrodistillation (NS)	Eugenol (24.3%), phenol (18.2%), caryophyllene (9.4%) [31].
S. malaccense	Selangor (**SML**)	Leaf	15 (64.1%)	Hydrodistillation (104.1mg)	Hexanoic acid (12.2%), methyl salicylate (8.3%), 3-hexen-1-*ol* (7.8%) [25].
	Selangor (**SMF**)	Fruit	11 (51.8%)	Hydrodistillation (89.2mg)	*n*-Hexadecanoic acid (18.6%), 9-octadecynoic acid (9.4%), (*Z*,*Z*)-9-12-octadecadien-1-*ol* (6.9%) [25].
S. polyanthum	Selangor (**SPOL1**)	Leaf	18 (62.2%)	Hydrodistillation (0.24%)	*Trans*-*β*-nerolidol (30.9%), farnesol (6.2%), viridiflorol (2.3%) [23].
	Selangor (**SPOS**)	Stem	23 (56.8%)	Hydrodistillation (0.09%)	Cubenol (14.2%), *n*-hexadecanoic acid (11.2%), *α*-cadinol (6.9%) [23].
	Terengganu (**SPOL3**)	Leaf	29 (95.2%)	Hydrodistillation (1.6%)	*α*-Pinene (38.5%), octanal (21.0%), (*E*)-methyl-cinnamate (7.2%) [24].
	Pahang (**SPOL2**)	Leaf	34 (93.9%)	Hydrodistillation (NS)	*α*-Pinene (30.9%), octanal (18.3%), caryophyllene (6.2%) [32].
S. cerinum	Pahang (**SCE**)	Leaf	39 (95.8%)	Hydrodistillation (0.2%)	*β*-Caryophyllene (22.2%), *α*-humulene (19.8%), *β*-selinene (7.2%) [33].
S. pyrifolium	Pahang (**SPYL**)	Leaf	32 (99.5%)	Hydrodistillation (0.9%)	Geraniol (73.8%), *β*-pinene (7.0%), *α*-pinene (5.7%) [34].
S. variolosum	Pahang (**SVL**)	Leaf	32 (98.9%)	Hydrodistillation (0.15%)	*β*-elemene (20.2%), bicyclogermacrene (13.5%), viridiflorol (11.1%) [35].
S. filiforme	Pahang (**SFL**)	Leaf	34 (96.1%)	Hydrodistillation (0.1%)	*α*-Cadinol (23.3%), *t*-muurolol (9.1%), geraniol (6.6%) [36].

NS - not stated

The main components of *Syzygium* essential oils were oxygenated monoterpenes and sesquiterpene hydrocarbons. Eugenol was identified as the predominant component in the clove oil of *S. aromaticum* [19, 21, 30,31]. Among sesquiterpene hydrocarbons, caryophyllene was also a major constituent, found significantly in the clove oil of *S. aromaticum* [19, 21, 30,31] and in the leaf oil of *S. polyanthum* [32]. Additionally, *β*-caryophyllene, an isomer of caryophyllene, was abundant in the clove oil of *S. aromaticum* [21] and in the leaf oil of *S. cerinum* [33]. Furthermore, *α*- and *β*-pinene were dominantly present in the leaf oils of *S. polyanthum* [32,24], *S. pyrifolium* [34], and *S. dyerianum* [4]. In other studies, *α*-humulene was found in the floral bud oil of *S. aromaticum* [30] and *S. cerinum* [33], while *β*-elemene was detected in the leaf oil of *S. variolosum* [35].

Additionally, oxygenated sesquiterpenes were found in several *Syzygium* essential oils. Viridiflorol was present in the leaf oil of *S. polyanthum* [23] and *S. variolosum* [35]. Geraniol was an abundant constituent in the leaf oil of *S. pyrifolium*, with a high percentage (73.8%) [34] compared to *S. filiforme*, which had only 6.6% [36]. Conversely, *α*-cadinol was the principal compound in the leaf oil of *S. filiforme* with 23.3% [36] compared to the stem oil of *S. polyanthum*, which contained only 6.9% [23]. Meanwhile, trans-*β*-nerolidol and cubenol were significant constituents in the leaf oil of *S. polyanthum* [23]. On the other hand, fatty acids were also found as major constituents in the oil. Hexanoic acid was identified in the leaves, while *n*-hexadecanoic acid was found in the fruits of *S. malaccense* oil [25].

