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Syzygium Samarangense: Review of Phytochemical Compounds and Pharmacological Activities

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Abstract: Jambu semarang (*Syzygium samarangense*), which belongs to *Myrtaceae* family, is widely cultivated in Asia and the Pacific region. This review systematically described the scientifically proven information about the plant's phytochemical contents, traditional usage, and pharmacological activities. Elucidated primary and secondary metabolites of *S. samarangense* mostly belong to flavonoids, phenolic compounds, resorcinol derivatives, acylphloroglucinols, tannins, terpenoids, and sterols. Various parts of the plant have been used traditionally to remedy cold, itches, cracked tongue, dysentery, and diabetes. It is also commonly consumed fresh or processed as wines, jams, nata, vinegar, and jellies. Currently, *in vitro* and *in vivo* experiments of the plant extract have demonstrated various pharmacological activities such as antioxidant, antimicrobial, anti-HIV, analgesic, anti-inflammatory, antihyperglycemic, antidiabetic, thrombolytic, spasmolytic, cytotoxic, hepatoprotective, anticancer, anthelmintic, anxiolytic, protease inhibitory, and immunomodulatory effect. Further research in standardization and clinical studies is highly expected for future development.

Keywords: *Syzygium samarangense*; jambu semarang; phytochemical compounds; traditional uses; pharmacological activities; toxicology.

1. Introduction

Natural products still contribute to drug developments nowadays, where up to 50% of approved drugs in the last 30 years isolated from natural products [1]. Natural products are well known to be used as food or spice, but some of them also have a significant effect as medicines [2]. Myrtaceae, in which the genus of *Syzygium* is placed, is one of the largest plant families that consists of 3,800-5,800 species in 140 genera [3]. Meanwhile, *Syzygium* is the largest woody genus of flowering plants and the 16th most diverse genus with 1,100-1,200 species widely spread in the tropical and subtropical regions of the world [4]. There are several metabolites commonly produced by the *Syzygium* genus, such as terpenoids sysamarins A-G), chalcones, (-)-epigallocatechin, samarangensis A-B, pinocembrin, samarone A-D, jasmonic acid, lignans, alkyl phloroglucinols, hydrolyzable tannins, and other derivates [3].

Syzygium samarangense is a native plant of Andaman and Solomon Island cultivated in Asia and the Pacific region, especially in Indonesia [2,5]. This plant is generally known as jambu semarang, java apple, java rose apple, mountain apple, samarang rose apple, wax jambu, wax apple, jamrul, malay apple, chompu-khieo, or makopa [6–8]. In Chinese, it is called jin shan pu tao, lián wù, lián-bū nan yang pu tao, yang pu tao [8]. Fruit of jambu semarang can be harvested at least three times a year [9]. The fruits are primarily consumed fresh, but they are

also made into wines, sauces, jams, desserts, liquors, vinegar, and jellies in a small percentage [9,10].

The evergreen tree of known to grow well in the land with a sea level above 1,200 m during a long dry season up to a height of 3-15 m with near ground branches. It can be propagated by cutting, grafting, seeding, and air-layering. Its leaves are opposite, oblong to elliptic shape, with a size of 6-30 cm length and 4-15 cm width [11], colored in dark green to yellowish, and consist of the thick petiole. Flower parts of jambu semarang usually consist of 3, 9, 15, or more flowers and can be found at the tip of the leaves, branches, or twigs. The stalk is estimated to have 3-5 mm length and 8-10 mm width size. Calyx of the flower has a yellow to green or white color with a semicircular form. The white corolla forms a round shape with a length estimated from 8-12 mm. Every flower contains 200-500 stamens approximately 3-4 cm long when the pistils only length around 4 cm with one mm diameter [11]. Its flowering period is in the early or late of the dry season and blooms a white to yellowish-white flower with a diameter of 2.5 cm. After several months of the flowering period, the ripping period with follow-up [12].

A comparative study of internal transcribed spacer (ITS) and trnL-F (UAA and GAA) sequences, an efficient tool to identify gametophytes, shows that different growth places will give slightly different molecular and morphological characteristics due to its color, size, and shape of the fruits [13]. The fruit is a berry with fruit skin color splits from white to pale green and pink to pinkish-red. Its fruits have pear-like or bell-shaped with an oval-obovate shaped in a size of 3.5-5.5 cm x 4.5-5.5 cm and crowned by the incurved lobes of fleshy calyx [9]. Some of the fruits were also examined as pseudo-stipe fruit [11]. The flesh is crisp, juicy, fresh, and fragrant with its sweet taste [12]. The skin of the fruit cannot be separated, so when it is cracked, the exocarp and mesocarp will be broken at the same time [14]. The fruit is commonly eaten after it is ripped [6] and only stored for up to a week in room conditions without preservatives [15].

Another molecular study summed the complete 159,109 bp long chloroplast genome, including 113 genes, of *S. samarangense*. The accession number of the genes is MH371141. Genome annotation of these full-length genes includes 79 protein-coding genes, 30 tRNA genes, and 4 rRNA genes. It was also known that their large single-copy (LSC), small single-copy (SSC), and inverted repeats (IR) regions are 88,533; 18,882; and 25,847 bp long. This information was validated through comparison with 9 other various Myrtaceae species through a phylogenetic tree study, in which *S. samarangense* forms a clade similarity with the other family members with 100% bootstraps values [16].

Plant-based products are widely used from the early stage of human civilization to cure various diseases [17]. *Syzygium* genus is also used traditionally to tackle several diseases and disorders, such as hemorrhage, dysentery, gastrointestinal disorder, diabetes, inflammation, bronchitis, thirst, and ulcers [7].

Syzygium genus is also well known for their various clinical scientific reports in medical treatment or prevention, such as antioxidant, antimicrobial (especially against herpes virus), antifungal, antivirus, analgesic, anti-inflammatory, antihypertensive, antihyperglycemic, anticonvulsant, sedative, spasmolytic, cytotoxic activity, and other activities [1,4].

This review systematically described the scientifically proven information of jambu semarang in the topic of phytochemical contents, traditional usage, and pharmacological activities. Hopefully, this article will be useful for future research towards the drug development of *S. samarangense*.

2. Materials and Methods

This review is based on articles collected through literature study from an international scientific journal written in English. Literature findings are conducted with several keywords and inclusion criteria. The keywords are *Syzygium samarangense;* jambu semarang; phytochemical compounds; traditional uses; pharmacological activities, toxicology. The inclusion criteria include 1) article published from 2010-2020; 2) article published from 2018-2020 with a minimum amount of 20 references; 3) article published in PubMed, Google Scholar, ScienceDirect, Scopus, and CrossRef portal; and 4) article must have DOI (digital object identifier). The selection of articles is conducted with PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) method to ensure that authors have a good quality of the article**.**

3. Results and Discussion

3.1. Phytochemical compounds of S. samarangense.

S. samarangense produces both primary metabolites and secondary metabolites. The primary metabolites of the plant consist of nutritional compounds, such as carbohydrates, proteins, lipids, amino acids, nucleic acids, fatty acids, vitamins, and minerals which are distributed in various parts of the plant. Metabolite production of the plant is highly affected by the environmental status, the use of growth regulators, local living pests, and storage methods [18]. The juicy content of the fruits' flesh consists of protein (92.9%), carbohydrate (6%), crude fiber (0.46%), and ash minerals (0.21%). A water-soluble polysaccharide fraction (WAFP) study isolated from the fruit also consists of rhamnose, arabinose, xylose, mannose, glucose, and galactose molar ratio of 1.88; 2.20; 6.37; 1.48; 5.47; and 2.82 [19]. Nutritional values of the fruit for every 100 g can be seen in Table 1 [12].

Table 1. Nutritional values of jambu semarang fruit **[**12].

Nutrition	Amount (for every 100 g fruits)
Calorie	34 Kcal
Water	90.6 g
Crude protein	0.5 g
Crude fat	0.2 g
Carbohydrate	8.6 g
Crude fiber	0.6 g
Dietary fiber	1 g
Ash	0.2 g
Vitamin B1	0.02 mg
Vitamin B2	0.03 mg
Vitamin B6	0.03 mg
Niacin	0.03 mg
Vitamin C	6 mg
Sodium	25 mg
Potassium	340 mg
Calcium	28 mg
Magnesium	13 mg
Phosphorus	35 mg
Iron	1.5 mg
Zinc	0.2 mg

Analysis of *S. samarangense* roots dry powder extracted in methanol and ethyl acetate solvents reported that there are several biochemical compounds obtained (w/w), which are amino acids (4.25 ± 0.28%), proteins (2.69 ± 0.17%), soluble sugars (1.11 ± 0.09%), crude fiber (0.41 ± 0.12%), crude fat (3.36 ± 0.23%), crude protein (5.81 ± 0.36%), nitrogen (2.71 ± 0.14 %), ash (6.49 ± 0.26%), and acid insoluble ash (0.37 ± 0.17%). There are metals and various minerals present in the roots of the plant extracted using acid digestion. Sodium and potassium content had the highest number compared to calcium, magnesium, iron, manganese, zinc, copper, cobalt, cadmium, mercury, and silver, based on atomic absorption spectrophotometry (AAS) and flame-photometer measurement [20].

