Arabian Journal of Chemistry (2021) **14**, 103346

King Saud University

Arabian Journal of Chemistry

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REVIEW ARTICLE

Phytochemical and pharmacological studies on the genus *Arcangelisia*: A mini review

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Received 8 May 2021; accepted 17 July 2021
Available online 24 July 2021

KEYWORDS

Arcangelisia;
Alkaloid;
Natural medicinal chemistry;
Pharmacological activity;
Folk medicine;
^{13}C NMR data

Abstract Only 3 plants in the genus *Arcangelisia*, belonging to the family Menispermaceae, are used as folk medicines for the treatment of various diseases by local residents. Alkaloids are main compounds of berberine analogues found in this genus and they demonstrate a wide range of pharmacological activities. The aim of this review is to compile the phytochemical progress including all the compounds isolated from this genus, their pharmacological activities together with the ^{13}C NMR spectral data of the main bioactive components, which will bring more attention of other researchers to this genus for further study to find new active compounds.

Contents

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https://doi.org/10.1016/j.arabjc.2021.103346

1. Introduction

The genus *Arcangelisia* (*A.*), which belongs to the family Menispermaceae, comprises 3 species (*A. gusanlung*, *A. flava* and *A. tympanopoda*) distributed in southeast Asia and south to Irian island (Zhang et al., 1995; Suzuki et al., 2011). These plants possess various medicinal properties and have wide-ranging applications in traditional and modern medicine. Among them, *A. gusanlung* H. S. Lo is the sole species of this genus found in the south of China including the provinces of Guangdong, Guangxi, and Hainan (Chinese Pharmacopoeia, 1977). As an important part of traditional Chinese medicine, it has a long history in the Dai and Li (Chinese national minorities) nationalities of China, and the Dai people in China use it to treat acute jaundice hepatitis (Chinese Pharmacopoeia, 1977; Peng et al., 2008). As a folk medicine, it has the functions of clearing away internal heat and detoxification, removing wind and relieving itching, promoting gangrene and reducing jaundice (Zhang et al., 1995; Chinese Pharmacopoeia, 1977; Hu et al., 2013; Li et al., 2019; Yu et al., 2014). However, the Li nationality has not its own character but the national language in history, the information of the herbs was transferred orally, which can lead to misinformation and unfounded rumor easily. To a certain extent, the inheritance and development of Li medicine are influenced (Hu et al., 2013). Another species, *A. flava* (L.) Merr. has been used as one of folk medicines (Jamu) in Indonesia. The medicinal plant is known locally as '*Akar kuning*', whose name derived from the yellow sap. *Fibraurea tinctoria* Lour. and *Cosinium fenestratum* Colebr. are also called '*Akar kuning*' in Indonesia, and they are distributed widely throughout Southeast Asia (Suzuki et al., 2011; Verpoorte et al., 1982; Wahyudi et al., 2016). It has been traditionally used by local people for the treatment of several diseases, such as malaria, dysentery, fever, abortion, the healing of hepatitis, indigestion and as atonic agent (Subeki et al., 2005; Niwat et al., 2005; Maryani et al., 2013; Ramadan et al., 2018; Julie et al., 2007). In addition, *A. flava* was used as an important component of folk medicines for the treatment of jaundice, smallpox, sore eyes, aphtha, water flea and as a stomachic and antihelminthic agent (Subeki et al., 2005; Setyowati et al., 2014; Kiss et al., 1988; Kaharap et al., 2016; Kusuma et al., 2011). *A. tympanopoda* (Lauberb. and K. Schum.) Diels., which is found only in New Guinea. *A. flava* and *A. tympanopoda* are distinguished by the different sizes of the fruits, the latter has larger fruits than the former (Suzuki et al., 2011; Verpoorte et al., 1982). Traditional uses of the genus *A.* are shown in Table 1.

In this review, we compile the phytochemical progress including all the compounds isolated from this genus, their pharmacological activities together with the ^{13}C NMR spectral data of the main biologically active compounds.

Table 1 Traditional uses of the genus *A.*

Plants	Traditional uses	Refs.
A. gusanlung	Acute jaundice hepatitis, clearing away internal heat and detoxification, removing wind and relieving itching, promoting gangrene and reducing jaundice	Peng et al., 2008; Zhang et al., 1995; Chinese Pharmacopoeia, 1977; Hu et al., 2013; Li et al., 2019; Yu et al., 2014
A. flava	Malaria, dysentery, fever, abortion, the healing of hepatitis, indigestion and as atonic agent, jaundice, smallpox , sore eyes, aphtha, water flea and as a stomachic and antihelminthic agent	Subeki et al., 2005; Niwat et al., 2005; Maryani et al., 2013; Ramadan et al., 2018; Julie et al., 2007; Subeki et al., 2005; Setyowati et al., 2014; Kiss et al., 1988; Kaharap et al., 2016; Kusuma et al., 2011

Fig. 1 The pictures of the two plants. The left is *A. gusanlung* and the right is *A. flava*.

