

Phytochemical account: *Phyllanthus reticulatus* Poir.

Md. Moshfekus Saleh-E-In^{1*} , Pallab Kar² , Ayan Roy⁴  and Radosław Kowalski^{4*} 

¹Division of Forest Resources, College of Forest and Environmental Sciences, Kangwon National University, Chunchon, South Korea

²Molecular Cytogenetics Laboratory, Department of Botany, University of North Bengal, Siliguri, West Bengal, India

³Department of Biotechnology, Lovely Professional University, Phagwara, Punjab, India

⁴Department of Analysis and Food Quality Assessment, University of Life Sciences in Lublin, Poland

Abstract

Phyllanthus reticulatus Poir has long been used in the traditional medications for the treatment of various human diseases most notably diarrhoea, asthma, diabetes and inflammation. Several chromatographic techniques were used to isolate the main active constituents from different parts of the plants using different solvents. Over the last few decades, 57 compounds have been isolated and identified from the *P. reticulatus* including 12 terpenoids, 4 steroids, 7 flavonoids, 8 phenolics, 8 lignins, 8 tannins, 5 megastigmane glycosides, 3 diterpenoids, 1 purine derivative, 2 acid derivatives and 1 fatty alcohol. This review provided a comprehensive overview of the phytochemistry of *P. reticulatus* based on the unified review of literature. The review suggests for further avenues of research on the phytochemistry of *P. reticulatus* to isolate and decipher the unidentified lead compounds for future pharmaceutical applications.

Article Information

Received: 30 May, 2022

Revised: 25 June, 2022

Accepted: 28, June 2022

Academic Editor

Marcello Iriti

Corresponding Author

Radosław Kowalski

radoslaw.kowalski@up.lublin.pl

Keywords

Friedelin, flavonoids, lignin megastigmane, *Phyllanthus reticulatus*, phytochemistry, terpenoids, tannin, steroids.

1. Introduction

Phyllanthus is a genus of 600 species that belongs to the family Euphorbiaceae. *Phyllanthus reticulatus* Poir. is a shrub tree growing up to 10 ft. in height. The plant grows throughout the tropical and subtropical areas of Africa, northern Australia, China, Malaysia, Indonesia, Malay Islands, India and Bangladesh [1]. The plant is used for traditional therapies with a variety of ailments, including diabetes, smallpox, diarrhoea, asthma, syphilis, bleeding from gums and inflammation [2,3]. The pharmacological investigation on *P. reticulatus* reported analgesic and anti-inflammatory, [4], antioxidant, [5], antidiabetic [6], antidiarrheal [7], hepatoprotective [8], anti-plasmodial [9], antiviral [10, 11] and skin healing activities [12]. The profound phytochemical investigation of this species encompasses various groups of secondary metabolites such as terpenoids, flavonoids, steroids, phenolic, lignin, tannins, megastigmane, glycosides, acid and alcohol derivatives. The first phytochemical study was

reported the isolation of polyphenols pyrogallol (25), *P*-coumaric (26) and ellagic (31) acids in 1966 [13]. The terpenoids were reported as the most predominant compounds of *P. reticulatus*. Apart from the phytochemical data, no review on the isolated metabolites of *P. reticulatus* exist. The different parts of the plant are shown in Fig. 1. The aim of this review is to provide a comprehensive phytochemical update of *P. reticulatus*. Perspectives on future phytochemical investigations of *P. reticulatus* are also discussed.

2. Materials and methods

Phytochemical data of *P. reticulatus* was surveyed with the main keywords *Phyllanthus reticulatus*, extraction, isolation and traditional use of *Phyllanthus* etc. SciFinderⁿ and Google Scholar[®] were used as electronic search engines. We have considered only phytochemical data, exactly for the isolated compounds of *P. reticulatus* which was the main attitude of the present review.





Fig 1: *Phyllanthus reticulatus* Poir and its different parts

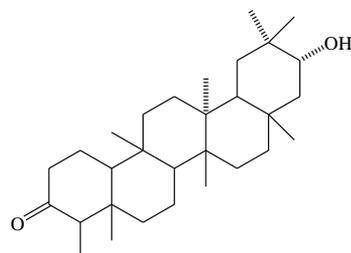
3. Results and discussion

3.1 Phytochemical data of *Phyllanthus reticulatus* Poir.

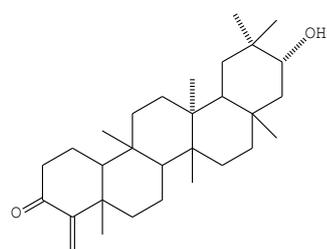
According to the critical study *P. reticulatus*, 57 compounds have been isolated from the various parts of the plants by extensive chromatographic procedures. The main compounds are classified as terpenoids, steroids, flavonoids, phenolic, lignin, aryl naphthalene lignin, lignin glycosides, tannins, megastigmane, purine, abscisic and geraniinic acid derivatives, glycosides and alcoholic compounds. The phytochemical data are compiled in Table 1.

