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Review article

Phytochemical and pharmacological profile of genus *shorea:* A review of the recent literature

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ABSTRACT

In tropical Southeast Asia, *Shorea* is the most economically important tree and the largest genus in the Dipterocarpaceae family. It comprises about 150–200 species, of which majority are distributed in Malaysia, with others found in Sumatra and Borneo (Kalimantan) in Indonesia. Research on the chemical constituents of *Shorea* plants has been ongoing for many years. To date, a total of 113 different compounds, including 83 stilbenes and their resveratrol oligomers, 18 triterpenes/terpenoids, 7 coumarins 3 flavonoids and 2 steroids have been isolated and successfully elucidated from 26 different species of this genus. The diversity of the stilbene resveratrol oligomers in the *Shorea* genus is primarily due to the difference in the amount of resveratrol constituent units, which include dimers, trimers and tetramers. In addition to the species' traditional usage in the treatment of illnesses, such as diarrhea, toothaches, skin diseases, ear troubles and wounds, the extracts and secondary metabolite compounds isolated from various parts of the plant species are known to have a very potent antioxidant, antimicrobial, anticancer, anti-diabetic, anti-obesity, antiulcer, hepatoprotective and nephroprotective activities. This review aims to summarize the most recent research made from 1999 to date on the secondary metabolite compounds isolated from different species of genus *Shorea*, as well as the bioactivity (in vitro and in vivo) of the crude extracts and the isolated secondary metabolite compounds.

1. Introduction

There are more than 250,000 species of flowering plants in existence worldwide. Over 6000 species of these plants are reported to exhibit medicinal value [1,2]. These medicinal plants, considered to have limited side effect and less toxic, are the foundation of both traditional and modern medicine [3]. Dipterocarpaceae is a relatively large family of tropical plants that consists of 14 genus namely: *Shorea, Anisoptera, Balanocarpus, Cotylelobium, Dipterocarpus, Doona, Drybalanops, Hopea, Isoptera, Neobalanocsrpus, Parashorea, Stemonoporus, Upuna* and *Vateria* [4]. The genus *Shorea* locally known as Meranti, is the main genus in this family with approximately 190

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species [5]. It represents tropical rain forest timber trees that are mostly found in Southeast Asia [6], primarily in Malaysia and Indonesia [29]. The majority of the species in this genus, particularly those found in Indonesia, are regarded as endemic. These might be due to their economic value, which includes their use in the plywood, building and furniture industries, as well as other economic sectors [5]. Shorea genus has been one of the research focus in the dipterocarpaceae family. This is due to the presence of variety of secondary metabolite compounds, such as coumarins, terpenoids and oligostilbenoid [7,8].

Numerous studies have proposed that oligostilbenoid, a polyphenolic stilbene which occurs in di-, tri- and tetra [9], demonstrates a wide range of biological activities, including antioxidant, chemopreventive, anti-inflammatory, anti-hepatotoxicity, anti-tumor, hepatoprotective, antimicrobial, and cytotoxic effects [10,39,46,79,93]. Various studies have been conducted on different species of the genus *Shorea*; with regards to this, the review aims to sum up the recent research made from 1999 to date on the crude extracts and secondary metabolite compounds isolated from different species of the *Shorea* genus and their bioactivities. The literature search involved reputable databases including Scopus, PubMed, Web of Science, ScienceDirect, and Google Scholar. Searches employed keywords related to '*Shorea* genus' as well as specific *Shorea* species names. The selection criteria favored studies with complete information relevant to the research questions.

2. *Shorea* species presentation

2.1. Description, distribution, and traditional uses of Shorea species

Dipterocarpaceae is a relatively large family of tropical plants that consists of 14 genera and approximately 600 species [11]. With approximately 190 species, *Shorea* or Meranti (Fig. 1) is one of the largest genera in this family, along with Hopea (100 species) and Dipterocarpus (75 species) [12].

According to Symington [6], the four color-based *Shorea* timber varieties legalized for use commercially are the Balau group, Red Meranti, Yellow Meranti, and White Meranti. These divisions are closely related to the four sections of the genus *Shorea*; Shorea, Rubroshorea, Richetioides, and Anthoshorea. However, the genus was previously divided into ten sections, namely; Richetioides, Anthoshorea, Rubella, Brachypterae, Pachycarpae, Mutica, Ovalis, Shorea, Pentacme, and Neohopea. Later on, he classified Richetioides into the yellow meranti timber group, Anthoshorea into the white meranti timber group, Rubella into the red meranti timber group, and *Shorea*, Pentacme, and Neohopea into the Balau timber group [5].

White meranti; they are known to have flowers with an anther that is filiform, rather long, and not noticeably ciliate or barbate. They have a laminated, usually yellowish, rarely pink, thick inner bark with soft to moderate hard wood that is coarse in texture. Some of the white meranti *Shorea* species include; *S. assamica* Dyer, *S. bracteolate, S. agami, S. hypochra, S. Polita, S. javanica, S. dealbat, S. gratissima* Dyer, *S. henryana* Pierre, *S. lamellate* Foxw and *S. roxburghii* G. Don [5,12].

Fig. 1. Tree of *Shorea beccariana*. (Source: Balikpapan Botanical Garden, East Kalimantan, 2023).

Yellow meranti; they are characterized by having a flower that has a club-shaped prominently barbate or ciliate anther with a thin inner bark that is usually brown or yellow and a very hard wood. Some of the yellow meranti *Shorea* species include; S. resina-nigra, S. balanocarpoides, S. gibbosa, S. maxima, S. multiflora, S. faguetiana, S. acuminatissima, S. blumutensis Foxw, S. longisperma [5,12].

Red meranti; they are characterized by having flower with an appendage filiform, rather long with an anther that is not prominently barbate or ciliate. They have a dull light brown grading to greenish yellow thin inner bark and a soft, moderate wood that is coarse in texture. Some of the red meranti *Shorea* species include; S. macrophylla, S. beccariana, S. acuminata, S. leprosula, S. parvifolia, S. macroptera, S. ovalis, S. dasyphylla, S. leprosula, S. palembanica, S. platycarpa, S. albida [5,12].

Balau groups; they are characterized by having a flower that has a club-shaped prominently barbate or ciliate anther with a thin inner bark that is usually brown or yellow and a very hard wood. Some of the balau *Shorea* species include; *S. guiso*, *S. cilliata* King, *S. foxworthyi* Sym, *S. balangeran S. glauca* King, *and S. maxwelliana* king [5,12].

The genus is widely distributed in Southeast Asian regions, especially in Malaysia and Indonesia. In Malaysia, *Shorea* is known by various names such as Balau, Meranti Pa'ang, Meranti Damar Hitam, and Meranti Merah [6]. According to Ashton [5], Indonesia is home to approximately 150 *Shorea* species, with the majority found in Kalimantan. Unfortunately, more than 76 of these species are listed in the IUCN Red Data Book, and recently, *Shorea falcate* from Vietnam was declared extinct [13].

The resin of *Shorea* has long been used in traditional medicine for the treatment of various ailments, including gonorrhea, dysentery, and diarrhea [14]. In Indian traditional medicine, specifically Ayurveda, *Shorea robusta* is employed to address a wide range of health issues spanning the circulatory, digestive, endocrine, respiratory, and skeletal systems. Additionally, it's resin is utilized in the traditional Siddha culture to manage conditions such as Menorrhagia, Leucorrhea, as well as for healing wounds and burns singes [15]. Moreover, it is used as an ingredient in ointments designed for ulcers, toothaches, skin ailments, ear problems, sore eyes and wounds. The wood of *Shorea* species serves as a valuable resource for constructing planks, buildings, and furniture [12]. Additionally, *Shorea* gum is used in preparing stain pastes, as a light fuel source [16]. In Malaysia and Indonesia, the seeds of *Shorea* species yield illipe nuts known as Engkabang or Tengkawang [17].

3. Secondary metabolite compounds from *Shorea* species

Shorea species plants have long been known to produce a variety of secondary metabolites, including stilbene and its resveratrol oligomers, coumarins, and terpenes [7,8,17]. From the present review, a total of 113 different compounds (Fig. 1A), including 83 stilbenes and their resveratrol oligomers (Fig. 1B), 18 triterpenes/terpenoids, 7 coumarins, 3 flavonoids and 2 steroids have been isolated from various *Shorea* species.

The major secondary metabolites found in the *Shorea genus* are the stilbenes and their resveratrol oligomers. They are polyphenolic compound naturally synthesized by plants in response to stressful conditions like UV radiation, fungal infections and physical attack [98]. In numerous plant species, resveratrol tends to accumulate more prominently in root, wood bark or stem tissues. This prevalence in roots or stems parts is often attributed to their increased vulnerability to attacks. Consequently, when resveratrol is produced, it is frequently transported to these parts of the plant, where it acts as a defense mechanism against pathogens and pests. The presence of resveratrol in these parts might be responsible for the potent activities of the stem, root and wood bark crude extract [20,98]. Moreover, resveratrol oligomers are known to possess complex mechanisms of action that vary depending on the specific activity under consideration [18]. Their diverse potent activities are attributed to factors such as the number of hydroxyl groups, the presence of catechol groups, the existence of an olefinic linkage, and their conjugated structure [18,19]. In addition to stilbenes and their resveratrol oligomers, coumarins, flavonoids and terpenes/terpenoids have also been identified, primarily extracted from n-hexane extract of the roots, stems, wood, leaves or twigs parts of the *Shorea* species. The vital structural heterogeneity of coumarins [7,21] and

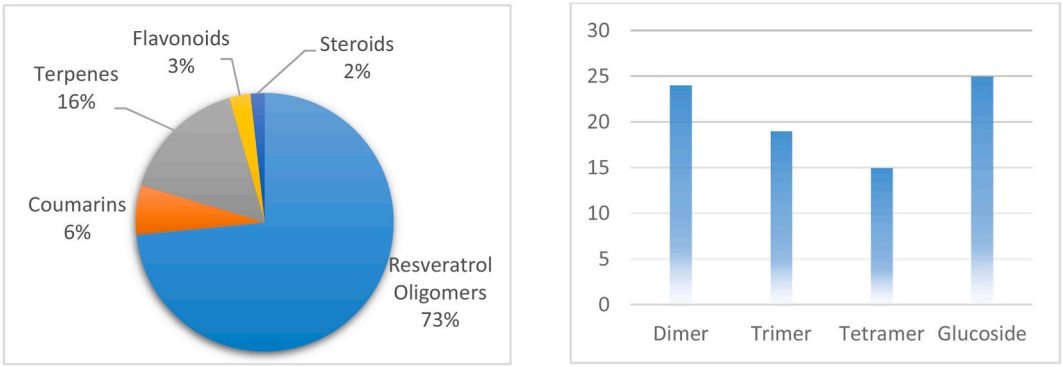

Fig. 1.2. A; Secondary metabolites isolated from Shorea genus from 1999 to 2023: B; Distribution of resveratrol oligomers isolated from Shorea genus.

Table 1
Shorea species isolated compounds.

