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Extraction, phytochemicals, bioactivities, and toxicity of *Syzygium polyanthum*: A comprehensive review

Nurlely[1,2], Aditya Maulana Perdana Putra[2], Arief Nurrochmad[3], Sitarina Widyarini[4], Nanang Fakhrudin[5,6*]

[1]Doctoral Study Programme of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara, Yogyakarta 55281, Indonesia
[2]Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Lambung Mangkurat, A.Yani Km. 36, Banjarbaru 70714, South Kalimantan, Indonesia
[3]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara, Yogyakarta 55281, Indonesia
[4]Department of Pathology, Faculty of Veterinary Medicine, Universitas Gadjah Mada, Jl. Fauna No.2 Karangmalang, Yogyakarta 55281, Indonesia
[5]Department of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara, Yogyakarta 55281, Indonesia
[6]Medicinal Plants and Natural Products Research Center, Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara, Yogyakarta 55281, Indonesia

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ABSTRACT

Medicinal plants are receiving much attention because they are traditionally used to treat common diseases. *Syzygium polyanthum*, an important medicinal plant, has been widely used in Southeast Asia, and numerous studies have published its chemical constituents and biological properties. Therefore, this study aimed to present the results of previous studies on extraction methods, chemical contents, and bioactivities of *S. polyanthum* published between 2011 and 2023. Some solvents have been predominantly used in the extraction of *S. polyanthum*, such as methanol, ethanol, ethyl acetate, n-hexane, and water. Maceration was the most commonly used method, followed by Soxhlet extraction, hydro-distillation, percolation, decoction, infusion, ultrasound-assisted extraction, and rapid solvent extraction. Furthermore, bioactivities of *S. polyanthum*, such as antioxidant, antihypertensive, antihyperglycemic, antibacterial, antifungal, cytotoxic, and antidementia properties, were reported. However, in the toxicity studies, no toxicity signs were observed after extended administration. Therefore, *S. polyanthum* might be an alternative natural product in treating some diseases. It also might be the main therapy when appropriate extraction method and solvent are used.

Implication for health policy/practice/research/medical education:
This review highlighted detailed information regarding the extraction methods, phytochemical constituents, pharmacology, and toxicology of *Syzygium polyanthum*. This plant might be an alternative for the treatment of inflammation, oxidative stress, hypertension, hyperglycemia, bacterial and fungal infections, cytotoxicity, and dementia.

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Introduction

Syzygium polyanthum is an evergreen tree of the Myrtaceae family that is widely distributed in Malaysia and Indonesia (1,2). *S. polyanthum* leaves have traditionally been used as a food flavor additive in Indonesia and Malaysia. In addition, the leaves and other parts of *S. polyanthum* have been evaluated for the treatment of various diseases such as diabetes mellitus (3), hypertension (4), diarrhea (5), dental plaque (6), fungal and bacterial infections (7,8), and Alzheimer's disease (9). Moreover, its chemical components have significantly contributed to some bioactivities (10).

The extraction of chemical compounds is the most significant stage in producing plant formulations. A previous study revealed that *S. polyanthum* leaf extract using a similar solvent, i.e., 96% ethanol, but a different extraction method possessed different antioxidant activities, which were dependent on the chemical compounds extracted (11). To achieve an acceptable reproducibility level, the most suitable process must also be standardized (12). However, Ismail et al reported that different solvents using modern extraction methods, such

***Corresponding author**: Nanang Fakhrudin,
Email: nanangf@ugm.ac.id

as ultrasound-assisted extraction (UAE), have different levels of inhibiting angiotensin-converting enzyme (ACE) and that distilled water showed the highest inhibition compared with other solvents (13). In this context, polar and nonpolar solvents extract polar and nonpolar substances, respectively. Maceration is the most common extraction method, and water, methanol, ethanol, ethyl acetate, chloroform, and n-hexane are frequently used to extract medically active components (12,14). In addition, solvent mixtures are applied to improve extraction efficiency, for example, the 70% ethanol (mixed with 30% water) extract of *S. polyanthum* leaves showed more potent antioxidant activity compared with the absolute ethanol extract (15). Furthermore, toxicity studies are important to obtain safety information of this plant as a new herbal medicine for further clinical uses (16).

In 2019, Ismail et al conducted an in-depth study of *S. polyanthum* as a potential phytomedicine related to its chemical compounds and bioactivities (1). Dogara also reviewed studies on the ethnopharmacology, morphoanatomy, biological evaluations, and chemical constituents of *S. polyanthum* until 2021 (14). However, no previous published studies have reviewed chemical constituents, bioactivities, and toxicity of *S. polyanthum* until 2023. Consequently, this study comprehensively summarizes the influence of solvents and extraction methods on the percentage yield, chemical constituents, bioactivities, and toxicity of *S. polyanthum* extracts. This study can inspire future researchers to determine the most appropriate extraction method and solvent and develop the main therapy of *S. polyanthum* to achieve healing.

Solvent selection

The appropriate choice of solvent for extraction is a prominent method to extract the chemical constituents of *S. polyanthum* expeditiously and its health benefits from bioactivities (17). The choice of solvent depends on the part of the plant used for extraction, solvent availability, and desired bioactive constituents. The extraction rate, diversity of the extracted compounds, convenience of extract handling, and cost-effectiveness influence the selection of solvents (18). Previous studies of *S. polyanthum* have used various solvents to extract the target chemical constituents and obtain the most effective bioactivity. The aqueous extract of *S. polyanthum* (AESP) was reported to exert vasorelaxation effect more prominently than the methanolic extract by mediating nitric oxide (NO); however, the vasorelaxation effect mediated by β-adrenergic receptor blockers was more significant than that in AESP (19). Because of high polarity, methanol can extract more polar molecules and increase the solubility of the nonpolar counterpart. Polar and nonpolar compounds can be extracted from *S. polyanthum*, which contribute to its activity (20). However, water, a highly polar solvent, is used to extract various polar compounds and sometimes requires a higher temperature to concentrate the extract (12). This high temperature may result in the oxidation and decomposition of the target chemical, reducing the extraction yield (21,22).