3.1.1 Triterpenoids

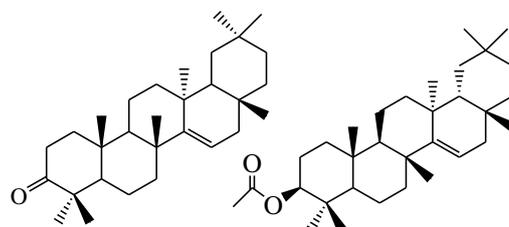
In 1976, Hui and his co-worker isolated pentacyclic triterpenoids 21 α -hydroxy friedelon-3-one (1), 21 α -hydroxy friedelon 4(23)-en-3-one (2), friedelin (7),



21 α -hydroxy friedelon-3-one (1)

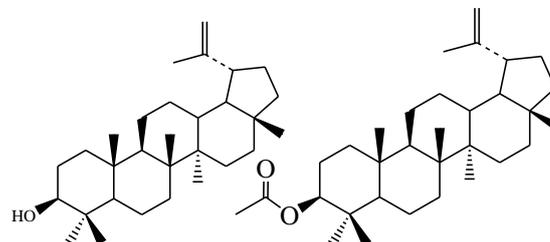


21 α -hydroxy friedelon-4(23)-en-3-one (2)



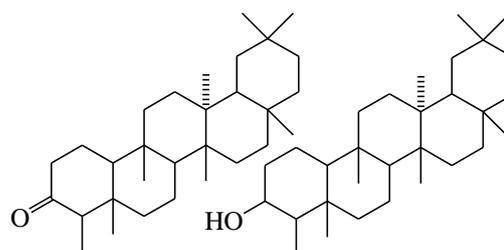
Taraxerone (3)

Taraxeryl acetate (4)



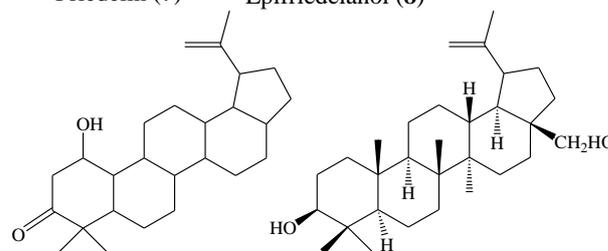
Lupeol (5)

Lupeol acetate (6)



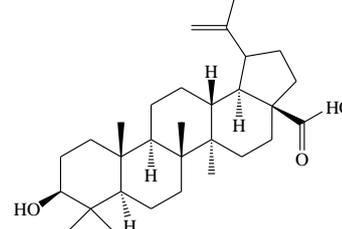
Friedelin (7)

Epifriedelanol (8)



Glochidonol (9)

Betulin (10)



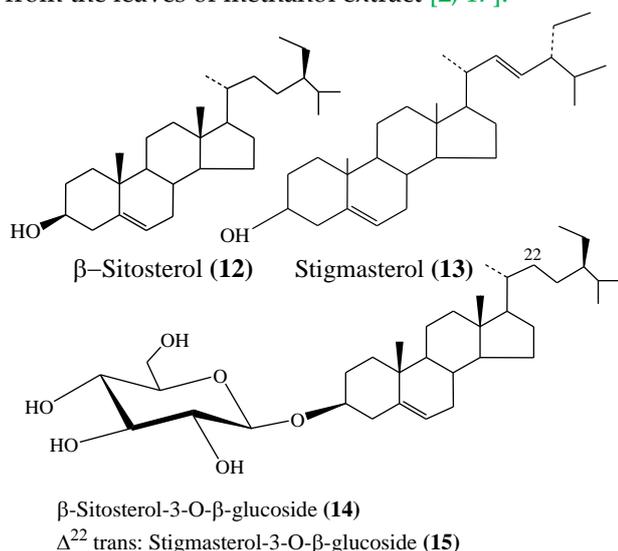
Betulinic acid (11)

epifriedelanol (8), glochidonol (9) and betulinic acid (11) from the petrol extract of the stems [14]. Later on Joshi et al., (1981) separated few pentacyclic triterpenoids from the benzene extract of the root such as 21 α -hydroxy friedelon-3-one (1), taraxerone (3) taraxeryl acetate (4), friedelin (7), epifriedelanol (8), glochidonol (9) and betulin (10) [15]. Those were almost found similar to the stem by Hui et al., (1976). On the other hand, methanol extract of the leaves

yielded two triterpenoids lupeol (5) and lupeol acetate (6) by the flash chromatographic technique [2].

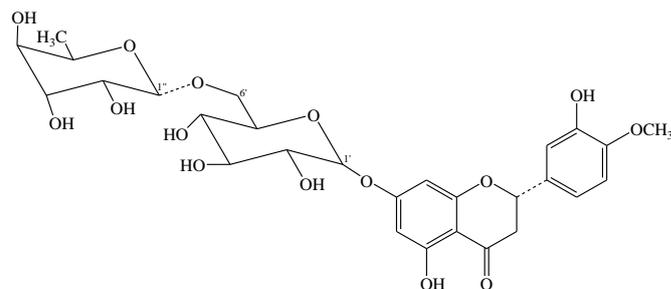
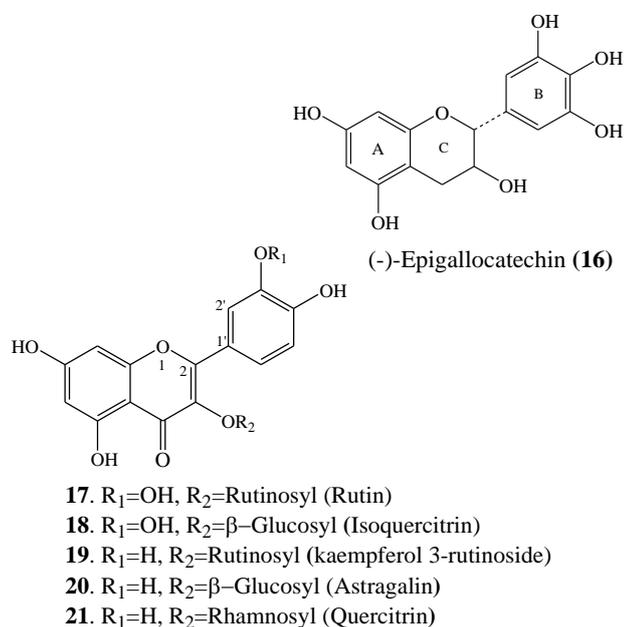
3.1.2 Steroids