The leaves of *S. samarangense* contained many compounds, which are flavonoids, phenolic compounds, tannins, terpenoids, and sterols. Other metabolite groups, such as volatile oils, sysamarins A-E [21], sysamarins F-G [22], phloroglucinols [23], essential oils [24], resorcinol derivatives [25], also were examined in the past study.

A study found that the first example of 23 long carbon chain aliphatic ester of ursane and oleanane triterpenoids were isolated from *Syzygium* genus. Those compounds were four unidentified ursane triterpenoids, sysamarins A-D, along with an undescribed oleanane triterpenoid, sysamarin E, isolated from leaves by ethyl acetate solvent. Elucidation of these structures was conducted by extensive spectroscopy method including High Resolution-Electrospray Ionization-Mass Spectrometry (HR-ESI-MS) spectroscopy[21]. Other oleanane triterpenoids, sysamarins F-G, were isolated from the leaves along with one known analog that have a long aliphatic chain at carbon 23 position. Oleanane triterpenoids could be developed as potential chemotaxonomic markers of *Syzygium* genus [22].

A systematic investigation utilizing HR-ESI-MS/MS analysis led to acylphloroglucinol, a rare phytochemical group in the higher plant yet common to be found *Syzygium* genus. The experiment revealed nine acylphloroglucinol derivatives isolated from the leaves of the plant. Four compounds among them were new acylphloroglucinol derivatives, samarones A-D, which are connected to alkyl side chain at C_{17} position and comprised a methylated 5,7-dihydroxy-chromone core [23].

Resorcinol derivatives with long aliphatic chain were isolated from jambu semarang leaves. There are nine resorcinol derivatives, with 5-[(8Z,11Z,14Z)-nonadeca-8,11,14-trienyl] resorcinol and 5-[(8Z,11Z,14Z)-heptadeca-8,11,14-trienyl] resorcinol reported as the newly discovered structure. Four of nine isolated resorcinol derivatives, which were 5-[(8Z,11Z,14Z)-heptadeca-8,11,14-trienyl] resorcinol, 5-[(9Z,12Z)-heptadeca-9,12-dienyl] resorcinol, 5-[(Z)-heptadeca-10-enyl] resorcinol, and 5-[(Z)-pentadecyl-10-enyl] resorcinol, demonstrated a significant inhibitory effect towards α-glucosidase. The other resorcinol derivatives were 5-[(Z)-nonadecyl-14-enyl] resorcinol, 5-pentadecyl resorcinol, and 5-heptadecane resorcinol [25].

A chalcone, namely aurentiacin, was isolated from jambu semarang leaves [26]. There were also novel proanthocyanins founded in the leaves with double-bond structures, which are samarangenins A and B [8]. Study n-hexane extract of the leaves confirmed the presence of α-carotene, β-carotene, lupeol, betulin, epibetulinic acid, 2',4'-dihydroxy-6'-methoxy-3'-methylchalcone, 2'-hydroxy-4',6'-dimethoxy-3'-methylchalcone, 2'-4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone, 2',4'-dihydroxy-6'-methoxy-3'-methyldihydrochalcone, 7-hydroxy-5-methoxy-6,8-dimethylflavanone, 2'-hydroxy-4',6'-dimethoxy-3'- methyl dihydro chalcone, and 2',4'-dihydroxy-6'-methoxy-3',5'-dimethyldihydrochalcone [3]. Sterols were also isolated (β-sitosterol and β-D-sitosteryl glucoside) [8].

Essential oils were represented in a study of hydro-distilled leaves of *S. samarangense* cultivated from Egypt's Cairo-Alexandria desert. The essential oil of the leaves mainly composed of mono- and sesquiterpenes. Those terpenes included germacrene D (21.62%), cuminyl aldehyde (10.56%), β-caryophyllene (5.93%), δ-cadinene (5.25%), spathulenol (4.53%), anethole (4.25%), caryophyllene oxide (3.35%), and 84 other minor components [24]. Another study on the plant cultivated from Mauritius confirmed the presence β-pinene (21.3%), *α*-pinene (8.9%), *γ*-terpinene (7.9%), limonene (7.7%), p-cymene (5.9%), β -selinene (3.8%), selin-11-en-4-*α*-ol (3.6%), β -caryophyllene (3.5%), *α*-selinene (3.4%), δ -cadinene (2.9%), 1-epi-cubenol (2.2%), terpinolene (2.1%), and *α*-terpineol (2.1%) [27].

Not only mono- and sesquiterpenes, other class terpenes, including triterpenoids and steroid groups, are also present in *S. samarangense*. These mainly consist of stearate, lupenyl stearate, sitosteryl stearate, and 24-methylenecycloartanyl stearate which were discovered from air-dried leaves of jambu semarang in dichloromethane extract [28]. A follow-up study carried out in the Philippines found that there were ursolic acid and lupeol in dichloromethane fractions of jambu semarang leaves. Ursolic acid was known for its anti-tumorigenic and chemo-preventive activity [29].

Several compounds were repeatedly founded in the various study. A study of *S. samarangense* leaves in methanol extract isolated 14 known compounds, lupeol, demethoxymatteucinol, cryptostrobin, betulinic acid, *β*-sitosterol glucoside, 2R-prunasin, myrciaphenone A, 1-feruloyl-*β*-D-glucopyranoside, (3*S*,5*R*,6*R*,7*E*,9*S*)- 3,5,6,9-tetrahydroxy megastigman-7-ene, guaijaverin, and myricetin 4′-methyl ether 3-*O*-*α*-L-rhamno-pyranoside. The same study also reported cyanogenic glucoside (taxiphyllin 6'-O-gallate), megastigmane glucoside (actinidioionoside 6′-*O*-gallate), and sulfated flavonoid rhamnoside (myricetin 2″-*O*-sulfate) as newly discovered compounds [30].

Phytochemical compounds investigation of *S. samarangense* bark extract indicated the presence of reducing sugar, tannins, flavonoids, saponins, gum, and alkaloids [7]. The flowers produce tannins [8], while the plant's fruits contain jasmonic acid and salicylic acid. During the post-harvesting process, the content of these components will be significantly reduced due to their roles in pathogenic resistance. The more duration of post-harvest shelf life, the more visible diseases appeared [15]. Two flavonol glycosides (epigallocatechin 3-O-gallate and epicatechin-3-O-gallate) also samarangenins A and B were found in the fruit parts. A study on fruits also traced the existence of anthocyanins cyanidin-3-glucoside, flavonoids, quercetin, quercitrin, myricetin, rutin, and ellagic acid [8].

Based on all the analyses below, there are many phytochemical compounds of jambu semarang summarized in Table 2.

Table 2. Phytochemical compounds of jambu semarang

Plant Parts	Metabolites Groups	Compounds	References
Leaves	Flavonoids	2′,4′-Dihydroxy-6′-methoxy-3′- methyl dihydrochalcone	[3]
		2′-Hydroxy-4′,6′-dimethoxy-3′- methyl dihydrochalcone	[3]
		2′,4′-Dihydroxy-6′- methoxy3′,5′- dimethyl dihydrochalcone	[3]
		2′-Hydroxy-4′,6′-dimethoxy-3′- methyl chalcone	[3]
		2′,4′-Dihydroxy-6′-methoxy-3′- methyl chalcone (Stercurensin)	[3]
		2′,4′-Dihydroxy-6′-methoxy- 3′,5′ dimethyl chalcone	[3]
		Pinocembrin	[3]
		(—)-Stropinin	[3]
		8-Methylpinocembrin	[3]
		Demethoxymatteutcinol	[3]
		7-Hydroxy-5-methoxy-6,8- dimethyl-flavanone	[3]