The differences in the chemical composition of *Syzygium* species can be attributed to a variety of factors, including the stages of development and the different habitats from which the plants were collected. The intricate interplay of climatic conditions, vegetation stages, and genetic variations influences the chemical and biological diversity observed in aromatic and medicinal plants such as those of the genus *Syzygium*. These factors shape the biosynthetic pathways in plants and thus change the relative proportions of the most characteristic compounds. As secondary metabolites, essential oils play a central role in plant adaptation by enhancing resistance to biotic (e.g., pathogens and herbivores) and abiotic (e.g., UV radiation and temperature extremes) stress factors. During periods of water stress and elevated temperatures, terpenes volatilize and generate air currents that contribute to cooling the plant and reduce transpiration, leading to increased terpene production. In addition, climatic conditions, including temperature and humidity, as well as edaphic factors such as altitude and soil conditions, significantly influence essential oil yield [37].

5. Biological Activities

The literature emphasises the need for extensive research into the pharmacological properties of the essential oils of *Syzygium* species. While some studies have revealed their biological activities, which include antimicrobial, antioxidant, and cytotoxic effects, there remains a great potential that has not yet been fully realized. The traditional use of the genus *Syzygium* reveals its rich medicinal diversity. However, many species traditionally used to treat various diseases are still largely unexplored regarding their bioactivity. This presents a promising avenue for the discovery of new pharmacological properties within this genus. The elucidation of the properties of essential oils is of great importance, as it is essential for functional food and pharmaceutical applications. In the case of Malaysian *Syzygium* essential oils, significant antibacterial [19-20,22,30,31] and cytotoxic [23,35,36] activities have been predominantly reported, with detailed results listed in Table 3.

Table 3. Bioactivity of the essential oils of Malaysian *Syzygium* species.

Bioactivity	Species	Description
Antifungal	*S. dyerianum*	The leaf oil showed activity against *Candida albicans* and *Streptococcus mutans* with MIC values of 125 and 250 µg/mL, respectively [4].
Antibiofilm	*S. dyerianum*	The leaf oil decreases the biofilm formation by 20.11% for *Candida albicans* and 32.10% for *Streptococcus mutans* at a concentration of 250 µg/mL [4].
Antibacterial	*S. aromaticum*	The flower bud (clove) oil showed activity against *Escherichia coli and Streptococcus agalactiae*, with MIC values 0.062 µg/mL and 0.015 µg/mL, respectively [19].
		The clove oil showed activity against *Enterococcus faecalis* and *Streptococcus mutans* with MIC values of 0.63 mg/ml and 1.25 mg/ml, respectively [20].
		The leaf oil showed activity towards *Streptococcus aureus* and *Klebsiella aerogenes* with inhibition zones of 27.18 mm and 19.45 mm, and MIC/MBC values of 0.125/0.125% and 0.125/0.125%, respectively [30].

Bioactivity	Species	Description
		The clove oil showed activity towards *Streptococcus mutans and S. anginosus* with inhibition zones of 10.33mm and 11.00mm, and MIC/MBC values of 100/400 µg/ml and 100/200 µg/ml, respectively [31].
Antioxidant	*S. cerinum*	The leaf oil showed DPPH radical scavenging with an IC_{50} value of 75.6 µg/mL [33].
Acetyl-cholinesterase	*S. pyrifolium*	The leaf oil showed strong inhibitory activity on acetylcholinesterase (AChE) enzyme with a percentage of inhibition of 82.5% [34].
	S. variolosum	The leaf oil showed AChE activity at a concentration of 1,000 µg/mL with 35.2% inhibitory activity [35].
Anti-tyrosinase	*S. variolosum*	The leaf oil showed activity of tyrosinase inhibition with 42.5% [35].
Anti-inflammatory	*S. variolosum*	The leaf oil showed activity at a concentration of 1,000 µg/mL with 48.6% inhibitory activity [35].
Cytotoxicity	*S. polyanthum*	The leaf oil showed toxicity against human peripheral blood mononuclear cells (PBMCs) with a maximum concentration of 11.0 mg/mL and a percentage of cell viability of 72.6-94.0% [23].
	S. filiforme	The leaf oil showed activity against three cancer cell lines, HepG2, MCF7, and A549, with the IC_{50} values of 95.2, 90.2, and 92.5 µg/mL, respectively [35].
	S. variolosum	The leaf oil showed toxicity against cancer cell lines HepG2, MCF7, and A549 with IC_{50} values of 88.1, 70.2, and 75.5 µg/mL, respectively [36].