Shorea species	Solvent Used	Part of Plant	Isolated compounds	References
S. ***accuminatissima***	Acetone	Stem bark	vaticanol A [36] davidiol A [39] α-viniferin [22] hopeaphenol [40] hemsleyanol D [51]	[13]
S. acuminatol	Acetone	Stem bark	acuminatol [2] laevifonol [18] (+)-α-viniferin [22] shoreaketone [41] vaticanol B [53] (−)-hopeaphenol [52]	[8]
S. assamica	Acetone	Stem bark	vaticanol A [36] α-viniferin [22] vaticanol B [53] isohopeafenol [46]	[23]
S. balangeran	Ethyl acetate	Stem bark	viticanol A [36] viticanol B [53] viticanol G [34]	[24]
S. brunnescens	Acetone	Stem bark	(+)-α-viniferin [22] (−)-laevifonol [20] vaticanol B [53] (−)-hemsleyanol D [43] (+)-isohopeaphenol [48] (−)-hopeaphenol [52]	[25]
	Acetone	Stem bark	(−)-davidiol A [27] (−)-vaticanol A [24] (+)-α-viniferin [22] (−)-ampelopsin E [29]	[26]
S. contorta	Dichloromethane	Twigs Leaves	lup-20 [29]-en-3-one [82] olean-12-en-3-one [83] urs-12-en-3-one [84] lutein [85] chlorophyll *a* [86] β-sitosterol [87]	[27]
S. cordifolia	Acetone	Stem bark	cordifoloside A [74] cordifoloside B [75]	[28]
***Shorea* species**	Solvent Used	Part of Plant	Isolated compounds	References
S. faguetiana	Acetone	Stem bark	(−)-ε-viniferin [10] (−)-α-viniferin [33] (−)-laevifonol [20] (−)-ampelopsin E [29] (−)-hopeaphenol [52]	[30]
S. gibbosa	Acetone	Stem bark	ε-viniferin [13] (−) ampelopsin A [12] diptoindonesin F [44] (−)-α-viniferin [33] ampelopsin E [28] vaticanol B [53]	[31]
	Methanol	Stem bark	ε-viniferin [13] ampelopsin A [3] balanocarpol [7] laevifonol [18] diptoindonesin G [19] (−)-α-viniferin [33] ampelopsin E [28] vaticanol G [34]	[32]
S. guiso	Dichloromethane	Leaves	shoreic acid [94]	[33]
S. hemsleyana	Acetone	Stem bark	hemsleyanoside A [54] hemsleyanoside B [55] hemsleyanoside C [56] hemsleyanoside D [57]	[34]
	Acetone	Stem bark	shorealactone [17]	[35]
	Acetone	Stem bark	shoreaketone [41]	[36]
	Acetone	Stem bark	(+)-α-viniferin 13b-*O*-β-glucopyranoside [73] 12-C-β-glucopyranoside [60] hemsleyanols A [16] hemsleyanols B [23]	[37]
	Acetone	Stem bark	(+)-α-viniferin [22] hemsleyanol B [23] hemsleyanol D [51] davidiol A [39] vaticanol B [53]	[38]
	Acetone	Stem bark	hemsleyanols C [50] hemsleyanols D [51] hemsleyanols E [15] hemsleyanosides E [58] hemsleyanosides F [62] (−)-ampelopsin H [49]	[39]

the flexible nature of the parent terpenoid backbones contribute to a wide range of structural variations within these groups. Consequently, this structural diversity leads to the modulation of various cellular targets in the body, depending on the specific activity being targeted [22,52,98]. Table 1 summarizes all the reported *Shorea* species isolated compounds.

Table 1 Cont.

Shorea species	Solvent Used	Part of Plant	Isolated compounds	References
S. hopeifolia	Acetone	Stem bark	(−)-ε- viniferin [10] (−)-ampelopsin E [29] (−)-hopeaphenol [52] shoreaphenol [8] scopoletin [76]	[40]
S. maxwelliana	Acetone	Stem bark	(+)-α-viniferin [22] maximol A [14] vaticanol A [36] suffruticosol A [37] vaticanol G [34]	[41]
	Acetone	Stem bark	ε-viniferin [13] laevifonol [18] davidiol A [39] stenophyllol B [35] hemsleyanol D [51] hopeaphenol A [47] hopeaphenol [40] isohopeaphenol [48]	[17]
S. multiflora	Acetone	Stem bark	(−)-hopeaphenol [52]	[42]
S. negrosensis	Acetone	Leaves	friedelin [88] 3β-friedelinol [89] oleanolic acid [90] ursolic acid [91] squalene [92] chlorophyll *a* [86]	[43]
	Acetone	Twigs	friedelin [88] 3β-friedelinol [89] ursolic acid [91]	
S. obtusa	Ethanol	Twigs	shoreanol A [25] shoreanol B [26]	[44]
S. parvifolia	Acetone	Stem bark	(−)-ampelopsin F [9] (−)-laevifonol [20]	[45]
S. pinanga.	Acetone/Diethyl ether	Wood bark	(−)-α-viniferin [33] laevifonol [18] (−)-ampelopsin A [12] (−)-hopeaphenol [52]	[46]
	Acetone	Stem bark	diptoindonesin C [31] gnetin H [32] hopeaphenol [40] scopoletin [76]	[47]

Table 1 Cont.

Shorea species	Solvent Used	Part of Plant	Isolated compounds	References
S. platyclados	Acetone	Stem bark	shoreaplatyclaphenols A [95] shoreaplatyclaphenols B [96] grandiphenol B [42] hopeaphenol A [47] α-viniferin [22]	[48]
S. roxburghii	Methanol	Stem bark	(−)-hopeaphenol [52] (+)-isohopeaphenol [48] hemsleyanol D [51] (−)-ampelopsin H [49] vaticanols A [36] vaticanols E [38] vaticanols G [34] (+)-α-viniferin [22] pauciflorol A [30] hopeafuran [21] (−)-balanocarpol [11] (−)-ampelopsin A [12] *trans*-resveratrol 10-C-β-D-glucopyranoside [61] phayomphenols A1 [77] phayomphenols A2 [78]	[49]
	Methanol	Stem bark	phayomphenols A1 [77] phayomphenols A2 [78] (−)-hopeaphenol [52] (+)- isohopeaphenol [48] hemsleyanol D [51] (−)-ampelopsin H [49] (−)-ampelopsin A [12] viticanol A [36] viticanol B [53] viticanol C [46]	[50]

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(*continued*)

Shorea species	Solvent Used	Part of Plant	Isolated compounds	References
			viticanol E [38] viticanol G [34] (+)-α-viniferin [22] pauciflorol A [30] hopeafuran [21] (−)-balanocarpol [11] malibatol A [4] malibato B [5] *trans*-resveratrol 10-C-β-D-glucopyranoside [61] *cis*-resveratrol 10-C-β-D-glucopyranoside [71] piced [72]	

Table 1 Cont.

Shorea species	Solvent Used	Part of Plant	Isolated compounds	References
S. roxburghii	Methanol	Stem bark	10S-dihydrophayomphenol A2 [79] phayomphenols B1 [80] phayomphenols B2 [81]	[50]
S. laeviforia	Methanol	Heartwood	(−) laevifonol [20] laevifonoside [97] (−)-ampelopsin A [12] (−)-ε-viniferin [10] (−)-hopeaphenol [52] (+)-Isohopeaphenol [48] Hemsleyanoside A [54]	[51]
S. robusta	Petroleum Ether	Root bark	asiatic acid [99], 3,25- epoxy-1,2,3,11-tetrahydroxyurs-12-en-28-oic acid [100], 3,25-epoxy-1, 2,3-trihydroxyurs-l2-en-28-oic acid **(101)**, Phayomphenol [98] 3,7-dihydroxy-8-methoxyflavone 7-*O*-α-L-rhamnopyranosyl-(1 → 4)-αL-rhamnopyranosyl-(1 → 6)-β-D-glucopyranoside **(112)**	[7]
	Ethanol	Seed	3, 7-dihydroxy-8- methoxyflavone7-*O*-α-L-rhamnopyranosyl-(1 → 4)-α-lrhamnonopyranosyl (1 → 6)-β-D-glucopyranoside **(112)**	[52]
	Acetone	Leaves	β-amyrin **(102)** friedelin [88] α-carotene **(104)** β-carotene **(105)** lutein [85] β-sitesterol [87] phenophytin A **(106)** dihydroxyisoflavone **(113)**	[53]
	Methanol	resin	Asiatic acid [99]	[90]

Table 1 Cont.

Shorea species	Solvent Used	Part of Plant	Isolated compounds	References
S. roxburghii	Chloroform	Root	roxburghiol A **(107)** melanoxylin A **(108)** caragaphenol A [45] ε-viniferin [13], hopeahainanphenol **(109),** vitisinol G **(110)** vaticanol A [36] (−)-hopeaphenol [52] isohopeaphenol [48] apigenin 7-*O*-arabinoside **(111)**, *trans*-piceid **(114)** *trans*-3,5,4′-trihydroxyresveratrol 2-C-glucoside **(103)**	[54]
S. rugosa	Acetone	Stem bark	(−)-davidiol A [27] (−)-vaticanol A [24] (+)-α-viniferin [22] (−)-ampelopsin E [29]	[55]
S. seminis	Ethyl acetate	Stem bark	diptoindonesin A [30] (−)-ampelopsin A [12] ε-viniferin [13] hopeaphenol [40]	[56]
	Ethyl acetate	Stem bark	laevifonol [18]	[57]
S. singkawang	n-hexane	Stem bark	campesterol [93]	[22]
S. uliginosa	Acetone	Stem bark	shoreaketone [41]	[58]
	Acetone	Stem bark	uliginoside H [70]	[59]
	Acetone	Stem bark	uliginosides D [66] hemsleyanoside A [54] hemsleyanoside B [55] hemsleyanoside C [56] shorealactone [17] laevifonol [18] diptoindonesin A [30] piceid [72] (−)-hopeaphenol [52] hemsleyanol A [16] hemsleyanol B [23] hemsleyanol D [50] hemsleyanol E [51] (+)-α-viniferin [22] ampelopsin A [3]	[60]

Table 1 Cont.

Shorea species	Solvent Used	Part of Plant	Isolated compounds	References
S. uliginosa	Acetone	Stem bark	(−) ampelopsin F [9] pauciflorol A [30] shoreaketone [41]	[60]
	Acetone	Stem bark	hemsleyanoloside B [55] uliginosides A [63]	[61]

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(*continued*)

Shorea species	Solvent Used	Part of Plant	Isolated compounds	References
	Acetone	Stem bark	uliginosides B [64] uliginosides C [65] shoreaketone [41] uliginosides E [67] uliginosides F [68] uliginosides G [69]	[62]

3.1. Stibenes and their resveratrol oligomers from Shorea species

Stilbenes are unique class of biologically active natural products produce primarily by plants [63,98]. A 14-carbon skeleton of two phenyl rings joined by an ethylene bridge forms the stilbene nucleus. The compound resveratrol is one of the most notable and generally conveyed stilbenes (3, 4, 5-trihydroxystilbene) [1]**.** Resveratrol is known to exist as trans [**1a**] and cis [**1b**] isomers (Fig. 2). The grape skin and leaf epidermis contain the most *trans*-resveratrol. Additionally, it was discovered to be present in wine, particularly red wine. *Trans*-resveratrol has been shown to have anti-inflammatory and anti-carcinogenic properties in both in vitro and in vivo studies. Contrary to *trans*-resveratrol, the cis isomer is not currently available commercially. Therefore, this isomer's pharmacological activity is less understood [64,65].