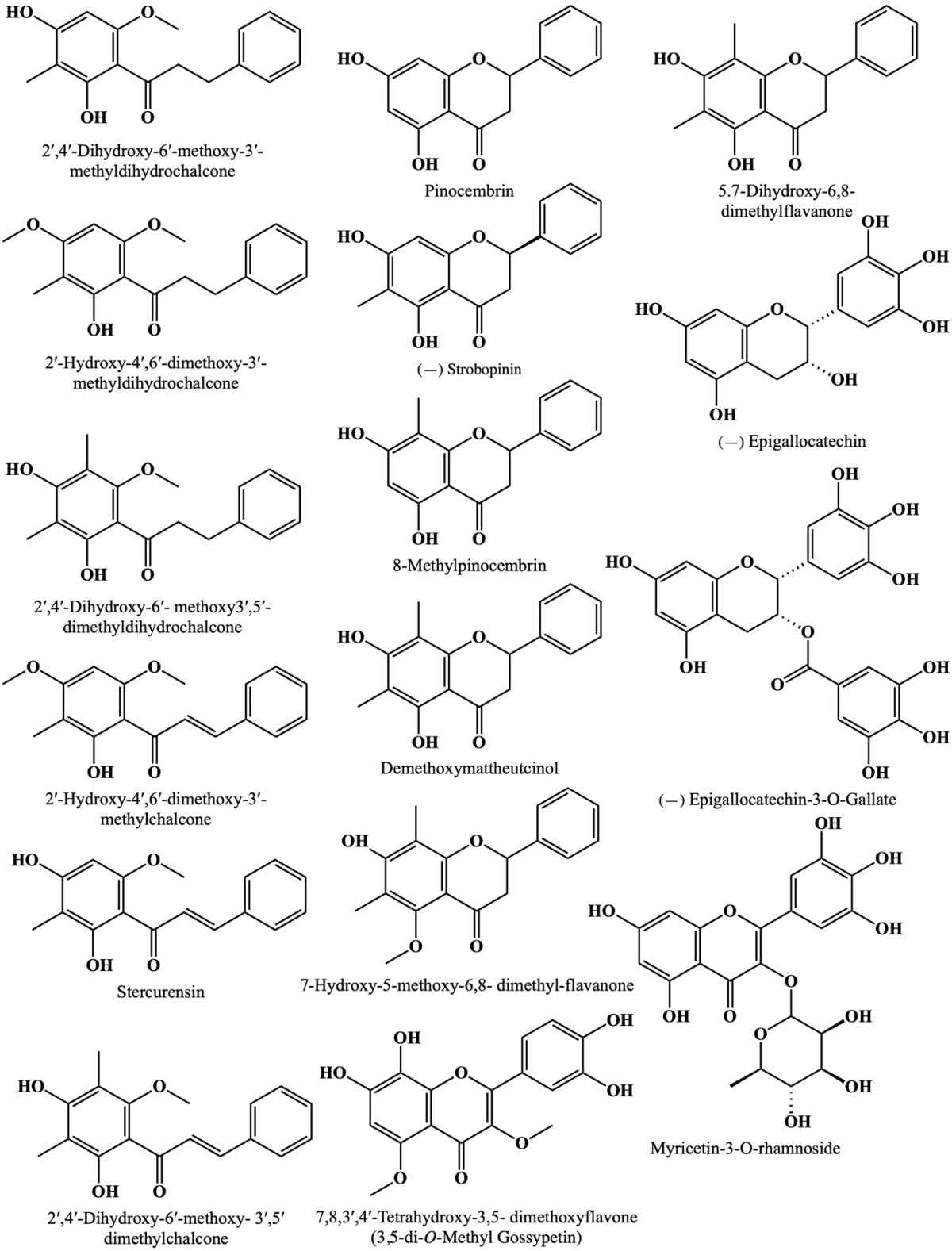
Plant Parts	Metabolites Groups	Compounds	References
		7,8,3′,4′-tetrahydroxy-3,5- dimethoxyflavone (3,5-di-*O*-Methyl Gossypetin)	[31]
		5.7-Dihydroxy-6,8- dimethyl flavanone	[32]
		(—)-Epigallocatechin	[3]
		(—)-Epigallocatechin 3-O- gallate	[3]
		Myricetin 4′-methyl ether 3-*O*-*α*-L-rhamno-pyranoside	[30]
		Myricetin 2′-*O*-sulfate	[30]
		Myricetin-3-O-rhamnoside	[31]
		Mearnsitrin	[3]
		Samarangenins A	[3]
		Samarangenins B	[3]
		Prodelphinidin B-2 3″-O- gallate	[3]
		Prodelphinidin B-2 3,3″-O- gallate	[3]
		Aurentiacin	[26]
		Cryptostrobin	[30]
		Guaijaverin	[30]
	Resorcinol	5-[(8Z,11Z,14Z)-nonadeca-8,11,14-trienyl] resorcinol	[25]
		5-[(8Z,11Z,14E)- heptadeca-8,11,14-trienyl] resorcinol	[25]
		5-[(8Z,11Z,14Z)-heptadeca-8,11,14-trienyl] resorcinol	[25]
		5-[(9Z,12Z)-heptadeca-9,12-dienyl] resorcinol	[25]
		5-[(Z)-nonadecyl-14-enyl] resorcinol	[25]
		5-[(Z)-heptadeca-10-enyl] resorcinol	[25]
		5-[(Z)-pentadecyl-10-enyl] resorcinol	[25]
		5-pentadecyl resorcinol	[25]
		5-heptadecane resorcinol	[25]
	Acylphloroglucinols	Samarone A	[23]
		Samarone B	[23]
		Samarone C	[23]
		Samarone D	[23]
		2-Pentadecyl-5,7- didydroxychromone	[23]
		Jamunone B	[23]
		Jambone E	[23]
		Jambone F	[23]
		Jambone G	[23]
	Alkaloids	2R-prunasin	[30]
	Glucose	(3*S*,5*R*,6*R*,7*E*,9*S*)- 3,5,6,9-tetrahydroxymegastigman-7-ene	[30]
		Taxiphyllin 6’-O-gallate	[30]
		Actinidioionoside 6′-*O*-gallate	[30]
	Phenolic compounds	Myrciaphenone A	[30]
		1-feruloyl-*β*-D-glucopyranoside	[30]
	Terpenoids	Sysamarin A	[21]
		Sysamarin B	[21]
		Sysamarin C	[21]
		Sysamarin D	[21]
		Sysamarin E	[21]
		Sysamarin F	[22]
		Sysamarin G	[22]
		Methyl 2α,3β,23-trihydroxyolean-12-en-28-formate	[22]
		Ursolic acid	[29]
		Ursane	[21]
		Oleanane	[21]
		Cycloartenyl stearate	[28]
		Lupenyl stearate	[28]
		24-methylenecycloartenyl stearate	[28]
		Lupeol	[29]
		Betulin	[3]
		Betulinic acid	[3]
		β-carotene	[8]

Plant Parts	Metabolites Groups	Compounds	References
		Epibetulinic acid	[8]
	Sterols	β- Sitosteryl stearate	[28]
		β-D- Sitosterol glucoside (Daucosterol)	[30]
		β-Sitosterol	[29]
	Volatile oils	Germacrene D	[24]
		Cuminyl aldehyde	[24]
		β-Carryophyllene	[24]
		δ-Cadinene	[24]
		Spathulenol	[24]
		Anethole	[24]
		Caryophyllene oxide	[24]
		β-Pinene	[27]
		α-Pinene	[27]
		γ-Terpinene	[27]
		Limonene	[27]
		p-Cymene	[27]
		β-Selinene	[27]
		Selin-11-en-4-α-ol	[27]
		α- Selinene	[27]
		δ -Cadinene	[27]
		epi-ubenol	[27]
		Terpinolene	[27]
		α-Terpineol	[27]
Fruits	Flavonoids	2′,4′-Dihydroxy-3′,5′-dimethyl- 6′-methoxychalcone	[3]
		2′,4′-Dihydroxy-6′- methoxchalcone (Cardamonin)	[3]
		Pinocembrin	[3]
		Quercetin	[3]
		Reynoutrin	[3]
		Hyperin	[3]
		Quercitrin	[3]
		Quercetin	[8]
		Myricetin	[8]
		Rutin	[8]
		Guaijaverin	[3]
		Epigallocatechin 3-O-gallate	[8]
		Epicatechin-3-O-gallate	[8]
		Samarangensis A	[8]
		Samarangensis B	[8]
	Anthocyanins	Cyanidin-3-glucoside	[8]
	Acids	Ellagic acid	[3]
		Gallic acid	[3]
		Jasmonic acid	[15]
		Salicylic acid	[15]

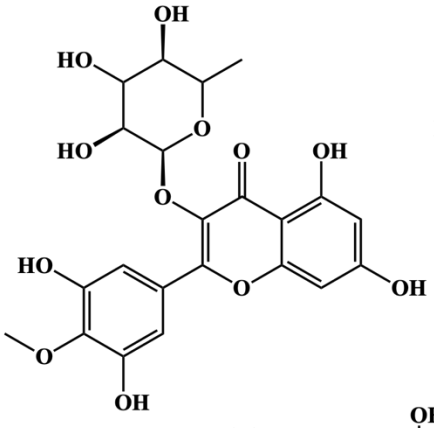
Several *S. samarangense* metabolites structures are available in Figures 1-3.

3.2. Traditional uses of S. samarangense.

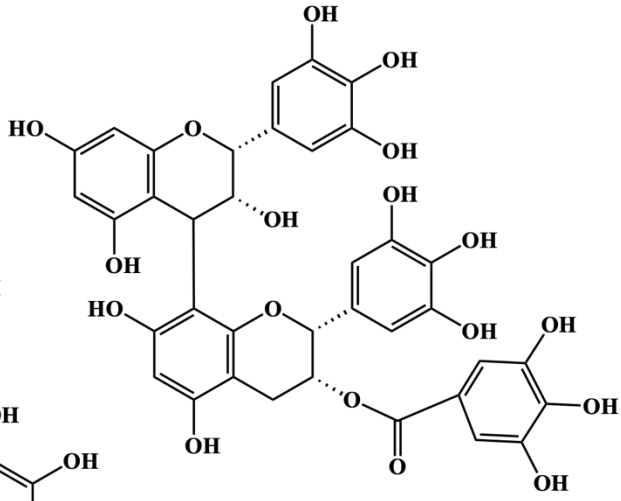
S. samarangense has been a part of traditional medicine in several countries in Asia. Bangladeshi used the leaves of *S. samarangense* for cold, itches, and waist pain treatment [33]. Malayan also used the roots preparations for itches to alleviate edema and as a diuretic. The leaves are used for fresh or dry as astringent, treating fever, and halt diarrhea [21]. The barks were prepared by the Indian tribe as an astringent for mouthwash [7]. The decoction of roots and barks was commonly used in dysentery, amenorrhea, menstrual flow stimulator, and abortifacient [3].