2. Morphological features

Since they share morphological similarity, botanical classification is required using different parts such as leaf, stem, flower and fruit. *A. gusanlung* is a woody rattan and reaches a length of about 30 m after several years of growth. Its root is cylindrical, twisted, occasionally branched, 0.5–3 cm in diameter. The surface is brownish yellow with obvious longitudinal wrinkles, lateral lenticels, root scars. The cork is easy to fall off. The cross section is hard, bright yellow, with chrysanthemum-like texture and cracks. Smell slightly and very bitter. The stem is cylindrical, with a few curved, up to 3 cm in diameter or more progenitor. The surface is dark grayish yellow to grayish green, the section emblem is raised, the section is bright yellow, and the center is pith. The leaves are ovoid or oblong, 11–23 cm long and 5.5–14 cm wide. Dark gray-green to dark yellow–brown, apex shortly pointed, blunt at base, entire, glabrous on both sides, 3–5 veins away from the base, veins protruding on both sides, the underside is obvious; petiole is 5–14 cm long, both ends are swollen, shield-shaped near base. Leathery and brittle. The smell and taste are weak. Inflorescence grow on old stem and peduncle is stout, 0.7–1.5 cm long, 0.5–0.7 cm in diameter, fruit subglobose, slightly flat, 2.5–3 cm wide. Yellow at maturity, black at last, mesocarp fleshy, nucleus nearly bony, oblate, rusty long hairy, without any protuberance. The roots and stems are preferably thick and yellow on the cross sections. (https://baike.sogou.com/v133052.htm?fromTitle = *Arcangelisia gusanlung*).

A. flava is a vigorous, climbing shrub producing twining stems up to 20 m long and 5 cm in diameter near their base (http://tropical.theferns.info/viewtropical.php?id = *Arcangelisia flava*). Plant glabrous apart from leaf-domatia. Leaves: inflorescences axillary or cauliflorous, paniculate, slender, 10–50 cm, lateral branches spicate or subspicate, 1–5 cm. Leaves apparently indistinguishable from those of *A. flava*, except for stomata. The difference between the two forms of infructescence is remarkable (http://portal.cybertaxonomy.org/flora-malesiana/cdm_dataportal/taxon/609d549e-cca5-4a6d-aa5a-4ffecb0d4005).

A. flava and *A. tympanopoda* are distinguished by the different sizes of the fruits, the latter has larger fruits than the former (Suzuki et al., 2011; Verpoorte et al., 1982). The pictures of two plants are shown in Fig. 1.

3. Phytochemistry

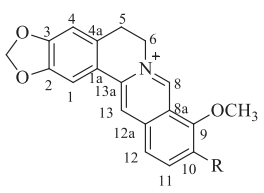
To the best of our knowledge, the first phytochemical investigation on the genus *A.* can be traced back to 1919. In 1919, Wells (Verpoorte et al., 1982) reported the presence of berberine (**1**) in the stem of *A. flava*. Garcia (Garcia et al., 1970) *et al* isolated berberine (**1**), palmatine (**4**) and jatrorrhizine (**3**) in the stem and berberine (**1**) and jatrorrhizine (**3**) in the roots of *A.* gusanlung for the first time in 1970. Up to the end of 2020, the total number of identified secondary metabolites from the genus *A.* amounts to 64, including alkaloids, phenylpropanoids, terpenoids, glycosides and some other components. The chemical structures of these compounds are shown in Figs. 2–6. Their names and the corresponding plant sources are compiled in Table 2.

3.1. Alkaloids

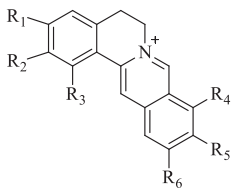
Previous chemical investigations have indicated that alkaloids are the most frequently occurring constituents in the genus *A.*. Thirty-two alkaloids, **1~32**, have been isolated and elucidated from the genus *A.*, most of which were isolated from *A. gusanlung*. Amongst, most alkaloids are protoberberine alkaloids, which belong to the type of isoquinoline alkaloids.

3.2. Phenylpropanoids

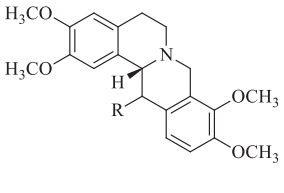
Up to date, twelve phenylpropanoids have been found in this genus. Among them, phenylpropanamides are the characteristic compounds, which are composed of a phenylpropionic acid structure and a phenylethylenediamine structure. Four phenylpropanamides were named as *N-cis*-feruloyltyramine (**33**), *N-trans*-feruloyltyramine (**34**), *N-trans*-coumaroyltyramine (**35**) and *N-trans*-feruloyl-3-methoxytyramine (**36**). Besides, eight



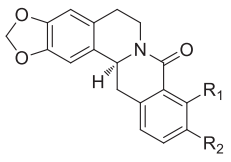
1 R=OCH_3
2 R=OH



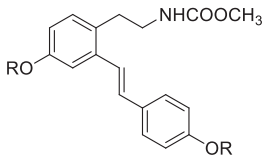
3 R_1=OH R_2=OCH_3 R_3=H R_4=OCH_3 R_5=OCH_3 R_6=H
4 R_1=OCH_3 R_2=OCH_3 R_3=H R_4=OCH_3 R_5=OCH_3 R_6=H
5 R_1=OCH_3 R_2=OCH_3 R_3=OH R_4=H R_5=OCH_3 R_6=OCH_3
6 R_1=OCH_3 R_2=OH R_3=H R_4=OCH_3 R_5=OCH_3 R_6=H
7 R_1=OCH_3 R_2=OCH_3 R_3=H R_4=OCH_3 R_5=OH R_6=H