Resveratrol oligomers contrast with most other polyphenols as they generally have less structural diversity due of their small varieties and limited pattern of functional groups. In each resveratrol unit, the research-friendly designating scheme has been used to standardize the first aromatic phenol rings as (A1), and the resorcinol rings as (A2). This is blended with a numbering system of 14 carbons [1–14] beginning from A1. Regarding additional resveratrol units, the next letter in the alphabet and the next numbering order are B1 B2 and C1 C2 [63]. Resveratrol oligomers typically occur as dimers, trimers, tetramers, and higher-order resveratrol oligomers, and they are primarily expressed as biological defense compounds with a wide range of biological activities [8,50,66].

3.1.1. Resveratrol dimers from Shorea species

ReResveratrol dimers isolated from different species of *Shorea* plants include acuminatol [2], ampelopsin A [3], malibatol A [4], malibatol B [5], parviflorol [6]**,** balanocarpol [7], shoreaphenol [8], (−)-ampelopsin F [9], (−)-ε-viniferin [10], (−)-balanocarpol [11], (−)-ampelopsin A [12], ε-viniferin [13]**,** maximol A [14], hemsleyanol E [15]**,** hemsleyanol A [16], shorea lactone [17], laevifonol [18], diptoindonesin G [19]**,** (−)-laevifonol [20], hopeafuran [21] roxburghiol A **(107)** melanoxylin A **(108)** hopeahainanphenol **(109)** and vitisinol G **(110)** (Fig. 3).

3.1.2. Resveratrol trimers from Shorea species

Resveratrol trimers reported to be isolated from different species of *Shorea* plants include (+)-α-viniferin [22], hemsleyanol B [23], (−)-viticanol A [24], shoreanol A [25]**,** shoranol B [26], (−)-davidiol A [27], ampelopsin E [28], (−) ampelopsin E [29], pauciflorol A [30], diptoindonesin C [31], gnetin H [32], (−)-α-viniferin [33], viticanol G [34], stenophyllol [35]**,** viticanol A [36], suffruticosol [37], viticanol E [38], davidiol A [39] and caragaphenol A [45] (Fig. 4).

3.1.3. Resveratrol tetramers from Shorea species

The highest form of resveratrol oligomers isolated from *Shorea* species is resveratrol tetramers containing four stilbene units. The resveratrol tetramers isolated from various species of *Shorea* include hopeaphenol [40] shorea ketone [41], grandiphenol [42], (−)-hemsleyanol D [43], diptoindonesin F [44], distichol [45]**,** viticanol C [46], hopeaphenol A [47], isohopeaphenol [48], (−)-ampelopsin H [49], hemsleyanol C [50], hemsleyanol D [51], (−)-hopeaphenol [52] and viticanol B [53]**,** shoreaplatyclaphenols A [95]**,** shoreaplatyclaphenols B [96] (Fig. 5).

3.1.4. Resveratrol oligomers glucosides from Shorea species

The chemical diversity of resveratrol oligomers in *Shorea* species comes from introducing glycoside groups, a six-carbon compound, into the resveratrol oligomers units (Fig. 6). The resveratrol oligomers glucosides consist of the O-glucosides and C-glucosides depending on the attachment of the glucoside to the resveratrol oligomer [63].

(1a) **(1b)**

Fig. 2. Structures of monomeric, 1a: trans (E) and 1b: cis (Z) resveratrol.

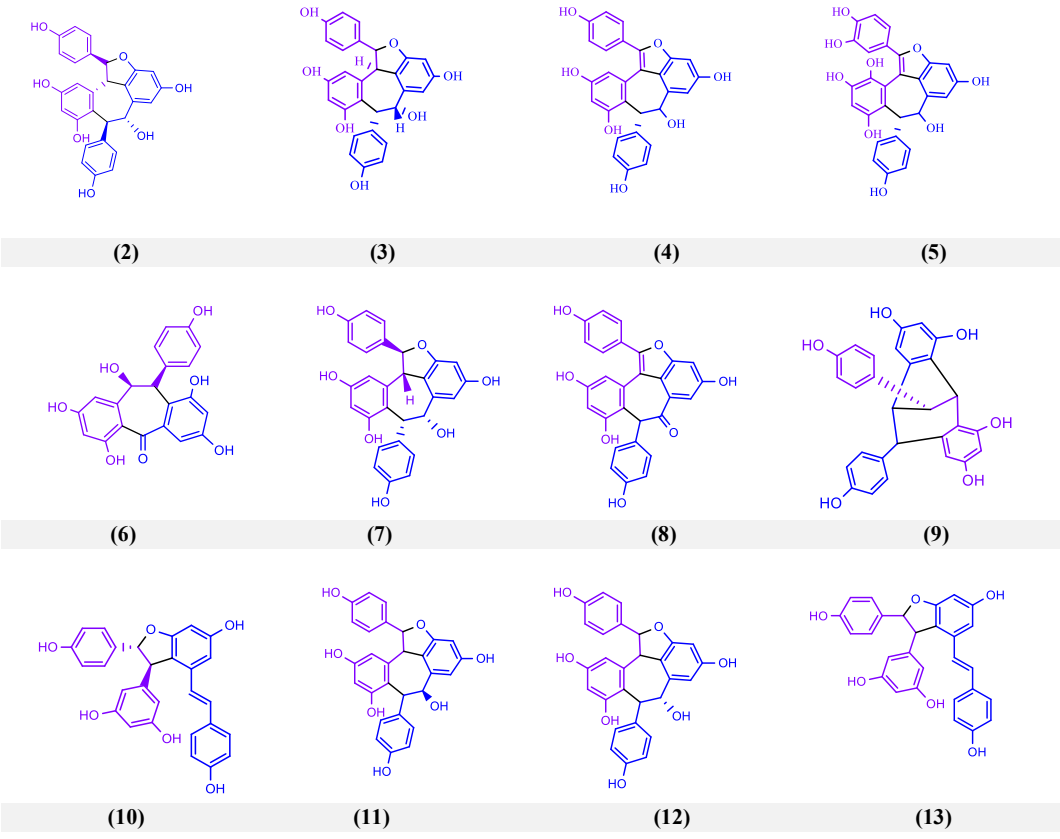


Fig. 3.1. Resveratrol dimers from Shorea species.

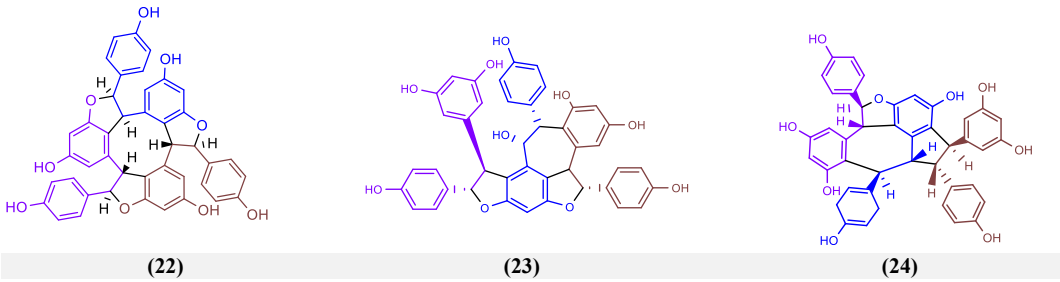


Fig. 4.1. Resveratrol trimers from Shorea species.

In C-glucosides, the building blocks are compounds [60,61,99]. C-glucosides compounds reported to be isolated include hemsleyanoside A [54], hemsleyanoside B [55], hemsleyanoside C [56], hemsleyanoside D [57], hemsleyanoside E [58] resveratrol 12-C-β-glucopyranoside [60], diptoindonesin A [59], F [62], uliginoside A [63], B [64], C [65], D [66], E [67], F [68], G [69], H [70], *trans*-resveratrol 10-C-β-D-glucopyranoside [61] and *cis*-resveratrol 10-C-β-D-glucopyranoside [71].

While in O-glucosides, compound [72] is the vital building block. O-glucosides compounds isolated from *Shorea* species include piced [72], (+)-α-viniferin 13b-*O*-β-glucopyranoside [73], cordifoloside A [74], B [75], laevifonoside [97], *trans*-piceid **(114)** and *trans*-3,5,4′-trihydroxyresveratrol 2-C-glucoside **(103)** (Fig. 7).

3.1.5. Structure elucidation of resveratrol oligomers

Modern spectroscopic techniques, including UV, IR, and NMR, are essential for determining the structures of naturally occurring resveratrol oligomers. To gain a comprehensive understanding of these structures, various 2D-NMR techniques like COSY, HMQC, HMBC, and NOESY play a crucial role in their elucidation.

3.1.5.1. UV Spectroscopy. The conjugation system within resveratrol and its oligomers significantly impacts their maximum

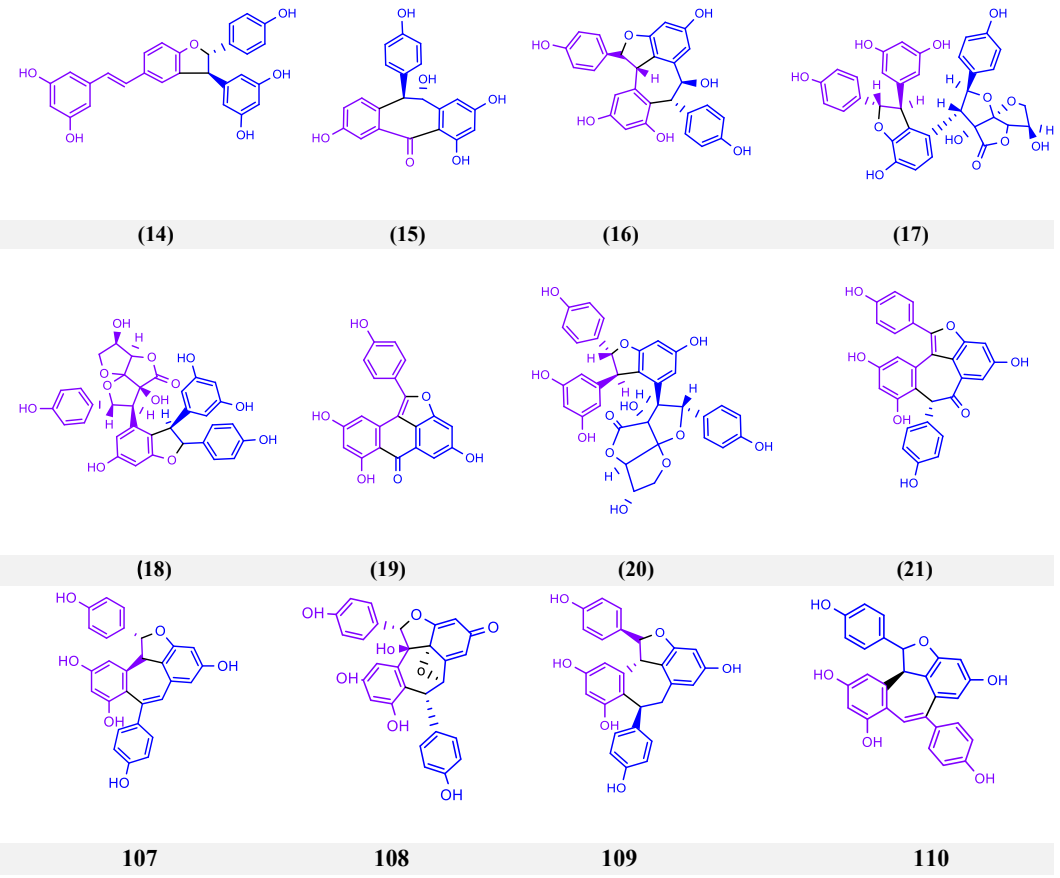


Fig. 3.2. Resveratrol dimers from Shorea species.