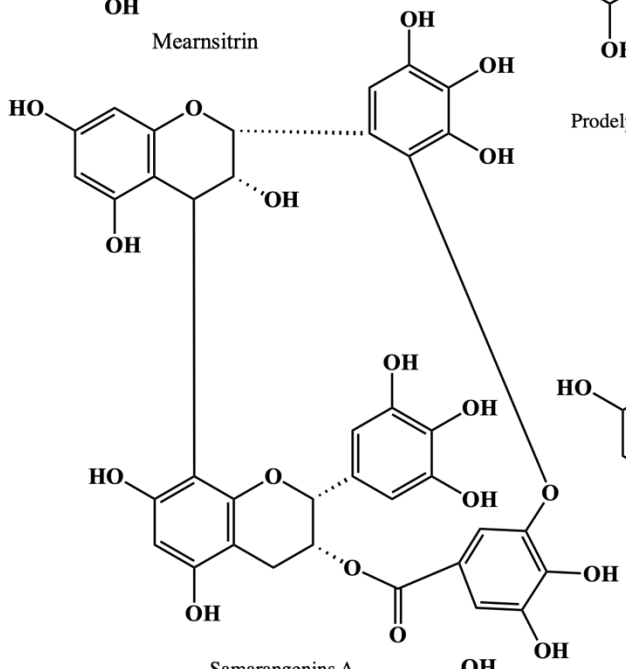
Taiwanese study reported that the leaves extract has a significant lure effect towards *Aedes albopictus* mosquito ovitraps. It was an ideal low-to-no-cost bait and simple vector management [34]. In South Asia, the fruit was served both as a hot dish and a cold dish. The hot dish was served as a soup added with crystal sugar to treat non-phlegmy cough. The fruit also was served cold dishes on banquets as an antidote to the alcoholic effect. Tannins, desmethoxymatteucinol, 5-O-methyl-40-desmethoxymatteucinol, oleanic acid, and *β*-sitosterol compounds of jambu semarang flower were used to reduce fever and also halt diarrhea [9].



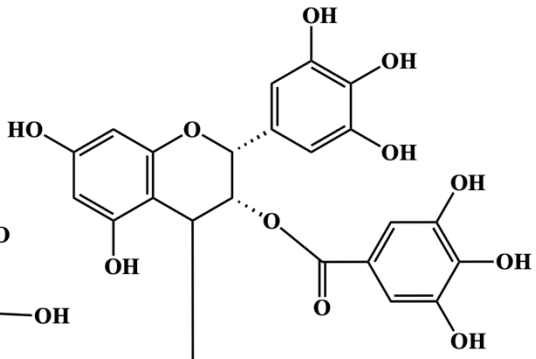
Mearnsitrin

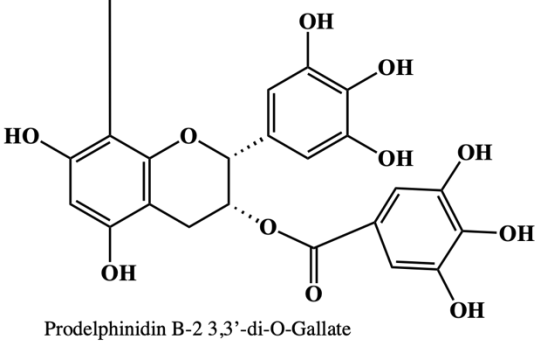


Prodelphinidin B-2 3'-O-Gallate

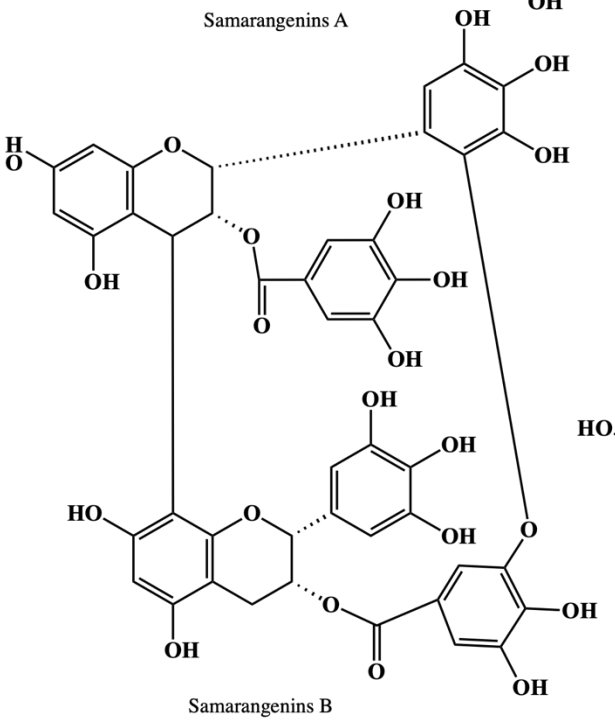


Samarangenins A

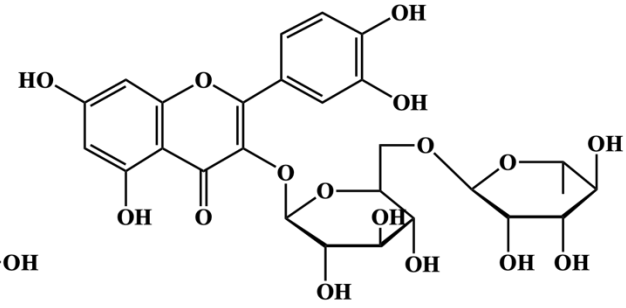




Prodelphinidin B-2 3,3'-di-O-Gallate



Samarangenins B



Rutin

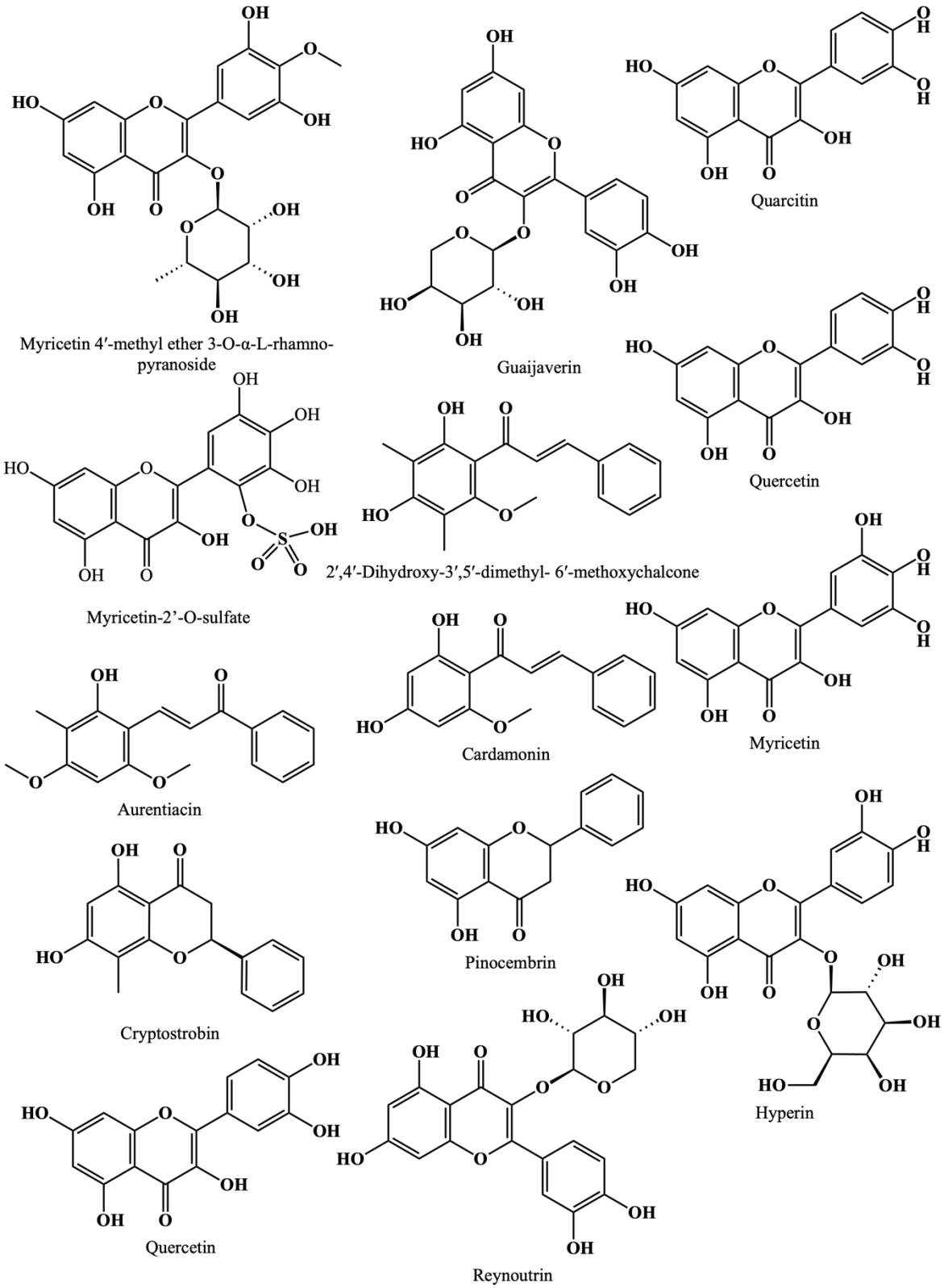


Figure 1. Representative chemical structures of flavonoids isolated from jambu semarang.

