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Review Paper

Notes on the genus *Paramignya*: Phytochemistry and biological activity

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ABSTRACT

Genus *Paramignya* belongs to Rutaceae family, with interesting secondary metabolites, comprising main classes of compounds coumarin and coumarin glycosides, acridone alkaloids, tirucallane and tirucallane glycosides, phenols, and flavonoids, as well as several compounds limonoid, lignin glycoside and sterol. *Paramignya* species has been employing as folk medicines against hepatitis, diabetes, cancer, nose infections. Many bioactive reported such as cytotoxic assay, antioxidant, antiinflammatory, antiumor cancer, α-glucosidase inhibitory activities indicated either *Paramignya* extracts, fractions, or isolated compounds to become valuable resources for natural new drug developments. However, no evidences are reported for general view about this genus. In current paper, we exhibit overview almost of isolated components and biological evaluations from this genus. These findings are important to improve the values of these medicinal plants for the health benefit, drug discovery and guideline for future researches.

1. Introduction

The genus *Paramignya*, was a member of Rutaceae family and was widely distributed in the tropical Southern Vietnam, Southern Philippines, Thailan, Malaysia, Java-Indonesia, Australia, dry and wet zones of Sri Lanka, including twenty 28 species [1–4]. *Paramignya* species established the values as traditional medicine of each country. The roots of *P. trimera* species, becoming as a folk Vietnamese medicine to treat hepatitis and diabetes [2,5], or Thai used the stems of *P. grithii* for the treatment of nose infections [6]. Chemical investigations have been reporting the existence of predominant coumarins, triterpenes, alkaloids, and their glycoside derivatives [1,2,4,6–13]. Significantly, apart from the easily available information on phytochemistry and bioassay for *P. trimera*, this species had also been concentrated on studied qualitative and quantitative experiments [14–18]. Although natural products from this genus has been increasingly playing important role in drug discovery programs, however, there is no supportive evidence to give general insight into phytochemical and biological activities of extracts, fractions, and isolated compounds. Subsequently, this current paper is an overview of almost naturally occurring compounds (total 67 compounds), including twenty-two coumarin and coumarin glycosides **1–22**, fifteen tirucallane and tirucallane saponins **23–37**, seven acridone alkaloids **38–44**, six flavanones, flavones and flavanone glycoside **45–50**, nine phenols **51–59**, two chromenes **60–61**, two megastigmane glycosides **62–63** and four others **64–67** from genus *Paramignya*, along with an extensive coverage their biological evaluation.

2. Botany

2.1. Nomenclature

According to database of the plant list (www.theplantlist.org, 2017), the following acceptable names, only two *Paramignya* species, which were *P. confertifolia* Swingle and *P. rectispinosa* W.G.Craib were listed at a level of medium confidence, whereas *P. brassii* C.T.White has been reported as a synonym of *Triphasia brassii* (C.T.White) Swingle species, with status of low confidence. Significantly, only five species were studied on phytochemistry and biology, including *P. trimera* (Oliv.) Burkill, *P. scandens* Craib, *P. griffithii* Hook.f., *P. monophylla* Wight, and *P. lobata* Burkill, along with twenty-two species *P. andamanica* Tanaka, *P. angulata* Kurz, *P. armata* Oliv., *P. beddomei* Tanaka, *P. blumei* Hassk., *P. citrifolia* Hook.f., *P. citrifolia* Oliv., *P. cuspidata* (Ridl.) Burkill, *P. dubia* Koord. & Valeton ex J.Moll & Janssonius, *P. glabra* Tanaka, *P. grandiflora* Oliv., *P. hainanensis* Swingle, *P. hispida* (Pierre ex Guillaumin) Pierre ex Guillaumin, *P. littoralis* Miq., *P. longipedunculata* Merr., *P. longispina* Hook.f., *P. micrantha* Kurz, *P. mindanaensis* Merr., *P. missionis* (Oliv.) Burkill, *P. petelotii* Guillaumin, *P. ridleyi* Burkill, and *P. surasiana* Craib were assigned as a status of unresolved and low confidence level [19].

2.2. Phylogeny

The Rutaceae were large and complex family, with commonly known as rue or citrus family of flowering plants, comprises of about

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158 genera and approximately 1900 species [20]. According to report of Epifano et al. [20], the Rutaceae were closest related to the Meliaceae and Simaroubaceae [20]. Almost species in the Rutaceae family that are trees or shrubs, a few are herbs, flowers had four or five petals and sepals, sometimes three, mostly separate, eight to ten stamen. Significantly, aromatic oils could be found in many species of this family, especially in terms of genus *Citrus* such as the orange (*C. sinensis*), lemon (*C. limon*), or grapefruit (*C. paradisi*). [21].

Paramignya belongs to Rutaceae family, commonly distributed in South East Asia [1–3], for instance, seven species named *P. armata* Oliv. var. *andamanica* King, *P. griffithii* Hook. F, *P. hispida* Pierre ex Guillaum, *P. monophylla* Wight, *P. petelotii* Guillaum, *P. scandens* (Griff.) Craib, and *P. trimera* (Oliv.) Guillaum, which were found in Vietnam [1,22]. Up to present, studies on phylogeny, morphological characterization, distribution, or pharmaceutical researches of this genus are quite limited. According to research paper of Mabberley (1998), the plants *Luvunga monophylla* (DC.) Mabb., *Atalantia* (?) *recurva* Benth., *Triphasia monophylla* DC, *Atalantia trimera* Oliver, could be considered as *P. trimera* (Oliver) Burkill [3]. Of note, general appearance showed that within the Rutaceae, *Paramignya* species is possibly congeneric with *Luvunga* species [23]. Additionally, morphological characterization of the genus *Luvunga* has been occurred with small different from *Paramignya* in its 3–5 petals, 6–10 stamens and 2–4 locules in the ovary, the simple leaves characteristic of *Paramignya,* including *P. trimera*, sometimes occur in *Luvunga*: petioles shorter than those of the usual trifoliolate leaves, so that *P. trimera* is more logically placed in *Luvunga* species [3].

3. Phytochemistry

Up to present, phytochemical investigations have been focused on various parts (roots, stems, barks, stem barks, leaves, twigs, and fruits) of four species *P. trimera*, *P. scandens*, *P. griffithii*, *P. monophylla*, especially in terms of roots and stems of *P. trimera*. With regards to total 67 compounds, chemical constituents of genus *Paramignya* were classified into a wide range of compounds, including coumarin and coumarin glycosides **1–22** [1,2,7,10–12,24], tirucallane and tirucallane saponins **23–37** [4,6,8,9,13], acridone alkaloids **38–44** [2,12], flavanones, flavones, and flavanone glycoside **45–50** [6,13,25], phenols **51–59** [2,25,26], chromenes **60–61** [2,6,7], and megastigmanes **62–63** [25] (Table 1 and Figs. 1a, 2a, 3a, and 4, 5). Beside, minor components **64–67** were also detected [11,25] (table 1 and Fig. 6). Among the total 67 different phytoconstituents, 24 new compounds were detected which belongs to the groups of coumarin and comarin glycosides **4**, **6–9**, **19–22**, tirucallane and tirucallane saponins **25–28**, and **31–37**, acridone alkaloids **43–44**, and flavanones **46–47**.Fig. 3b.

3.1. Coumarin and coumarin glycosides

Coumarin derivative compounds **1–22** were obtained as dominant components from *P. trimera* and *P. monophylla* species (Fig. 1a and Table 1). Article in phytochemistry of these species revealed most of naturally occurring coumarins **1–5** and **8–22** as free [1,2,7,10–12,24], whereas only two dimeric monoterpene-linked coumarin glycosides compounds **6–7** were reported [1]. Significantly, the most striking features for both major free compounds and their glycosides were that chemical isolated compounds have been found in the 6,7-disubstituted pattern in general molecular formula (Fig. 1a). Comprehensive analysis of free compounds, side chains were built from some typical characteristics such as methoxy, hydroxyl, geranyl, or with pyranyl moieties, meanwhile, glycosyl parts of coumarin glycosides paratrimerins A-B (**6–7**), which spectroscopic data elucidated their detail chemical structures as β-D-glucopyranosyl and β-D-apiofuranosyl (1 → 6)-β-D-glucopyranosyl moieties [1]. In addition, biscourmarin glycosides, with typical monoterpene bridge, which were found in other genus of rutaceous family, such as bisparasin from *Citrus paradise* or thamnosin from *Thamnosma montana* [27]. Consequently, they could be seen as a

Table 1
Chemical structures from *Paramygnia* species sources.