absorption bands. For *trans*-resveratrol, which has a trans double bond, the maximum absorption bands are observed at around 320–330 nm. In contrast, resveratrol oligomers lacking trans double bonds exhibit a shift in their maximum absorption bands to a lower wavelength, approximately 280–290 nm. However, the presence of a benzofuran ring, as seen in resveratrol oligomers like ε-viniferin [13], shifts the absorption band to a higher wavelength, approximately 340 nm [66].

3.1.5.2. IR Spectroscopy. In the IR spectra of resveratrol oligomers, absorption bands for hydroxyl groups exhibit a broad stretch between 3200 and 3500 cm-1, benzene groups are evident at 1450-1600 cm-1, and double bonds can be observed in the range of 1610–1670 cm-1. Notably, structures featuring trans double bonds display a distinct absorption band at 965 cm-1 [67].

3.1.5.3. 1H NMR and 13C NMR Spectroscopy. In the 1H and 13C NMR spectra of resveratrol oligomers, the signals from various monostilbenes are valuable for determining the polymerization degrees of higher stilbene and their oligomers. Fig. 8A

The ethylene bridge forming a trans double bond between (H-7, H-8) in a resveratrol unit typically appears in two forms following polymerization.

(i) As a trans double bond (Fig. 8A), where the proton signals manifest as two doublets at δ 6.4–7.2 (J = 15.0–17.0 Hz). Carbon signals are observed at δ 128–135 (C-7) and δ 120–125 (C-8), respectively.

(ii) As part of a dihydrobenzofuran moiety (Fig. 8B), where H-7a and H-8a are in a trans relationship, and C-7a is usually bonded to the oxygen atom. In 1HNMR spectra, the signals of H-7a and C-7a appear at a lower field of δ 5.2–6.0 and δ 85–95, respectively, potentially due to the deshielding effect of the oxygen atom. Meanwhile, H-8a and C-8a appear at a much lower field of δ 4.2–4.8 and δ 45–60, respectively.

Additionally, the 4-hydroxybenzene groups (ring A1) in Fig. 8A display two coupled doublets at δ 7.0–7.5 for H-2 and H-6 and at δ 6.4–6.9 for H-3 and H-5 (J = 7.5–9.0 Hz) in the 1H NMR spectra after polymerization. In the 13C NMR, the signals of C-2 and C-6 are observed at δ 127–130, with C-3 and C-5 at δ 114–117. Furthermore, for the 3, 5-dihydroxybenzene group (ring A2) in Fig. 8A, the 1H NMR proton signals of H-12a appear as a triplet with a coupling constant between 1.0 and 2.5 Hz. H-10a and 14a proton signals appear as symmetrical doublets with the same chemical shift and coupling constant. In the 13C NMR, C-10a and 14a exhibit the same chemical

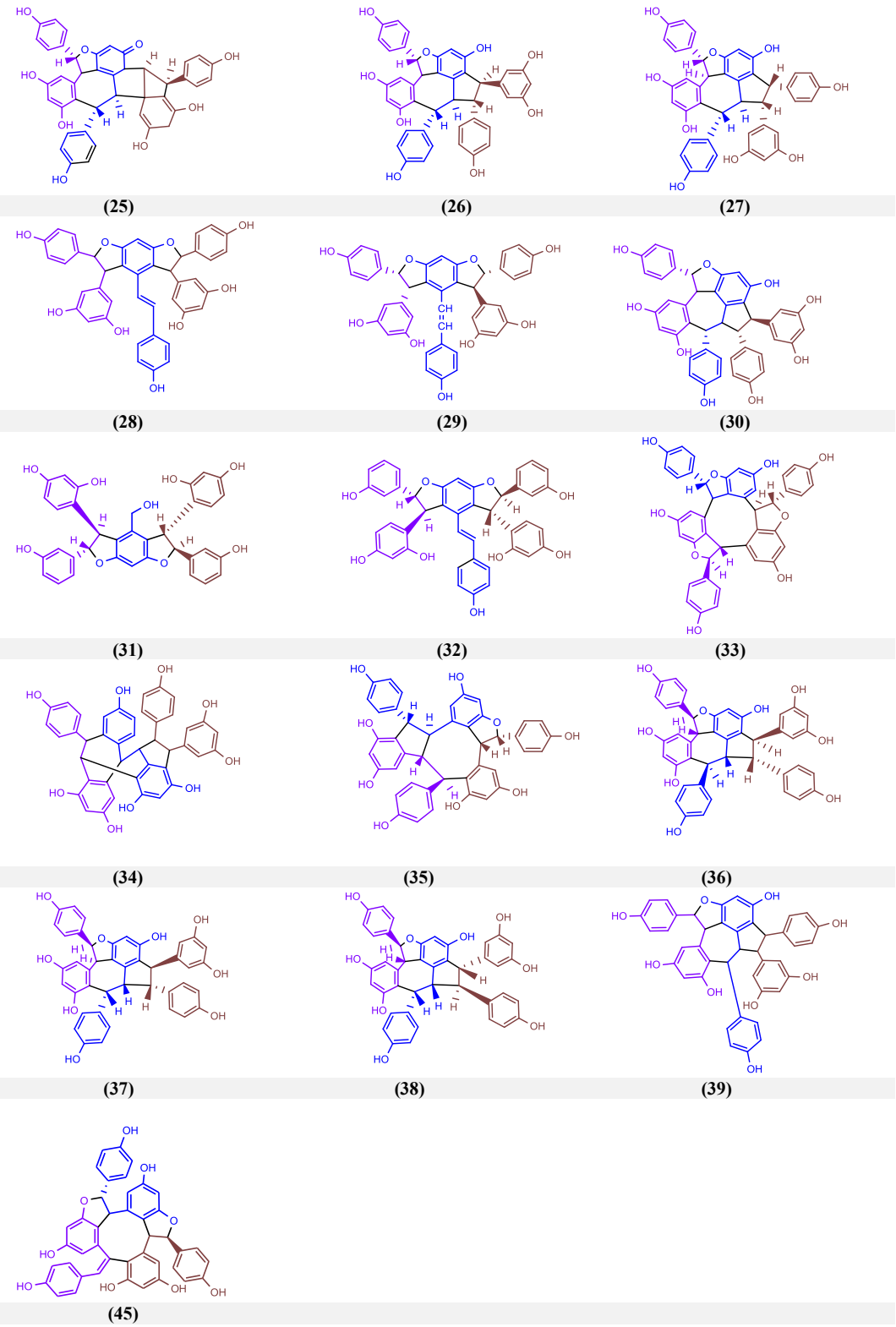
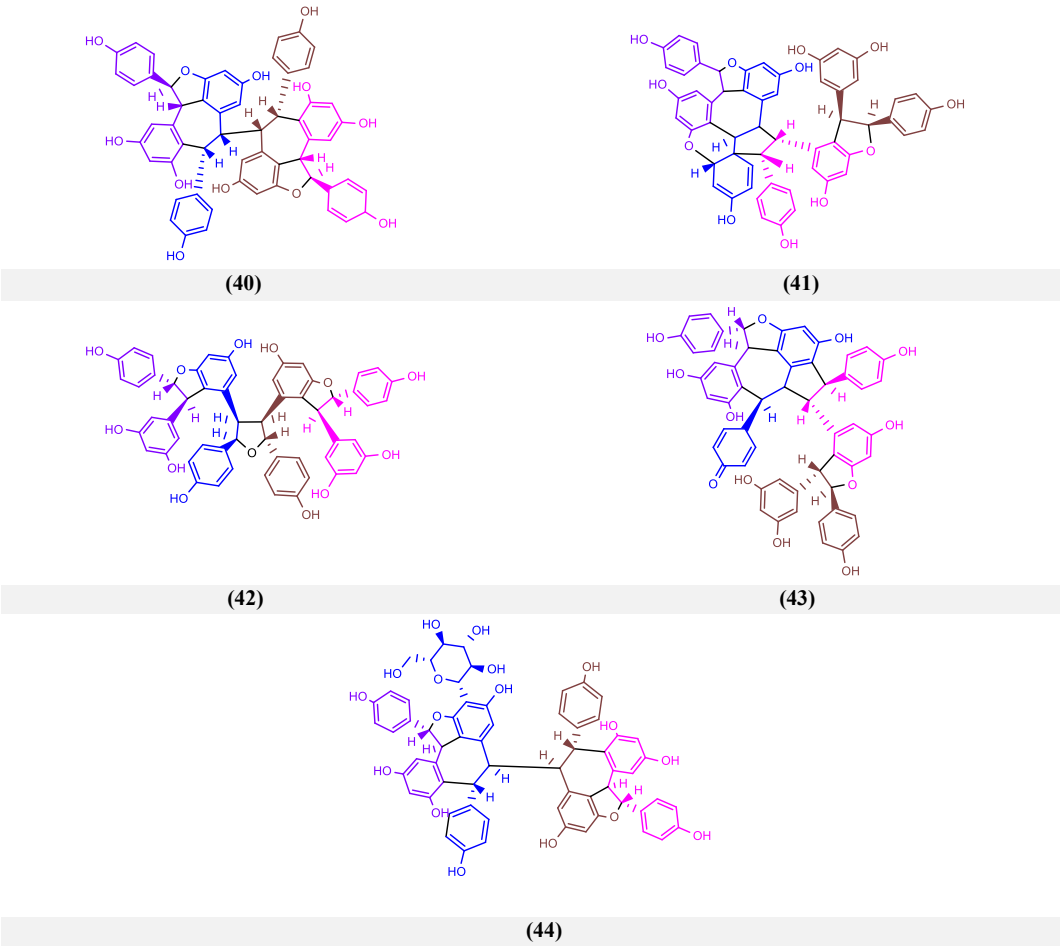


Fig. 4.2. Resveratrol trimers from Shorea species.