Notably, two essential oils from *Syzygium* have shown promising antibacterial activities against Gram-negative bacteria (*Escherichia coli* and *Salmonella enteruica*): *S. aromaticum* [19] and *S. polyanthum* [22]. Meanwhile, *S. aromaticum* from Kuala Lumpur, sourced from local markets, showed remarkable activity against Gram-positive bacteria, including *Streptococcus mutans*, *S. anginosus*, *S. oralis*, *S. mitis*, *S. pneumoniae*, *S. salivaris*, and *S. aureus* [30,31]. Eugenol, the main component most commonly identified in the above-mentioned essential oils of *Syzygium*, has a bacteriostatic effect against Gram-positive and Gram-negative bacteria by damaging the cell membrane, resulting in a low static effect on bacterial growth [38,39]. The cytotoxicity of the essential oils of three *Syzygium* species has already been reported. In particular, the leaf oil of *S. polyanthum* showed toxicity towards human peripheral blood mononuclear cells (PBMCs) [23].

Meanwhile, the leaf oils of *S. filiforme* and *S. variolosum* showed toxicity against various cancer cell lines, including HepG2, MCF7, and A549 [35,36]. In eukaryotic cells such as PBMCs, essential oils have been observed to cause depolarisation of mitochondrial membranes, thereby lowering the membrane potential and contributing to the observed cytotoxic effects [40]. In addition, the composition of these essential oils includes a variety of bioactive compounds, including terpenes and phenols, which can disrupt cellular processes by interacting with cell membranes, proteins, and DNA, thereby triggering cell death. Terpenes, for example, can affect the integrity of cell membranes, while phenols have the ability to generate reactive oxygen species (ROS), which trigger oxidative stress and damage cellular components. This complex mechanism is likely responsible for the cytotoxic effects observed in both normal and cancer cells [41]. Other reported biological activities of *Syzygium* essential oils include inhibition of acetylcholinesterase, antioxidant, antifungal, antibiofilm, antityrosinase, and anti-inflammatory properties.

6. Molecular Docking Analyses

Molecular docking of the main components of the Malaysian *Syzygium* essential oils was performed on the active sites of the enzymes associated with the reported bioactivities. The 3D structures of the main essential oil compounds from each *Syzygium* species, as shown in Table 4 and Figure 3, were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in SDF format [42]. Then, optimization of the structures,

including energy minimization and molecular dynamics, was performed separately using the OpenBabel tool in PyRx software with default parameters [43]. The parameters used included 100 steps of the steepest descent with a step size of 0.02 (Å), followed by 100 steps of the conjugate gradient, also with a step size of 0.02 (Å), and an update interval of 10 [44]. To validate the docking protocol, redocking was performed using the co-crystallized ligands of selected target proteins. The root-mean-square deviation (RMSD) between the docked and crystallographic ligand poses was calculated. All RMSD values were within acceptable limits (2.0 Å), confirming the reliability of the docking protocol.

Table 4. Binding free energy of major components in Malaysian *Syzygium* essential oils against key enzymes.