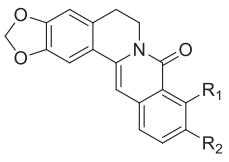
8 R=CH_3
9 R=H



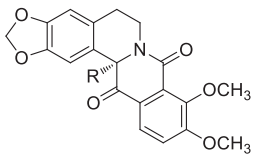
10 R_1=OH R_2=OCH_3
11 R_1=$OCOCH_3$ R_2=OCH_3
12 R_1=OCH_3 R_2=OCH_3
13 R_1=H R_2=H



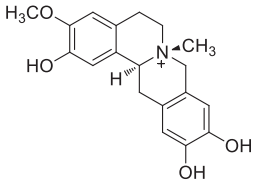
14 R=H
15 R=$COCH_3$
16 R=CH_3



17 R_1=OCH_3 R_2=OCH_3
18 R_1=OCH_3 R_2=OH
19 R_1=OCH_3 R_2=$OCOCH_3$
20 R_1=OH R_2=OCH_3



21 R_1=OH
22 R_2=OCH_3



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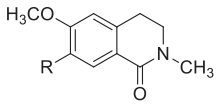
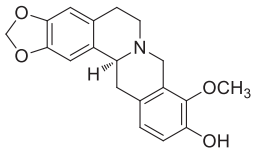


24 R=OCH_3
25 R=OH



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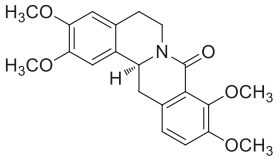
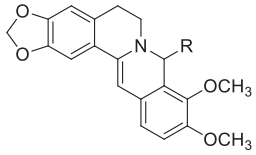
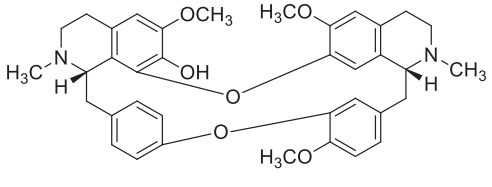


27



28 R=H
29 R=OH



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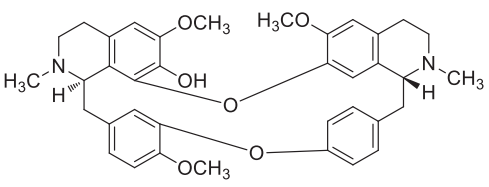

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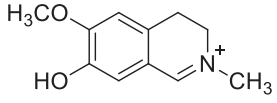

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Fig. 2 The chemical structures of the isolated alkaloids.