(40) **(41)** **(42)** **(43)** **(44)**

Fig. 5.1. Resveratrol tetramers from Shorea species.

shift at δ 105–108, while the chemical shift of C-12a is around δ 100–103. When the 3,5-dihydroxybenzene group is involved in a dihydrobenzofuran moiety, the two meta-coupled protons, i.e., H-10b and H-12b, exhibit two doublets at δ 6.0–6.6. In 13C NMR, the signals of C-10b and C-12b are observed at δ 95–100 and δ 105–110, respectively.

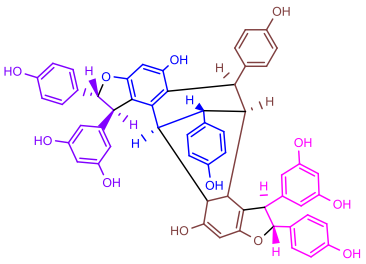
Furthermore, the quaternary carbons of C-l and C-9 (not attached to a double bond) in resveratrol oligomers display signals at δ 130–136 and δ 141–149, respectively. Quaternary carbons attached to a hydroxyl group exhibit signal at δ 155–162 [66,67].

3.1.5.4. Optical activity. Optical activity refers to a compound's ability to rotate the plane of polarized light. It's a phenomenon used to determine if a sample is racemic (containing equal amounts of both enantiomers) or if one enantiomer predominates. Resveratrol oligomers like ε-viniferin exhibit optical activity in nature, existing as enantiomers: (+) ε-viniferin [13] and (−) ε-viniferin [10]. They cause the plane-polarized light to rotate, making them chiral and optically active [68].

Polarimetric measurements are conducted using an instrument called a polarimeter. A positive rotation value is called dextrorotary, designated as d or (+), indicating a clockwise rotation of the plane-polarized light. Conversely, a negative value is laevorotary, labeled as l or (−), indicating an anti-clockwise rotation. When only one enantiomer is present, the sample is considered optically pure [68]. The degree of rotation measured by the polarimeter is known as the observed rotation (α), and it depends on factors like the sample tube's length, sample concentration, and temperature. To compare optical rotations consistently between different compounds, specific rotation is used. This is the rotation caused by a solution with a concentration of 1.0 g/mL in a sample tube of 1.0 dm length at a standard temperature, usually 20 °C. It can be calculated using the equation below (Fig. 8.1).

$$(\propto)\frac{t}{\lambda} = \frac{\propto}{c\,x\,\ell}$$

Where $(\propto)$ = Specific rotation, t = temperature (°C), λ = wavelength, $\propto$ = observed rotation, C = concentration (g/ml) and ℓ = pathlength (dm).



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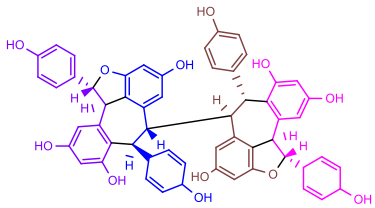

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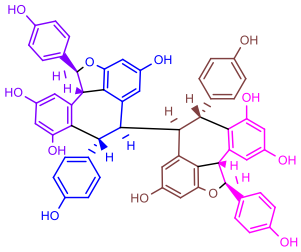

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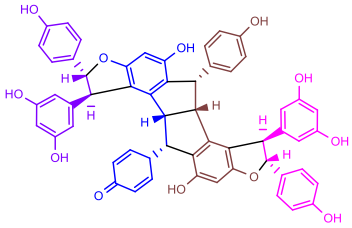

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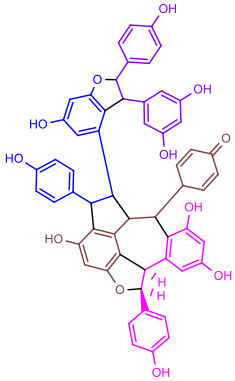

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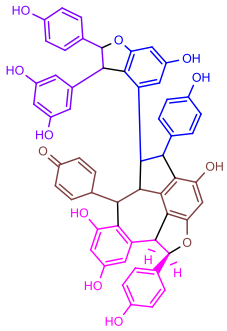

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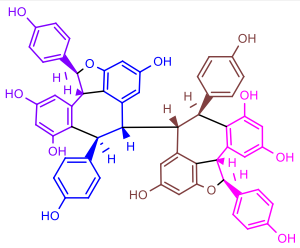

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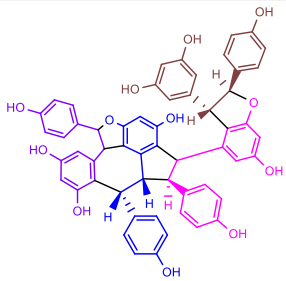


(53)

Fig. 5.2. Resveratrol tetramers from Shorea species.

3.2. Coumarins from Shorea species

Coumarins are secondary metabolites found in several plants. They purportedly have calming, anticoagulant, anticancer, antibacterial, antimalarial, antifungal, antiviral, anticonvulsant and antihypertensive properties [69]. Coumarins reported to be isolated from different species of *Shorea* plants include scopoletin [76], phayomphenols A_1 [77], phayomphenols A_2 [78], 10S dihydrophayomphenol [79], phayomphenols B_1 [80], phayomphenols B_2 [81] and phayomphenol [98] (Fig. 9).

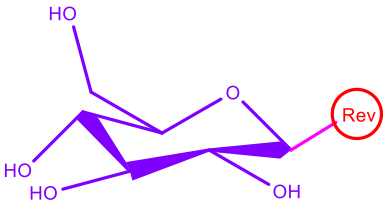


Fig. 6. Resveratrol glucoside.

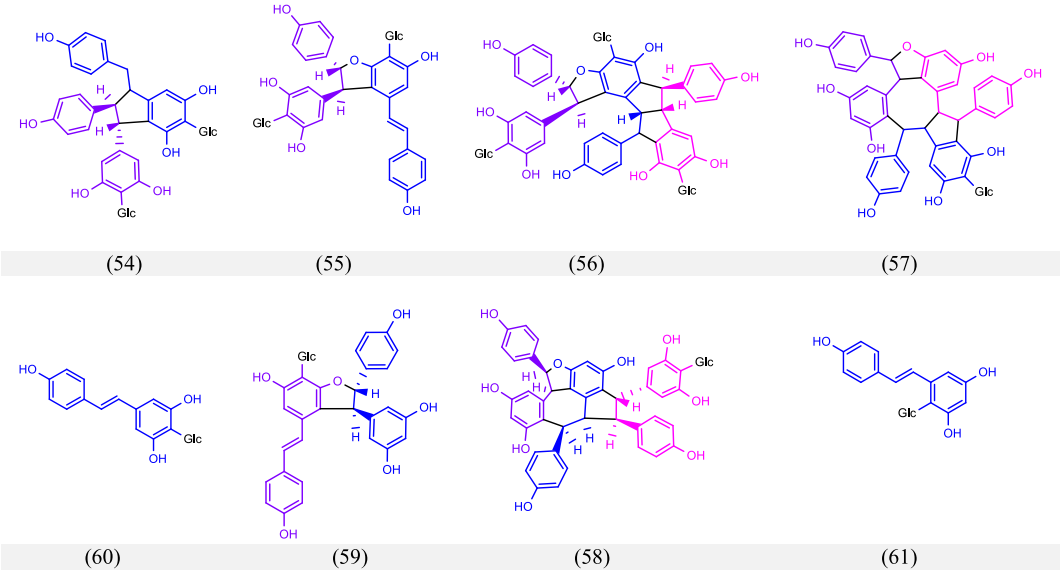


Fig. 7.1. Resveratrol Oligomer glucosides from Shorea species.

3.3. Terpenes and terpenoids from Shorea species

Terpenes and terpenoids are large group of phenolic compounds found in flowers, stems, roots, leaves and other parts of numerous plant species with a building block of 2-methylbuta-1, 3-diene (C_5H_8 or C_5H_8O) commonly known as isoprene unit [22,98]. Terpenes and terpenoids reported to be isolated from different species of *Shorea* plants include lup-20 [29]-en-3-one [82], olean-12-en-3-one [83], urs-12-en-3-one [84], lutein [85], chlorophyll *a* [86], friedelin [88], 3β-friedelinol [89], oleanolic acid [90], ursolic acid [91], squalene [92], asiatic acid [99], 3,25- epoxy-1,2,3,11-tetrahydroxyurs-12-en-28-oic Acid [100], 3,25-epoxy-1,2,3-trihydroxyurs-l2-en-28-oic acid **(101)**, β-amyrin **(102)**, α-carotene **(104)**, β-carotene **(105)** and phenophytin A **(106)** (Fig. 10.1)

3.4. Steroids from Shorea species

Steroids are diverse group of natural products that exert a wide range of biological activities [100]. While over 250 steroids and related compounds have been reported from different plant species, only few have been reported to be isolated from *Shorea* genus. Among them are β-sitosterol [87], and compesterol [93] (Fig. 11).

3.5. Flavonoids from Shorea species

Flavonoids reported to be isolated from *Shorea* species include 3, 7-dihydroxy-8-methoxyflavone7-*O*-α-L-rhamnopyranosyl-(1 → 4)-α-lrhamnonopyranosyl (1 → 6)-β-D-glucopyranoside **(112)**, dihydroxyisoflavone **(113)** and apigenin 7-*O*-arabinoside **(111)** reported to be isolated from *Shorea* species (Fig. 12).