No	Compounds	Species	Refs.
Coumarins and coumarin glycosides			
1	7-Hydroxycoumarin	*P. trimera*	[12]
2	7-Methoxycoumarin	*P. trimera*	[12]
3	Ostruthin	*P. trimera*	[1,2,7,12,24]
4	Ninhvanin (8-Methoxyostruthin)	*P. trimera*	[1,2,7,12,24]
5	6-(6-Hydroxy-3,7-dimethylocta-2,7-dienyl)-7-hydroxycoumarin	*P. trimera*	[1]
6	Paratrimerin A	*P. trimera*	[1]
7	Paratrimerin B	*P. trimera*	[1]
8	Paratrimerin E (**8a**) 6-(6′,7′-Dihydroxy-3′,7′ -dimethylocta-2′-enyl)-7-hydroxycoumarin (**8b**)	*P. trimera*	[2,7]
9	Paratrimerin F	*P. trimera*	[2]
10	Umbelliferone	*P. trimera*	[2]
11	Scopoletin	*P. trimera*	[2]
12	Xanthyletin	*P. trimeraP. monophylla*	[2,10,24]
13	Pandanusin A	*P. trimera*	[2]
14	8-Geranyl-7-hydroxycoumarin	*P. trimera*	[7]
15	6-(7-Hydroperoxy-3,7-dimethylocta-2,5-dienyl)-7-hydroxycoumarin	*P. trimera*	[7]
16	Luvangetin	*P. trimera*	[7]
17	Poncitrin (dentatin)	*P. monophylla*	[11]
18	Nordentatin	*P. monophylla*	[11]
19	5-Hydroxy-8,8-dimethyl-10-(3′,7′-dimethyocta-1′,6′-dimethylocta-1′,6′-dien-3′-yl) pyranocoumarin	*P. monophylla*	[11]
20	5-Methoxy-8,8-dimethyl-10-(3′,7′-dimethyocta-1′,6′-dimethylocta-3′-dien-3′-yl) pyranocoumarin	*P. monophylla*	[11]
21	5-Methoxy-8,8-dimethyl-10-(7-hydroxy-3,7-dimethylocta-1,5-dien-3-yl) pyranocoumarin	*P. monophylla*	[10]
22	5-Hydroxy-8,8-dimethyl-10-(7-hydroxy-3,7-dimethylocta-1,5-dien-3-yl) pyranocoumarin	*P. monophylla*	[10]
Tirucallanes and tirucallane saponins			
23	Flindissone	*P. monophylla*	[4]
24	Deoxyflindissone	*P. monophylla*	[4]
25	Tirucalla-7,24-diene-3β,23-diol	*P. monophylla*	[4]
26	Tirucalla-7,24diene-3β,2123-triol	*P. monophylla*	[4]
27	3-Oxotirucalla-7,24-diene-2123-diol	*P. monophylla*	[4]
28	3-Oxo-tirucalla-7,24-dien-23-ol	*P. monophylla*	[4]
29	2424-Dimethyl-lanosta-25-en-3β-ol	*P. monophylla*	[13]
30	3-Oxo-tirucalla-7,24-diene-21-al	*P. grithii*	[6]
31	Paramignyol A	*P. scandens*	[9]
32	Paramignyol B	*P. scandens*	[9]
33	Paramignyosides A	*P. scandens*	[8]
34	Paramignyosides B	*P. scandens*	[8]
35	Paramignyosides C	*P. scandens*	[8]
36	Paramignyosides D	*P. scandens*	[8]
37	Paramignyosides E	*P. scandens*	[8]
Acridone alkaloids			
38	Citrusinine-I	*P. trimera*	[2,12]
39	Glycocitrine-III	*P. trimera*	[2,12]
40	Oriciacridone E	*P. trimera*	[2]
41	Oriciacridon	*P. trimera*	[12]
42	5-Hydroxynoracronycin	*P. trimera*	[2,12]
43	Paratrimerin C	*P. trimera*	[2]
44	Paratrimerin D	*P. trimera*	[2]
Flavanones, flavones, and flavanone glycoside			
45	Amoradicin	*P. grithii*	[6]
46	3′,4′-Dihydroxy-7-methoxy-8-(3-methylbut-2-enyl)-furano-(4″,5″:6,5)-flavanone	*P. grithii*	[6]
47	3′,4′-Dihydroxy-7-methoxy-8-(3-methylbut-2-enyl)-2‴-(1-hydroxy-1-methylethyl)-furano-(4″,5″:6,5)-flavanone	*P. grithii*	[6]
48	Carpachromene	*P. monophylla*	[13]
49	3′-Methoxycarpachromene	*P. monophylla*	[13]
50	Atripliside B	*P. scandens*	[25]
Phenols			

(*continued on next page*)

Table 1 (*continued*)

No	Compounds	Species	Refs.
51	Methyl 4-hydroxybenzoate	*P. trimera*	[26]
52	Methyl p-(*E*)-coumarate	*P. trimera*	[26]
53	Methyl syringate	*P. trimera*	[26]
54	Vanillin	*P. trimera*	[26]
55	(*E*)-Methyl3-(4′-hydroxy-3′,5′-dimethoxyphenyl) acrylate	*P. trimera*	[26]
56	Methyl ferulate	*P. trimera*	[26]
57	Methyl 4-hydroxy-3-methoxybenzoate	*P. trimera*	[26]
58	Vanillic acid	*P. trimera*	[2]
59	*Trans*-N-*p*-coumaroyl tyramine	*P. scandens*	[25]
Chromenes			
60	Daedalin A	*P. trimera*	[2]
61	6-(2-Hydroxyethyl)-2,2-dimethyl-2H-1-benzopyran	*P. trimeraP. grithii*	[6,7]
Megastigmane glycosides			
62	Gusanlungionoside C	*P. scandens*	[25]
63	(6*R*,9*S*)-Roseoside	*P. scandens*	[25]
Other compounds			
64	Limonoid Methyl isolimonate	*P. scandens*	[25]
65	Lignin glycoside Syringaresinol di-*O*-β-d-glucopyranoside	*P. scandens*	[25]
66	Nucleoside Adenosine	*P. scandens*	[26]
67	Sitosterol	*P. monophylla*	[11]

remarkable signal for medicinal plant in the family Rutaceae. Taking chemical structure of compound **8** (**8a** and **8b**) into consideration, absolute configuration of carbon C-6′ in the genaryl side chain could not determine, it therefore show that paratrimerin E (**8a**) and 6-(6′,7′-dihydroxy-3′,7′-dimethylocta-2′-enyl)-7-hydroxycoumarin (**8b**) had the same depict [2,7]. Finally, the relationship among compounds **3–4** and **8–13** was proposed by plausible biosynthetic scheme (Fig. 1b) [2].

3.2. Tirucallane and tirucallane saponins

Phytochemical investigations also reported the presence of typical structures tirucallane and tirucallane saponins **23–37** (Table 1 and Fig. 2a), comprising seven tirucallanes **23–29** from fruits, leaves and stems of *P. monophylla* species [4,13], one tirucallane **30** from ground stems of *P. grithii* species [6], seven glycosyl derivatives **31–37** from stems and leaves of *P. scandens* species [8,9]. Of the tirucallane saponins, the combination between (13*S*,14*R*,17*S*,20*S*)-lanostane aglycone and β-D-glycopyranosyl glycone via *O*-acetyl bridge, and/or glycosylated phenomena at carbon C-25 in compounds **33–37** might already be a remarkable marker for *P. scandens* and other relative species in genus *Paramignya* (Fig. 2b) [8].

3.3. Acridone alkaloids

The research result in describing the isolation and structural characterization, biosynthesis, bioactive experiences of alkaloids was published by Duong et al. and Dang et al. [2,12]. In terms of alkaloids, including seven compounds **38–44** (Table 1 and Fig. 3a), all of them were found in only *P. trimera* species with interesting characteristic skeleton acridone [2,12]. Their molecules consist of some general features, comprising spin systematic protons ABX at H-6, H-7, and H-8, methylation of amine group, hydroxyl groups at C-1 and C-5. Furthermore, the side chains in acridone alkaloids **38–44** usually occur at C-2, C-3, and C-4, for instance, paratrimerin C (**43**) was designated as a novel acridone alkaloid with the typical furano-cyclization at C-3 and C-4 [2], or genaryl side chain evidently attached at C-2 in known acridone alkaloid glycocitrin-III (**39**) throughout ^{1}H–^{13}C HMBC spectrum confirmation [2,12]. Hence, acridone alkaloids offered the significant value for differences between *P. trimera* and other *Paramignya* species. Last but one least, plausible biosynthetic scheme for acridone alkaloids **38–39** and **40–44** was suggested as Fig. 2b [2].