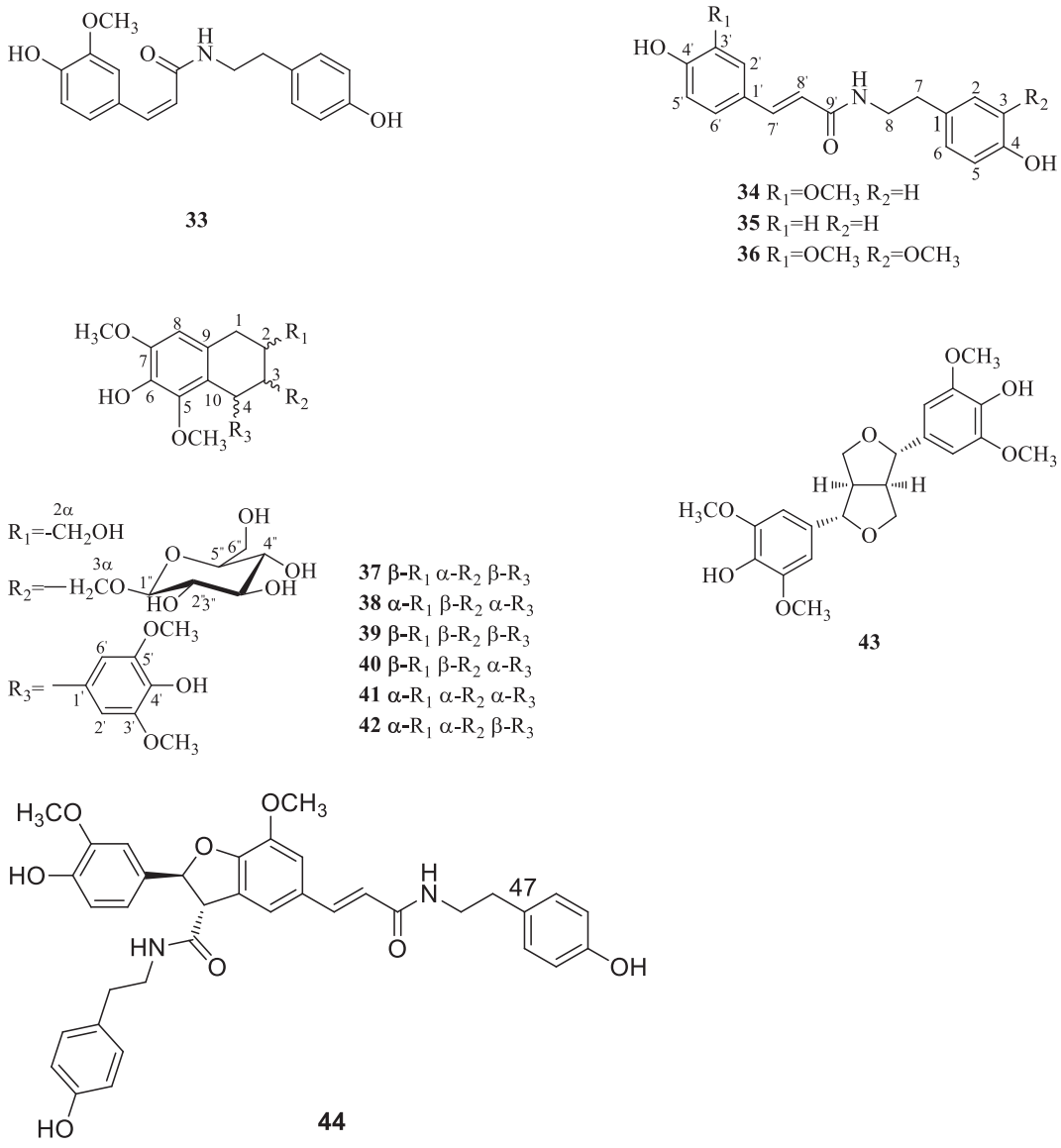

Fig. 3 The chemical structures of phenylpropanoids.

lignans were also obtained from this genus. Take compound **44** as an example, it has a lignan linked to two phenylethylenediamine homologues.

3.3. Terpenoids

One sesquiterpenoid, aduncin (**45**) and ten furanoditerpenes (**46~55**) were identified from the genus *A.*. These furanoditerpenes are bicyclic diterpenoids, whose molecular skeletons consist of four isoprene units and most of these diterpenes contain ester ring or oxygen ring, which is also a very interesting phenomenon found in this genus.

3.4. Glycosides

Interestingly, four megastigane glycosides (**56~59**) have been found in the genus *A.*. Such compounds are rare in nature, whose aglycones are isomers that appear in pairs.

3.5. Other compounds

Simple phenolic compounds were found in this genus, and sterols and anthraquinones were also found.

3.6. *^{13}C NMR spectral data of some active compounds isolated from the genus A.*

^{13}C NMR spectroscopy is used to determine the type of carbon atoms in the molecules. Since ^{13}C NMR chemical shifts are widely distributed in the spectrum, there is little signal overlap between carbon atoms except for the chemical and/or magnetic equivalences. ^{13}C NMR signals are more easily discriminated than ^{1}H NMR signals because they generally appear as singlets through the use of proton decoupling. In addition, ^{13}C NMR chemical shifts are quite sensitive to structural features, although structurally similar compounds may have similar chemical shifts.