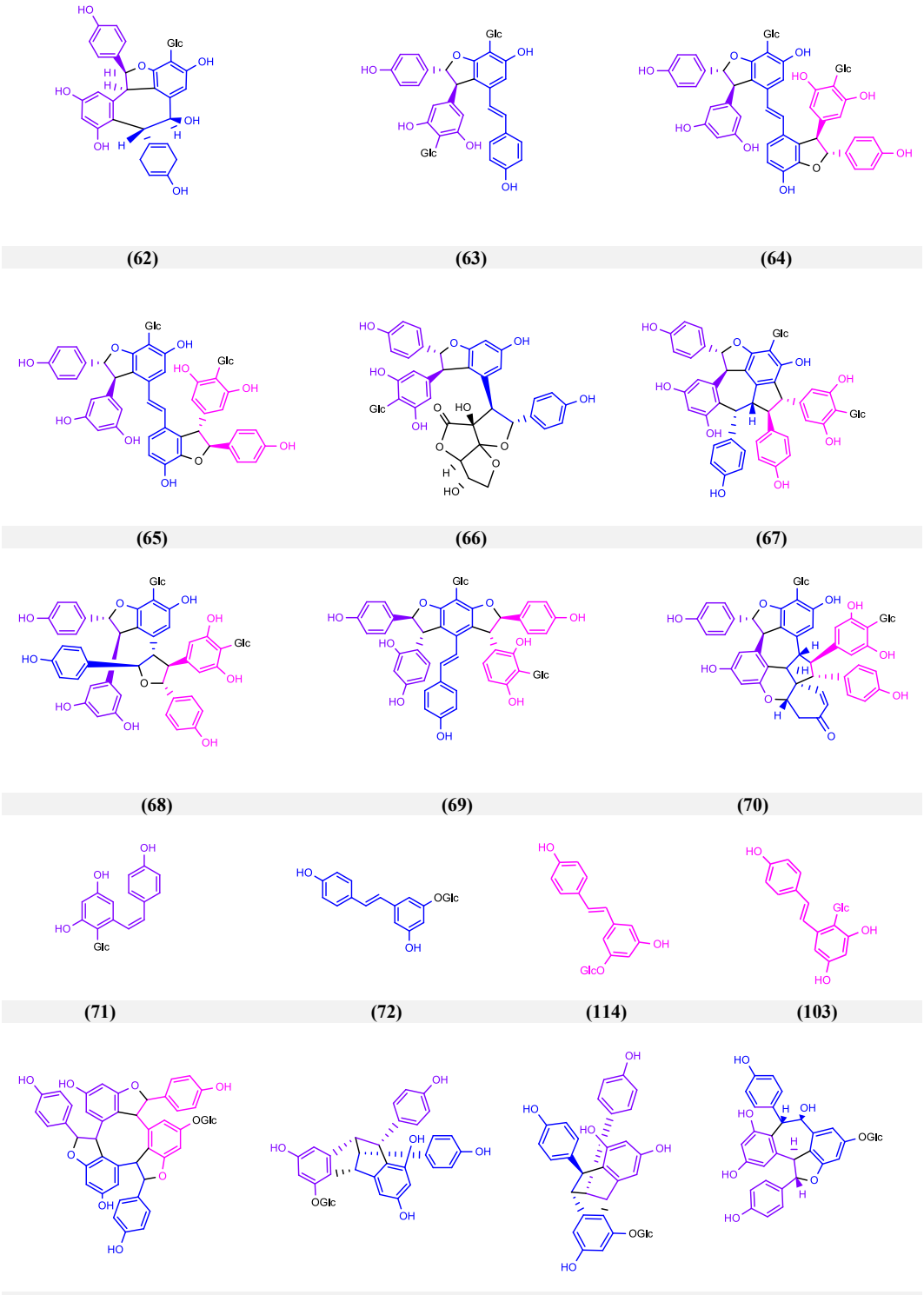


Fig. 7.2. Resveratrol Oligomer glucosides from Shorea species.

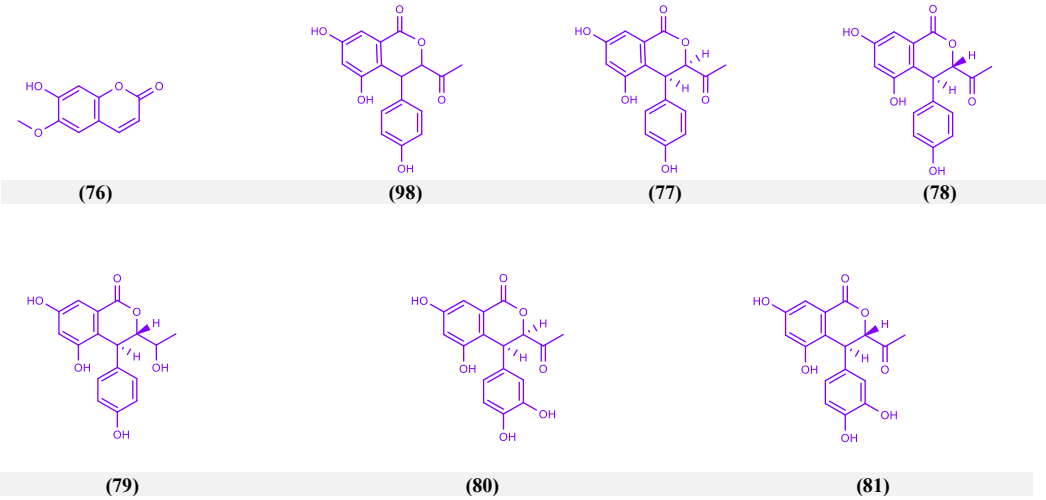
A B

Resveratrol **(1)** ε-viniferin **(13)**

Fig. 8. Numbering pattern of monomeric and dimeric resveratrol.

$$(\propto)\,{}^{t}_{\lambda} = \frac{\propto}{c\,x\,\ell}$$

Fig. 8.1. Equation for the Specific rotation of compounds.



(76) **(98)** **(77)** **(78)**

(79) **(80)** **(81)**

Fig. 9. Coumarins from Shorea species.

4. Bioactivities of *Shorea* species

4.1. In vitro activities of Shorea species

4.1.1. Cytotoxicity effect

Muhammad et al. [8] evaluated the cytotoxic potency of laevifonol [18], (+)-α-viniferin [22], shoreaketone [41], vaticanol B [55], and (−)-hopeaphenol [52] against the Vero cell line. All the compounds were found to be non-cytotoxic, with LC50 values ranging from 161 to 830 μM. Moreover, Nazri et al. [17] conducted experiments that revealed the significant cytotoxic potency of ε-viniferin [13] and davidiol A [39] against HL-60 and HeLa cell lines. Furthermore, Haryoto et al. [25] discovered the cytotoxic potential of (−) hopeaphenol [52], which exhibited higher inhibition on murine leukemia P-388 cells. In addition, Rohaiza [70] carried out a similar investigation on four oligostilbene compounds: (−)-ε-viniferin [10], (−)-ampelopsin E [29], (−)-hopeaphenol [52], and one coumarin, shoreaphenol [8]. Surprisingly, the same (−) hopeaphenol [52] was found to be very potent against HepG2 cells, with a CC50 value of 4.5 μg/ml.

Zawawi et al. [41] conducted a phytochemical study on the stem bark of *Shorea maxwelliana*, which yielded (+)-α-viniferin [22], maximol A [14], vaticanol A [36], suffruticosol A [37], and vaticanol G [34]. They investigated the neurotoxic and cytotoxic effects of each compound. It was found that none of the tested compounds exhibited neurotoxicity in cultured cells. However, compounds [14, 34] demonstrated active cytotoxic activity against the HL60 cell line, with IC50 values ranging from 2.7 to 78 mg/mL. Saroyobudiono et al. [31] conducted research on the methanolic extracts of *Shorea leprosula* leaves. Surprisingly, they reported isolating similar

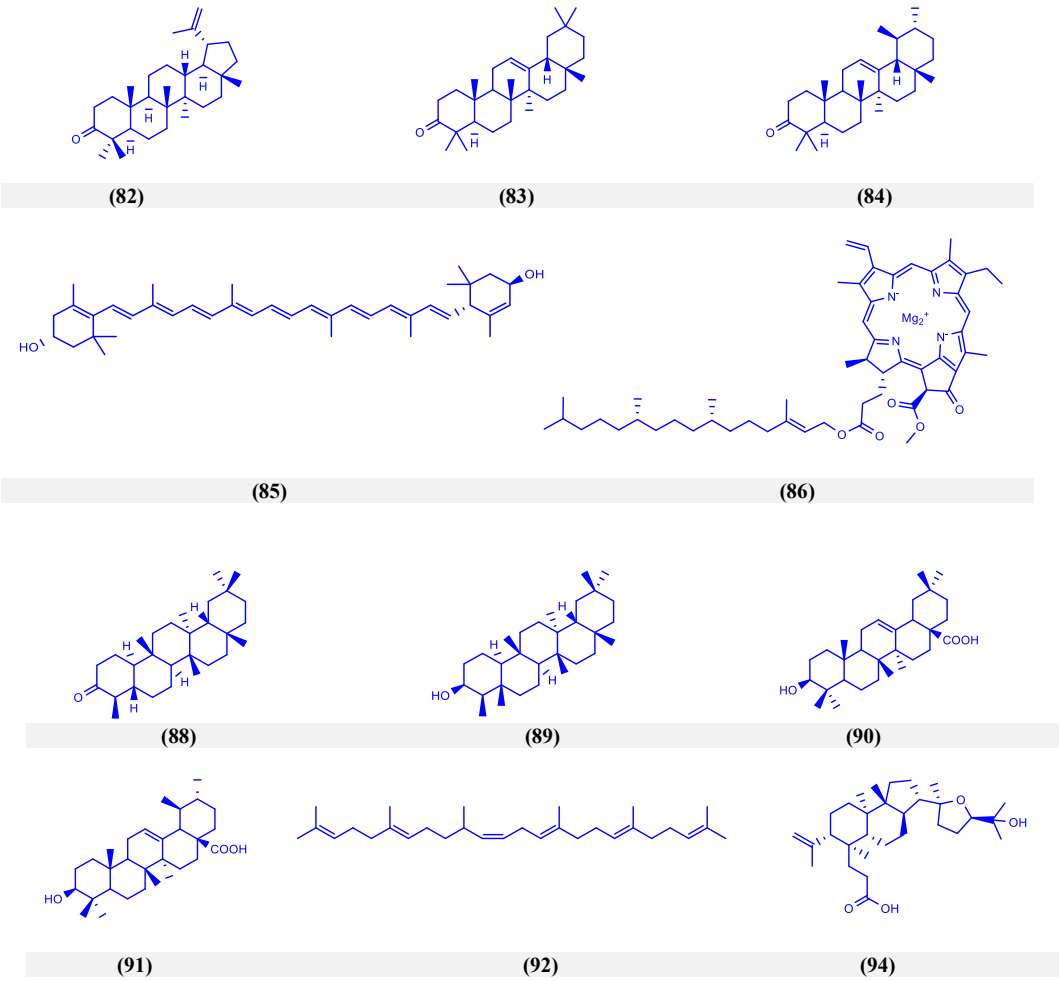


Fig. 10.1. Terpenes and terpenoids from Shorea species.

compounds as those found by Bastri et al. [32], with diptoindonesin G [19] being the only new compound isolated from the experiment. The cytotoxic potential of the isolated oligostilbenoids was tested on P-388 cells from murine leukemia. All compounds were found to exhibit activity, with ampelopsin A [3] and laevifonol [18] being reported as having the highest cytotoxic potency against the tested cell lines.

The acetone extract of the stem bark of *Shorea assamica* Dyer was reported to contain four resveratrol oligomers: two trimers and two tetramers. Cytotoxicity tests were conducted on the isolated compounds against murine leukemia P-388 cells. The results showed that vaticanol A [36], α-viniferin [22], vaticanol B [53], and isohopeaphenol [48] exhibited IC50 values of 27.0, 17.5, 46.4, and 36.0 ppm, respectively, against the tested cells. Interestingly, the findings indicated that resveratrol trimers were more cytotoxic than resveratrol tetramers [23]. In a report by Syah et al. [47], the cytotoxicity potency of gnetin H [32] was highlighted. It was found to exhibit significant activity (LC50 = 57 mg/mL), while diptoindonesin C [31] and hopeaphenol [40] demonstrated moderate activity. In contrast, scopoletin [76] with an LC50 of 4500 mg/mL was deemed inactive. Furthermore, the first steroid compound, campesterol [93], was successfully isolated from the n-hexane fraction of the bark of *Shorea singkawang* Miq. Subsequent cytotoxicity assays of the isolated compound revealed activity with an LC50 > 100 m/mL [22].