3.4. Flavanones, flavones, and flavanone glycoside

Taking flavonoids into consideration, three flavanones, two flavones, and one glycosyl derivative **45–50** were isolated (Table 1 and Fig. 4) [6,13,25]. Two new prenylated flavanones 3′,4′-dihydroxy-7-methoxy-8-(3-methylbut-2-enyl)-furano-(4″,5″:6,5)-flavanone (**46**), and 3′,4′-dihydroxy-7-methoxy-8-(3-methylbut-2-enyl)-2″-(1-hydroxy-1-methylethyl)-furano-(4″,5″:6,5)-flavanone (**47**), together with known one amoradicin (**45**) were isolated from methanol extract of the *P. grithii* stems whereas a flavanone diglycoside atripliside B (**50**) was derived from aqueous extract of *P. scandens* twigs and leaves. Of these flavones, Bowen and Patel (1998) reported the existence of flavones **48–49** in the petroleum and chloroform extracts of *P. monophylla* air dried stems [13]. Admittedly, flavonoids have not been finding in the tropical-medicinal plant *P. trimera* sepcies.

3.5. Phenols, chromenes, and megastigmane glycosides

In the work of Linh et al. [26], the stems of *P. trimera* species were

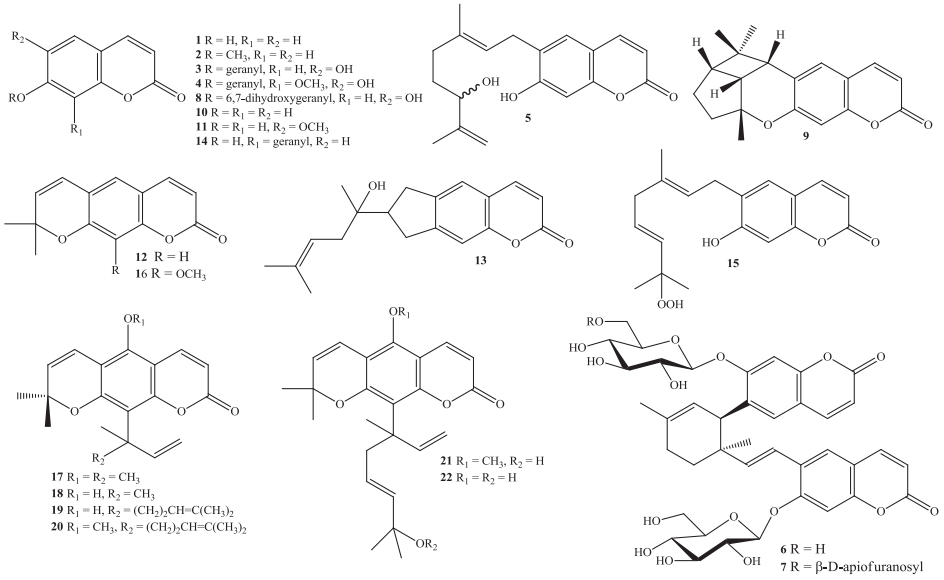

Fig. 1a. Coumarins and coumarin glycosides (**1–22**) from genus *Paramignya*.

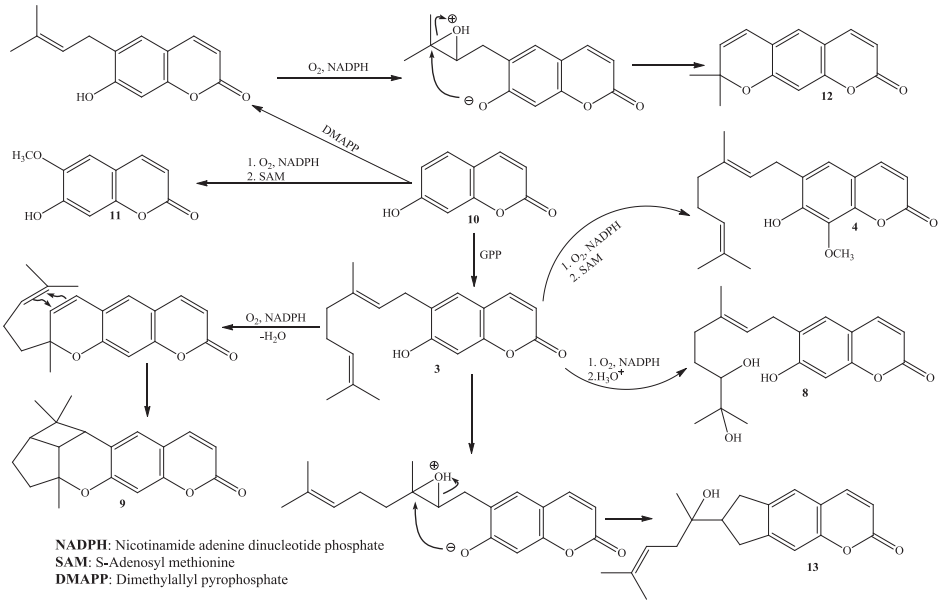

Fig. 1b. Pausible biosynthetic schemes for compounds **3–4** and **8–13.**

selected for chemical investigation, phytochemical analysis of chloroform extract led to the isolation of seven phenolic compound **51–57** [26]. All of these showed the simple structure with type of 1246-tetrasubstituted derivatives (table 1 and Fig. 5). Beside, vanillic acid (**58**) and *trans*-N-*p*-coumaroyl tyramine (**59**) were isolated from *P. trimera* methanolic extract and *P. scandens* aqueous extract, respectively, which might also be identified as phenolic compounds [2,25].

A few sesquiterpene glycosides in genus *Paramignya* occured as megastigmane glycosides, which only two compounds named gusanlungionoside C (**62**) and (6*R*,9*S*)-roseoside (**63**), were isolated from the aqueous extract of *P. scandens* dried twigs and leaves [25]. Herein, comprehensive NMR spectroscopies of **62–63**, megastigmane glycosides were performed by the connectivity between glycopyranosyl moieties and terminal methyl group of prenyl side chain (Fig. 5). Moreover, based on chemical shifts and *J*-coupling constants of anomeric protons, to be [δ_H 4.42 (d, 8.0 Hz), δ_C 100.36] in **62**, and [δ_H 4.30 (d, 7.5 Hz), δ_C 101.25] in **63** that were usually confirmed sugars as β-D-glucopyranosyl units [25].

3.6. Other compounds

According to the work of Thuan et al. [25], apart from atripliside B (**50**), *trans*-N*p*-coumaroyl tyramine (**59**), and megastigmane glycosides **62–63**, minor compounds such as limonoid methyl isolimonate (**64**),