Species	Major component (PubChem CID)	EOs	Drug target protein	Binding energy (kcal/mol)
S. aromaticum	Eugenol **(3314)**	**SAC1**	1C14 (*E. coli*)	-6.1
			6YOC (*S. agalactiae*)	-5.5
		SAC2	3L9T (*S. mutans*)	-5.0
			3B1E (*S. anginosus*)	-5.3
		SAL	7RWZ (*S. aureus*)	-5.3
			1FWJ (*K. aerogenes*)	-3.8
	Isobornyl propanoate **(23617864)**	**SAC3**	3CLQ (*E. faecalis*)	-4.3
			3L9T (*S. mutans*)	-4.3
S. polyanthum	Trans-*β*-nerolidol **(8888)**	**SPOL1**	5GMM (Human peripheral blood mononuclear cells)	-6.2
S. filiforme	*α*-Cadinol **(10398656)**	**SFL**	8SZL (HepG2)	-5.4
			6HQU (MCF7)	-5.8
			6O1T(A549)	-6.4
S. variolosum	*β*-elemene **(6918391)**	**SVL**	8SZL (HepG2)	-4.6
			6HQU (MCF7)	-5.3
			6O1T (A549)	-6.2
			6TT0 (AChE)	-8.7
			2Y9X (Tyrosinase enzyme)	-5.6
			1YPQ (5-LOX)	-4.7
S. pyrifolium	Geraniol **(637566)**	**SPYL**	6TT0 (AChE)	-6.6
S. cerinum	*β*-Caryophyllene **(5281515)**	**SCE**	3N2S (DPPH)	-5.6
S. dyerianum	*β*-Pinene **(14896)**	**SDL**	1IYL (*C. albicans*)	-5.9
			3L9T (*S. mutans*)	-5.2

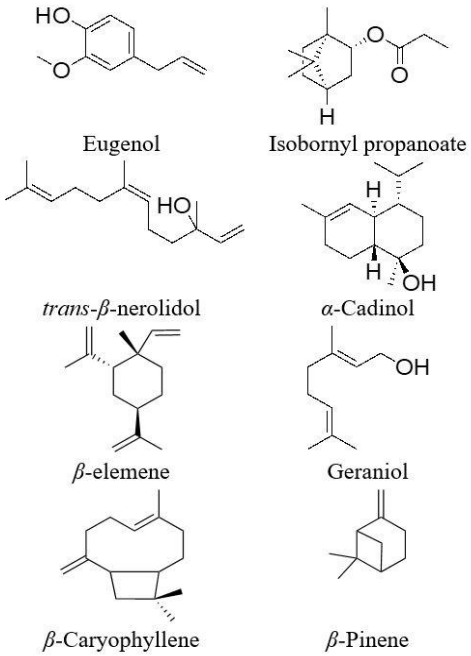

Figure 3. Chemical structures of major components of Malaysian *Syzygium* essential oils.

The 3D crystal structures of the target enzymes were downloaded from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) (https://www.rcsb.org/) in PDB format [45]. The PDB codes for the enzymes were as follows: 1C14 (*E. coli*), 6YOC (*S. agalactiae*), 3L9T (*S. mutans*), 3B1E (*S. anginosus*), 7RWZ (*S. aureus*), 1FWJ (*K. aerogenes*), 3CLQ (*E. faecalis*), 5GMM (Human peripheral blood mononuclear cells), 8SZL (HepG2 cell line), 6HQU (MCF7 cell line), 6O1T (A549 cell line), 6TT0 (AChE), 2Y9X (tyrosinase enzyme), 1YPQ (5-LOX), 3N2S (DPPH), and 1IYL (*C. albicans*). Docking of the optimized structures to the active sites of these enzymes was performed using the PyRx virtual screening tool with the AutoDock Vina Wizard approach to evaluate the interactions between the major components and enzyme receptors. The X, Y, and Z grid box center values were adjusted to ensure sufficient coverage of the binding pocket residues, allowing the ligands to move freely [44]. The optimal binding free energy values were determined using the PyRx virtual screening tool, both from the GUI and log files. The selected docking poses were determined by comparing their alignment with the X-ray structure of the reference ligand for each respective enzyme [46].