4.1.2. Antioxidant activity

Muhammad et al. [8] reported the antioxidant activities of laevifonol [18], (+)-α-viniferin [22], shoreaketone [41], vaticanol B [55], and (−)-hopeaphenol [52] isolated from the acetone extract of the stem bark of *Shorea acuminata*. In the DPPH assay, all isolated compounds showed strong inhibition of β-carotene oxidation and good to moderate antioxidant activity. These results were in consistent with previous antioxidative studies conducted on the same resveratrol oligomers obtained from the roots of *Vitis thunbergii* (Vitaceae) [71]. Furthermore, Muhammad et al. [72] investigated the essential oil from the leaves and stems of the same plant species for their antioxidant potency. The investigation revealed that the essential leaf oils, primarily containing caryophyllene oxide and β-caryophyllene, exhibited very potent antioxidant activity with an EC50 value of 0.64 mg/ml in the DPPH free radical-scavenging assay and 89.27 % inhibition in the β-carotene/linoleic acid assay. Conversely, the stem essential oils, which mainly contains

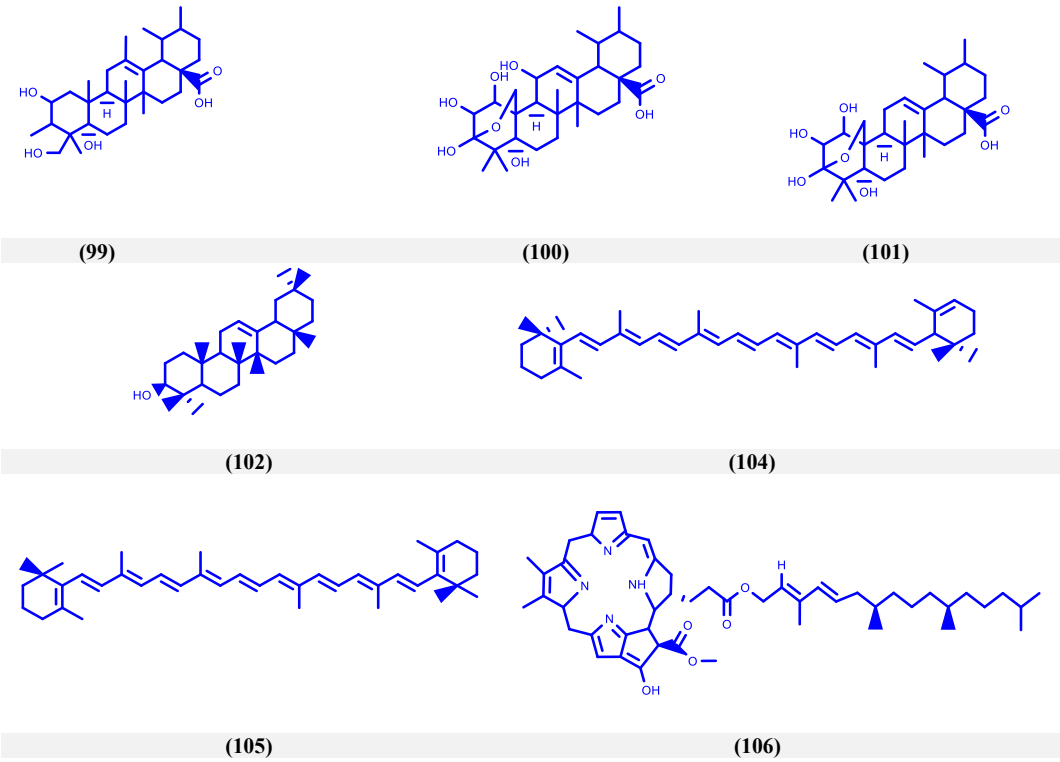


Fig. 10.2. Terpenes and terpenoids from Shorea species.

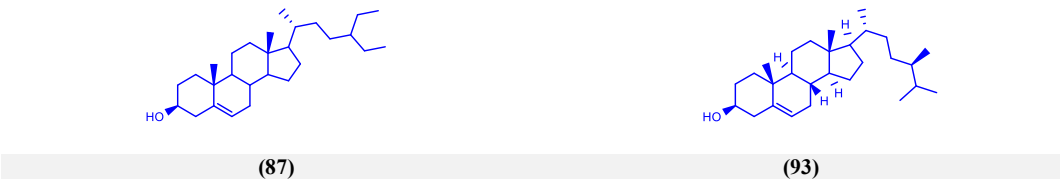


Fig. 11. Steroids from Shorea species.

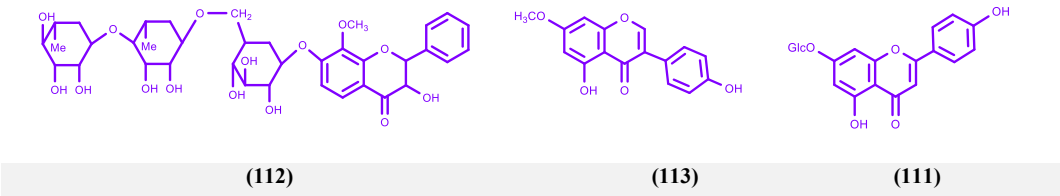


Fig. 12. Flavonoids from Shorea species.

germacrene D, also demonstrated potent antioxidant activity with an EC50 value of 0.72 mg/ml in the DPPH free radical-scavenging assay and 88.78 % inhibition in the β-carotene/linoleic acid assay. The significant presence of germacrene D (35.0 %) in the stem oil, caryophyllene (13.9 %), and caryophyllene oxide (36.0 %) in the leaf oil may be related to the antioxidant properties of the stem and leaf extracts. This outcome also indicates the strong scavenging power of sesquiterpene hydrocarbons and oxygenated sesquiterpenes.

Nazrizawati et al. [73] similarly investigated the antioxidant potency of five different *Shorea* species. The trial results indicated a positive correlation between radical scavenging activity and total phenolic content, with *S. acuminata* having the highest total phenolic content (TPC) and exhibiting the strongest antioxidant potential. Overall, all tested plant extracts displayed potent antioxidant activity, as evident from their higher absorbance values, which were all greater than those of the negative controls. Norizan et al. [74]

reported in vitro antioxidant and radical scavenging properties (DPPH) activities of methanolic extracts from five *Shorea* species. *S. macroptera* displayed the highest percentage of inhibition in both the ferric thiocyanate method (FTC) and thiobarbituric acid method (TBA) analyses, with *S. macroptera* exhibiting the highest percentage of inhibition in the DPPH analysis as well. These two studies highlight the potential of *Shorea macroptera* as a natural source for new antioxidant drugs. A study performs to explore the potentials of *Shorea roxburghii's* acetone and methanol stem bark extracts towards reducing silver nanoparticles results in the formation of spherical particles ranging from 4 to 50 nm. Both acetone and methanol extracts used in the studies exhibited strong antioxidant properties, suggesting potential applications in treating diseases associated with free radicals. Furthermore, the plant extract showed potential as a green reducing agent for synthesizing silver nanoparticles [89].

Furthermore, Nazri et al. [17] conducted an experiment that displayed the significant free radical scavenging activity of hemsleyanol D, with an IC50 of 63.2 μg/ml. Additionally, the crude extract exhibited very high activity at 59.1 μg/ml. Siti et al. [78] investigated the antioxidant activities of n-hexane, dichloromethane, and methanol extracts isolated from the stem bark of *Shorea kunstleri*. The results indicate methanol extract had the highest free radical scavenging activity. Suksungworna et al. [75] also performed an in-vitro antioxidant activity assessment of the bark and wood extracts of *S. obtusa*. The experiment revealed that the bark extract had potent inhibitory concentrations against DPPH radical scavenging, superoxide radical scavenging, and ferric-reducing antioxidant power, with higher levels of quercetin and gallic acid compared to the wood extract. Consequently, the bark extract of *S. obtusa* can be considered as a potential source of novel antioxidant plant-based drugs. Mathavi et al. [76] conducted antioxidant screening of *Shorea robusta* methanolic leaf extract using DPPH and superoxide scavenging assays. The results indicated a promising activity with IC50 values of 36.61 μg/ml for the DPPH assay and 43.20 μg/ml for the superoxide assay. Suganya et al. [77] conducted an experiment revealing the antioxidant capacity of *Shorea robusta* leaves (200 and 400 μg/ml) in CCl4-induced oxidative stress in hepatocytes. Additionally, the methanolic extract of *Shorea robusta* resin exhibited higher antioxidant activity (IC50 value of 35.60 μg/ml) than ascorbic acid (IC50 value of 31.91 μg/ml).

4.1.3. Antimicrobial activity

Norizan et al. [74] reported the in vitro antimicrobial activities of methanolic extracts from five *Shorea species*. Among them, only *S. resinosa* exhibited moderate inhibition against *Escherichia coli, Streptococcus pyogenes, Staphylococcus aureus*, and *Bacillus subtilis*. Nazri et al. [17] reported that Davidiol A [39] repressed the growth of *S. uberis* and *B. subtilis* at 20 μg/ml per disc. Nitta et al. [38] isolated five compounds from the stem barks of *Shorea hemsleyana* and found that the root extract and the isolated compounds were effective against methicillin-resistant *Staphylococcus aureus* (MRSA), with the extract being highly potent. Notably, hemsleyanol D [57], one of the stilbene tetramers isolated, exhibited the most active antimicrobial activity with a minimum inhibitory concentration (MIC) of 2 μg/ml. Muhammad et al. [72] investigated the essential oils from the leaves and stems of the same plant species for their antimicrobial potency. The essential leaf oil showed very low antibacterial activity, while the stem essential oil showed no activity against all the tested bacteria.

In addition, Siti et al. [78] investigated the antibacterial properties of n-hexane, dichloromethane, and methanol extracts from the stem bark of *Shorea kunstleri*. The methanol extract showed remarkable inhibition against *Staphylococcus aureus* and *Candida albicans*, while the dichloromethane extracts exhibited the highest inhibition against *Candida tropicalis*. Suksungworna et al. [75] conducted in vitro studies on the antimicrobial potency of the bark extract of *Shorea obtusa*. The extract exhibited greater inhibitory concentrations against all the tested microbes, except *M. luteus*. It showed the highest antimicrobial activity against E. coli (MIC = 1 μg/mL, compared to ampicillin at 10 μg/mL), *B. subtilis* strains (MIC at 4 μg/mL, compared to gentamicin at 10 μg/mL), *S. aureus* strains (MIC at 2 μg/mL; compared to penicillin G at 1 μg/mL), and *C. albicans* (MIC at 20 μg/mL, compared to nystatin at 1 μg/mL). Overall, the bark extract of *S. obtusa* appears to be a promising source for developing novel plant-based drugs with antimicrobial properties.