The use of solvents, where the addition of water to organic solvents will increase the solubility of more polar compounds, also affect the difference in the activity potential (23). This process induces the enlargement of the cellular matrix and improves access to deeper places within the matrix (24,25). Dewijanti et al reported that combining organic and water solvents in the 70% ethanolic extract of *S. polyanthum* more significantly inhibited 2,2-diphenyl-1-picrylhydrazyl (DPPH) than that in the 96% ethanolic extract (26). Furthermore, the 70% ethanolic extract of *S. polyanthum* has shown a higher antioxidant activity compared with absolute ethanol. The increase in water content of the 50% ethanolic extract induced lower antioxidant activity than the absolute extract despite having the highest total phenolic content (TPC) (15). This study is similar to that of Do et al in that the 50% ethanolic extract of *Limnophila aromatica* had less antioxidant activity (27). Furthermore, the crude extract showed a more significant hypoglycemic effect on other bioactivities than in fractions and subfractions. This is related to the findings of Widyawati et al in that only methanolic extracts experienced the highest decrease in hypoglycemic effects compared with fractions and subfractions of extracts (28). This study implies that the hypoglycemic effect is likely caused by a combination of several chemicals present in the plant.

Jumaat et al evaluated the effect of various solvents on the percentage yield of *S. polyanthum* to show cytotoxic and genotoxic evidence. The methanolic extract of *S. polyanthum* leaves revealed the highest percentage yield of extraction (11.7%), followed by hexane extract (0.6%) and essential oils (0.24%), respectively. Furthermore, the methanolic extract of *S. polyanthum* stem had the highest extraction yield (1.0%), followed by hexane (0.2%) and essential oils (0.09%) (29). Ismail et al also reported the influence of solvent on the percentage yield of *S. polyanthum* extraction. In their study, the methanolic extract had the highest percentage yield of extraction (6.39% ± 1.25%) compared with aqueous, ethanolic, and n-hexane extracts (5.00% ± 2.59%, 3.62% ± 1.97 %, and 1.72% ± 0.83%, respectively). This result was due to the insolubility of neutral lipids (nonpolar hydrophobic) in water. Still, methanol dissolves greater amounts of polyphenols than water because of its natural ability to break down nonpolar cell wall components. AESP leaves exhibited the most prominent antihypertensive effect compared with methanolic and ethanolic extracts. Conversely, the n-hexane extract had no significant antihypertensive effect (4). A related study by Darusman et al confirmed that the ethyl acetate extract of *S. polyanthum* provided the highest percentage yield of extraction, followed by methanolic and n-hexane extracts. According to the results, the extract demonstrated the

strongest acetylcholinesterase inhibitory and antioxidant properties (30).

Extraction methods of *Syzygium polyanthum*

The amounts of active substances in natural remedies are typically quite limited. The laboratory-intensive and time-consuming extraction and isolation procedure have been the bottleneck in developing drugs derived from herbal medicines such as *S. polyanthum*.

Maceration

Maceration is a very easy and widely used method, with drawbacks of a long extraction time and low efficiency. Thermolabile components can be extracted using this method (31). It is ideally performed in a closed container to minimize solvent loss caused by evaporation, and a concentrated extract resulting from solvent evaporation is undesirable (32). Luliana et al evaluated the extraction efficiency of total phenol and antioxidant activity, where maceration produced the highest TPC and the most prominent antioxidant activity compared with Soxhlet extraction and infusion methods (33). Some disadvantages emerged, such as low efficiency and long extraction duration (34). These were observed in the study by Sandikapura et al using the ferric ion reducing antioxidant power (FRAP) assay, in which the inhibition rates of the antioxidant contents of the *S. polyanthum* extract were lower with maceration than with sonication and Soxhlet extraction. This may be due to the long extraction process during maceration that hydrolyzes phytochemicals and reduces antioxidant activity (3).

Percolation

Percolation involves a continuous process of replacing saturated solvents and offers enhanced extraction of secondary metabolites owing to a continuous and fresh flow of solvent. This increases the concentration difference and yields above other approaches (35). Hartanti et al compared percolation and Soxhlet extraction methods for *S. polyanthum* leaves using 96% ethanol as a solvent. The percentage yields of extraction by percolation and Soxhlet extraction were 25.05% and 23.62%, respectively. No differences in chemical constituents were found between the two methods, and both extracts contained alkaloids, flavonoids, saponins, tannins, and steroids (11).

Soxhlet extraction

Soxhlet extraction is an efficient automatic continuous extraction and requires less solvent volume and time. Furthermore, it allows for the extraction of molecules with moderate to low solubility when an appropriate solvent is selected carefully (36). With high temperature and a long extraction period, Soxhlet extraction increases the destruction of some thermolabile compounds (31).

Ismail et al found that the reduction in blood pressure using *S. polyanthum* extract by decoction at 80°C–90°C heat was less than that by Soxhlet extraction in spontaneously hypertensive rats. This showed that separate active constituents mediated the hypotensive effects of the two extracts through different mechanisms. However, the percentage yield with Soxhlet extraction was lower than that with decoction (37). The inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase of ethanolic extracts was also three times higher using Soxhlet extraction than using percolation. This showed that Soxhlet extraction successfully isolated more active components, inhibiting HMG-CoA reductase and showing thermal stability (11). Various compounds, including gallic acid, eugenol, kaempferol, quercetin, luteolin, and isorhamnetin, inhibit HMG-CoA reductase, increasing this inhibitory activity (38-40).

Decoction

The decoction extract has a high concentration of water-soluble contaminants. Therefore, this method cannot extract thermolabile or volatile components (31). Simplisia is usually boiled in water for 15–60 minutes during decoction depending on the plant tissue used and the chemical compound to be extracted. The useful parts of the plant, such as the leaves, flowers, roots, and stems, are boiled for 15 minutes. Flavonoids as well as phenols from fruits, rhizomes, and leaves are extracted by decoction and infusion at 100 °C (41,42). As an alternative, hard plant materials, such as bark and branches, can be boiled for one hour. Subsequently, the mixture is cooled and filtered, and the necessary amount of solution is added (32).