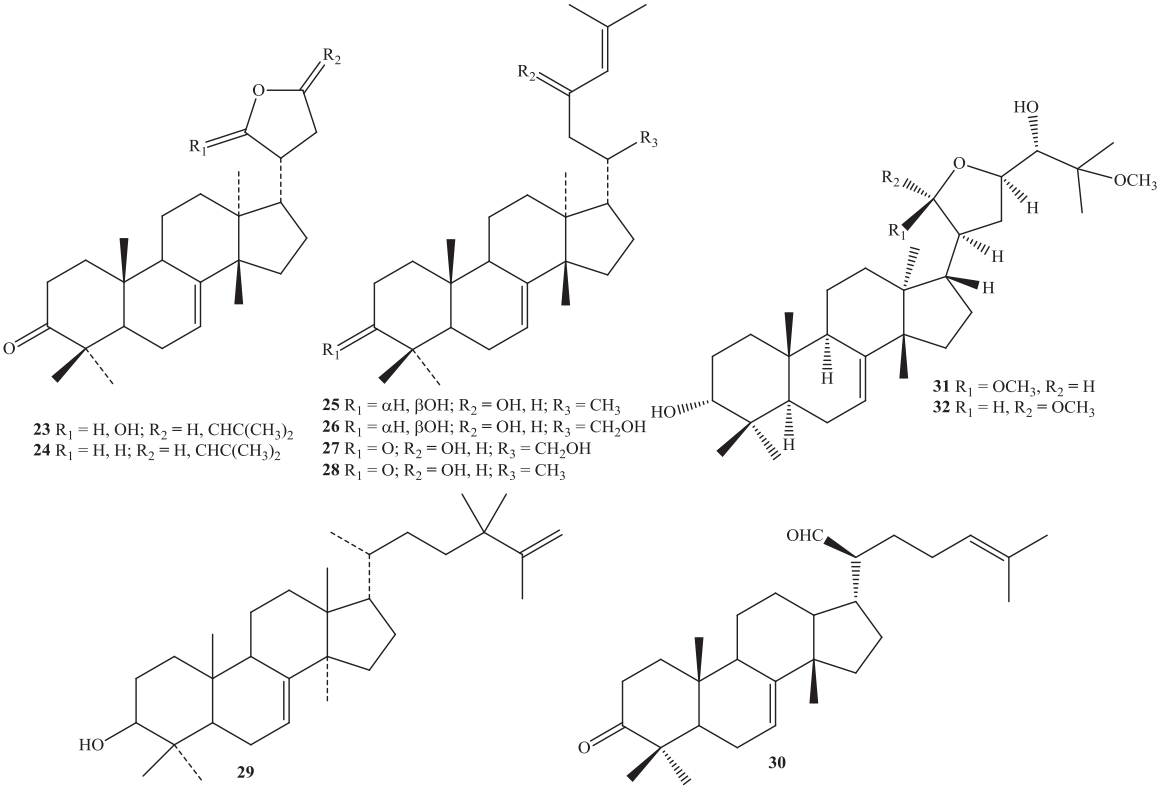

Fig. 2a. Tirucallanes (**23–32**) from genus *Paramignya.*

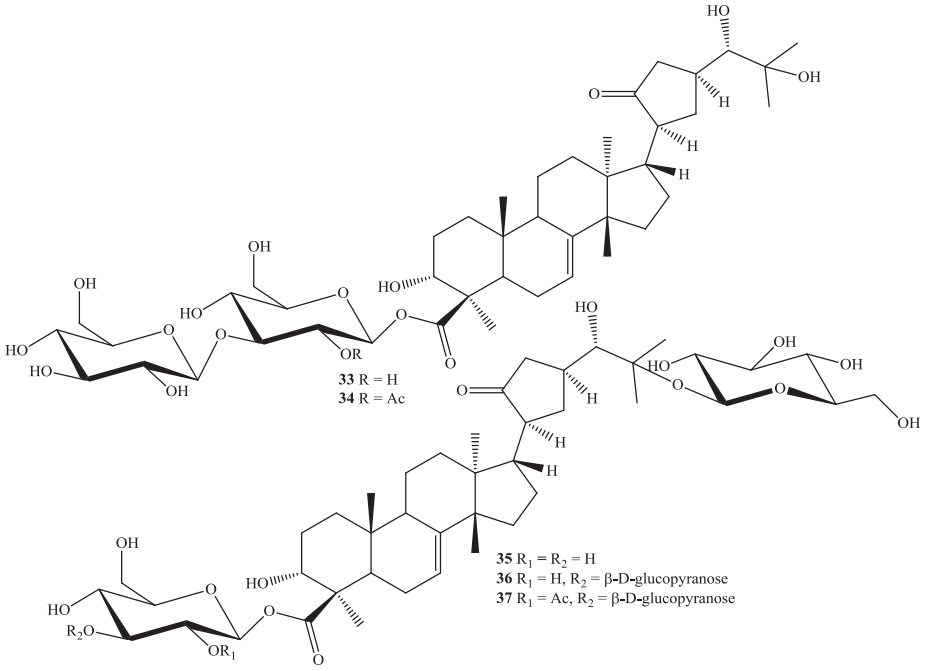

Fig. 2b. Tirucallane saponins (**33–37**) from genus *Paramignya*.

lignin glycoside syringaresinol di-*O*-β-D-glucopyranoside (**65**), nucleoside adenosine (**66**) were also detected from the *P. scandens* dried twigs and leaves (Table 1 and Fig. 6) [25]. Final, a commonly chemical compound named *β*-sitosterol (**67**) from the stem bark of *P. monophylla* species was also reported [11].

4. Qualitative and quantitative analyses

4.1. Qualitative analyses

The phytochemical screenings detected revealed beneficial values in phytochemistry and pharmacology. Based on this work, it helps us understand the traditional values of these medicinal plants, and guideline for future researches. In the genus *Paramignya*, only Kuala Lumpur *P. lobata* species of Malayan Rutaceae plant was being observed the phytochemical screenings in 1978 [28]. To take alkaloids survey into consideration, it suggests that methanol-chloroform (1:1) extract of stems showed faint positive with Dragendorff reagent/chromatographic system alumina/$CHCl_3$:cyclohexane-ethanol-diethylamine 70:30:0.5:0.5, whereas leaves gave this one in Dragendorff/silica gel/toluene:EtOAc:MeOH 12:12:1. Of steroids-triterpenes-saponins survey, 70% methanol extract of stem displayed the positive reaction with 50% H_3PO_4 or 1.5% phosphomolybdic acid or Lieberman-Burchard/silica gel PF_{254}/cyclohexane-ethyl acetate 3:7 or isopropanol-water-formic acid 70:24:6. Similarly, 70% methanol extract of leaf revealed positive signals with 50% H_3PO_4/silica gel PF_{254}/cyclohexane-ethyl acetate 3:7 or isopropanol-water-formic acid 70:24:6 and Lieberman-Burchard/silica gel PF_{254}/isopropanol-water-formic acid 70:24:6. In general, the phytochemical analysis carried out revealed the presence of alkaloids, steroids, triterpenes, and saponins in the stems and leaves of Kuala Lumpur *P. lobata* species.

Take notes of qualitative high performance liquid chromatography (HPLC) analysis for *P. trimera* species, by comparing with authentic compounds, the appearance of seven individuals was in roots, including kaempferol, chlorogenic acid, gallic acid, rutin, p-coumaric acid, (−)-epicatechin, (+)-catechin, myricetin, syringic acid, quercetin, and caffeic acid, while five ones were for leaves, comprising gallic acid, protocatechuic acid, ellagic aicd, rutin, and quercetin, however, major compound ostruthin **3**, which has yet to be found [14,18].

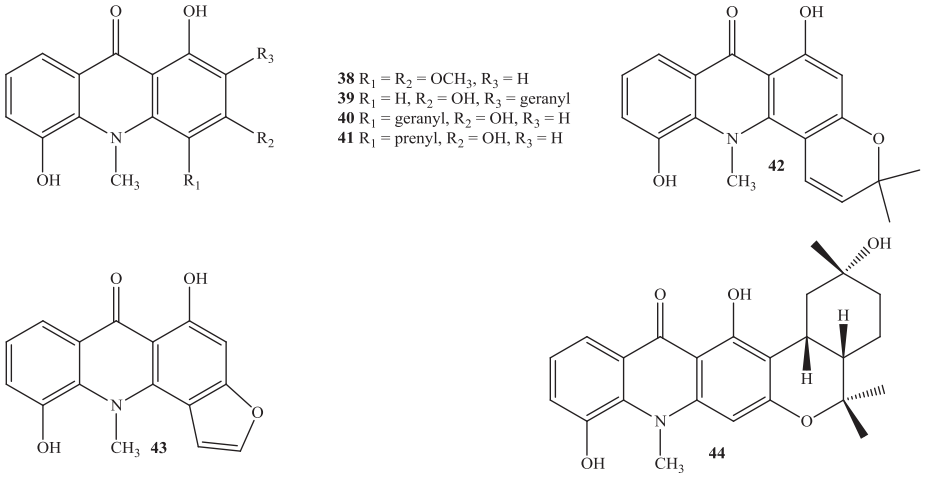

Fig. 3a. Acridone alkaloids (**38–44**) from genus *Paramygnia*.