3.3. Pharmacological activities of S. samarangense.

Alongside the traditional uses, phytochemicals of jambu semarang are reported to have several pharmacological actions with prospective medical benefits such as antioxidant, antimicrobial (especially against herpes virus), analgesic, anti-inflammatory, antihypertensive, antihyperglycemic, anticonvulsant, sedative, astringent, spasmolytic, inhibitor of histamine release, potential inhibitor on peripheral blood mononuclear cells, cytotoxic activity,

immunomodulator, diabetes or glucose tolerance impairment, skin diseases, tuberculosis, diarrhea, stomach, and respiratory complaints management [12].

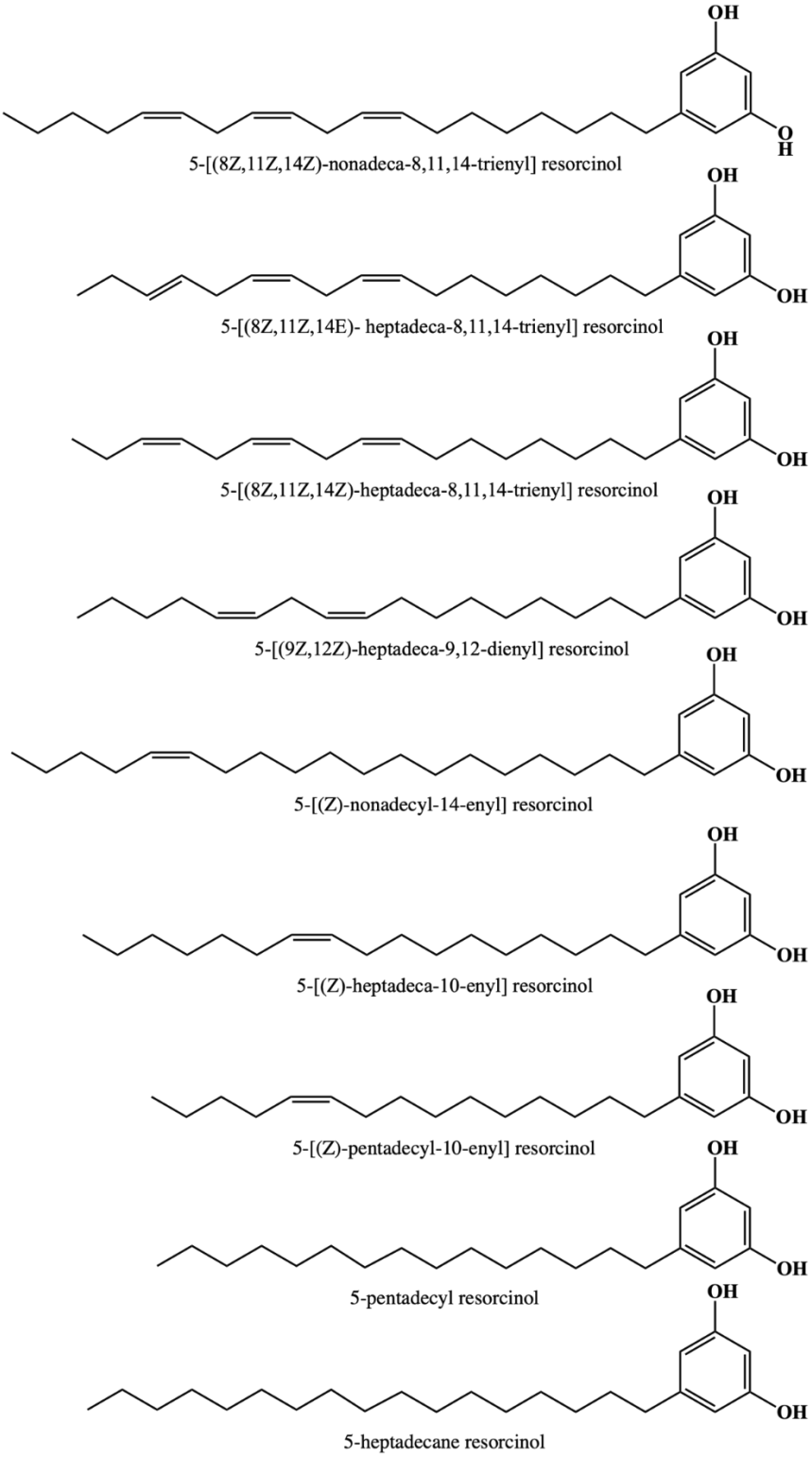


Figure 2. Representative chemical structures of resorcinol derivatives isolated from jambu semarang.

3.3.1. Antioxidant activity.

The antioxidant activity is commonly linked to the presence of phenolic compounds with numerous hydroxyl moieties such as flavonoids and coumarins [32]. Being rich in flavonoids, jambu semarang provides an effective antioxidant measure [31].

A study with ethyl acetate extract of *S. samarangense* reported the presence of antioxidant activity using the DPPH method with IC_{50} estimated 74.37 µg/ml. Myricitrin (myricetin-3-O-α-rhamnoside) compound of leaves crude extract was reported to modulate the mitogen-activated protein kinase (MAPK) signaling pathway to counter the activation of oxidative stress.

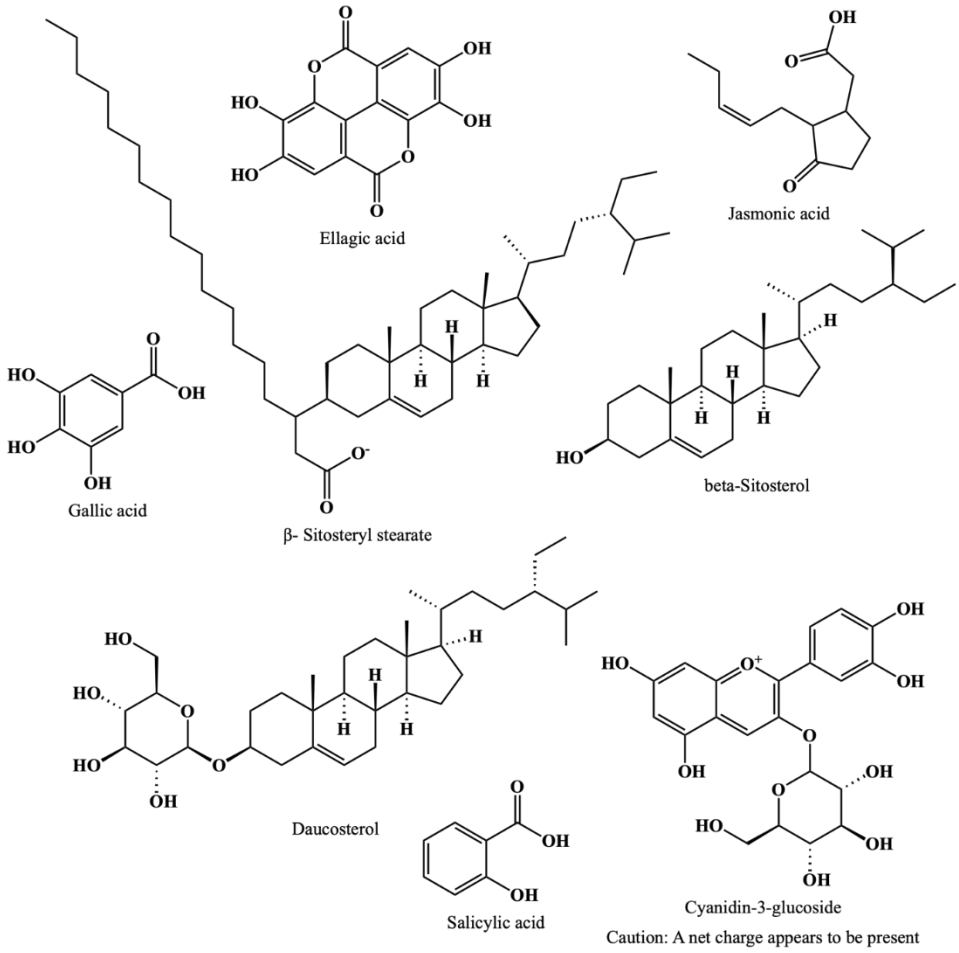


Figure 3. Representative chemical structures of sterols, anthocyanins, and acids isolated from jambu semarang.