Table 4 summarises the binding free energy values (in kcal/mol) of the main components of the different Malaysian *Syzygium* essential oils against various target proteins (enzymes) from different species. The free energy of binding reflects the strength of the interaction between a ligand (in this case, the major component of the oil) and a particular target protein, with lower (more negative) values indicating stronger binding [47]. The range of binding energies observed in this study highlights the varying strength of interactions between the essential oil components and their respective protein targets. Compounds exhibiting strong binding (below -6.0 kcal/mol), such as *β*-elemene with the AChE enzyme (-8.7 kcal/mol), *α*-cadinol with the A549 cell line (-6.4 kcal/mol), and geraniol with AChE (-6.6 kcal/mol), show high affinity for their target proteins, suggesting potential efficacy in inhibiting these proteins. Moderate binding energies (between -6.0 and -5.0 kcal/mol), such as those observed for eugenol against various bacteria (-5.0 to -5.5 kcal/mol) and *β*-elemene with the MCF7 cell line and the enzyme tyrosinase (-5.3 to -5.6 kcal/mol), indicate moderate affinity. These compounds may still be effective, though higher concentrations might be required to achieve optimal biological activity. Weak binding energies (above -5.0 kcal/mol), as observed with eugenol against *K. aerogenes* (-3.8 kcal/mol) and multitarget isobornyl propanoate (-4.3 kcal/mol), indicate fewer effective interactions that may benefit from further chemical optimisation to improve efficacy at lower concentrations.

Numerous components show activity against multiple targets, indicating potential broad-spectrum biological activities. The binding energy data (kcal/mol) allow the study and comparison of the binding affinity between different ligands or compounds and their respective target receptor molecules. The binding energy is defined as the total internal energy minus the energy associated with the unbound system [48]. A lower binding energy indicates a stronger affinity of the ligand for the receptor, which makes it appear more favourable in the docking results and suggests its potential as a drug candidate for further research [49]. *β*-Elemene from *S. variolosum* (**SVL**) shows the strongest binding to the AChE enzyme (6TT0) with a binding energy of -8.7 kcal/mol. Eugenol from *S. aromaticum* (**SAC**) demonstrated binding to multiple bacterial enzymes, highlighting its potential antibacterial properties. Additionally, *α*-cadinol from *S. filiforme* (**SFL**) and *β*-elemene from *S. variolosum* (**SVL**) showed significant binding energies against cancer cell line targets (HepG2, MCF7, A549), indicating potential anticancer activity. The binding free energy data emphasise the diversity of binding affinities among the

components of Malaysian *Syzygium* essential oils for a range of enzyme targets. This diversity not only indicates their potential as versatile bioactive compounds but also emphasises their prospective therapeutic utility in a range of conditions, including bacterial infections, cancer, and other diseases. The strong binding of *β*-elemene to AChE, in particular, indicates a promising area for further exploration of its potential applications.

7. Multivariate Chemometric Analyses

Interpretation of the results and evaluation of the influence of geographical origin on chemical composition were carried out by subjecting the major constituents of *Syzygium* essential oils from different Malaysian locations to multivariate chemometric analyses, specifically hierarchical cluster analysis (HCA) and principal component analysis (PCA). HCA and PCA were performed using MINITAB Version 16.2.3 statistical software (Minitab Incorporated, State College, PA, USA). Prior to the chemometrics analyses, the spectral data of the Malaysian *Syzygium* essential oils were recorded in a Microsoft Excel spreadsheet. These statistical analyses were used for calculations to point out some considerations regarding the similarities between each of the *Syzygium* species. The data for the diagrams were first created using the PCA technique, which depicts both the oil samples (objects) and the first three main components of the oil (variables). The HCA was then performed to create a classification tree that organized the locations of the samples (objects). By combining these two methods, it was possible to determine the relationship between all the Malaysian *Syzygium* species studied and their essential oil compositions [50].

The HCA technique shows three clusters: Cluster I, Cluster II, and Cluster III (Figure 4). The first cluster (Cluster I) contained *S. aromaticum* from clove oil (**SAC1**, **SAC2**, **SAC4**), floral oil (**SAF**), and leaf oil (**SAL**) due to a similar high abundance of eugenol (24.3-74.0%) and caryophyllene (7.5-19.4%).