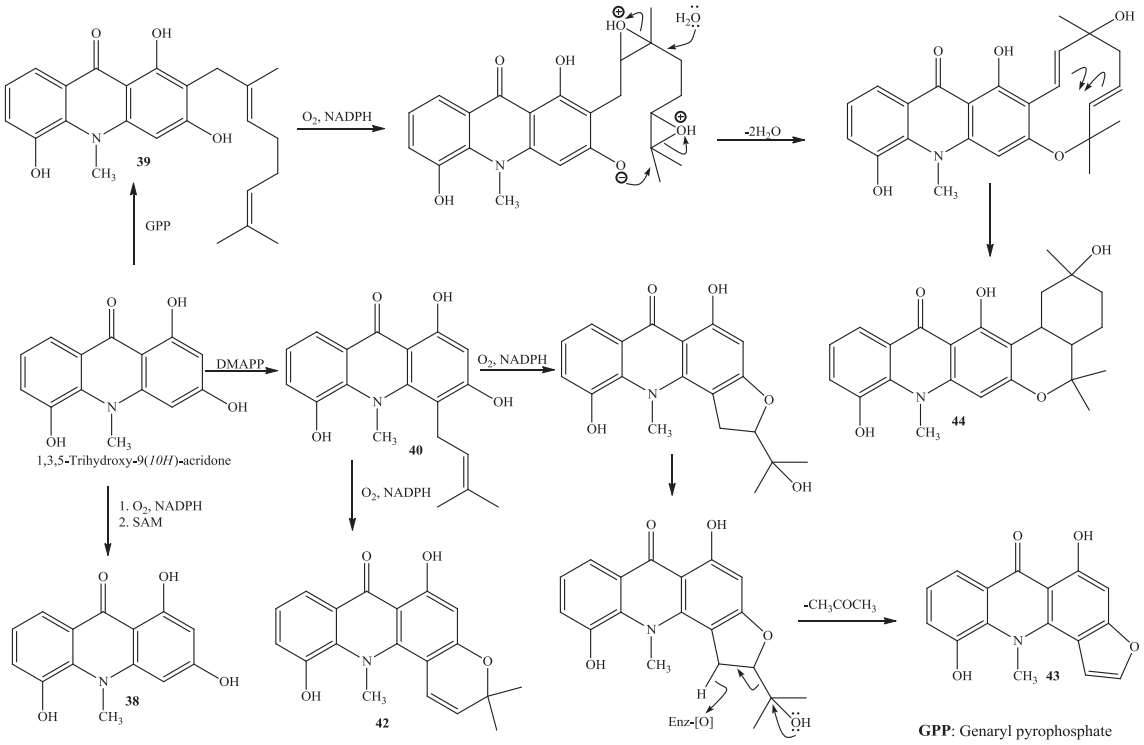

Fig. 3b. Pausible biosynthetic schemes for compounds **38–39** and **40–44.**

4.2. Quantitative analyses

Besides the studies on phytochemistry, structure elucidation, or with biological evaluation for *Paramignya* species, it may be mentioned here that only plant *P. trimera* was specialized in the quantitative analyses. Until now, there had five research articles from the work of Nguyen et al. [14–18], which involved the studies on phytochemicals (total phenolic content (TPC) total flavonoid content (TFC), saponin content (SC), saponin extraction efficiency (SEE), proanthocyanidins, and antioxidant capacity (ABTS (2,2′-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid) radical scavenging capacity (ARSC), DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) radical scavenging capacity (DRSC), cupric ion reducing antioxidant (CUPRAC), and ferric reducing antioxidant power (FRAP)), together with efficacious evaluations of various solvents and extraction methods, extraction optimized parameters, and different drying methods, and quantitative HPLC analysis [14–18].

With regards to solvents and extraction methods, studying on effects of the various solvents (water, acetonitrile, methanol, ethyl acetate, and hexane) and three extraction methods (conventional (CE), ultrasound-assisted (UAE), and microwave-assisted (MAE)) concerned about the extraction processed for *P. trimera* root [18]. The same amounts of dried sample (0.2 g) were possessed the first with selected solvents for 20 min and 20 °C and then using various methods for the second stage at 60 min. As far as the paper reported, the general observation of the results suggested that methanol and MAE have taken good advances in the yield extraction (14.39 g dried extract for MAE and methanol/100 g dried sample, 12.02 g for CE and 10.93 g for UAE), TPC (33.36 mg gallic acid equivalents for methanol/g dried

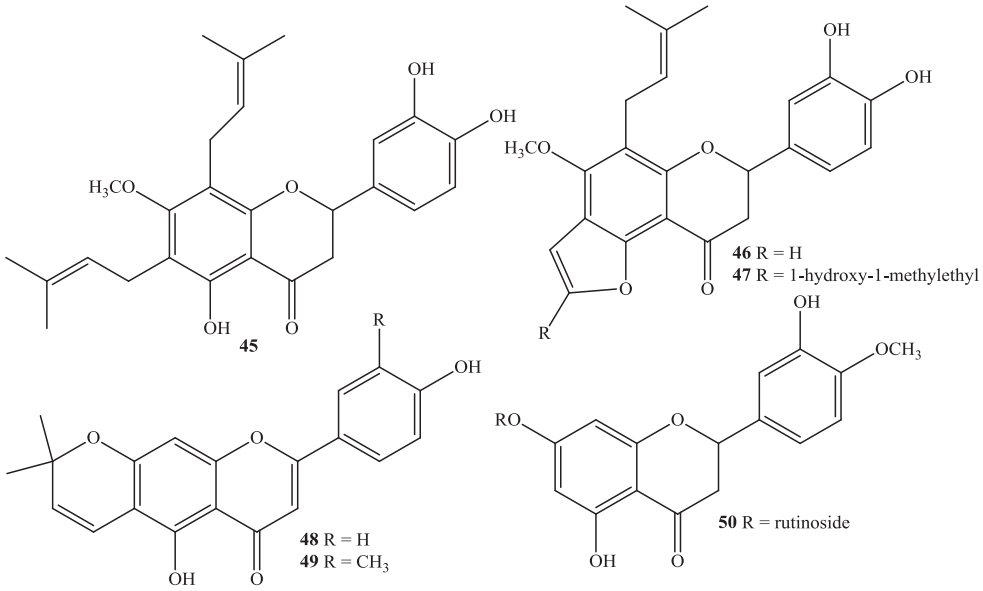

Fig. 4. Flavanones, flavones, and flavanone glycoside (**45–50**) from genus *Paramygnia.*

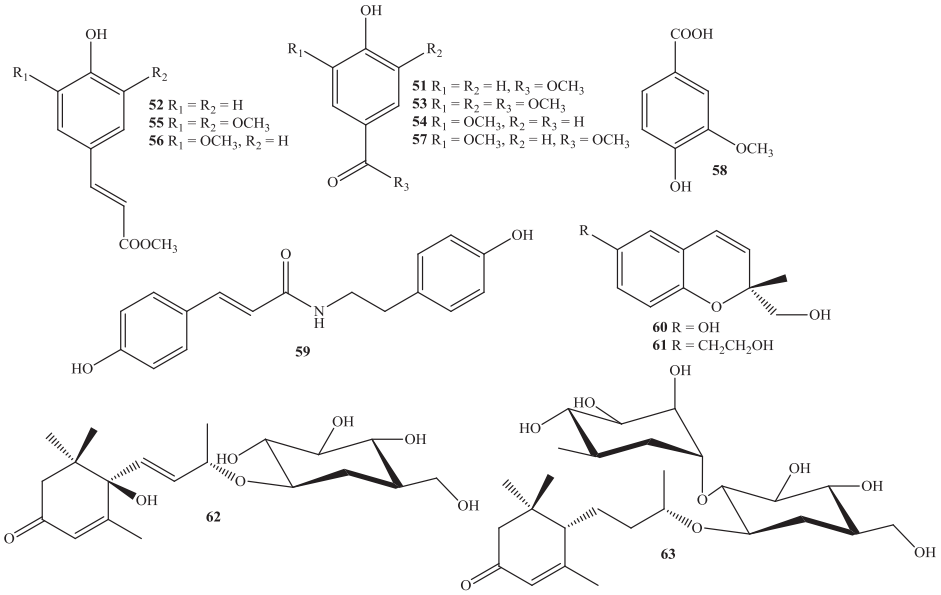

Fig. 5. Phenols, chromenes, and megastigmane glycosides (**52–63**) from genus *Paramygnia*.

sample, 25.06 mg for water and 22.33 mg for acetonitrile, together with 42.25 mg for MAE, 39.86 mg for EC, and 37.91 mg for UAE), TFC (14.11 mg rutin for methanol/g dried sample to compare with 12.00 mg for acetonitrile, 3.76 mg for hexane, 2.72 for water, and 2.27 mg for ethyl acetate, further no significant differences were for three extraction methods with range from 13.63 to 15.74 mg rutin for methanol/g dried sample), proanthocyanidin content (MAE, CE and UAE methods did not show significant values with 5.66, 5.51 and 5.54 mg catechin equivalents/g dried sample respectively, so far ethyl acetate could be the best choice with 5.28 mg and following by using solvents methanol (5.00 mg), acetonitrile (3.92 mg), water (2.99 mg) and hexane (1.77 mg)), SC (414.49 mg escin equivalents for methanol/g dried sample, 221.85, 155.30, 141.31, and 114.3 mg for ethyl acetate, water, hexane, and acetonitrile respectively, whereas three extraction methods were 500.18, 401.29, and 321.76 mg for MAE, CE, and UAE respectively), ARSC (the highest contents 174.31 mg and 171.42 mg trolox equivalents for methanol and water respectively/g dried sample, three extraction ways was found 196.72 mg for CE > 162.62 mg for UAE > 91.08 mg for MAE), DRSC (66.99 mg trolox equivalents for methanol/g dried sample > 35.59 mg for acetonitrile > 29.81 mg for ethyl acetate > 26.82 mg for water > 0.43 mg for hexane, along with 73.17, 71.66, and 66.72 mg were for CE, MAE, UAE respectively), CUPRAC (18.72 mg trolox equivalents for methanol/g dried sample was found significantly higher than remainder solvents trialed, among three extractions MAE possessed the highest with 21.61 mg), and FRAP (the highest value conducted by methanol with 71.82 mg trolox equivalents/g dried sample and the lowest rank belongs to hexane with 7.12 mg, while 88.98 mg for MAE generated over 80.61 mg for UAE and 79.80 mg for CE).