The same research also found where 3,5-di-O-methyl gossypetin (7,8,3 ,4 -tetrahydroxy-3,5-dimethoxyflavone) reported the same mechanism by modulating the nuclear transcription factor-2 (Nrf-2) signaling pathway and stimulate the phase II detoxifying enzymes expression, such as HO-1 enzyme and Mn-SOD-3 enzyme. Both metabolites showed an *in vitro* antioxidant activity by lowering the negative effects of oxidative stress in HaCaT cells. Glutathione level was observed from a constant amount of reactive oxygen species (ROS) [31].

The methanolic extract of *S. samarangense* roots showed a moderate antioxidant activity using DPPH and FRAP assays with gallic acid as the biomarkers [3]. The roots of the plant extracted continuously in three different solvents (ethyl acetate, methanol, and water) by the Soxhlet apparatus method, reported an antioxidant activity that was evaluated by DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging compared with ascorbic acid. Methanolic extracts with the highest scavenging percentage contained flavonoids at 33.687 µg/ g extract [3].

There are three variants of *S. samarangense* based on their fruit color (red, pink, and green). Antioxidant activity measurement using the DPPH method with ascorbic acid as the standard showed that the extract of the red fruit variants had the highest antioxidant activity,

followed by the pink and green variants, respectively [9]. Further studies need to be conducted to analyze the correlation between fruit pigmentation and antioxidant activity.

Antioxidant effect was also found in eight phytochemicals that were identified from the fruits. Those compounds are six quercetin glycosides (reynoutrin, hyperin, myricitrin, quercitrin, quercetin, and guaijaverin), (S)-pinocembrin, and phenolic acid (gallic acid and ellagic acid) [3]. Another study also showed that fruit ethanolic extract expressed moderate antioxidant activity with IC_{50} of 77.51 mg/ml, TAC (total anthocyanins content) of 0.07 mg C3G/g dry weight, and TPC (total phenolic content) of 18.04 mg GAE (gallic acid equivalent)/g dry weight. The same report with DPPH assay exhibit an IC_{50} of 200 mg/ml [8].

Antioxidant activity of jambu semarang twigs and leaves extract was examined with DPPH, ABTS (2,2-azino-bis (3-ethyl-benzthiazoline-6-sulfonic acid)), DMPD (dimethyl-4-phenylenediamine), nitrite radical scavenging, and ferrous-ion chelating activity. This study also measured the activity by several assays, including cupric reducing antioxidant capacity, reducing power, ferric reducing antioxidant power, total phenol content, and total flavonoid content. The results dominantly showed that the twigs extract had a stronger antioxidant activity than the leaves due to its higher total phenol and flavonoid contents [36].

3.3.2. Antimicrobial activity.

Antimicrobial activities are generally correlated with several phenolics killing the bacteria or suppress virulence factors. The phenolic compound will decrease the amount of important substrate for microbial growth, enzyme inhibition, and chelate complex formation by modifying cytoplasmic membrane permeability [37]. Antimicrobial activity claims can be made by *in vitro* assay. A molecule is considered antibacterial activity whenever the minimum inhibitory concentrations (MIC) fall below 1000 µg/mL[3].

Volatile oils of *S. samarangense* leaves extract showed antimicrobial activity towards a wide range of enteric and nosocomial pathogenic bacteria that cause diarrhea, such as *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella enteritidis*, *Salmonella paratyphi*, *Salmonella typhimurium*, *Shigella dysenteriae* and *Shigella sonnei* [1]. Antibacterial activity of *S. semarangense* volatile oil was assessed by microdilution method and reported that it was most active toward *S. typhimurium* with IC_{50} of 0.17±0.005% v/v [38]. Recent evaluation towards antimicrobial effect in volatile oil of jambu semarang leaves showed the inhibition on E. coli 25922 growth with IC_{50} of 0.42% (v/v) [39].

Another study on volatile oil of *S. samarangese* showed the higher activity of the oil against Gram-positive, where *Bacillus spizizenii* was the most susceptible one, compared to Gram-negative bacteria. The oil composed of terpenes including β-pinene (21.3%), α-pinene (8.9%), γ-terpinene (7.9%), limonene (7.7%), p-cymene (5.9%), β-selinene (3.8%), selin-11-en-4 α-ol (3.6%), β-caryophyllene (3.5%), α-selinene (3.4%), δ -cadinene (2.9%), 1-epi-cubenol (2.2%), terpinolene (2.1%), and α-terpineol (2.1%) [27]. The antibiotic potentiating effect of this extract showed a synergic antibacterial efficacy by reducing concentration due to its combination with antibiotic in a 1:1 ratio. Ciprofloxacin, chloramphenicol, and streptomycin were used in this experiment. These findings were valuable for further studies to tackle antimicrobial resistance after safety was established [27]. Further pharmacological investigations will be necessary to validate its medical applications.

A previous antibacterial study found that the ethanolic extract of jambu semarang leaves consisted of flavonoids, tannins, alkaloids, and terpenoids. This study was conducted using the microdilution method to obtain minimum inhibitory concentration (MIC). The sample of this study were *E. coli*, *Bacillus cereus*, *Enterobacter aerogenes*, and *Salmonella enterica*. It was shown that there was an effective antibacterial activity against B. cereus and *S. enterica* compared to chloramphenicol as a biomarker, where both the MIC value obtained were 78 µg/ml [39].

Desmethoxymatteucinol, 5-O-methyl-4'-desmethoxymatteucinol, oleanic acid, and β-sitosterol of the flower demonstrated a weak antibiotic action against S. aureus, Mycobacterium smegmatis, and Candida albicans [8]. Further study needs to be conducted to find the specific phytochemical compound with antibacterial activity.

3.3.3. Antiviral (anti-HIV) activity.

Oleanic acid was well known as an effective anti-HIV compound. These compounds are also present in the leaves of *S. samarangense*. *In vivo* study was conducted by cultures of human peripheral mononuclear cells (PBMC) and monocyte (macrophage) showed that oleanic acid inhibited replication event of human immunodeficiency virus-1 (HIV-1) in the cellular systems [8]. Further study needs to be conducted with an animal model *in vitro* assay.

3.3.4. Analgesic activity.

Cycloartenyl stearate, lupenyl stearate, sitosteryl stearate, and 24-methylenecycloartanyl stearate were discovered from air-dried leaves of jambu semarang in dichloromethane extract. These components demonstrated a potent analgesic activity respectively at 6.25 mg/kg body weight [28].

Analgesic activity of ethanolic extract of jambu semarang bark was measured using acetic acid-induced writhing and formalin test. The results at the dose 100 mg/kg and 200 mg/kg significantly showed that the extract reduced the writhing and the licking repetition number induced by acetic acid and formalin, respectively, in a dose-dependent manner. A preclinical experiment of ethanolic extract of the barks at the dose of 100 mg/kg and 200 mg/kg body weight on swiss-albino mice showed a significant depressant activity manifesting in the reduction of locomotor, exploratory in the open field, and hole cross test activity [40].

Stercuresin (2', 4'-dihydroxy-6'-methoxy-3'methylchalcone), an isolated compound of *S. semarangense* leaves, has anti-inflammatory activity by *in vivo* assay with a mouse model. Expression of lipopolysaccharide-induced iNOS (inducible nitric oxide synthase) and cyclooxigenase-2 (COX-2) of isolated mouse peritoneal macrophages were reduced during pretreatment. Thereby, it inhibited nitric oxide (NO) and prostaglandin E(2) production. Stercuresin downregulated NF-**κ**B dependent pro-inflammatory mediators and cytokines pathways through the attenuated complex formation of TAK-1 and TAB1 (activator subunit of TAK1) [8].

3.3.5. Anti-inflammatory activity.

The same study was discovered cycloartenyl stearate, lupenyl stearate, sitosteryl stearate, and 24-methylenecycloartanyl stearate from air-dried leaves of jambu semarang in dichloromethane extract revealed a potent anti-inflammatory activity respectively at 12.15 mg/kg body weight [28]. *In vitro* experiment reported that oleanic acid and ursolic acid

effectively protect the liver from chemical-induced injury, anti-inflammatory, and antihyperlipidemic. Oleanic acid and ursolic acid were qualified to be non-toxic compounds and had been used in cosmetic and health products [8].

The previous research also found that myricetin-3-O-α-rhamnoside and 3,5-di-O-methyl gossypetin (7,8,3,4 -tetrahydroxy-3,5-dimethoxyflavone) expressed an *in vitro* anti-inflammatory activity by strongly reduced intracellular reactive oxygen species (ROS) accumulation, carbonyl content and protected the glutathione (GSH) levels in human keratinocyte cells (HaCaT) after exposure to the sodium arsenite ($NaAsO_2$) as a toxic agent. Therefore, both compounds contributed to lower the adverse effects from oxidative stress in HaCaT, inhibit I-**κ**B-α degradation, and protecting cells from UVA-induced inflammation [31].