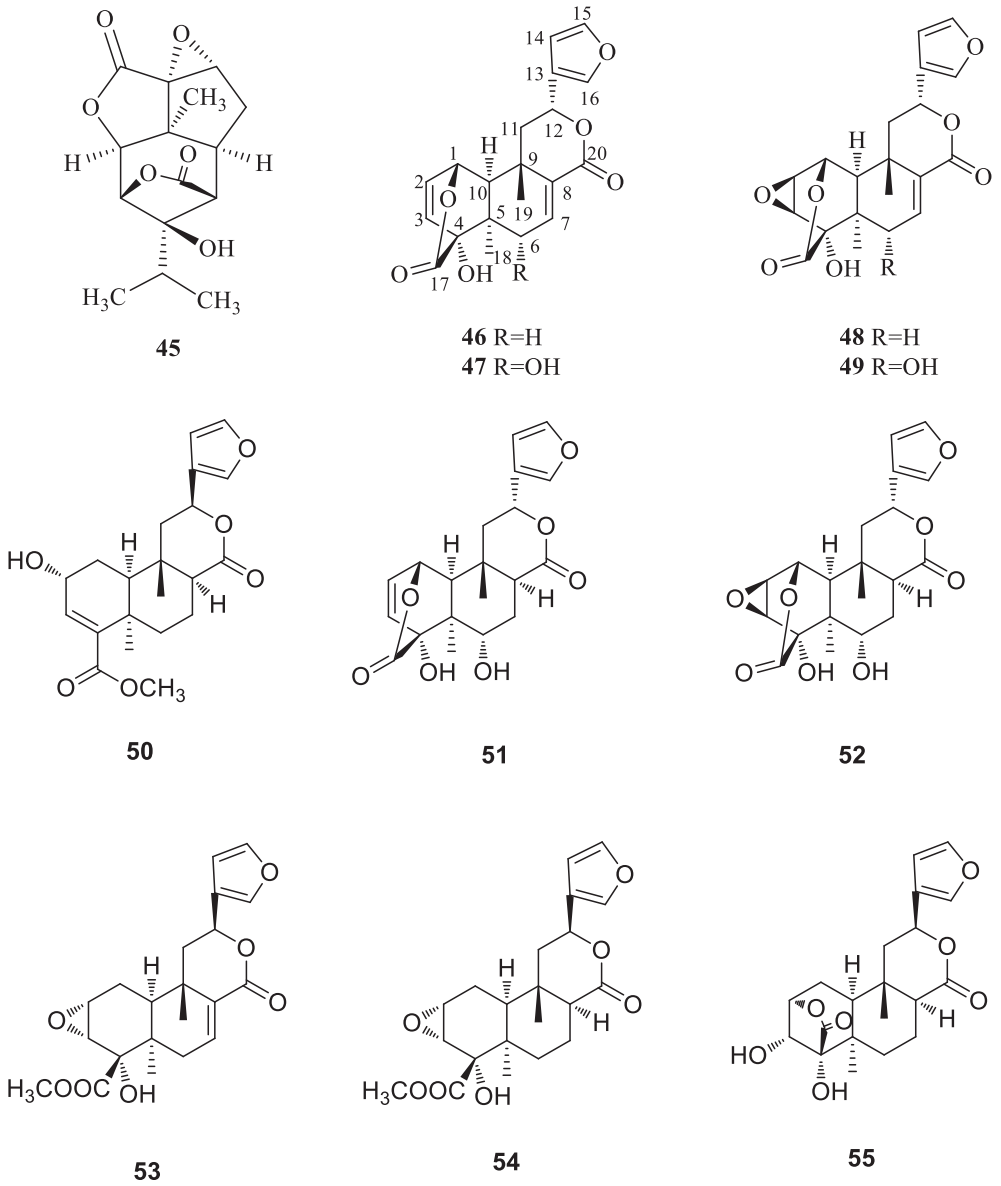

Fig. 4 The chemical structures of terpenoids.

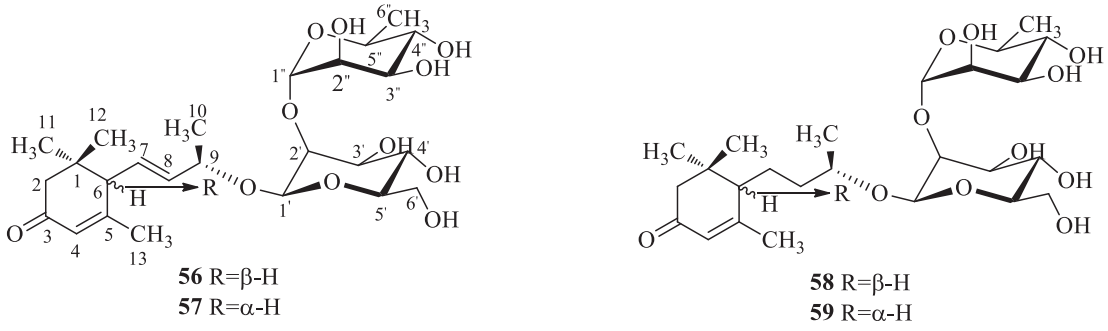

Fig. 5 The chemical structures of glycosides.

In order to help the chemical workers find the ^{13}C NMR data of the isolated compounds more quickly, we specially summarized the ^{13}C NMR spectral data of the main biologically active compounds from the genus *A*. (Tables 3–8).

First of all, we take berberine (**1**) as an example to analyze the carbon spectral data of alkaloids. Its ^{13}C NMR spectrum gives twenty carbon signals, including fifteen olefinic carbon signals at δ_C 108.4 (C-4), 105.4 (C-1), 120.2 (C-13), 120.4 (C-

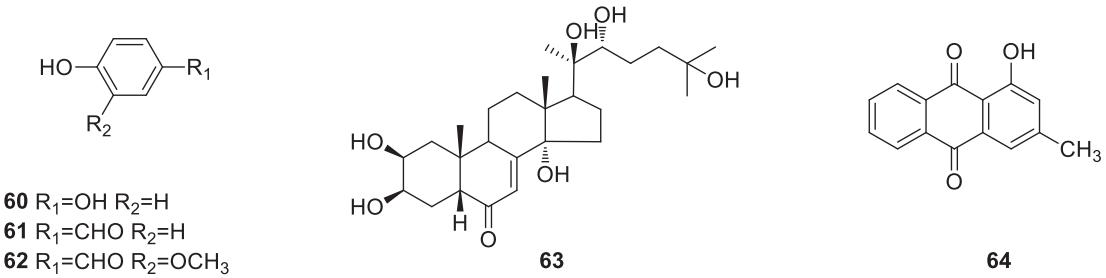

Fig. 6 The chenmical structures of other compounds.

1a), 121.4 (C-8a), 123.5 (C-12), 126.7 (C-11), 130.6 (C-4a), 132.9 (C-12a), 137.4 (C-13a), 143.6 (C-9), 145.4 (C-8), 147.6 (C-2), 149.7 (C-3), 150.4 (C-10); a methylene carbon signal (-OCH_2O-) at δ_C 102.1; two methylene carbon signals at δ_C 26.4 (C-5) and 55.2 (C-6) and two methoxy carbon signals at δ_C 62.0 (9-OCH_3) and 57.1 (10-OCH_3).