Obviously, microwave-assisted extraction (MAE) method and methanol solvent were consistent with *P. trimera* root. Continued surveys for this plant, using Box-Behnken Design-Response Surface Methodology (RMS) to optimize the MAE conditions (based on the changes of three main variables methanol concentration (X_1, %), extraction time (X_2, min), ratio of solvent to sample (X_3, mL/g)) for SC, SEE, ARSC, DRSC, CUPRAC, and FRAP [16]. In terms of SC and SEE, the highest SC (520.5 mg escin equivalents/g dried sample) and SEE (62.6%) were obtained at X_1 = 100%, X_2 = 40 min, X_3 = 100 mL/g, meantime, the lowest SC (214.5 mg) and SEE (25.8%) scored at X_1 = 60%, X_2 = 40 min, X_3 = 50 mL/g. The greatest ARSC (216.2 mg trolox equivalents/g dried sample) and lowest ARSC (193.8 mg) was found at X_1 = 60%, X_2 = 60 min, X_3 = 75 mL/g and at X_1 = 100%, X_2 = 40 min, X_3 = 50 mL/g, respectively. Of CUPRAC and FRAP items, the numbers of CUPRAC and FRAP reached to maximum at 24.7 mg trolox/ g dried sample and 121.7 mg, respectively when employing the condition of saponin extraction process at X_1 = 100%, X_2 = 40 min, X_3 = 100 mL/g, whereas minimal experimental CUPRAC (17.5 mg) attained at X_1 = 60%, X_2 = 20 min, X_3 = 75 mL/g and FRAP (70.1 mg) showed at X_1 = 100%, X_2 = 40 min, X_3 = 50 mL/g.

In case of drying method, the preparation of dried sample from fresh materials was implemented with four differential methods, comprising conventional drying: drying oven-25 °C-humidity 65%, hot air drying: heating oven-100 °C-humidity 23%, vacuum drying: vacuum drying

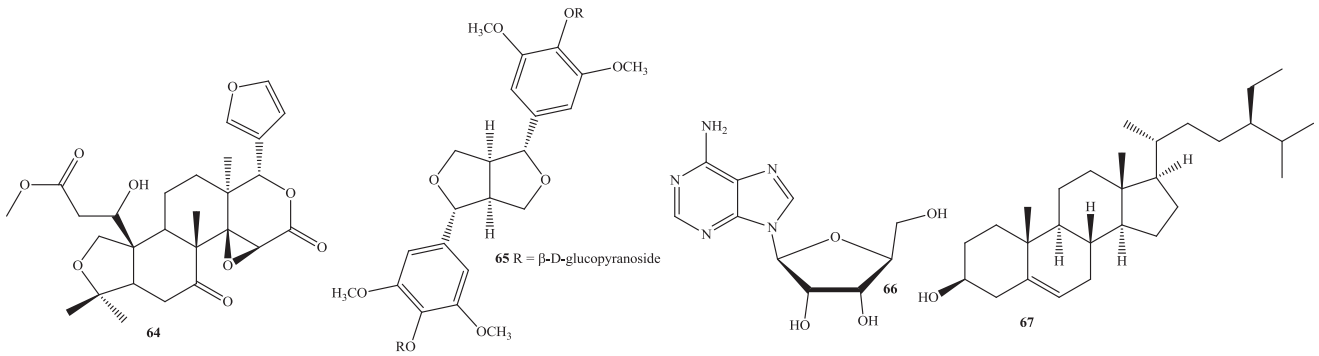

Fig. 6. Limonoid, lignin glycoside and nucleoside, and sterol (**64–67**) from genus *Paramygnia*.

oven, 60 °C-humidity 40%, microwave drying: microwave oven-400 W [15]. The same amounts of dried sample (0.2 g) was firstly extracted with methanol for 18 °C and 20 min, and second stage with microwave extraction method for 60 min and 360 W in microwave oven. Among the four drying methods tested, microwave established the beneficial conditions (drying time 0.28 h, the least energy of consumption 0.28 kWh) for TPC, TFC, proanthocyanidin, and SC, to be 11.27 mg gallic acid, 19.88 mg rutin, 3.98 mg catechin, and 267.15 escin equivalents/g dried sample, respectively. In addition, effects of drying methods on the antioxidant capacity of *P. trimera* root were found that had comparable levels with other drying methods, including 56.73 mg trolox equivalents for vacuum > 55.55 mg for convention > 55.30 mg for hot air > 53.52 mg for microwave in ARSC analysis, 51.89 mg trolox equivalents for vacuum > 47.12 mg for microwave > 41.28 mg for convention > 40.45 mg for hot air in DRSC qualification, 10.10 mg trolox equivalents for hot air > 9.73 mg for vacuum > 9.77 mg for convention > 9.96 mg for microwave in CUPAC amount, and 45.12 mg trolox equivalents for convention > 44.68 mg for hot air > 43.70 for microwave > 43.00 for vacuum in FRAP target.

Of the other adjust, dried sample (10 g) was soaked with methanol for 20 min and 21 °C, and followed by microwave extraction using microwave oven for 40 min and 360 W [17]. The results indicated that methanol extract of *P. trimera* root contained rich in SC, TPC, TFC, and proanthocyanidins (7731.05 mg escin, 238.13 mg gallic acid, 81.49 mg rutin, and 58.08 mg catechin equivalents/g dried extract, respectively), adding that, these phytochemical contents showed much more impressive than those of leaf (702.1 mg escin, 25.4 mg gallic acid, 86.3 mg rutin, and 5.6 mg catechin equivalents/g dried sample, respectively), or with bitter melon power (77.1–113.6 mg escin, 17.0–22.4 mg gallic acid, 2.8–5.8 mg rutin, 1.9–3.2 mg catechin equivalents/dried power, respectively [17]. Meantime, ARSC and DRSC indices were obtained from methanol extract of *P. trimera* root as 898.03 mg and 164.31 mg trolox equivalents/g dried sample and being significantly higher than those of ostruthin 667.35 mg and 7.52 mg, respectively, while antioxidant capacity of *P. trimera* leaf was assignable to 119.2 mg (ARSC), 28.0 mg (DRSC), 13.1 mg (CUPRAC), and 52.2 mg (FRAP) trolox equivalents/g dried sample [14].

Ostruthin **3** was identified as a major compound of *P. trimera* species and was biosynthesized from umbelliferone **10** by Orf2 in the presence of Mg^{2+} [2,29]. This one in roots and stems of medicinal plant *P. trimera* collected in Khanhhoa-Vietnam was analyzed qualitatively and quantitatively by rapid and sensitive HPLC coupled with UV detector [29]. Following by using a Versitep C18 column (4.6 × 250 nm × 5 μm), mobile phase water-acetonitril 25:75, flow rate 0.7 mL/min, detector photodiode array at λ = 340 nm, the percentage of predominant coumarin ostruthin in roots accounted for 0.050–5.091%, while 0.008–1.364% was for stems [29].

Further investigation in quantitative HPLC analysis (C18 column, 250 mm × 4.6 mm × 5 μm, mobile phase acetonitrile–water, UV detector at λ = 340 nm), eleven compounds were identified and quantified in the methanolic extract of *P. trimera* roots, including kaempferol (16.72 mg/g dried sample) > chlorogenic acid (7.72 mg) > gallic acid (2.79 mg) > rutin (2.27 mg) > *p*−coumaric acid (2.14 mg) > (−)-epicatechin (1.22 mg) > (+)-catechin (1.16 mg) > myricetin (1.03 mg) > syringic acid (0.66 mg) > quercetin (0.57 mg) > caffeic acid (0.34 mg/g) [18].