Aurentiacin, a chalcone isolated from jambu semarang leaves, was reported to have an anti-inflammatory effect. *In vivo* study showed this activity towards lipopolysaccharide (LPS)-stimulated mouse macrophages by inhibiting the production of LPS-induced nitric oxide in RAW264.7 cell parallel with suppressing the expression of inducible nitric oxide synthase (iNOS). Electrophoretic mobility shift and reporter gene assay at the molecular level reported that there was a reduction of pro-inflammatory cytokines (tumor necrosis factor-α and interleukin-6). Aurentiacin alleviated DNA binding, transcriptional activities of NF-**κ**B, also attenuated phosphorylation and acetylation of p65 and MAPKs. *In vitro* study with animal model injected by intraperitoneal also showed a decrease in the number of pro-inflammatory cytokine release. Ex vivo experiment also reported a decent decrease of iNOS protein level related to the inhibition of NF-**κ**B activation [26].

Evaluation of ethyl acetate, methanol, and water root extract showed the anti-inflammatory effect following albumin denaturation assay. Methanolic extract showed the highest activity, followed by water and ethyl acetate extract, respectively [3]. Ethanolic extract of barks also gave a potential anti-inflammatory in mice. Carrageenan induced hind paw edema model was used in this study, and the inhibition appeared after 4 h at the dose 100 mg/kg and 200 mg/kg in a dose-dependent manner [40]

3.3.6. Antidiabetic activity.

Flavonoids isolated *S. samarangense* was reported to have antihyperglycemic activity on alloxan-induced diabetic mice [3]. Further study finds that vescalagin is responsible in ameliorating hyperglycemia and hypertriglyceridemia effect on high-fructose diet-induced diabetic rats [41].

Flavonoids isolated from leaves significantly affected lowering the blood glucose level (BGLs) in glucose-hyperglycemic mice. The extract was administrated 15 min after a glucose load. Those flavonoids were 2',4'-dihidroxy-3',5'-dimethyl-6'-methoxychalcone and its isomeric flavanones (5-O-methyl-4'-desmethoxhymatteucinol and 2',4'-dihidroxy-6'-methoxy-3'-methylchalcone) [8].

In carbohydrates metabolism, the aqueous fruit extract of jambu semarang had the potential to mitigate the hyperglycemia of diabetes mellitus (DM) type 2 by increasing the glycogen storage, glycolysis and gluconeogenesis activity, expression of glycogen synthase (GS), hexokinase (HXK), glucose-6-phosphate dehydrogenase (G6PD), phosphofructokinase (PFK), and aldolase. The study was conducted using FL83B mouse hepatocytes that treated with TNF-α to induce insulin resistance and evaluated by examining the uptake of 2-[N-(7-

nitrobenz-2-oxa-1, 3-diazol-4-yl)amino]-2-deoxyglucose (2 NBDG), a fluorescent D-glucose derivative, and analyzed with Western blot assay [42].

An ellagitannin called vescalagin decreased the expression of pro-inflammatory factors that may cause the excessive metabolism of insulin secretion in β-cells of rats—this metabolism in human-caused the excessive formation of methylglyoxal (MG), a derivate of pyruvic acid. Further studies of vescalagin on MG metabolism signaling pathway need to be done[43].

A study on the diabetic rat model showed that oral administration of vescalagin alleviated hyperglycemic shown by reducing the glucose level following oral glucose tolerance test. It also reduced cardiovascular risk index, advanced glycation end products (AGEs), and tumor necrosis factor-α contents. Antiglycation was facilitated by increasing D-lactate that retard AGE formation and decreasing cytokine release to prevent β-cell damage of MG-induced carbohydrate metabolic disorder in rats. This study has proven that vescalagin has a preventive effect on MG-induced inflammation and carbohydrate metabolic disorder in rats [43].

Another vescalagin study showed an ameliorative effect on hepatic insulin resistance cascades and abnormal carbohydrates in the high-fructose diet (HFD)-induced hyperglycemic Wistar rats. The hypoglycemic activity of the compound was confirmed in oral glucose tolerance test and homeostasis model assessment of insulin resistance index. Abnormal carbohydrate metabolism was improved by modulating hepatic gluconeogenesis, glycolysis, and glycogenesis [44].

Methanolic leaves extract was evaluated to have an antihyperglycemic potential carried oral glucose tolerance test in glucose-loaded mice. Methanol extract administered at different doses an hour after glucose administration and BGLs are measured with the glucose oxidase method. The results stated that there was a 59.3% reduction in serum glucose level. Meanwhile, glibenclamide, as a controlled drug, only reduced 57.3% [33].

S. samarangense extract could reduce insulin resistance by inhibiting inflammatory pathways, insulin signaling activation, glucose uptake improvement in insulin-resistance mouse hepatocytes [3,42,45].

Fruit of jambu semarang had a big role in the antidiabetic activity. A study against streptozotocin reported protective properties of jambu semarang fruit extract (STZ)-induced pancreatic ß-cell apoptosis in diabetic rats for 30 days. The results were an alleviation of pancreatic ß-cell apoptosis with significant expression of upregulated Bcl2 and Bcl-xl protein, also down-regulated cleaved caspase-3 and Bax protein expression. The extract also improved pancreatic ß-cell function, possibly caused by inhibiting oxidative stress and pro-inflammatory cytokine also activating anti-apoptotic proteins [46]. Water-soluble polysaccharide fraction (WAFP) isolated from fruit exhibited an effective inhibitory effect on α-glucosidase activity [19].

Fruit extract was also known to enhance the glucose uptake ability of insulin-resistant FL83B rat hepatocytes. A recent study evaluated the hypotriglyceridemic and hypoglycemic effect of fruit extract in a high-fructose diet (HFD)-induced diabetic Wistar rats. Vescalagin, which was administered 30 mg/kg body weight for a 4 weeks period, demonstrated a respectively decrease in the number of fasting blood glucose (44.7%), c-peptide (46.2%), fructosamine (4%), triglyceride (42.5%), and free fatty acid (10%) contents. Also, it be mentioned that there was an increase of high-density lipoprotein-cholesterol content by 14.4% [41].

A different study was also conducted using FL83B mouse hepatocytes, where the fruit fraction of jambu semarang was evaluated to enhance glucose uptake in TNF-α-induced insulin resistant Wistar rats. Fruit fraction increased expression of insulin receptor (IR), insulin receptor substrate-1 (IRS-1), protein kinase B (Akt/PKB), phosphatidylinositol-3 kinase (PI3K), and glucose transporter 2 (GLUT-2), and IR tyrosyl phosphorylation. The same cell also decreased phosphorylation of c-Jun N-terminal kinases (JNK), but not the expression of the intercellular signal-regulated kinases **(**ERK). There was an alleviation of insulin resistance in TNF-α-treated FL83B cells by activating PI3K-Akt/PKB signaling and inhibited inflammatory response via suppression of JNK cascade activation [45].

The antidiabetic activity was determined at jambu semarang roots extracted by ethyl acetate, methanol, and water solvents by continuous extraction in the Soxhlet apparatus. The results stated that water extract showed the highest percentage of α-amylase inhibitory, followed by methanol and ethyl acetate extract [3].

Resorcinol derivatives with long aliphatic chains were isolated from jambu semarang leaves. There are nine resorcinol derivatives that have been reported before, demonstrating a significant inhibitory effect towards *α*-glucosidase as a promising antidiabetic alternative with IC_{50} value 3.16, 3.16, 2.34, and 0.99 mM, respectively [25].

Further study needs to be conducted to develop the potential drug or food supplement against diabetes.

3.3.8. Thrombolytic and spasmolytic activity.

Methanolic extract of jambu semarang leaves had effectively show a thrombolytic activity by its significant clot lysis activity (32.73 ± 2.57%) compared to streptokinase drug positive control (75.00 ± 2.60%) and distilled water as a negative control (5.55 ± 1.20%) [47].

In vivo spasmolytic activity study showed that n-hexane extract of jambu semarang relaxed the contracting isolated rabbit jejunum. Flavonoids that were isolated from this extract: 2’-hydroxy-4’,6’-dihydroxy-3’-methylchalcone, 2’,4’-dihydroxy-6’-methoxy-3’,5’-dimethyl chalcone, 2’,4’-dihydroxy-6’-methoxy-3’-methylchalcone, and 7-hydroxy-5-methoxy-6,8-dimethyl-flavanone. The most potent compound (2’,4’-dihydroxy-6’-methoxy-3’,5’-dimethylchalcone) was reported in a dose-dependent study (10-100 mg/ml) with spasmolytic activity was [8].

3.3.9. Cytotoxic activity.

Ethanolic extract of jambu semarang leaves showed a cytotoxicity activity towards human breast cancer (HeLa) cells. Viable cancer cells were incubated with different extract concentrations and demonstrated a dose-dependent pattern effect with an IC_{50} value of 40.5 mg/ml. Preliminary screening found that fatty acids, alkaloids, flavonoids, terpenoids, saponins, tannins, and steroids of *S. samarangense* extract are responsible for the cytotoxicity activity[17]. Cytotoxic activities were also examined from this extract against two other tumor cell lines, HepG2 and MDA-MB-231 cells, which displayed potent cytotoxic activities ranging from 1.73 to 32.90 µM and 4.02 to 37.83 µM, respectively [23].