Ismail et al reported that the *S. polyanthum* extract by decoction and Soxhlet extraction methods had a significant vasorelaxation potency through the NO pathway and reduced blood pressure. However, different blockage systems induce vasorelaxation. The decoction extract induced vasorelaxation by α-adrenergic receptor blockers, whereas Soxhlet extraction has shown a prominent role in inducing vasorelaxation by including β-adrenergic receptor blockers (19).

Infusion

This extraction process is similar to maceration, where the plant is pulverized into a fine powder and placed in a container. Hot or cold extract solvent is poured over the plant material and soaked for 15 minutes. This method is suitable for soluble bioactive compounds, and the extract is prepared fresh. Furthermore, the solvent used is usually in a 4:1 or 16:1 ratio, depending on the desired use (43-45), and the extract is subjected to decantation (32). Luliana et al reported that the infusion of *S. polyanthum* leaves made by freeze-drying had the lowest percentage yield of extract and antioxidant activity compared with maceration and Soxhlet extraction methods (33). However, Sandikapura et al stated that *S. polyanthum* infusion made from fresh juice by soaking for 15 minutes and stirring at 1500 rpm had the highest percentage yield and antioxidant

activity compared with the infusion made by maceration, sonication, and Soxhlet extraction methods (3). These results were comparable with those of *Satureja nepeta* L. infusion, which had the highest total flavonoid content (TFC) and TPC and antioxidant activity compared with decoction and hydroalcoholic extracts (46).

UAE or sonication extraction

UAE initially creates openings and fissures in cells, which are broken down by ultrasonic waves that convert electromagnetic energy to heat to liberate and dissolve intracellular components (47). Cavitation created by ultrasound with frequencies ranging from 20 to 2000 kHz in the solvent speeds up solute heat transfer, solubility, and diffusion, contributing to increased extraction yields. Other benefits of UAE include low solvent and energy usage, shorter extraction time, and lower temperature requirements. This method is suitable for thermolabile and unstable compounds (12,31).

Pratama et al achieved the best conditions for extracting *S. polyanthum* using the UAE method with the solvent-to-sample ratio of 12:1 for 15 minutes of extraction. This method had an extraction yield of 18.90% and high TPC and TFC (48). Furthermore, Alipieva et al reported that UAE was the optimal method to extract phenolic and flavonoid compounds from mountain tea (49).

Accelerated solvent extraction (ASE)

ASE, or pressurized liquid extraction or pressurized fluid extraction, is an automated method conducted under high temperature and pressure to quickly remove the chemicals from solid or semisolid materials. Phytochemical solubility is also essential for the efficacy of the ASE method. High solubilities typically increase the extent of extraction and recovery yield of phytochemicals. To promote reproducibility, this method uses a meticulously regulated system that allows the precise control of pressure, temperature, extraction length, and solvent composition while preventing the detrimental effects of light and oxygen (32). Syabana et al used the ASE method and reported that the *S. polyanthum* leaf extract contained trans-aconitic acid, gallic acid, and myricetin, which had high antioxidant potential (50).

Hydro-distillation and steam distillation

Hydro-distillation and steam distillation methods are suitable for extracting volatile oils and natural chemicals. In steam distillation, a reservoir flask containing the herb is placed above boiling water, and the herb is in the path of the ascending steam flow. In the condenser, the steam providing the extracted volatile compounds is condensed to obtain the distillate. However, in hydro-distillation, the herb is immersed in boiling water. In both methods, the steam from the boiling water of the mixture is drained into a condenser, and the distillate is collected (51). Jumaat et al extracted essential oils from the leaves and stems of *S. polyanthum* using the hydro-distillation extraction method with a Clevenger-type apparatus. The percentage yield of *S. polyanthum* leaves was higher (0.24) than that of stem (0.09) (29).

Chemical constituents of *Syzygium polyanthum*

Some parts of *S. polyanthum* have various essential chemical constituents extracted using some solvents. Some phytochemicals are very beneficial active molecules with therapeutic properties. One of the chemical contents of *S. polyanthum* is essential oils. They are a complex mixture of monoterpenes and sesquiterpenes and have a distinctive odor (14). Fatty aldehydes, such as 1-decyl aldehyde, cis-4-decanal, dodecanal, nonanal, octanal, and capryl aldehyde, are more commonly observed in essential oils of *S. polyanthum* leaves using hydro-distillation procedures. According to Hamad et al, cis-4-decanal, 1-decyl-aldehyde, and capryl aldehyde, which have antimicrobial capabilities, are the primary components of the oil extracted from *S. polyanthum* leaves (52). This information was derived from Aljaafari et al, where decanal fatty aldehydes showed antimicrobial and immunomodulatory properties (53).

Fatty acids (hexadecanoic acid and palmitic amide) were found in the leaves and stems by maceration and hydro-distillation using polar and nonpolar solvents. n-Hexadecanoic acid showed anti-inflammatory properties by inhibiting phospholipase A2. In the traditional Indian Ayurvedic medical system, therapeutic oils with high acid levels are used to treat rheumatic symptoms. Furthermore, palmitic amide was reported to have antibacterial activity (54).

Terpenes are also widely found in *S. polyanthum* leaves, stems, and bark. Monoterpenes such as geraniol acetate, nerol, o-cymene, α-pinene, geranial, α-bergamotene, 1-limonene, and β-linalool were found in the leaves and stems by maceration and steam distillation (52,55-57). Annisa et al used linalool, a monoterpene of *S. polyanthum*, in a formula of herbal toothpaste (55). Seol et al also stated that the inhalation of linalool, an essential oil component with antioxidant activity, reduced blood pressure in patients with cardiovascular disorders (58). Furthermore, diterpenes, neophytadiene, and phytol were found in *S. polyanthum* leaves by maceration using several solvents, including methanol, ethanol, ethyl acetate, and n-hexane (56,57,59). Ramli et al investigated the antimicrobial activity of the absolute alcohol extract of *S. polyanthum* leaves containing phytol (59). This study was also reinforced by Saha et al, who revealed that phytol also possessed antimicrobial activity both *in vivo* and *in vitro* (60).