In other case of *P. trimera* roots, based on using the same HPLC procedure (C18 column HPLC, 250 mm × 4.6 mm × 5 μm, mobile phase acetonitrile–water, UV detector at λ = 340 nm), individual phytochemical compounds quercetin and kaempferol were the highest levels at 4.31 mg and 6.84 mg/g dried sample for conventional drying method, hot air drying way gave the greatest numbers of caffeic acid, syringic acid, rutin, and myricetin (0.58, 0.70, 0.66, and 1.23 mg/g dried sample, respectively), vacuum drying condition possessed the highest amounts of gallic acid, chlorogenic acid, (−)-epicatechin, and *p*-coumaric acid (1.23, 3.10, 0.43, and 0.62 mg/g dried sample, respectively), as well as final method microwave drying obtained the significant content of (+)-catechin (3.73 mg/g dried sample) [15].

5. Biological activities

5.1. Cytotoxic activities

The cytotoxic activity of chemical constituents of *Paramignya* species related to their structure and the organisms that they affect. Phan et al. [9] identified the presence of two new tirucallane derivatives, paramignyols A-B (**31**–**32**) in the stems and leaves of *P. scandens* species, which can be claimed responsible for activity against human cancer cell lines: KB (epidermoid carcinoma), SK-Mel-2 (melanoma), LU-1 (lung adenocarcinoma), and MCF-7 (breast cancer) [9]. Following by this article, the natural tirucallane paramignyol A (**31**) illustrated the significant IC_{50} values of 6.43 ± 0.17 μM for KB, 6.02 ± 0.17 μM for SK-Mel-2, 10.50 ± 0.17 μM for LU-1, 7.22 ± 0.23 μM for MCF7, whereas paramignyol B (**32**) had been shown the IC_{50} values of 5.25 ± 0.17 μM for KB, 3.55 ± 0.15 μM for SK-Mel-2, 6.48 ± 0.17 μM for LU-1, 5.98 ± 0.09 μM for MCF-7, to compare with these things of positive control ellipticine 2.07 ± 0.28, 1.09 ± 0.24, 1.75 ± 0.24, and 1.87 ± 0.20 μM, respectively.

To take notes on cytotoxic activity of isolated compounds from *P. trimera* species, four coumarins **1**–**4**, and four acridone alkaloids **38**–**39**, and **41**–**42** were subjected to test cytotoxic activity against hepatocellular carcinoma Hep-G2 cell line by using sulforhodamin B assay [12]. Two coumarins ostruthin (**3**) and its 8-methoxy derivative (**4**), along with four acridone alkaloids citrusinine-I (**38**), glycocitrine-III (**39**), oriciacridon (**41**), and 5-hydroxynoracronycin (**42**) established the low IC_{50} values of 30.53 ± 0.61, 62.90 ± 2.58, 51.40 ± 1.19, 31.66 ± 0.46, 52.50 ± 5.25, and 32.81 ± 0.87 μM/mL respectively, while neither compound **1** nor **2** was inactive, when compared with significant IC_{50} value of 0.051 ± 0.007 μM/mL for positive control camptothecin.

In accordance with above mention, major component ostruthin (**3**) was also reported the insignificant IC_{50} values of > 50 μM/mL for Hep-G2 (hepatocellular carcinoma cell), 55.78 μM/mL for HTC-116 (colon cancer cell), 48.74 μM/mL for MDA-MB-231 (breast adenocarcinoma cell), 57.7 μM/mL for OVCAR-8 (human ovary carcinoma cell), and the moderate IC_{50} values of 18.4 μM/mL for Hela (human epithelial cervial carcinoma cell), meanwhile, the significant IC_{50} values of positive control adriamycin were assignable to be 1.50, 0.50, 1.82, 1.21, and 1.48 μM/mL, respectively [5].

Finally, for determination cytoprotective effects by using MTT (tetrazolium salt, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) in glutamate-induced toxicity in mouse hippocampal HT22 cell experiment, five coumarins **3**–**4**, **8b**, **14,** and **16** as well as chromene **61** revealed not to have any significant protections [7].

5.2. Antiinflammatory

Neurodegenerative diseases such as Alzheimer, Pakinson, or Hungtington have been increasing in recent decades, which related to the activity of pro-inflammatory mediators, such as nitric oxide (NO) and protagladin E2 (PGE_2) in microglia [30]. Antiinflammatory drugs from medicinal plants have received attention of researchers and scientists. Recently, the latest report of antiinflammatory effects of phytochemical constituents from *P. trimera* species was performed in the work of Anh et al. [7]. Herein, compounds **3**–**4**, **8b**, **14, 16,** and **61** were applied for inhibiting inflammatory products NO and PGE_2, and inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) protein expressions in lipopolysaccharide (LPS)-stimulated BV2 microglia cells. According to this paper, the selective concentrations were ranging from 5 to 40 μM of tested compounds of which did not show significant cytotoxic for the tested cells, BV2 microglia cells were firstly pretreated with those concentrations of tested compounds for 3 h and

then stimulated with LPS (1 μg/mL) for 18 h. Generally, chromene **61**, which a compound was considered inactive with the IC_{50} value of > 80 μM for reducing NO and PGE_2 productions. In other case, coumarin ostruthin (**3**) and its 8-methoxy derivative (**4**) showed the highest capacity, with the IC_{50} values of 9.8 and 12.3 μM for decreasing the level of NO concentration, and 9.4 and 13.4 μM for reducing the level of PGE_2, respectively. While three remainders **8b**, **14**, and **16** indicated the moderate IC_{50} values of 36.8, 36.5, and 46.8 μM for NO, together with 34.7, 32.1, and 52.8 μM for PGE_2. Furthermore, by Western blot analysis (pretreated with the compounds for 3 h and then stimulated for 24 h with LPS (1 μg/mL), compounds **3–4** also possessed to inhibit pro-inflammatory mediators through suppressing iNOS and COX-2 protein expression in LPS-stimulated BV2 cells [7].

In the other model, the continuous antiinflammatory improvement of isolated compounds from *Paramignya* species, [8]) implemented with five unusual tirucallane saponins paramignyosides A-E (**33–37**) on pro-inflammatory cytokines throughout measuring the production of interleukin (IL)-12 p40, IL-6, and tumor necrosis factor-α (TNF-α) in LPS-stimulated bone marrow-derived dendritic cells (BMDCs) [8]. Notably, all tested compounds established insignificant inhibition, with the IC_{50} value > 100 μM for IL-6 and TNF-α in LPS stimulated BMDCs, but both of them showed selective effects on the modulation of interleukin (IL)-12 p40. Deeply, the most potential effect was assignable to paramignyoside C (**35**) (the IC_{50} value of 5.03 ± 0.19 μM), which was estimated equation with positive control SB203580 (the IC_{50} value of 5.00 ± 0.16 μM), the remainders were paramignyoside D (**36**) (19.57 ± 0.97 μM) > paramignyoside E (**37**) (14.09 ± 0.65 μM) > paramignyoside B (**34**) (29.15 ± 1.33 μM) > paramignyoside A (**33**) (48.68 ± 1.89 μM).

5.3. Alpha-glucosidase inhibitory activities

As can be seen, alpha-glucosidase inhibitors were used in the treatment of patients with diabetes mellitus type 2 because these inhibitors reduced the impact of carbohydrates on blood sugar. Pseudotetrasaccharide acarbose, with commercial brand name Precose**,** has been employing as alpha-glucosidase inhibitor for managing diabetes mellitus type 2. Naturally occurring compounds **3–4**, **8a**, **9–13**, **38–40**, **42–44**, **58**, and **60** were subjected to evaluate α-glucosidase inhibitory activity when acarbose was used as positive control [2]. The result showed that all compounds of test displayed the significant IC_{50} values (the lowest IC_{50} value of 106.9 μM for paratrimerin E (**8a)**, the highest IC_{50} value of 14.6 μM for 5-hydroxynoracronycin (**42**) and paratrimerin C (**43**), and more active than positive control acarbose (the IC_{50} value of 214.5 μM). Regarding to highlight structure activity relationship, authors suggested that cyclization of a prenyl or a geranyl moiety being reasonable for reducing the inhibition activity, for instance ostruthin (**3**) (the IC_{50} value of 17.1 μM) > paratrimerin F (**9**) (31.7 μM) > pandanusin A (**13**) (95.3 μM), oriciacridone E (**40**) (45.5 μM) > paratrimerin C (**43**) (70.0 μM), 5-hydroxynoracronycin (**42**) (63.9 μM) > daedalin A (**60**) (14.6 μM), as well as the methoxy group causes for the insignificant IC_{50} values **3** (17.1 μM) > > ninhvanin (**4**) (84.6 μM), umbelliferone (**10**) (34.4 μM) > scopoletin (**11**) (69.0 μM).