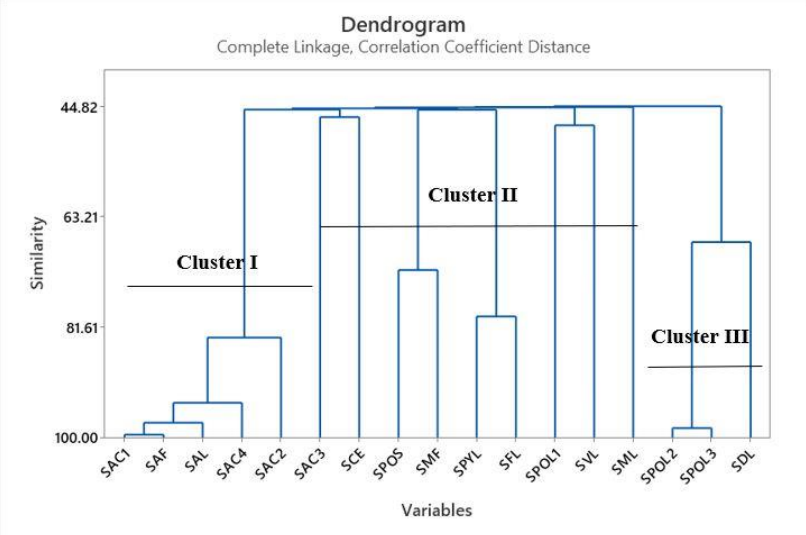

Figure 4. HCA analyses of Malaysian *Syzygium* essential oils.

In addition, the second cluster (Cluster II) had the highest number of species, namely, *S. aromaticum* (**SAC3**), *S. cerinum* (**SCE**), *S. polyanthum* (**SPOS**, **SPOL1**), *S. malaccense* (**SMF**, **SML**), *S. pyrifolium* (**SPYL**), *S. fliforme* (**SFL**), and *S. variolosum* (**SVL**). PCA biplot analysis revealed that the main compounds in this group were 2-propanone, methylhydrazone, phenol, isobornyl propanoate, (*E*)-isoeugenol, *γ*-muurolene, *β*–caryophyllene, eugenol acetate, *α*-humulene, *trans*-*β*-nerolidol, farnesol, viridiflorol, cubenol, *n*-hexadecanoic acid, *α*-cadinol,

geraniol, *β*-selinene, *τ*-muurolol, hexanoic acid, methyl salicylate, 3-hexen-1-*ol*, 9-octadecynoic acid, (*Z*, *Z*)-9-12-octadecadien-1-*ol*, *β*-elemene, and bicyclogermacrene. The third cluster (Cluster III) consisted of *S. polyanthum* (**SPOL2**, **SPOL3**) and *S. dyerianum* (**SDL**), which were characterised by the presence of *α*- and *β*-pinene, octanal, (*E*)-methyl-cinnamate, and *α*-terpineol. PCA scatter biplot (Figure 5) showed the same results as HCA, affirming the differentiation of the three clusters.