A total of four steroids were isolated and identified from the various parts of the plant with different solvent system. β -sitosterol (12) was isolated from the stems, leaves, aerial parts and roots of the hot benzene, petrol and 75% ethanol extracts [14-16]. Rest of steroids stigmasterol (13), β -sitosterol glucoside (14) and stigmasterol-3-O- β -glucoside (15) were reported from the leaves of methanol extract [2, 17].



3.1.3 Polyphenols (Flavonoids)

Out of the 7 isolated flavonoids, (-)-epigallocatechin (16) and hesperetin 7-O-[(α -L-rhamnopyranosyl-(6 \rightarrow 1)]- β -D-glucopyranoside (22) were isolated from the whole plant of 75% ethanol extract [16]. The another research group reported the rest of 5

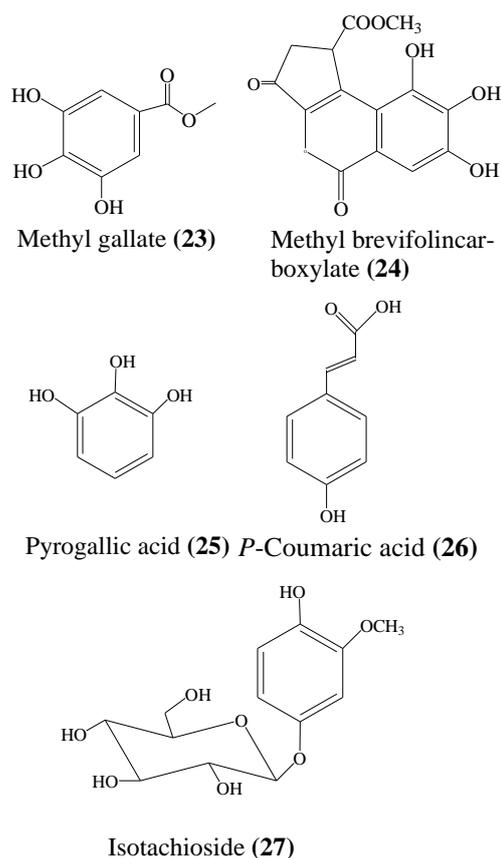


Hesperetin 7-O-[(α -L-rhamnopyranosyl-(6 \rightarrow 1)]- β -D-glucopyranoside (22)

flavonoids rutin (17), isoquercitrin (18), kaempferol 3-rutinoside (19), astragalin (20) and quercitrin (21) from the butanol soluble fraction of the methanolic extract of the leaves [17].

3.1.4 Polyphenols and Phenolic glucosides

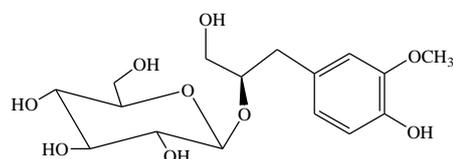
A rigorous chemical investigation of *P. reticulatus* leaves isolated two phenolics methyl gallate (23) and methyl brevifolincarboxylate (24) from the leaves of butanol soluble fraction of the methanolic extract [17]. Methyl gallate (23) was also isolated from the dichloromethane fraction of methanolic extract of the leaves [19]. In the very earlier study, pyrogalllic acid (25) and *P*-coumaric acid (26) were separated from the leaves of methanolic extract [13]. The phenolic glycosides isotachioside (27), carthamoside B5 (28),



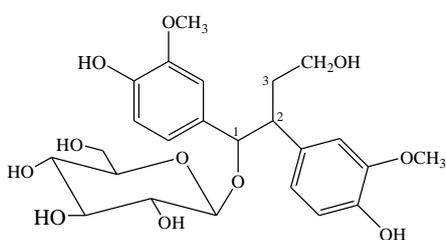
hovetrichoside A (29) and 3, 4-dihydroxyphenylpropanol 3-O-β-D-glucopyranoside (30) were successively isolated from the Butanol fraction of 75% ethanol extract of the whole plant [18].

3.1.5 Polyphenols (Tannins)

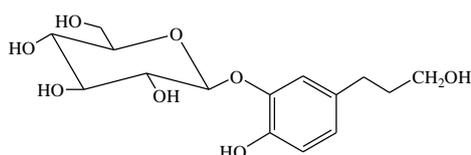
Tannins are water-soluble polyphenols and mentioned to as tannic acid, which are important for antioxidant, anti-inflammatory antimicrobial activities [22].