Triterpenes such as asiatic acid (59,61), madecassic acid (36), quillaic acid (59), and squalene (28,56,57,59) are also distributed in the leaves and stem bark of *S. polyanthum*. Squalene obtained by maceration with solvents such as methanol, absolute ethanol, ethyl acetate, chloroform,

and n-hexane showed great potential as an antidiabetic and antioxidant. This finding was reinforced by the results of the in silico and in vivo studies by Widyawati et al, which revealed that squalene had antioxidant and antidiabetic effects on type 2 diabetes model rats (62,63). Furthermore, sesquiterpene is very abundant in *S. polyanthum* stem and leaves by maceration and hydro-distillation, including sesquiterpene hydrocarbons and oxygenated sesquiterpene. The compound is a key component of several essential oils that are important commercially for fragrance and flavor (64). Sesquiterpene hydrocarbons found included valencene, α-panasinsen, α-copaene, α-cubebene, α-farnesene, α-guaine, α-gurjunene, α-humulene, α-muurolene, α-selinene, γ-cadinene, and δ-cadinene (29,52,55-57). Oxygenated sesquiterpenes, including cubenol, elemol, nerolidol, farnesol, caryophyllene oxide, globulol, hinesol, spatulenol, humulene oxide II, viridiflorol, β-spathulenol, and α-cadinol were also quite abundant (29,52,55-57,59).

In Soxhlet extraction, several compounds such as alkaloid (theobromine), benzodioxole (apiole), amine (sphinganine), carbohydrate (disialyllactose), phenolic (syringic acid and salvianolic acid), and lignan (eudesmin) and other chemicals such as aminofurantoin, exserohilone, 2-amino-3-methyl-1-buthanol, 3,4-dihydroxybenxylamine Gln Cys Asp, and salvianolic acid were obtained (3). The fresh juice of *S. polyanthum* contained amine (sphinganine), arylpropionic acid (tiaprofenic acid), benzodioxole (apiole), fatty acid (palmitic acid), flavonoid (karanjin), alkaloid (adifoline), mallic acid (3-propylmalic acid), and others (exserohilone, 1-deoxy-D-xylulose, a-methyl-3,4-dihydroxyphenylpropionic acid, proanthocyanidin A2, and anthraquinone) (3). Several flavonoids, phenols, tannins (gallo-tannin and hydrolysable tannin), lignins, phytosterols, and vitamins were also found. *S. polyanthum* is abundant in flavonoids such as cyclocurcumin, myricetin, quercetin, tachioside, isotachioside, karanjin, 2,7-dihydroxy-4- methoxyphenanthrene-2-O-glucoside, 4,2',4'-trihydroxy-3-methoxydihydrochalcone, 8-hydroxy-6-methoxy-3-pentylisocoumarin, gallocatechin 3-O-gallate, and mulberrofuran C (3,50,59,61,65,66). Phenols, namely, syringic acid, salvianolic acid, polydatin, aspidinol, ellagic acid, eugenol, methylgallate, norbergenin, proanthocyanidin A2, pyrogallic acid, pyrogallol and yakuchinone A, are also widely found in *S. polyanthum* (3,4,57,61,66). Tannins included 1-galloyl-glucose, 1-O-galloylpedun-culagin, 2, 3-(S)-hexahydroxydiphenoyl D-glucose, 2,6-Di-O-galloyl-β-D-glucose, 5-desgalloylstachyurin, and gemin D (4,66), and lignins were burseran and eudesmin (3). Table 1 shows the chemical constituents, extraction methods, and parts of *S. polyanthum* used.

Bioactivities of *Syzygium polyanthum*

Many studies have investigated the bioactivities of *S. polyanthum* (leaves, bark, stems, fruits, and roots) against free radicals, bacteria, fungi, and enzymes that cause diabetes and dementia. Compared with other plant parts, the leaves have had the most bioactivities. Previously, the secondary metabolites produced in the leaves had the most medicinal effects. To extract the component, a wide range of polarity, from nonpolar to polar, should be adopted. Extraction using solvents of varying polarities is more effective in releasing compounds and producing extracts with semi-overlapping components (14,65,67). All bioactivities of *S. polyanthum,* extraction methods, and solvents are shown in Figure 1, and the mechanisms of action of these bioactivities are shown in Figure 2.

Antioxidant activity

All parts of *S. polyanthum*, namely, leaves, ripen fruits, unripe fruits, rootbark, and stembark, have been studied for their antioxidant activity using various solvents and extraction methods. The methanolic extract of *S. polyanthum* leaves possessed the highest antioxidant activity using the DPPH and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) methods compared with the ethyl acetate, dichloromethane, and n-hexane extracts (68). Furthermore, these results were reinforced by the findings of Ramadhania et al, who revealed that by maceration, the methanolic extract showed the highest antioxidant activity with an IC_{50} of 26.03, followed by ethyl acetate (IC_{50}: 73.15) and n-hexane (IC_{50}: 3121.37) extracts. However, the methanolic leaf extract using sonication revealed lower antioxidant activity with an IC_{50} of 21.24 µg/mL than ethyl acetate with an IC_{50} of 13.7 µg/mL (3). Kusuma et al. (2011) also reported that ripe fruits showed the most active antioxidant activity (90%) at a concentration of 100 ppm compared with unripe fruits (88%) and leaves (83%) (7). In addition, the methanol extracts of the roots and stem bark contained the highest TPC of 187.5 gallic acid equivalent/g compared with the methanolic, ethyl acetate, and petroleum ether extracts (61). Furthermore, phenolic compounds (polar) have important roles in eliminating free radicals, and the methanolic extract (polar) has high antioxidant activities (68,69). In a recent study, Aditya et.al (2023) reported that the 96% ethanolic extract of *S. polyanthum* leaves extracted using UAE possessed antioxidant activity of IC_{50} and TPC more potent than that using maceration. UAE might enhance more phenolic compounds from plants (70).