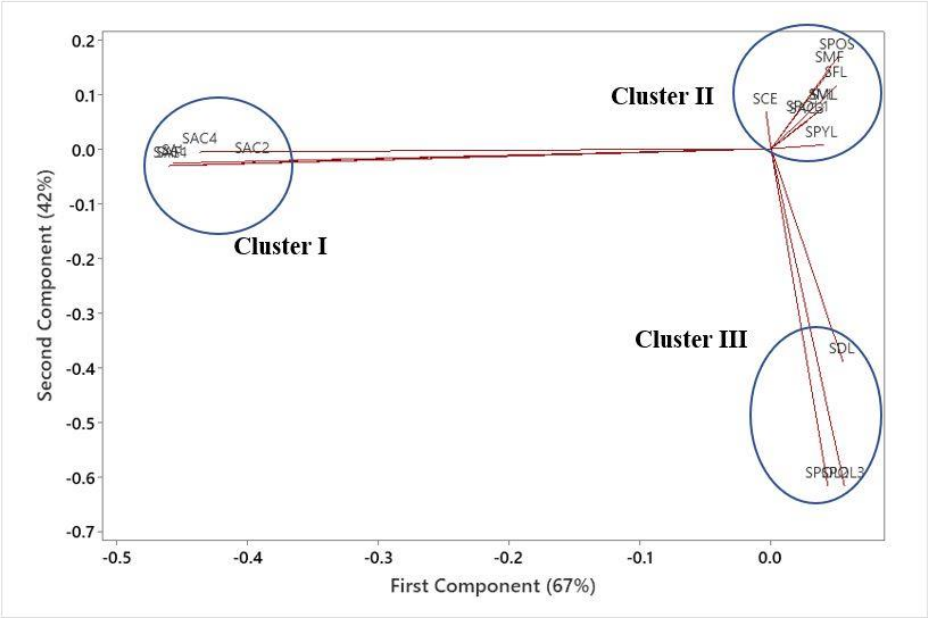

Figure 5. PCA analyses of Malaysian *Syzygium* essential oils.

Five factors were identified that account for the cumulative variation (12.60%-54.30%) in the data, each with a corresponding eigenvalue and variance (Table 5). The first principal component, accounting for 12.60% of the variation with an eigenvalue of 3.92, was considered the most significant. The main contributors to this factor were 3-hexen-1-*ol*, 9-octadecynoic acid, and (*Z*, *Z*)-9-12-octadecadien-1-*ol*, all with an eigenvalue of 3.92 and a significance level of 12.60%. Viridiflorol was the only significant contributor to factor 3, explaining 10.40% of the variance with an eigenvalue of 3.22. For factor 5, *α*-pinene was the only significant contributor, explaining 10.00% of the variance with an eigenvalue of 3.09. The fourth principal component explained 10.30% of the variance with an eigenvalue of 3.10 and represented isobornyl propanoate, (*E*)-isoeugenol, *γ*-muurolene, *τ*-muurolol, hexanoic acid, and methyl salicylate. The second main component had no significantly related components.

Table 5. Eigenvalues and cumulative variance of the factors derived from principal component analysis (PCA) of the chemical composition of essential oils from Malaysian Syzygium species

Composition	Factors				
	1	2	3	4	5
Eugenol	0.19	-0.36	-0.08	0.01	-0.23
Caryophyllene	0.18	-0.32	-0.06	0.01	-0.08
2-Propanone, methylhydrazone	0.07	-0.14	-0.03	0.01	-0.08
Phenol	0.08	-0.14	-0.03	0.01	-0.08
Isobornyl propanoate	0.02	0.17	0.31	0.41*	-0.13
(*E*)-Isoeugenol	0.02	0.17	0.31	0.41*	-0.13
γ-Muurolene	0.02	0.17	0.31	0.41*	-0.13
β–Caryophyllene	0.09	-0.16	-0.04	0.01	-0.17
Eugenol acetate	0.11	-0.20	-0.05	0.01	-0.15
α-Humulene	0.09	-0.17	-0.04	0.01	-0.15
Trans-*β*-nerolidol	0.02	0.26	-0.26	0.01	-0.07
Farnesol	0.02	0.26	-0.26	0.01	-0.07

Composition	Factors				
	1	2	3	4	5
Viridiflorol	0.03	0.38	-0.48*	0.01	-0.11
Cubenol	-0.15	-0.01	0.01	0.01	0.01
n-Hexadecanoic acid	-0.45	-0.07	-0.01	0.01	-0.01
α-Cadinol	-0.14	0.01	0.01	0.01	0.01
α-Pinene	0.08	0.01	0.05	0.01	0.54*
Octanal	0.07	-0.03	0.03	0.01	0.34
(*E*)-methyl-cinnamate	0.04	0.01	0.03	0.01	0.29
Geraniol	0.04	0.04	0.04	0.01	0.36
β-Pinene	0.05	-0.10	-0.03	0.01	-0.11
β-Selinene	0.03	0.03	0.03	0.01	0.29
α-Terpineol	-0.03	0.02	0.01	0.01	0.01
t-Muurolol	0.01	0.17	0.31	-0.41*	-0.13
Hexanoic acid	0.01	0.17	0.31	-0.41*	-0.13
Methyl salicylate	0.01	0.17	0.31	-0.41*	-0.13
3-Hexen-1-*ol*	-0.46*	-0.10	-0.02	0.01	-0.02
9-Octadecynoic acid	-0.46*	-0.09	-0.02	0.01	-0.02
(*Z*, *Z*)-9-12-octadecadien-1-*ol*	-0.46*	-0.09	-0.02	-0.01	-0.02
β-elemene	0.02	0.23	-0.31	0.01	-0.07
Bicyclogermacrene	0.02	0.23	-0.26	0.01	-0.07
Eigenvalue	**3.92**	**3.40**	**3.22**	**3.19**	**3.09**
% of variance	**12.60**	**11.00**	**10.40**	**10.30**	**10.00**
Cumulative (%)	**12.60**	**23.60**	**34.00**	**44.30**	**54.30**