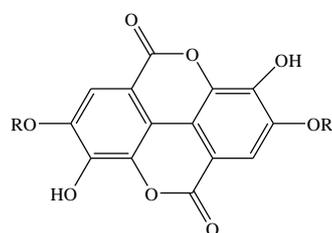
Carthamoside B5 (28)



Hovetrichoside A (29)

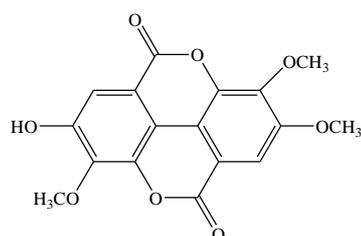


3,4-Dihydroxyphenylpropanol
3-O-β-D-glucopyranoside (30)



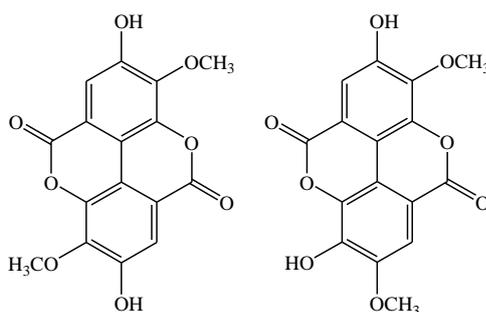
R=H, Ellagic acid (31)

R=CH₃, 2,7-di-O-methylellagic (32)

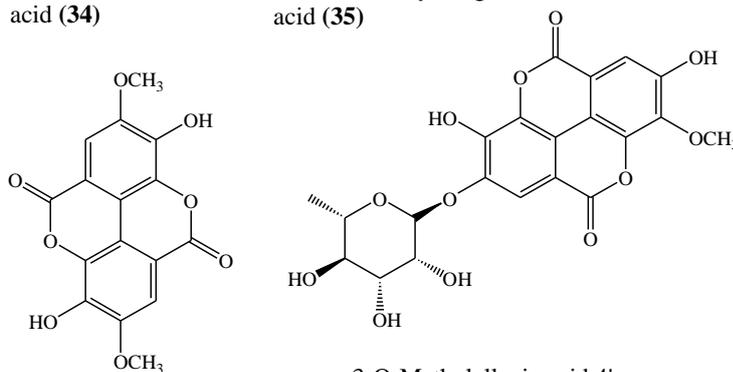


3, 3', 4'-Tri-O-methyl-
ellagic acid (33)

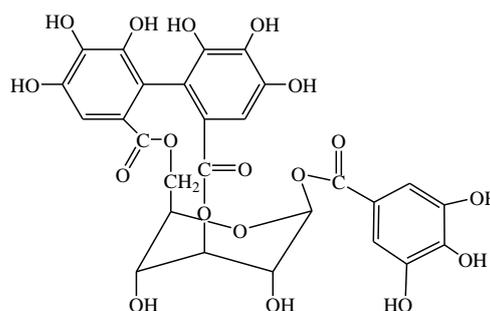
The investigation of leaves of *P. reticulatus* has led to the isolation and identification of few tannins such as ellagic acid (31), 2,7-di-O-methylellagic (32) and corilagin (38) acids from the butanol soluble fraction of the methanolic extract [17]. In addition Sangkasila (1998) and Pojchaijongdee (2010) isolated 3, 3', 4'-tri-O-methylellagic acid (33) from the methanol extract of the leaves and stems by Sephadex LH 20 coloum [19, 20]. In the other extraction, 3, 3'- di-O-methylellagic (34), 3,4-di-O-methylellagic (35) and 4,4'-di-O-methylellagic (36) acids along with a glycosidic compound 3-O-methylellagic acid 4'-O-α-L-rhamnopyranoside (37) were extracted from the 75% ethanol extract of the whole plant [16]



3,3'- Di-O-methylellagic acid (34) 3,4-Di-O-methylellagic acid (35)



3-O-Methylellagic acid 4'-
O-α-L-rhamnopyranoside (37) 4,4'-Di-O-methylellagic acid (36)



Corilagin (38)

Table 1 Compounds isolated from the different parts of *Phyllanthus reticulatus* Poir.