3.3.10. Hepatoprotective activity.

Methanolic leaves extract had a hepatoprotective activity in carbon tetrachloride (CCl_4)-treated rats. Carbon tetrachloride induces severe hepatic toxicity because of its

metabolism by cytochrome P450s in the liver into halogenated free radicals. These metabolites destruct the hepatic tissue and result in serious lipid peroxidation. It also attributes to covalent bonds with membrane lipids formation. This extract was reported to increase the reduced glutathione by 84.75% and superoxide dismutase activities by 26/27% and decrease in total bilirubin 37%, total cholesterol 13.26%, and total cholesterol glycerides by 15.15%. Histopathological analyses also confirmed this report [48].

S. samarangense fruits were also reported to have a hepatoprotective activity towards alcohol-induced liver injury mice. Alcohol chronic treatment increased the level of aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin (TB), triglyceride (TG), malondialdehyde (MDA), also respectively decreased the total protein (TP). The fruit extract normalized these biochemical markers [49].

3.3.11. Anticancer activity.

An anti-colon cancer activity of *S. samarangense* pulp in methanol extract was examined on SW-480 human colon cancer cell line using MTT (3-(4,5- dimethylthiazol-2-yl)-2-5-diphenyltetrazolium bromide) assay with epigallocatechin gallate as a positive control. The results showed high toxicity towards cancer cell, and further toxicity study yet to be conducted [50].

Another study expressed that dimethyl cardamon isolated from the leaves could inhibit HCT 116 and LOVO human colorectal carcinoma cell proliferation and induce G_2/M cell cycle arrest. The effects attributed to the induction of autophagy respectively [51].

Castalagin and vestalagin isolated from the leaves of *S. samarangense* demonstrated dual *in vitro* inhibitory activity towards PARP1 and DNA topoisomerase II (Top2) of SH-SY5Y cells. These compounds attenuated cellular PARP1 activity with IC_{50} values at 0.86 μM and 2.67 μM for castalagin and vestalagin, respectively, without any sign of cell death characterized by the emergence of floating or changing shape of the cell. Analysis of castalagin and vestalagin structures described that different OH-orientation affected this difference inhibition activity. Top2 had a big role in cancer chemotherapy development due to its DNA topological changes that required DNA replication, transcription, and chromosomal segregation alongside topoisomerase I (Top1). Castalagin and vestalagin significantly suppressed Top2-dependent conversion from supercoiled DNA to various relaxation degrees [51].

3.3.12. Anthelmintic activity.

The anthelmintic study was normally investigated base on the paralysis and death rate effect of living parasites. Polyphenolic compounds played a major role in these studies, especially tannins. Tannins facilitate energy depletion in helminths by performing uncoupling oxidative phosphorylation. Methanolic extract of jambu semarang leaves revealed a comparable effect with albendazole in an animal model. Ethanolic extract of barks also demonstrated anthelmintic activity compared with the standard anthelmintic drug albendazole. Both studies evaluated the extract in 25, 50, 100, and 200 mg/ml. Time estimation of these two studies reported a quicker paralysis and death effect on a higher extract concentration. The vermicidal activity of methanolic leaves extract was measured by their effect on paralysis and death of anthelmintics parasite at 200 mg/dl [47]. *In vitro* evaluation resulted in a dose-

dependent manner and a significant effect statistically [7]. The mechanism action of the extract needs to be studied later.

3.3.13. Anxiolytic activity.

Anxiolytic activity of *S. samarangense* methanol extract measured using a light and dark box test (LDB) at doses 200 and 400 mg/kg body weight. The extract showed an increasing number of animal model crossing movement and time spend in either light or dark box 29.67 ± 2.71 and 230.80 ± 16.39 second compared to diazepam 28.50 ± 2.31 and 254.00 ± 7.34 second, as the standard. The anxiolytic activity was also measured by elevated plus maze (EPM). The test showed that this extract increased the percentage of entries and duration needed into the open arm compared to the negative control group. Statistically, this study also displays a significant effect in a dose-dependent manner [47].

3.3.14. Protease inhibitory activity.

N-hexane extract of *S. samarangense* leaves exhibited inhibitory activity towards serine proteases, such as trypsin, thrombin, and prolyl endopeptidase (PEP). Lupeol, betulin, epibetulinic acid, 2',4'-dihydroxy-6'-methoxy-3'-methylchalcone, 2'-hydroxy-4',6'-dimethoxy-3'-methylchalcone, 2'-4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone, and 7-hydroxy-5-methoxy-6,8-dimethylflavanone responsible for significant PEP inhibition. PEP has a role in several neuropeptides degradation, such as vasopressin, substance P, and thyrotropin-releasing hormone (TRH), involved in the learning and memory process. PEP inhibition improved memory by blocking the endogenous neuropeptides metabolism. This inhibition might be a potential target for antidementia drug development[8].

Volatile oils of leaves inhibited the purified extracellular protease enzyme of Salmonella typhimurium. Inhibition was observed from the enzyme-substrate kinetic method using a line-weaver burke plot [37]. Another study demonstrated that the same method resulted in the same inhibition activity of volatile oils towards purified Escherichia coli. This volatile oils inhibited with IC_{50} value of 0.42% (v/v) [38]. Further isolation and identification of these bactericidal-specific volatile oil constituents would be impactful towards antimicrobial chemotherapy development.

3.3.15. Immunomodulatory activity.

Sixteen flavonoids were isolated from acetone extract of *S. samarangense*. Four of them described an inhibitory potency on human peripheral blood mononuclear cells (PBMC) proliferation activated by phytohemagglutinin (PHA). Those flavonoids, (−)-strobopinin, myricetin 3-O-(2′-O-galloyl)-a-rhamnopyranoside, (−)-epigallocatechin 3-O-gallate, and myricetin 3-O-a-rhamnopyranoside, were reported to reduce IL-2. The inhibitory mechanism involved by IL-2 blockage and Interferon-g (IFN-g) production in a dose-dependent manner [8].

3.4. Toxicity study.

With its no toxicity events until the dose of 1000 mg/kg toxicity test toward albino Swiss mice, methanolic extract of *S. samarangense* leaves was reported to be safe [40]. Another study upon the administration of dichloromethane extract of the leaves containing mainly

cycloartenyl stearate, lupenyl stearate, sitosteryl stearate, and 24-methylenecycloartanyl stearate also reported no toxicity event. Toxicity examination with dechorionated embryos of zebrafish showed no mortality and teratogenicity effect. There was no necessary abnormality of all treatments. There was a delay in the hatching of embryos with intact chorion treated with extract. Hence there was no toxicity compared to diclofenac as a positive control [28]. Taken together, these results underline the safety of *S. samarangense* at the preclinical level. Further safety evaluation at the clinical level yet to be done.

3.5. Further development of S. samarangense.

Research on pharmacological activities of *S. samarangense* contributed to the development of the natural produce of the plant. A *in silico* study showed a promising docking score, glide model, and glide energy of jambu semarang isolate obtained from SwissADME database, where the docking value would give a potential novel drug [47].

Cell viability of hot water leaves and twigs extract of *S. samarangense* measured by MTT assay in human keratinocyte cells (HaCaT). The cell viability of these extracts was lowered due to their low stimulation level. The test observed that a slight irritation appeared. The lower concentration should be evaluated to have more comprehensive data on this irritation. This study showed a possible candidate for topical application [35]. Effective formulation by concentration and excipient adjustment needs to be done for further development.

The pharmaceutical formulation had been conducted from *S. samarangense* fruit extracts as an anti-acne cream. This formulated cream showed antibacterial activity, including acne vulgaris. The evaluation of this formula reported stability for two months duration. Further clinical and toxicological studies were recommended to develop this product into commercial standards [52].

Besides pharmaceutical usage, the study of *S. samarangense* was also conducted from lots of perspectives. Other studies of this plant focused on developing this extract as a DNA fingerprint [53], bio-semiconductor [54], and other studies.

Modernized natural product development gives a bigger picture of what challenges might be seen towards future novel drug development. Isolation, standardization, and quality control will focus on developing medicine that meets the safety, quality, and efficacy requirements [47]. Harmonization and modernization of scientific research need to be done in a multidisciplinary field [1].

4. Conclusions

S. samarangense produces diverse metabolites, including flavonoids, phenolic compounds, resorcinol derivatives, acylphloroglucinols, tannins, terpenoids, sterols, and other metabolite groups. Past studies of this plant extract showed various pharmacology activities by *in vivo* and *in vitro* experiments. Negligible toxicity was reported. Other development was also exhibited an *in-silico* assay, topical formulation assay, and other biological studies. Modern challenges of this natural product development will be focused on isolation, standardization, and quality control to develop a novel medicine that meets the safety, quality, and efficacy requirements. Multidisciplinary scientific research needs to be done for further drug development and discovery.

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Conflicts of Interest

The authors declare no conflict of interest.

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