Then, we take *N-trans*-feruloyltyramine (**34**) and (+)-lyoniresinol 3α-*O*-β-D-glucopyranoside (**37**) as examples to analyze the carbons of phenylpropanoids, the ^{13}C NMR spectrum of *N-trans*-feruloyltyramine (**34**) gives eighteen carbon signals, include fifteen olefinic carbon signals at δ_C 111.8 (C-2′), 116.5 (C-3, 5), 116.7 (C-5′), 118.9 (C-8′), 123.4 (C-6′), 128.5 (C-1′), 131.0 (C-2, 6), 131.5 (C-1), 142.4 (C-7′), 149.5 (C-3′), 150.0 (C-4′), 157.1 (C-4), 169.4 (C-9′); two methylene carbon signals at δ_C 36.0 (C-7) and 42.7 (C-8) and a methoxy carbon signal at δ_C 56.6 (3′-OCH_3). (+)-lyoniresinol 3α-*O*-β-D-glucopyranoside (**37**) gives twenty-eight carbon signals, include twelve olefinic carbon signals at δ_C 107.1 (C-2′, 6′), 108.0 (C-8), 126.5 (C-10),130.3 (C-9), 134.6 (C-1′), 139.0 (C-6), 139.4 (C-4′), 147.7 (C-5), 148.7 (C-7), 149.1 (C-3′, 5′); an anomeric carbon signal at δ_C 104.9 (Glu-1″); six methylene carbon signals at δ_C 33.8 (C-1), 40.7 (C-2), 42.8 (C-4), 46.7 (C-3), 66.4 (C-2α) and 71.6 (C-3α) and four methoxy carbon signals at δ_C 56.7 (7-OCH_3), 57.0 (3′, 5′-OCH_3) and 60.3 (5-OCH_3).

In addition, we take fibleucin (**46**) as an example to analyze the carbons of terpenoids, its ^{13}C NMR spectrum gives twenty carbon signals, include two carbonyl group signals at δ_C 162.4 (C-17), 174.2 (C-20); eight olefinic carbon signals at δ_C 109.1 (C-14), 124.8 (C-13), 131.0 (C-2), 132.1 (C-8), 135.9 (C-3), 140.5 (C-15), 143.8 (C-16), 146.6 (C-7); two methyl carbon signals at δ_C 19.4 (C-19) and 20.8 (C-18); two methylene carbon signals at δ_C 41.8 (C-11) and 71.1 (C-6); three tertiary carbon signals at δ_C 57.3 (C-10), 69.9 (C-12) and 73.5 (C-1) and three quaternary carbon signals at δ_C 35.6 (C-5), 46.5 (C-9) and 81.9 (C-4).

Finally, we take gusanlungionoside A (**56**) as an example to analyze the carbon signals of glycosides, its ^{13}C NMR spectrum gives twenty-five carbon signals, include a carbonyl group signals at δ_C 202.2 (C-3); four olefinic carbon signals at δ_C 126.4 (C-4), 129.0 (C-7), 138.4 (C-8) and 166.0 (C-5); two anomeric carbon signal at δ_C 101.0 (Glu-1′) and 102.2 (Rha-1″); four methyl carbon signals at δ_C 21.2 (C-10), 24.0 (C-13), 27.8 (C-11) and 28.3 (C-12); a methylene carbon signals at δ_C 48.6 (C-2); two tertiary carbon signals at δ_C 56.9 (C-6) and 76.9 (C-9) and a quaternary carbon signals at δ_C 37.3 (C-1).

4. Pharmacological activities

According to the above chemical constituents, this genus is rich in alkaloids, diterpenoids and other chemical components, so their biological activities are also quite rich, such as antimicrobial, anti-inflammatory, antimalarial, antidiabetic, antibabesial, antioxidant, antitumor, cardiotonic and antihypertensive activities, *et al*. Consequently, their main pharmacological activities are summarized as Table 9.

4.1. Antimicrobial activity

Serveral studies have shown that the ethanol extract of *A. flava* stems has excellent antimicrobial activity against various microbes both bacteria and fungi (Setyowati et al., 2014; Pratama, 2016). The antimicrobial spectrum of *A. flava* extracts is even quite extensive including some Gram-positive and Gram-negative bacteria (Maryani et al., 2018; Hesty et al., 2015). This activity is mainly associated with the ability of secondary metabolites as antimicrobials through various pathways including inhibition of cell wall, protein, nucleic acid synthesis and antimetabolites (Alves et al., 2014; Cheng et al., 2009; Dharani et al., 2016). Maryani (Maryani et al., 2018) *et al* showed that *A. flava* leaf possessed inhibition activity on the growth of bacteria *Pseudomonas fluorescens*. In addition, Pratama (Pratama et al, 2018) *et al* found that the main mechanism of action for the selected secondary metabolites of *A. flava* was the inhibition of protein and cell wall synthesis, which was shown by berberine (**1**). Berberine (**1**) has been claimed to be therapeutically useful for the treatment of malaria and as an antimicrobial agent (Iwasa et al., 1997; Sarma et al., 1999; Singh et al., 2010; Subeki et al., 2005; Vennerstrom and Klayman, 1988). And its mechanism of berberine (**1**) as antimicrobial agent could be changing the arrangement of amino acid chain on DNA that rises balances changes of genetics on DNA, so that the DNA of microbial will be defeat, this causes a core of microbial cell to be defeat and dead (Setyowati et al., 2014). Yu (Yu et al., 2005) *et al* reported that berberine (**1**) showed antimicrobial activity against all tested strains of MRSA (methicillin-resistant *Staphylococcus aureus*). Futhermore, *A. flava* had antibacterial capability against *Aeromonas hydrophila* (Maryani et al., 2013). Pachybasin (**64**), a major metabolite from culture broth of endophytic Coelomyceteous AFKR-18 fungus, was isolated from *A. flava* (Wulansari et al., 2014). Crude extract of *A. flava*

Table 2 Chemical constituents isolated and identified from the genus *A*.