Antihyperglycemic activity

Diabetes mellitus is a degenerative disease, and its treatment receives increasing attention because of its high prevalence and characteristics (65,71). A previous study showed that *S. polyanthum* leaves could lower blood sugar levels by inhibiting alpha-glucosidase. The enzyme plays a role in reducing the absorption of carbohydrates in food to decrease blood sugar levels. This property was suspected to be due to the presence of myricetin-3-O-rhamnoside (myricitrin), epigallocatechin-3-gallate,

Table 1. Chemical constituents extracted and percentage yield from all parts of *Syzygium polyanthum* using different extraction methods and solvents

Class	Part of the plant	Compound	Extraction method	Solvent	Percentage yield	Ref.
Flavonoids	Leaf	Myricetin	ASE	Acetone and water		(50)
		Karanjin	Fresh juice	Water	10.07	(3)
			Maceration	Water	7.44	
		Gallic acid, gallocatechin 3-O-gallate, quercetin 3-(6'' galloylgalactoside)	Maceration	Ethanol		(59)
		2-Hydroxy-3-4-dimethoxy-isoflavan7-O-β-D-glucoside, 2,7-dihydroxy-4- methoxyphenanthrene-2-O-glucoside, mulberrofuran C, tachioside, isotachioside, and 8 brazilein	Maceration with sonication	Water		(66)
		Cyclocurcumin and brazilin	Maceration with UAE	Water		(4)
Monoterpenoids	Leaf	α-Bergamotene, geraniol acetate, and geranial	Hydro-distillation	Water		(52)
		Octanal	Maceration	n-Hexane		
		Octanal	Maceration with UAE	n-Hexane	1.72	(57)
		Octanal and α-pinene		Ethyl acetate	3.62	
		Octanal and α-pinene	Steam hydro-distillation	Water	0.021	(55)
		o-Cymene	Maceration	n-Hexane	0.6	(29)
		Nerol	Maceration	Methanol	11.7	(29)
		1-Limonene	Steam hydro-distillation	Water	0.021	(55)
		α-Pinene	Maceration	n-Hexane		(56)
	Stem	Nerol	Maceration	Methanol		(29)
		o-Cymene	Maceration	n-Hexane	0.2	
Diterpenoids	Leaf	Neophytadiene and phytol	Maceration	Ethyl acetate		(56)
		Phytol	Maceration with UAE	b-Hexane, ethyl acetate, and methanol	1.72, 3.62, 6.39	(57)
Triterpenoids	Leaf	Quillaic acid, squalene, asiatic acid, madecassic acid, propapyriogenin A2, trans-BTP dioxolane	Maceration	Ethanol		(59)
		Squalene	Maceration	n-Hexane, ethyl acetate, and methanol	1.72, 3.62, 6.39	(57)
		Oleanolic acid	Maceration	96% ethanol		(28)
	Stem bark	Asiatic acid and arjunolic acid	Maceration	Methanol		(61)

Table 1. Continued

Class	Part of the plant	Compound	Extraction method	Solvent	Percentage yield	Ref.
Sesquiterpenoids	Leaf	β-Farnesene, α-farnesene, α-humulene, 6,10,14-trimethyl-2-pentadecanone, tumerone, α-bisabolene, α-copaene, α-curcumene, α-murulene, α-selinene, α-zingiberene, β-bisabolene, β-caryophyllene, β-sesquiphellandrene, α-cadinol, α-elemene, α-guaiene, and caryophyllene oxide	Steam hydrodistillation	Water	0.021	(17)
		Trans-β-nerolidol, cubenol, germacrone, spatulenol, viridiflorol, β-spathulenol, τ-cadinol, γ-selinene, aromadendrene, copaene, germacrene D, longifolene, β-gurjunene, β-maaliene, β-selinene, and β-eudesmol	Maceration	Methanol	11.7	(29)
		Nerolidol, azulene, valencene, α-cubebene, α-panasinsene, β-panasinsene, and farnesol	Maceration with UAE	n-Hexane	1.72	(29,56)
		Dihydrophaseic acid and vernoflexuoside flavor	Maceration with sonication	Ethanol		(59)
		Nootkatone, caryophyllene oxide, and (+)-ar-turmerone	Maceration and UAE	96% ethanol		(28)
	Leaf	δ-Cadinene	Maceration with UAE	n-Hexane		(57)
			Steam hydro-distillation	Water		(55)
	Stem	δ-Cadinene	Hydro-distillation	Water	0.24	(29)
	Leaf	α-Gurjunene	Steam hydro-distillation	Water		(55)
	Leaf	Trans-caryophyllene, elemol, humulene oxide, veridiflorol, 4,11-selinadiene, hexahydrofarnesyl acetone, selina-4(14), 11-diene, α-copaene, γ-cadinene, Juniper camphor, α-panasinsen	Steam hydro-distillation	Water		(55)
	Stem	τ-Muurolol, cadalene, cubenol, elemol, humulene oxide II, spatulenol, α-cadinol, nerolidol, α-elemene, β-guainene, β-selinene, δ-cadinene, and ledol	Hydro-distillation	Water	0.09	(29)
		Ledol, β-eudesmol, globulol, hinesol, spatulenol, β-spathulenol, τ-cadinol, allo-aromadendrene, germacrene D, isocaryophyllene, α-Cubebene, α-gurjunene, α-murulene, α-ylangene, and caryophyllene oxide	Maceration	Methanol	1.0	
		Trans-β-nerolidol, farnesol, longifolene, and α-famesene	Maceration	n-Hexane	0.2	
Alkaloids	Leaf	Adifoline	Maceration	Water		(3)
		Kukoamine A	Maceration with UAE	Water		(4)
		Theobromine	Soxhlet extraction	Water	8.7	(3)
			Maceration	Water	7.44	(3)
			Sonication	Water	8.22	(3)
Coumarins	Leaf	Laserpitin and bergenin	Maceration	Ethanol		(59)
	Stembark	8-Hydroxy-6-methoxy-3-pentylisocoumarin	Maceration	Methanol	12	(61)
Kuinons	Leaf	Anthraquinone	Fresh juice	Water	10.07	(3)
Aldehydes	Leaf	2,6-Octadienal, capryl aldehyde, cis-4-decenal, n-nonaldehyde, and 1-Decyl aldehyde	Hydro-distillation	Water		(52)
		Dodecanal, nonanal, octanal	Steam hydro-distillation	Water	0.021	(55)
		Octanal	Maceration	n-Hexane	0.021	(55)
			Maceration with UAE	n-Hexane and ethyl acetate	1.72, 3.62	(57)