Name of compounds	Extracts/Fractions	References
Triterpenoids		
21 α -hydroxy friedelon-3-one (1) (C ₃₀ H ₅₀ O ₂)	Petrol extract, Hot	[14]
	Benzene	[15]
21 α -hydroxy friedelon 4(23)-en-3-one (2) (C ₃₀ H ₄₈ O ₂)	Petrol extract	[14]
Taraxerone (3) (C ₃₀ H ₄₈ O)	Hot benzene	[15]
Taraxeryl acetate (4) (C ₃₂ H ₅₂ O ₂)	Hot benzene	[15]
Lupeol (5) (C ₃₀ H ₅₀ O)	Methanol	[2]
Lupeol acetate (6) (C ₃₂ H ₅₂ O ₂)	Methanol	[2]
Friedelin (7) (C ₃₀ H ₅₀ O)	Petrol extract,	[14]
	Hot benzene	[15]
	75% ethanol	[16]
Epifriedelanol (Friedelan-3 β -ol) (8) (C ₃₀ H ₅₂ O)	Petrol extract, Hot	[14]
	Benzene	[15]
Glochidonol (9) (C ₃₀ H ₄₈ O ₂)	Petrol extract, Hot	[14]
	benzene	[15]
Betulin (10) (C ₃₀ H ₅₀ O ₂)	Hot benzene	[15]
Betulinic acid (11) (C ₃₀ H ₄₈ O ₃)	Petrol extract	[14]
Steroids		
β -Sitosterol (12) (C ₂₉ H ₅₀ O)	Petrol extract	[14]
	Hot benzene	[15]
	75% Ethanol,	[16]
Stigmasterol (13) (C ₂₉ H ₄₈ O)	Methanol	[2]
β -Sitosterol glucoside (β -Sitosterol-3-O- β -glucoside) (14) (C ₃₅ H ₆₀ O ₆)	Methanol	[17]
Stigmasterol-3-O- β -glucoside (15) (C ₃₅ H ₅₈ O ₆)	Methanol	[17]
Polyphenols (Flavonoids)		
(-)-Epigallocatechin (16) (C ₁₅ H ₁₄ O ₇)	75% EtOH extract	[18]
Rutin (Quercetin 3-rutinoside) (17) (C ₂₇ H ₃₀ O ₁₆)	Methanol	[17]
Isoquercitrin (Quercetin 3-O- β -D-glucopyranoside) (18) (C ₂₁ H ₂₀ O ₁₂)	Methanol	[17]
Kaempferol 3-rutinoside (3-O- α -L-rhamnopyranosyl-(6 \rightarrow 1)- β -D-glucopyranoside) (19) (C ₂₇ H ₃₀ O ₁₅)	Methanol	[17]
Astragalin (kaempferol 3-O- β -D-glucopyranoside) (20) (C ₂₁ H ₂₀ O ₁₁)	Methanol	[17]
Quercitrin (Quercetin 3-O- α -L-rhamnopyranoside) (21) (C ₂₁ H ₂₀ O ₁₁)	Methanol	[17]
Hesperetin 7-O-[(α -L-rhamnopyranosyl-(6 \rightarrow 1))- β -D-glucopyranoside (22) (C ₂₈ H ₃₄ O ₁₅)	75% ethanol	[16]
	Methanol	[17]
Polyphenols and phenolics		
Methyl gallate (23) (C ₈ H ₈ O ₅)		
Methyl brevifolincarboxylate (24) (C ₁₄ H ₁₀ O ₈)	Dichloromethane fraction of methanol extract	[19]
Pyrogalllic acid (25) (C ₆ H ₆ O ₃)	Methanol	[13]
<i>P</i> -Coumaric acid (26) (C ₉ H ₈ O ₃)	Methanol	[13]

(continued on next page)

Table 1 (Continued)

Name of compounds	Extracts/Fractions	References
Phenolic glucosides		
Isotachioside (27) (C ₁₃ H ₁₈ O ₈)	Butanol fraction of 75% EtOH extract	[18]
Carthamoside B5 (28) (C ₁₆ H ₂₄ O ₉)	Butanol fraction of 75% EtOH extract	[18]
Hovetrichoside A (29) (C ₂₃ H ₃₀ O ₁₁)	BuOH fraction of 75% EtOH extract	[18]
3, 4-Dihydroxyphenylpropanol 3-O-β-D-glucopyranoside (30) (C ₁₅ H ₂₂ O ₈)	Butanol fraction of 75% EtOH extract	[18]
Polyphenols (Tannins)		
Ellagic acid (31) (C ₁₄ H ₆ O ₈)	Methanol	[17] [13]
2,7-di-O-methylellagic (32) (C ₁₆ H ₁₀ O ₈)	Methanol	[17]
3, 3, 4'-tri-O-methylellagic acid (33) (C ₁₇ H ₁₂ O ₈)	Methanol Dichloromethane fraction of methan-ol extract	[20] [19]
3,3'- Di-O-methylellagic acid (34) (C ₁₆ H ₁₀ O ₈)	75% ethanol	[16]
3,4-di-O-methylellagic acid (35) (C ₁₆ H ₁₀ O ₈)	75% ethanol	[16]
4,4'-di-O-methylellagic acid (36) (C ₁₆ H ₁₀ O ₈)	75% ethanol	[16]
3-O-methylellagic acid 4'-O-α-L-rhamnopyranoside (37)(C ₂₁ H ₁₈ O ₁₂)	75% ethanol	[16]
Corilagin(β-1-O-galloyl-3,6-(R)-hexahydroxydiphenoyl-D-glucose) (38) (C ₂₇ H ₂₂ O ₁₈)	Methanol	[17]
Polyphenols (Lignan)		
(+)-Lyoniresinol (39) (C ₂₂ H ₂₈ O ₈)	Ethyl acetate fraction of 95% Ethanol extract	[21]
Syringaresinol (40) (C ₂₂ H ₂₆ O ₈)	Ethyl acetate fraction of 95% Ethanol extract	[21]
Pinoresinol (41) (C ₂₀ H ₂₂ O ₆)	Methanol	[20]
Lignin (glycoside)		
Mananthoside I (42) (C ₃₂ H ₃₄ O ₁₆)	75% EtOH extract	[18]
Lignin (Arylnaphthalene lignan glycosides)		
Reticulatusides A (3',4'-methylenedioxy-4, 5-dimethoxy-7-hydroxy-2,7'- cycloigna-7,7'-dien-9', 9-olide 7-O-α-L-arabinofuranosyl (1→6)- β-D-glucopyranoside) (43) (C ₃₂ H ₃₄ O ₁₆)	Butanol fraction of 95% EtOH extract	[21]
Reticulatusides B (3', 4'-methylenedioxy-4-methoxy-5-α-L-arabinofurano- syloxy- 7-β-D-glucopyranosyloxy-2,7'-cycloigna-7,7'-dien-9', 9-olide) (44) (C ₃₁ H ₃₂ O ₁₆)	Butanol fraction of 95% EtOH extract	[21]
Phyllanthusmins B (45) (C ₂₈ H ₂₆ O ₁₁)	Ethyl acetate fraction of 95% Ethanol extract	[21]