NO.	Names	Source	Refs.
Alkaloids			
1	berberine	*A. gusanlung*	(Yu et al., 2014; Garcia et al., 1970; Zhang and Chen, 1991)
		A. flava	(Suzuki et al., 2011; Verpoorte et al., 1982; Subeki et al., 2005; Niwat et al., 2005; Pratama et al., 2018; Pratama, 2016; Watthanachaiyingcharoen et al., 2010; Subeki et al., 2004)
2	thalifendine	*A. gusanlung*	(Yu et al., 2014)
		A. flava	(Verpoorte et al., 1982; Subeki et al., 2005; Subeki et al., 2004)
3	jatrorrhizine	*A. gusanlung*	(Yu et al., 2014; Garcia et al., 1970; Zhang and Chen, 1991)
		A. flava	(Verpoorte et al., 1982; Subeki et al., 2005; Niwat et al., 2005; Pratama et al., 2018; Watthanachaiyingcharoen et al., 2010; Subeki et al., 2004; Mohammad, 2017)
4	palmatine	*A. gusanlung*	(Yu et al., 2014; Garcia et al., 1970)
		A. flava	(Verpoorte et al., 1982; Subeki et al., 2005; Niwat et al., 2005; Pratama et al., 2018; Watthanachaiyingcharoen et al., 2010; Mohammad, 2017; Yu et al., 2011)
5	stephabine	*A. gusanlung*	(Yu et al., 2014)
6	columbamine	*A. flava*	(Suzuki et al., 2011; Verpoorte et al., 1982; Pratama et al., 2018; Pratama, 2016; Subeki et al., 2004; Mohammad, 2017)
7	dehydrocorydalmine	*A. flava*	(Verpoorte et al., 1982; Subeki et al., 2005; Pratama et al., 2018)
8	corydaline	*A. gusanlung*	(Yu et al., 2014)
9	tetrahydropalmatine	*A. gusanlung*	(Yu et al., 2014)
10	gusanlung A	*A. gusanlung*	(Zhang and Chen, 1991)
11	acetyl gusanlung A	*A. gusanlung*	(Zhang and Chen, 1991)
12	gusanlung B	*A. gusanlung*	(Yu et al., 2014; Zhang and Chen, 1991)
13	gusanlung D	*A. gusanlung*	(Zhang et al., 1995)
14	gusanlung C	*A. gusanlung*	(Zhang et al., 1995; Yu et al., 2014)
15	acetyl gusanlung C	*A. gusanlung*	(Zhang et al., 1995)
16	trimethyl gusanlung C	*A. gusanlung*	(Zhang et al., 1995)
17	8-oxyberberine	*A. gusanlung*	(Zhang et al., 1995; Yu et al., 2014)
18	8-oxythalifendine	*A. gusanlung*	(Zhang et al., 1995)
19	acetyl 8-oxythalifendine	*A. gusanlung*	(Zhang et al., 1995)
20	8-oxyberberrubine	*A. gusanlung*	(Zhang et al., 1995)
21	8,13-dioxo-14-hydroxycanadine	*A. gusanlung*	(Yu et al., 2014)
22	8,13-dioxo-14-methoxycanadine	*A. gusanlung*	(Yu et al., 2014)
23	gusanlung E	*A. gusanlung*	(Yu et al., 2014)
24	*N*-methylcorydaldine	*A. gusanlung*	(Yu et al., 2011; Yu and Zou., 2012)
25	thalifoline	*A. gusanlung*	(Yu et al., 2011; Yu and Zou., 2012)
26	tetrahydrothalifendine	*A. gusanlung*	(Yu et al., 2014)
27	8-oxotetrahydroplamatine	*A. gusanlung*	(Yu et al., 2014)
28	dihydroberberine	*A. flava*	(Subeki et al., 2005; Watthanachaiyingcharoen et al., 2010)
29	8-hydroxy-berberine	*A. flava*	(Verpoorte et al., 1982; Subeki et al., 2005; Pratama et al., 2018)
30	homoaromoline	*A. flava*	(Verpoorte et al., 1982; Subeki et al., 2005; Pratama et al., 2018)
31	limacine	*A. flava*	(Verpoorte et al., 1982; Subeki et al., 2005; Pratama et al., 2018)
32	pycnarrhine	*A. flava*	(Verpoorte et al., 1982; Subeki et al., 2005; Pratama et al., 2018)
Phenylpropanoids			
33	*N-cis*-feruloyltyramine	*A. gusanlung*	(Yu and Zou, 2012)
34	*N-trans*-feruloyltyramine	*A. gusanlung*	(Yu and Zou, 2012; Jiang et al., 2015)
35	*N-trans*-coumaroyltyramine	*A. gusanlung*	(Yu et al., 2011; Yu and Zou, 2012)
36	*N-trans*-feruloyl-3-methoxytyramine	*A. gusanlung*	(Yu et al., 2011; Yu and Zou, 2012)