Meanwhile, Ito et al. [60] reported the antiviral potency of (−)-hopeaphenol [52], (+)-α-viniferin [22], shoreaketone [41], vaticanol B [5], and G [34] against herpes simplex virus types 1 and 2. Moreover, (−)-hopeaphenol [52] and shoreaketone [41] were further reported to had showed an inhibitory effect on influenza A virus replication. Ragasa et al. [33] isolated shoreic acid [94] from the dichloromethane extract of *Shorea guiso*, which exhibited antimicrobial activity against *E. coli, P. aeruginosa, S. aureus, B. subtilis, C. albicans,* and *T. mentagrophytes*. Daud et al. [80] reported the effectiveness of *S. kunstleri* methanol extract against *C. albicans* and *S. aureus* at MIC values of 40 μg/mL and 80 μg/mL respectively. In addition, Jatuporn et al. [81] further reported the inhibition of *E. coli, S. aureus,* and *L. monocytogenes* by *S. tolura* extract. Duddukuri et al. [82] investigation on the antibacterial properties of the floral part of *Shorea robusta's* aqueous extract against *S. aureus*, *B. subtilis, K. pneumonia, and S. marcescens,* were reported to have shown a significant inhibitory activity. Murthy et al. [83] further tested gram-positive and gram-negative bacteria against the aqueous, petroleum, benzene, and methanolic extracts of *Shorea robusta* resin. The results revealed that the extracts exhibited a very potent antimicrobial activity.

4.1.4. Antiparasitic activity

Subeki et al. [84] also reported the anti-babesial potency of vaticanol A [36] and G [34] against an intraerythrocytic apicomplexan parasite, *Babesia gibsoni*, at a concentration of 25 mg/mL and 50 mg/mL respectively.

4.1.5. Analgesic activity

Chattopadhyay et al. [85] investigated the analgesic effect of the ethanolic extract of *S. robusta* resin (SRE) using various central and peripheral pain models. The study revealed a significant central and peripheral analgesic effect at doses of 30, 100, and 300 mg/kg of the extract. Furthermore, the ethanolic extract of *S. robusta* resin (at 400 mg/kg) demonstrated significant analgesic effects in rats and mice in both the acetic acid-induced writhing test and tail flick test [86].

4.2. In vivo activities of Shorea species

4.2.1. Anti-diabetes and Hypoglycemic effect

Zhang et al. [87] conducted an in vivo study to investigate the hypoglycaemic effect of the methanol extract from *Shorea roxburghii* leaves in a rat model with streptozotocin-induced type 2 diabetes mellitus (T2DM), induced by a high-fat diet and high-fructose solution. The results showed a significant improvement, including reduced fasting blood glucose (FBG) levels, weight, and decreased food and water consumption in the diabetic rats treated with the extract. These findings highlight the anti-diabetes potential of *Shorea roxburghii* leaf extract and suggest its consideration for future treatments of T2DM. Morikawa et al. [50] reported the isolation of two new 3-acetyl-4-phenyl-3,4-dihydroisocoumarins, phayomphenols A1 [77] and A2 [78], along with twenty-two known compounds from the methanol extract of *Shorea roxburghii* stem bark. In vivo experiments with the extracts and secondary metabolites revealed their ability to suppress the rise in plasma triglycerides in mice treated with olive oil and inhibit pancreatic lipase activity. Morikawa et al. [50] further fractionated the methanol extract of *S. roxburghii* bark, resulting in the isolation of 24 compounds, including three new 3-ethyl-4-phenyl-3,4-dihydroisocoumarins. In vivo examinations of these isolates demonstrated their ability to restrain the rise in plasma glucose levels in sucrose-loaded mice. Among the isolated compounds, (+)-hopeaphenol [40], hemsleyanol D [51], (+)-alpha-viniferin [22], and (+)-balanocarpol [7] significantly inhibited the elevation of plasma glucose in sucrose-loaded mice at doses of 100–200 mg/kg, p.o., while (+)-isohopeaphenol [48] showed inhibitory effects at a dose of 200 mg/kg, p.o.

4.2.2. Anti-obesity activity

Supriya et al. [88] investigated the anti-obesity effect of *Shorea robusta* hydro-alcoholic leaf extract on monosodium glutamate-induced obesity in albino rats. Initially, obesity was induced by monosodium glutamate and a normal diet for 7 days. Subsequently, for the next 41 days, the obese rats were administered *Shorea robusta* extract at doses of 200, 400, and 600 mg/kg orally. Various physical parameters, including body weight, fat tissue weight, and biochemical parameters such as triglycerides, cholesterol, LDL-C, HDL-C, VLDL-C, serum glucose, atherogenic index, SGPT, and SGOT, were assessed and compared with both normal and obesity control groups. The findings indicated that the hydro-alcoholic *Shorea robusta* leaf extract may effectively treat obesity and normalize lipid profiles.

4.2.3. Antiulcer activity

The gastroprotective action of *S. robusta* resin was evaluated in rats using two models: the ethanol-induced model and pyloric ligation (PL)-induced gastric ulcer model. Pretreatment with the resin at doses of 150 and 300 mg/kg body weight orally provided significant protection against gastric mucosal damage in both the ethanol-induced and PL-induced models, similar to the reference medication omeprazole. In the ethanol-induced model, the antioxidant indicators, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione-S-transferase (GST), and lipid peroxidation (LPO), returned to normal levels, demonstrating the protective effect of the resin. Additionally, in the PL-induced model, *S. robusta* resin extract significantly reduced gastric juice volume (by 65.44 %), free acidity (by 33.06 %), total acidity (by 26.98 %), pepsin (by 44.39 %), and protein (by 23.82 %), while increasing the levels of carbohydrate (by 22.67 %) and mucin (by 41.46 %). Furthermore, the pH of the gastric juice also increased from 1.23 to 4.54. This study provided pharmacological evidence of the gastroprotective properties of *S. robusta* resin preparations used in traditional medicine [91].

4.2.4. Hepatoprotective effect

A quantitative and logical investigation of the bark and wood parts of *S. roxburghii* led to the isolation of 13 stilbenoids and 2 dihydroisocoumarins. The hepatoprotective properties of the methanol-extracted compounds were examined. The results revealed that the main polyphenols exhibited hepatoprotective effects against D-galactosamine (D-galN)/lipopolysaccharide (LPS)-induced liver injury in mice at doses of 100 or 200 mg/kg orally. Additionally, the isolates were tested for their effects on LPS-induced nitric oxide (NO) production in mouse peritoneal macrophages, tumor necrosis factor-α (TNF-α)-induced cytotoxicity in L929 cells, and D-GalN-induced cytotoxicity in primary cultured mouse hepatocytes to determine their potency. It was suggested that the inhibition of LPS-induced macrophage activation and reduction of hepatocyte sensitivity to TNF-α were important mechanisms of action for these polyphenol compounds. However, none of the isolates reduced D-GalN's cytotoxicity [49].

4.2.5. Nephroprotective effect

Hu et al. [92] conducted a study to evaluate whether *Shorea roxburghii* phenolic extract (SRPE) could protect rats from cyclophosphamide (CTX)-induced nephrotoxicity. Rats were simultaneously given CTX and treated with SRPE (100 and 400 mg/kg) for five weeks. The experiment demonstrated that SRPE treatment significantly reduced renal malondialdehyde (MDA), IL-6, TNF-α, IL-1β, NF-kB, and caspase-3 levels, as well as serum creatinine, blood urea nitrogen (BUN), and uric acid. Furthermore, SRPE enhanced renal superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and glutathione peroxidase (GPx) activities. SRPE also improved the renal histopathological effects caused by CTX administration. These findings indicate that SRPE's antioxidant and anti-inflammatory properties effectively mitigate renal toxicity induced by CTX.

4.2.6. Other protective effects

Wang H. et al. [93] explores the potential protective properties of *Shorea roxburghii* polyphenol extract (SRPE) in countering peripheral neuropathy induced by Cyclophosphamide (CYP), a commonly used antineoplastic and immunosuppressive drug known for its harmful side effects. Rats were treated with SRPE alongside CYP, and the study identified 54 polyphenolic compounds in SLPE using

advanced analytical techniques. The findings demonstrated that CYP caused significant increases in mechanical and thermal hyperalgesia, nociceptive responses, and reduced locomotive activity and motor coordination. However, SLPE treatment effectively mitigated these adverse effects induced by CYP, indicating its potential as a therapeutic remedy for chemotherapy-induced peripheral neuropathy.

4.2.7. Anti-inflammatory activities

Wani et al. [96] revealed the anti-inflammatory potential of methanolic and aqueous leaf extracts of *S. robusta* in the carrageenan and dextran-induced paw edema models, as well as the cotton-pellet-induced granuloma model. Additionally, Nainwal et al. [94] conducted an experiment using the HRBC (Horse Red Blood Cell) membrane stabilization model, comparing aqueous extracts of *Shorea robusta* leaves at doses of 100, 200, and 500 μg/ml with the standard Diclofenac at doses of 20 and 40 μg/ml. They also analyzed these extract doses at 200 μg/ml using the heat-induced hemolytic method. In both models, the results indicated that only the 500 μg/ml extract was effective against inflammation.

4.2.8. Immunomodulatory activity

The administration of *Shorea robusta* bark ethanolic extract at a dose of 300 mg/kg to rat models (administered orally daily) demonstrated the significant potential of the extract as a potent natural remedy for immune system modulation Kalaiselvan et al. [95].

4.2.9. Wound healing activity

Wani et al. [97] conducted an experiment to evaluate the activity of an ethanolic extract of *S. robusta* resin. The results indicated that the extract increased the hydroxyproline content and tensile strength of wounds in rats and accelerated wound contraction in a dose-dependent manner. These findings suggest that the ethanolic extract of *S. robusta* resin possesses wound-healing properties.

5. Conclusion

According to the current review, numerous of the plant's crude extracts and secondary metabolite compounds isolated from this genus, including (−) hopeaphenol [52], vaticanol B [55], (+)-α-viniferin [22] and shoreaketone [41] were found to have a very potent antioxidant, antimicrobial and cytotoxicity effects. However, these compounds were only screened for their preliminary in vitro activities. As a result, the advanced clinical trial of these compounds deserves to be further investigated. The genus *Shorea* has been the subject of much research, underscoring its substantial medicinal and economic importance. However, the alarming number of endangered *Shorea* species, with some already reported as extinct, calls for urgent action. Phytochemical investigations on the species that are yet to be phytochemically investigated, particularly focusing on critically endangered *Shorea* species, can unveil their hidden phytochemical potentials. This, in turn, can stimulate conservation efforts by promoting their cultivation and preventing their extinction. Furthermore, a wide range of future research projects on this genus remains feasible, making it highly valuable from a scientific perspective to isolate more new active compounds from these species.

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CRediT authorship contribution statement

Abdullahi Musa: Writing – review & editing, Writing – original draft. **Nanik Siti Aminah:** Validation, Supervision, Funding acquisition, Data curation, Conceptualization. **Alfinda Novi Kristanti:** Methodology, Formal analysis. **Imam fathoni:** Software, Project administration. **Rizka Tazky Amalia:** Software, Project administration. **Tin Myo Thant:** Visualization, Data curation. **P. Rajasulochana:** Supervision. **Yoshiaki Takaya:** Supervision, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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