*significant ≥ 0.4

The separation emphasized by the HCA and PCA analyses of the investigated essential oils can be attributed to the significant influence of geographical variations on the chemical composition of the essential oils. The composition of essential oils is shaped by multiple determinants, such as genetic and evolutionary traits, environmental and geographical factors, physiological conditions, socio-political influences, and the timing of harvest [13]. Consequently, genetically and climatically diverse plants grown in their natural habitats can serve as valuable sources for the discovery of new chemotypes, which is particularly important for the cosmetic, perfume, pharmaceutical, and food industries. Understanding metabolite diversity in plants from different natural habitats helps to determine the optimal growing conditions for plant domestication and breeding. In addition, the chemical variability of *Syzygium* essential oil due to geographical differences should be considered for different pharmaceutical applications [51-53].

Evidence from other geographical regions reinforces this observation. A comparison of Malaysian *Syzygium* essential oils with those reported from other regions reveals distinct chemotypic patterns. For instance, clove bud oil from Indonesia and Madagascar consistently contains very high eugenol content (77-82%), along with differing levels of eugenol acetate (2.8-10.6%) and caryophyllene (2.8-8.6%). In contrast, Malaysian *S. aromaticum* exhibits a broader composition diversity, with eugenol ranging from 24.3% to 74.0%, and notable proportions of other minor oxygenated terpenoids. Similarly, leaf essential oils of *S. cumini* from India are dominated by *τ*-cadinol and *τ*-muurolol (21.4% and 12.0% respectively), while samples from Brazil and Egypt predominantly feature *α*-pinene, *β*-pinene, (*E*)-*β*-caryophyllene, *α*-terpineol, and caryophyllene oxide [55]. These differences illustrate the influence of ecological, climate, and genetic factors on essential oils chemotype and underscore the uniqueness of Malaysian *Syzygium* species as potential sources of novel bioactive compounds.

8. Conclusions

This article reviews the relevant literature on the medicinal uses, chemical composition, and bioactivity of essential oils from Malaysian *Syzygium* species. Research shows that the

essential oils of *Syzygium* species contain monoterpenes and sesquiterpenes that exhibit potential bioactivities such as antibacterial and cytotoxic properties. Significant differences in the chemical composition of the essential oils of *Syzygium* species collected from different locations were highlighted. Molecular docking was employed to elucidate the interactions between the bioactive components of these oils and target proteins. Hierarchical cluster analysis (HCA) and principal component analysis (PCA) were used to identify three different clusters based on their similarities. The observed diversity in quantitative and qualitative components may be attributed to genetic variations or environmental conditions affecting the plant material from different geographic locations. Further pharmacological studies are necessary to explore the full therapeutic potential of *Syzygium* species. Additionally, preclinical analyses and clinical trials, similar to those conducted for essential oils from other species, are needed to assess the potential of *Syzygium* essential oils for drug development. The data collected in this review may prove valuable in selecting species with high potential for applications in the pharmaceutical industry.

Author Contributions

Conceptualization, W.M.N.H.W.S.; methodology, A.S.S.; writing original draft preparation, F.A.M.R.; review and editing, S.G., N.J.A., and M.H.A. All authors have read and agreed to the published version of the manuscript.

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Not applicable.

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors declare no conflict of interest.

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