Table 1. Continued

Class	Part of the plant	Compound	Extraction method	Solvent	Percentage yield	Ref.
Fatty acids	Leaf	n-Hexadecanoic acid, methyl tetradecanoate, pentadecanoic acid, and tetradecanoic acid	Maceration	Methanol	11.7	(29)
		9,12-Octadecadienoic acid and hexadecanoic acid	Maceration	Chloroform		(28)
		Decanoic acid, palmitic acid, and palmitic acid ester	Maceration with sonication	Ethanol		(59)
		10-Methylnonadecane	Maceration and hydro-distillation	n-Hexane and water	0.6, 0.24	(29)
		Methyl tetradecanoate	Maceration	Methanol	11.7	(29)
	Stem	n-Hexadecanoic acid	Hydro-distillation	Water	0.4	
			Maceration	Methanol and n-hexane	0.2, 1.0	(29)
			Hydro-distillation	Water	0.09	(29)
Tannins	Leaf	6-Di-O-galloyl-β-D-glucose, 1-O-galloylpedun-culagin, gemin D, 2, 3-(S)-hexahydroxydiphenoyl D-glucose, and 5-desgalloylstachyurin	Maceration with sonication	Water		(66)
		1-Galloyl-glucose (glucogallin)	Maceration with UAE			(4)
Lignins	Leaf	Thannilignan	Maceration with sonication	Water		(66)
		Eudesmin	Maceration	Water (1:8)		(3)
			Soxhlet extraction	Water (1:20)		
Phenols	Leaf	2,4,5-Trihydeoxybenzaldehyde, 4 darendoside A, norbergenin, aspidinol, 2,3,5,4-tetrahydroxystilbene-2-O-(6'-O-α-D-glucopyranosyl)-β-Dglucopyranoside	Maceration with sonication	Water		(66)
		Ellagic acid, sesamol, polydatin, and eugenol	Maceration with UAE	Water	5.0	(4)
		Syringic acid and salvianolic acid	Soxhlet extraction	Water	8.7	(3)
	Stem bark	Methylgallate and 3,3'-di-O-methylellagic acid	Maceration	Methanol	12	(61)
Phytosterols	Leaf	β-Sitosterol	Maceration	Ethyl acetate and absolute ethanol (1:4)		(56,59)
			Maceration with UAE	n-Hexane, ethyl acetate, and methanol	1.72, 3.62, 6.39	(57)
		Stigmasterol	Maceration (40°–60°)	n-Hexane		(28)
	Stem bark	Daucosterol and stigmasterol	Maceration	Methanol	12	(61)
Glucosides	Leaf	Polydatin	Maceration with UAE	Water		(4)

UAE, Ultrasound assisted extraction.

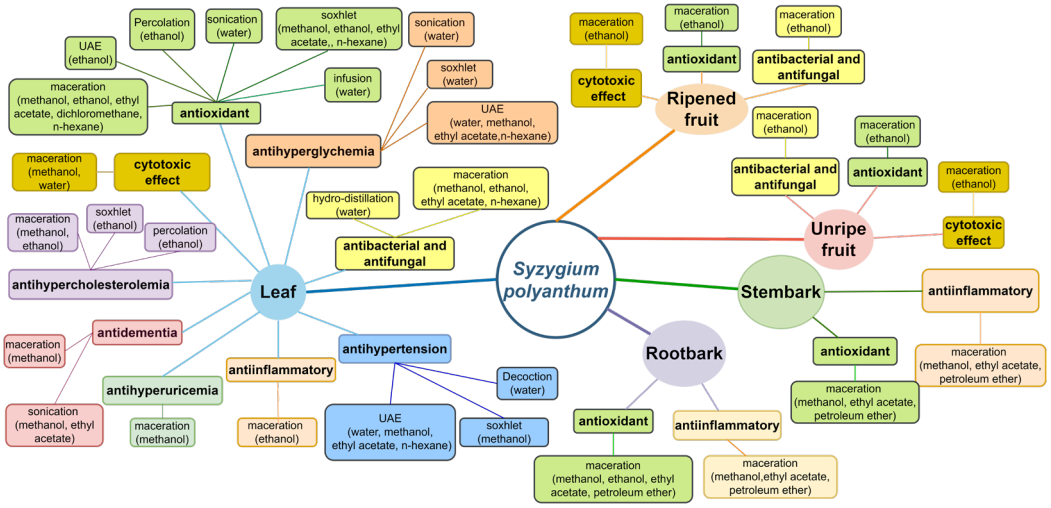

Figure 1. Summary of the biological activities of all parts of *Syzygium polyanthum* along with the extraction methods and solvents used. UAE: Ultrasound assisted extraction.

4-hydroxy-3-methoxy-benzoic acid, and 4-hidroxy-3,5-dimethoxy-benzoic acid, which play important roles. In addition, a squalene compound acts by increasing glucose uptake in muscle tissue (65,71,72). The fresh juice of the *S. polyanthum* leaf extract also showed the highest inhibition of α-glucosidase and α-amylase compared with those extracted by sonication, Soxhlet extraction, and maceration (3).