5.4. Biological activities of extracts

The first biological evaluation was performed in screening anti-tumor activity of Kuala Lumpur *P. lobata* stems and leaves [28]. Both of them had been shown to have the ED_{50} value of 100 μg/ml for KB cell line. Remarkably, the same result had been found in various species of different genus in the Rutaceae family such as *Acronychia porter*, *Burkillanthus malacensis*, *Euodia roxburghiana*, *Glycosmis calcicola*, *Merope augulata*, *Tetractomia roxburghii*, *Triphasia trifolia*, and *Zanthoxylum myriacanthum* species [28].

The medicinal plant *Paramignya trimera* (Oliv.) Guillaum, local name Xao tam phan, has been known as marvellous plant in Vietnam [1,5]. Studying on acute toxicity for methanol extract of *P. trimera* roots, Khoi et al. [5] proposed that LD_0 (least dose did not kill any animal in test) of was less than 329.0 g/kg weight by oral administrations and not to determine LD_{50} (median lethal dose) [5].

As above result, apart from the result in describing cytotoxic assay *in vitro* against five cancer Hep-G2, HTC-116, MDA-MB-231, OVCAR-8 and Hela cell lines of major component ostruthin **3**, methanol extracts and partitioned *n*-hexane and butanol fractions of *P. trimera* roots were also tested in which *n*-hexane fraction indicated the moderate IC_{50} value of 39.61 μg/mL for Hep-G2, meanwhile, kinds of butanol and methanol extracts showed insignificant or no toxicity to all five cancer cell lines [5].

Numerous saponins, phenolics, flavonoids, and anthocyanidins advocated that parts of *P. trimera* species could be have cancer chemopreventive property. Experimental evidences, twelve cancer cell lines, which MiaPaCa2 (pancreas), HT29 (colon), A2780 (ovarian), H460 (lung), A431 (skin), Du145 (prostate), BE2-C (neuroblastoma), MCF-7 (breast), MCF-10A (normal breast), and U87, SJ-G2, SMA (glioblastoma) were treated with methanol extract of *P. trimera* root at 100 μg/mL, in which the result was observed with the GI_{50} values (the concentration that inhibited cell growth by 50%) ranging from 15 to 32 μg/mL [17]. Particularly, A2780 gave the GI_{50} values of only 15 μg/mL, followed by MiaPaCa2, Du145, MCF-7, and SMA cells (23 μg/mL), and SJ-G2 (24 μg/mL). Furthermore, within the concentration at 100 μg/mL, growth inhibition on above cancer cell lines of methanol extract of *P. trimera* leaves was identical with roots, for instances, the lowest GI_{50} value was observed for A2780 (31 μg/mL), followed by SMA (40 μg/mL), and HT29 (47 μg/mL), whereas the highest GI_{50} value was determined for SJ-G2 (81 μg/mL) [14]. Notably, these values of both roots and leaves on all cancer cell lines were being lower than those of extracts from *E. robusta* leaves (77–183 μg/mL) and *S. spinescens* (28–110 μg/mL), except for MCF-7 (12 μg/mL) and SJ-G2 20 (μg/mL) [14,17]. In addition, methanol extract of *P. trimera* roots with various concentrations (200–12.5 μg/mL), and its four HPLC fractions F_1-F_4 (F_1: 36.5–37.0 min, F_2: 39.9–40.5 min, F_3: 41.35–41.85 min, and F_4: 42.85–43.35 min) at 50 μg/mL, methanol extract of *P. trimera* leaves at 200 μg/mL, and ostruthin (**3**) at 20 μg/mL were further subjected to test viability of pancreatic cancer (MiaPaCa-2) and normal human pancreatic ductal epithelial (HPDE) cells [14,17]. The results suggested that the concentrations of 200, 100, and 50–12.5 μg/mL of roots extract, 50 μg/mL of four fractions, 200 μg/mL of leaf extract, and 20 μg/mL of ostruthin gave viability of MiaPaCa2 to be 4.22, 5.83, 86.38–97.93, 96.68–97.92, 6.6, and 86.34%, respectively, while these things in the publications such as chemotherapy medication gemcitabine (50 nM), or with other plants Quillaja bark extract (200 μg/mL), *S. paniculatum* extract (200 and 100 μg/mL), papaya leaves water extract (100 μg/mL), *E. robusta* leaves extract (100 μg/mL) were 27.22, 4.20, 23, 90, 96, and 15% respectively [14,17]. Regarding viability of HPDE cells, *P. trimera* roots methanol extract had comparable with leaf extract at 100 μg/mL, to be 2.4 and 2.2%, respectively, but being much lower than those of four fractions F_1-F_4 (55.69–85.62%, 50 μg/mL) and *S. paniculatum* extract (58%, 100 μg/mL). Further research also pointed out viability of other human pancreatic cancer BxPc3 cell were 2.3, 20.5–98.9, 15.2, 60.9, and 2.2% for the concentrations at 200 μg/mL, and 100–12.5 μg/mL of *P. trimera* leaves extract, 50 nM of gemicitabline, 20 μg/mL of ostruthin, 200 μg/mL of Quillaja extract, respectively, whereas the results had received for CFPAC1 cell to be 7.9, 16.4–71.2, 16.0, 81.4, and 7.9%, respectively. In conclusion, four HPLC fractions F_1-F_4 indicated weak activity on both MiaPaCa2 and HPDE cells, meanwhile root and leaf methanol extracts showed great influences due to the presences of individual contents phenolics, saponins, flavonoids, and proanthocyanidins [14–18].

Liver can be seen as vital organ in which takes place of important metabolism endotoxins, exotoxins, responsible for the breakdown bilirubin via glucuronidation and excretion of many waste products. Paracetamol and carbontetrachloride CCl_4 are widely applied for

inducing experimental hepatotoxicity in *in vivo* experiments. In order to further establish the pharmacological properties of *Paramignya* species, the extracts of *P. trimera* roots were then studied on hepatoprotective activity against paracetamol induced hepatic damage in rats. According to the latest paper in the work of Cuong et al. [31], the boiled aqueous extract at the oral dose of 10 g/kg weight has reduced serum AST (aspartate transaminase) and ALT (alanine aminotransferase) concentrations, decreased liver histopathological injury by paracetamol (only single dose 400 mg/kg, oral) in *BALB/c* rats after 9 days treatment, whereas the methanol extract exhibited high effect which was similar to those of the positive control silymarin at the dose of 50 mg/kg weight daily [31]. However, by using the same model of paracetamol (400 mg/kg) induced hepatic damage in *Swiss albino* rats, Khoi et al. [5] further suggested that methanol extract at doses 10 and 20 g/kg did not show any change the levels of AST, ALT, or bilirubin after 8 days experiment.

The latest term of biological evaluation for extract was implemented by Dang et al. [2], methanol extract of Vietnamese *P. trimera* roots also exhibited significant alpha-glucosidase inhibitory activity with an IC_{50} value of 36.6 μg/mL, when compared with some Vietnamese plant roots such as *Antidesma ghaesembilla* Gaertn. (IC_{50} value of 145.8 μg/mL), *Lasia spinosa* (L.) Thw. (IC_{50} value of 79.8 μg/mL), and *Dendrobium crumenatum* Sw. (IC_{50} value of 55.5 μg/mL) [2,32].

6. Conclusion

In conclusion, the phytochemical investigations on the only five *Paramygnia* species led to the isolations and structure elucidations that were identified as a wide range of major coumarin and coumarins, tirucallane and tirucallane saponins, acridone alkaloids, and flavonoids, together with minor chromene, sesquiterpene glycoside, limonoid, lignin, and sterol. Coumarin ostrtuthin (**3**) and its 8-methoxy derivative (**4**) were most frequently found medicinal plant *P. trimera* and was the most investigated in both qualitative and quantitative researches. Isolated compounds and extracts also possessed the experiments of cytotoxicity, antioxidant, antiinflammatory, anticancer, alpha-glucoside inhibitory, and liver prevention activity. It therefore concludes that genus *Paramignya* was a rich source of various biological active products for application in the medicinal and pharmaceutical fields.

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Conflict of interest

The authors declare no conflict of interest.

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