(continued on next page)

Table 1 (Continued)

Name of compounds	Extracts/Fractions	References
Phyllanthusmins C (46) (C ₂₆ H ₂₄ O ₁₁)	Ethyl acetate fraction of 95% Ethanol extract	[21]
Megastigmane glycosides		
(3S,5R,6S,9R)-megastigman-3,9-diol 3-O- α -L-arabinofuranosyl-(1 \rightarrow 6)- β -D-glucopyranoside (47) (C ₂₄ H ₄₃ O ₁₁)	Butanol fraction of 95% EtOH extract	[21]
7-megastigmen-3-ol-9-one 3-O- α -L-arabinofuranosyl-(1 \rightarrow 6)- β -D-glucopyranoside (48) (C ₂₄ H ₃₉ O ₁₁)	Butanol fraction of 95% EtOH extract	[21]
Turpenionosides A (49) (C ₁₉ H ₃₄ O ₈)	Butanol fraction of 75% EtOH extract	[18]
Turpenionosides B (50) (C ₁₉ H ₃₄ O ₈)	Butanol fraction of 75% EtOH extract	[18]
Diterpenoids (Cleistanthane-type)		
Diterpenoid glucoside		
19-Hydroxyspruceanol 19-O- β -D-glucopyranoside (51) (C ₂₆ H ₃₈ O ₈)	BuOH fraction of 75% EtOH extract	[18]
Diterpene alcohols		
Cleistanthol (8,11,13,15-Cleistanthatetraene-2,3,12-triol) (52) (C ₂₀ H ₂₈ O ₅)	Ethyl acetate fraction of 95% Ethanol extract	[21]
Spruceanol (8,11,13,15-Cleistanthatetraene-3,12-diol) (53) (C ₂₀ H ₂₈ O ₂)	Ethyl acetate fraction of 95% Ethanol extract	[21]
Purine derivative		
3-(3-methylbut-2-en-1-yl) isoguanine (54) (C ₁₀ H ₁₃ N ₅ O)	BuOH fraction of 75% EtOH extract	[18]
Glycosylated abscisic acid derivative		
Dihydrophaseic acid 4'-O- β -D-glucopyranoside (55) (C ₂₁ H ₃₀ O ₁₀)	75% ethanol	[16]
Glycosylated abscisic acid derivative		
(5R*,6R*)-4,6-Dimethoxycarbonyl-5-[2',3',4'-trihydroxy-6'-(methoxycarbonyl) phenyl]-5,6-dihydro-2H-pyran-2-one (56) (C ₁₇ H ₁₆ O ₁₁)	Dichloromethane fraction of methanol extract	[19]
Fatty alcohols		
Octacosanol (57) (C ₂₈ H ₅₈ O)	Hot benzene	[15]

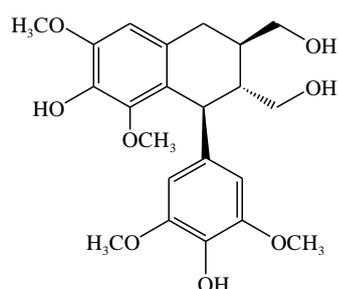
3.1.6 Polyphenols (Lignans and lignin glycosides)

Lignans are phenolic dimers with the strong antioxidant, anti-inflammatory and anticancer potentials. Lignans are common in food and woody

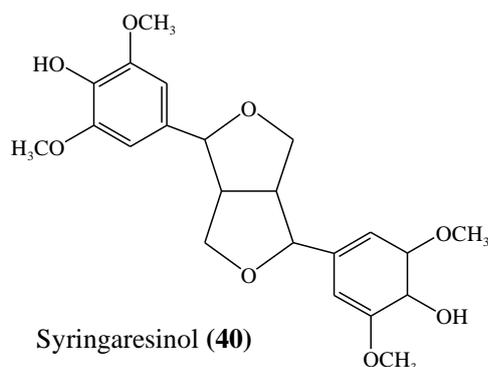
plants. Thus far, eight lignans (39-46) have been identified in *P. reticulatus*. The lignans such as (+)-lyoniresinol (39) and syringaresinol (40) were detected and quantified from the whole plant of 95%



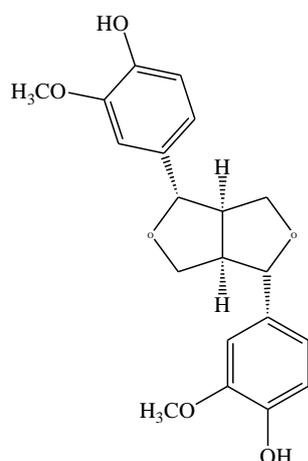
ethanol extract (Ethyl acetate fraction) [21], whereas pinoresinol (41) was isolated from the stem of methanolic extract [20]. In the case of lignin glycosides, Lan et al., (2010) isolated mananthoside I (42) from the 75% ethanolic extract of the whole plant [18]. Again, arylnaphthalene lignan glycosides reticulatusides A (43) and reticulatusides B (44) were isolated from the butanol fraction along with phyllanthusmins B (45) and phyllanthusmins C (46) from the ethyl acetate fraction of 95% ethanol extract [21].