Ramli et al reported that the *S. polyanthum* leaf extract had antibacterial effects, specifically against foodborne bacteria such as *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Vibrio cholera,* and *methicillin-resistant S. aureus*. Grape extracts were also tested for bacterial growth, and a decrease in bacterial abundance was reported (73). Various bacterial strains were also investigated using disc, agar, and well-diffusion methods. *Bacillus subtilis* growth was significantly inhibited, whereas the growth of *Salmonella typhimurium*, *S. aureus*, and *V. cholera* was mildly inhibited by essential oils of the leaf extract. Aldehydes and

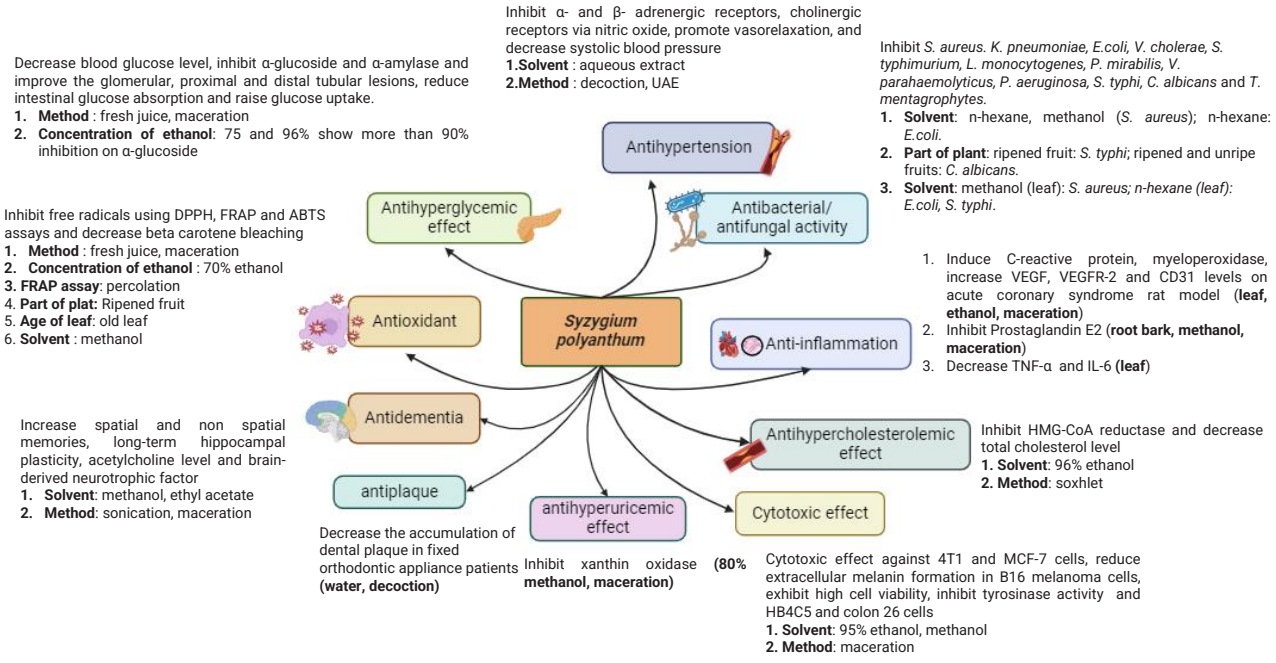

Figure 2. Mechanism action of the bioactivities of *Syzygium polyanthum* along with the best method, part of the plant, and solvents used. UAE: Ultrasound assisted extraction; TNFα: Tumor necrosis factor-α; IL-6: Interleukin-6; HMG-CoA: β-Hydroxy β-methylglutaryl-CoA; FRAP: Ferric reducing antioxidant power; VEGF: Vascular endothelial growth factor; VEGFR-2: Vascular endothelial growth factor receptor-2.

eugenol, primary chemical components, were responsible for these antibacterial properties (52). Kusuma et al also stated that ripe and unripe fruit extracts possessed more effective antifungal properties against *Candida albicans* infection than the leaf extract (7). Wong et al reported that leaf extracts showed strong antifungal activity against *Aspergillus flavus*, *Aspergillus niger*, *Rhizopus oligosporus*, and *Rhizopus oryzae* (74). Furthermore, the n-hexane extract had potent antibacterial activity against *S. aureus*, *E. coli,* and *Salmonella sp.* (56,69). Khan et al reported that the absolute ethanolic fraction using maceration revealed strong antibacterial activity against foodborne microorganisms such as *E. coli*, *K. pneumoniae*, and *S. typhimurium* (75).

Antihypertension

Decoction of *S. polyanthum* has been reported to lower blood pressure. The main content of gallic acid, a phenolic compound, contributed the most to the reduction of systolic blood pressure after 3 weeks of administration of the aqueous extract (76). A previous study revealed that the methanolic and aqueous extracts of *S. polyanthum* leaves induced significant vasorelaxation in normal and hypertensive rats. Acute treatment with the decoction (2.50–3.00 g/kg) and methanolic extract (2.00–3.00 g/kg) lowered blood pressure (19,76).

Ismail et al identified multiple bioactive substances linked to antihypertensive mechanisms. These compounds included 1-galloyl-glucose (glucogallin), polydatin, sesamol, brazilin, eugenol, elagic acid, kukoamine A, and cytocurcumin. The inhibitory effects of 1-galloyl-glucose (glucogallin) and eugenol on the activity of ACE-I were demonstrated by the development of a chelate complex inside the active site of ACE-I. Meanwhile, polydatin was found to increase NO levels and simultaneously decrease endothelin and angiotensin II levels, reducing blood pressure in rats subjected to pressure overload. Sesamol and brazilin exerted vasorelaxation effects on rat aortic rings through the endothelium-dependent pathway and an independent mechanism, which activated calcium-dependent NO production. Ellagic acid can reduce the expression of the β-nicotinamide adenine dinucleotide phosphate oxidase subunit p47phox, which is responsible for the increased production of vascular oxygen radicals. This mechanism potentially mitigates oxidative stress and restores NO availability (4).

Anti-inflammatory activity

Sabandar et al also reported the anti-inflammatory effect of the stem bark extract of *S. polyanthum*, which was attributed to its contents of stigmasterol, 8-hydroxy-6-methoxy-3-pentylisocoumarin, 3,3'-di-O-methylellagic acid, methylgallate, asiatic acid, arjunolic acid, and daucosterol (61). Furthermore, the 70% ethanolic leaf extract was evaluated to treat rheumatoid arthritis by reducing the scores of hindpaw rats with arthritis. The extract also has anti-inflammatory properties and can treat rheumatoid arthritis by reducing leg scores. This finding has been attributed to the presence of flavonoids, saponins, tannins, and essential oils in *S. polyanthum* leaves (77). Furthermore, Aditya et al stated that the leaf extract (150 mg/kg) inhibited the inflammatory process by decreasing tumor necrosis factor-α and interleukin-6 levels in polycystic ovarian syndrome rat models (78).

Antidiarrhea

The ethanolic leaf extract of *S. polyanthum* had also been reported to inhibit diarrhea induced by castor oil (88.08%) in animal studies. Furthermore, the potency of the extract was comparable to that of loperamide (89.72%), which was suspected to be due to the contents of tannins, flavonoids, 10-epigazanioplid, gazaniolid, spirafolide, costunolid, reinosin, and santamarin (5).

Antihyperuricemia

Sakti et al reported that *S. polyanthum* leaves of ethyl acetate fraction from 80% methanol extracted by maceration could reduce uric acid levels by inhibiting xanthin oxidase (79). This activity was supported by its chemical constituents in methanolic extract, such as linalool, α-pinene, nerolidol, caryophyllene oxide, α-tocopherol, β-tocopherol, phytol, farnesol, α-humulene, hentriacontane, octanal, neophytadiene and β-sitosterol (57).

Antidementia

The administration of the methanolic extract at a dose of 100 mg/kg increased acetylcholine and brain-derived neurothrophic factor levels, whereas the ethyl acetate and methanolic extracts had moderate acetylcholinesterase activity (9,30). The *S. polyanthum* leaf extract contains caffeic acid and gallic acid that can improve the function of the cholinergic nervous system and reduce cholinesterase activity, providing a nootropic effect that can improve memory function (80). Caffeic acid improves cognitive function through its antioxidant effect and improves cholinergic function, and gallic acid reduces damage to the nervous system by scavenging free radicals and inhibiting the oligomerization of aggregated beta-amyloid (81,82). Furthermore, caffeic acid in *M. officinalis* enhanced memory retrieval by increasing step-through latency and decreasing the time spent in the dark compartment (83).

Antihypercholesterolemic activity

Atherosclerosis, an inflammatory disease of the arterial walls marked by atheroma formation, is one of the risk factors for hypercholesterolemia. The ethanolic extract of *S. polyanthum* leaves inhibited the activity of HMG-CoA reductase, which was attributed to the phenolic contents of the extract (11). Squalene, an important hydrocarbon in *S. polyanthum* leaves, at a dose of 1 g/kg, may increase high-density lipoprotein cholesterol levels (84).

Cytotoxic effect

The isolate of 3,(4E)-1-(2,3,5-trihydroxy-4-methylphenyl) decan-1-one from the methanolic extract of *S. polyanthum* leaves decreased melanin formation by inhibiting melanogenesis and tyrosinase activity with high cell viability in B16 melanoma cells (85). Tyrosinase, an enzyme of the melanogenic process, increases during tumorigenesis; thus, an approach that can inhibit this enzyme is needed (86). Eugenol and yakuchinone A found in *S. polyanthum* play an important role in inhibiting tyrosinase activity (4,66,87).

Toxicity studies

The ethanolic extract of *S. polyanthum* leaves did not show any toxicity 90 days after administration at a dose of 100 mg/kg of body weight or cause hematologic and biochemical changes between male and female rats (88). Meanwhile, the methanolic extract of *S. polyanthum* leaves at a dose of 400 mg/kg for 28 days did not cause changes in body weight, biochemical and hematological functions, estrous cycle, and liver histological characteristics (16).

Conclusions

Syzygium polyanthum exhibits a range of bioactivities that can effectively treat various diseases. These activities include antioxidant, antihypertensive, antihypercholesterolemic, anti-inflammatory, antimicrobial, anti-hyperuricemia, antiplaque, and anticytotoxic effects. These therapeutic properties are supported by a wide range of chemical constituents. These activities are predominantly observed in the leaves, roots, stems, stem bark, and fruits. To achieve the required pharmacological activity while using some parts of *S. polyanthum*, the extraction procedure that employs a suitable solvent should be selected carefully. This process will allow the extraction of some chemical constituents that can potentially provide bioactivity targets. Furthermore, studies that compare different extraction methods using different solvents are warranted to find the optimal bioactivity of *S. polyanthum*. Furthermore, current knowledge of the chemical constituents of *S. polyanthum*, specific bioactivity, and toxicity should be improved.

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Authors' contribution

Conceptualization: Nurlely.
Data curation: Nurlely, Aditya Maulana Perdana Putra.
Formal analysis: Nurlely, Aditya Maulana Perdana Putra, Nanang Fakhrudin, Arief Nurrochmad, Sitarina Widyarini.
Investigation: Nurlely, Aditya Maulana Perdana Putra, Nanang Fakhrudin, Arief Nurrochmad, Sitarina Widyarini.
Methodology: Nurlely, Nanang Fakhrudin.
Project administration: Nurlely, Nanang Fakhrudin, Arief Nurrochmad.
Resources: Nurlely, Nanang Fakhrudin, Aditya Maulana Perdana Putra.
Software: Nurlely, Aditya Maulana Perdana Putra.
Supervision: Nanang Fakhrudin.
Validation: Nurlely, Nanang Fakhrudin.
Visualization: Nurlely, Nanang Fakhrudin.
Writing-original draft: Nurlely, Nanang Fakhrudin.
Writing-review & editing: Nurlely, Aditya Maulana Perdana Putra, Nanang Fakhrudin, Arief Nurrochmad, Sitarina Widyarini.

Conflict of interests

The authors have declared that there are no competing interests.

Ethical considerations

The authors have completely observed ethical issues including double publication, plagiarism, and data fabrication.

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