(+)-Lyoniresinol (39)



Syringaresinol (40)



Pinoresinol (41)

3.1.7 Megastigmane glycosides

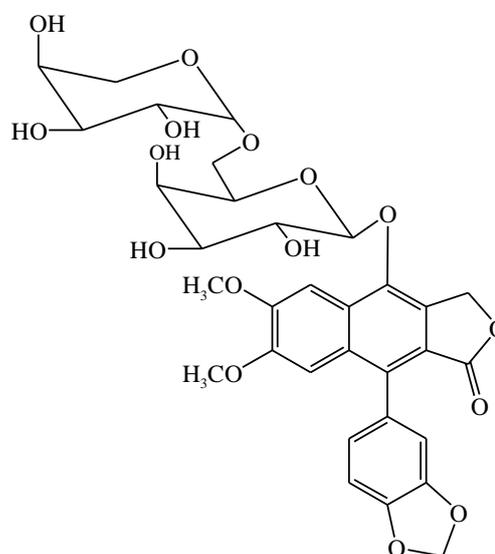
Megastigmanes are rare and expanding class of chemical compounds distributed in the plant kingdom. Ma et al., (2012) reported two megastigmane glycosides (3S,5R,6S,9R)-megastigman-3,9-diol 3-O- α -L-arabinofuranosyl-(1 \rightarrow 6)- β -D-glucopyranoside (47) and 7-megastigmen-3-ol-9-one 3-O- α -L-arabinofuranosyl-(1 \rightarrow 6)- β -D-glucopyranoside (48) with other phenolic compounds from the butanol fraction of 95% ethanol extract of the dried whole plant [21]. In another investigation, 75% ethanol extract of butanol fraction yielded two megastigmane glycosides turpenionosides A (49) and turpenionosides B (50) from the whole plant [18].

3.1.8 Diterpenoids

Lan and his colleagues in 2010, were able to isolate a cleistanthane-type diterpenoid glucoside 19-hydroxyspruceanol 19-O- β -D-glucopyranoside (51) from the 75% ethanol extract of butanol fraction of the whole plant [18]. There are also two diterpene alcohols cleistanthol (52) and spruceanol (53) have been detected in whole plant and isolated from the ethyl acetate fraction of 95% ethanol extract as the known compounds [21].

3.1.9 Purine derivative

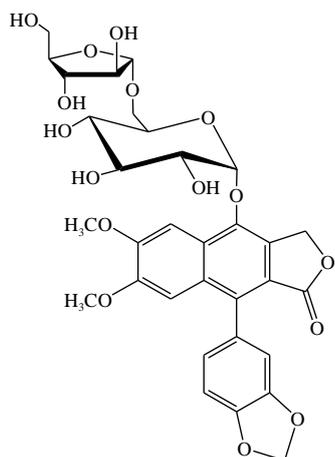
Again, Lan et al., (2010) reported a new purine derivative 3-(3-methylbut-2-en-1-yl) isoguanine (54) from the 75% ethanol extract of the butanol fraction as a white amorphous powder [18].



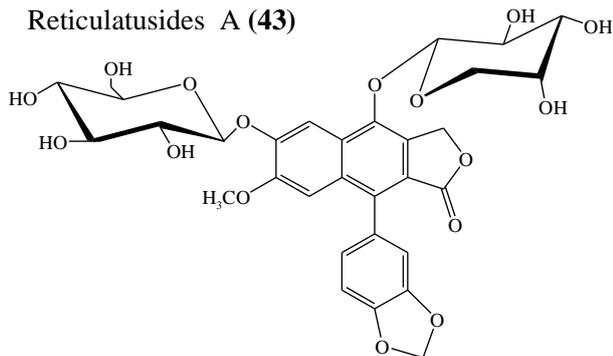
Mananthoside I (42)

3.1.10 Glycosylated abscisic and Geraniinic acid derivative

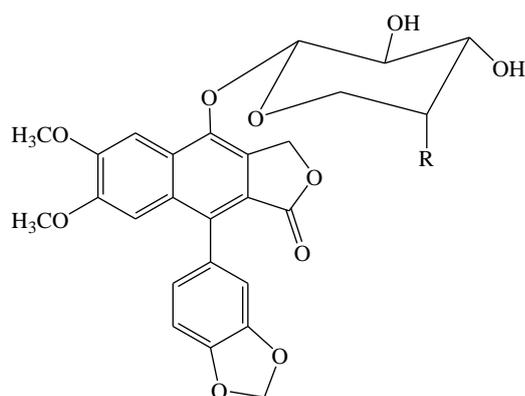
Dihydrophaseic acid 4'-O-β-D-glucopyranoside (**55**) was isolated as glycosylated abscisic acid derivative obtained from the whole plant of 75% ethanol extract [16]. On the other investigation, a new geraniinic acid derivative (5*R**,6*R**)-4,6-Dimethoxycarbonyl-5-[2',3',4'-trihydroxy-6'-(methoxycarbonyl) phenyl]-5,6-dihydro-2*H*-pyran-2-one (**56**) was isolated as colorless needle from the leaves of dichloromethane fraction of methanol extract [19].



Reticulatusides A (**43**)



Reticulatusides B (**44**)

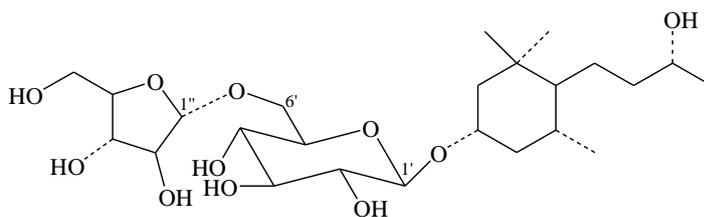


R=OCOCH₃, Phyllanthusmins B (**45**)

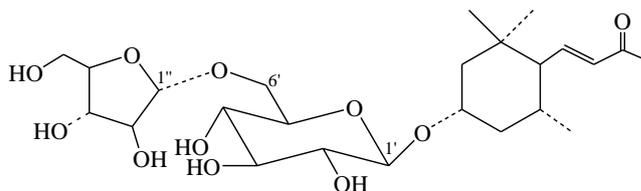
R=OH, Phyllanthusmins C (**46**)

3.1.11 Fatty alcohols

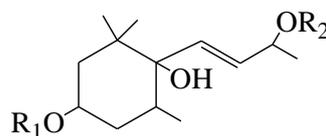
A light petroleum ether extract of the roots yielded a crystalline solid fatty alcohol octacosanol (**57**) at the scheme of triterpenoids separation [15].



(3*S*,5*R*, 6*S*, 9*R*)-megastigman-3, 9-diol 3-O-α-L-arabinofuranosyl-(1→6)-β-D-glucopyranoside (**47**)

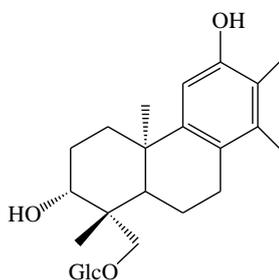


7-Megastigmen-3-ol-9-one 3-O-α-L-arabinofuranosyl-(1→6)-β-D-glucopyranoside (**48**)

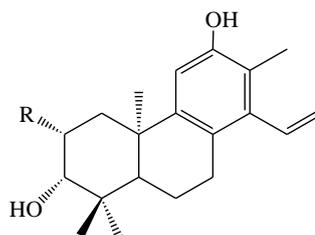


R₁=Glc, R₂=H, (Turpenionosides A) (**49**)

R₁=H, R₂=Glc, (Turpenionosides B) (**50**)

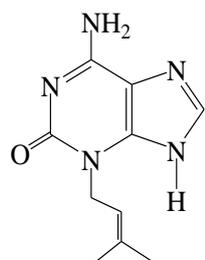


19-Hydroxyspruceanol 19-O-β-D-glucopyranoside (**51**)

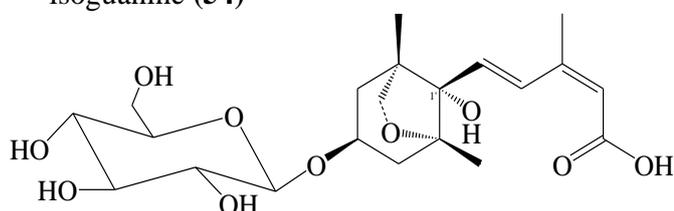


R=OH (Cleistanthol) (**52**)

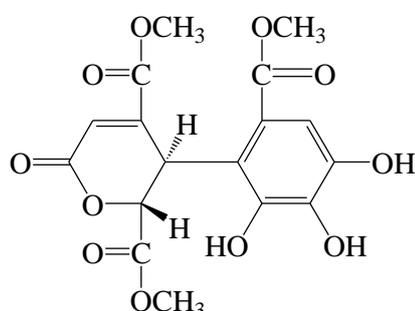
R=H (Spruceanol) (**53**)



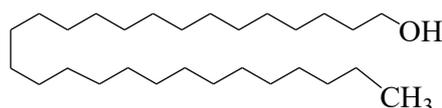
3-(3-methylbut-2-en-1-yl)
isoguanine (**54**)



Dihydrophaseic acid
4'-O- β -D-glucopyranoside (**55**)



(5R*, 6R*)-4, 6-
Dimethoxycarbonyl-5-
[2', 3', 4'-trihydroxy-
6'-(methoxycarbonyl)
phenyl]-5, 6-
dihydro-2H-pyran-2-
one (**56**)



Octacosanol (**57**)

4. Conclusions and future remarks:

The current review is intended to evaluate the isolated secondary metabolites from *P. reticulatus*. It is noted that the typical compounds are mainly triterpenoids and polyphenols. Among the isolated compounds, 21

α -hydroxy friedelon 4(23)-en-3-one (**2**), reticulatusides A (**44**), reticulatusides B (**45**), 19-hydroxyspruceanol 19-O- β -D-glucopyranoside (**52**), 3-(3-methylbut-2-en-1-yl) isoguanine (**55**) and (5R*,6R*)-4,6-dimethoxycarbonyl-5-[2',3',4'-trihydroxy-6'-(methoxycarbonyl)phenyl]-5,6-dihydro-2H-pyran-2-one (**57**) have been reported as new compounds in this plant. It is striking that no alkaloids have been reported. Moreover, the pharmacological activities of the isolated compounds have been less studied and yet many of those remain untouched. In addition, the number of secondary metabolites reported from this plant is very limited. Therefore, the species warrants more attention in the future phytochemical investigation in the aspect of pharmacological point of view. Future studies should be focused on the seed, flower and bark part for the isolation of more triterpenoids and unidentified alkaloids. The reported compounds might have potential pharmaceutical importance for the synthesis of new series of bioactive molecules.

5. Author Contributions:

MMS: data collection, design and drafted the manuscript; PK & AR: revised and improve the manuscript; RK: Supervised the work.

6. Funding: No Fund Received

7. Conflicts of Interest:

There is no conflict of interest among the authors

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