Table 2 (*continued*)

NO.	Names	Source	Refs.
37	(+)-lyoniresinol 3α-*O*-β-D-glucopyranoside = (2R,3R,4S)-3α-[(β-D-glucopyranosyl)oxy]lyoniresinol	*A. gusanlung*	(Yu and Zou, 2012)
38	(-)-lyoniresinol 3α-*O*-β-D-glucopyranoside =(2S,3S,4R)-3α-[(β-D-glucopyranosyl)oxy]lyoniresinol	*A. gusanlung*	(Yu and Zou, 2012)
39	(2R,3S,4S)-3α-[(β-D-glucopyranosyl)oxy]lyoniresinol	*A. gusanlung*	(Yu et al., 2011)
40	(2R,3S,4R)-3α-[(β-D-glucopyranosyl)oxy]lyoniresinol	*A. gusanlung*	(Yu et al., 2011)
41	(2S,3R,4R)-3α-[(β-D-glucopyranosyl)oxy]lyoniresinol	*A. gusanlung*	(Yu et al., 2011)
42	(2S,3R,4S)-3α-[(β-D-glucopyranosyl)oxy]lyoniresinol	*A. gusanlung*	(Yu et al., 2011)
43	syringaresinol	*A. gusanlung*	(Yu et al., 2011; Yu and Zou, 2012)
44	grossamide	*A. gusanlung*	(Yu and Zou, 2012)
Terpenoids			
45	aduncin	*A. gusanlung*	(Yu and Zou, 2012)
46	fibleucin	*A. flava*	(Suzuki et al., 2011; Pratama et al., 2018; Pratama, 2016; Mohammad, 2017; Kunii et al., 1985; Kawakami et al., 1987)
47	6-hydroxyfibleucin	*A. flava*	(Pratama et al., 2018; Pratama, 2016; Mohammad, 2017; Kunii et al., 1985; Kawakami et al., 1987)
48	fibraurin	*A. flava*	(Suzuki et al., 2011; Pratama et al., 2018; Pratama, 2016; Mohammad, 2017; Kunii et al., 1985; Kawakami et al., 1987)
49	6-hydroxyfibraurin	*A. flava*	(Pratama et al., 2018; Pratama, 2016; Mohammad, 2017; Kunii et al., 1985; Kawakami et al., 1987)
50	tinophyllol	*A. flava*	(Pratama et al., 2018; Mohammad, 2017; Kunii et al., 1985; Kawakami et al., 1987)
51	2-dehydroarcangelisinol	*A. flava*	(Pratama et al., 2018; Pratama, 2016; Mohammad, 2017; Kunii et al., 1985; Kawakami et al., 1987)
52	6-hydroxyarcangelisin	*A. flava*	(Pratama et al., 2018; Pratama, 2016; Mohammad, 2017; Kunii et al., 1985; Kawakami et al., 1987)
53	2α,3α-epoxy-2,3-dihydropenianthic acid methyl ester	*A. flava*	(Suzuki et al., 2011)
54	2α,3α-epoxy-2,3,7,8α-tetrahydropenianthic acid methyl ester	*A. flava*	(Suzuki et al., 2011)
55	2β, 3α-dihydroxy-2,3,7,8α-tetrahydropenianthic acid-2,17-lactone	*A. flava*	(Suzuki et al., 2011; Fun et al., 2011)
Glycosides			
56	gusanlungionoside A	*A. gusanlung*	(Yu et al., 2011; Yu and Zou, 2012)
57	gusanlungionoside B	*A. gusanlung*	(Yu et al., 2011; Yu and Zou, 2012)
58	gusanlungionoside C	*A. gusanlung*	(Yu et al., 2011)
59	gusanlungionoside D	*A. gusanlung*	(Yu et al., 2011)
Others			
60	p-hydroxybenzyl alcohol	*A. gusanlung*	(Yu et al., 2011)
61	p-hydroxybenzaldehyde	*A. flava*	(Suzuki et al., 2011)
62	vanillin	*A. flava*	(Suzuki et al., 2011)
63	20-hydroxyecdysone	*A. flava*	(Subeki et al., 2005)
64	pachybasin	*A. flava*	(Wulansari et al., 2014)

was also active against *Staphylococcus aureus* and *Bacillus cereus* (Soonthornchareonnon et al., 2012). And Suzuki (Suzuki, et al., 2011) *et al* found that 2β, 3α-dihydroxy-2,3,7,8α-tetrahydropenianthic acid-2,17-lactone (**54**) showed the highest antifungal activity of the five isolated furanoditerpenes against a white-rot fungus (*Trametes versicolor*) and a brown-rot fungus (*Fomitopsis palustris*). Hesty (Hesty et al., 2015) *et al* found that water extract of *A. flava* exhibited a positive respond against *Salmonella typhii*, *Staphylococcus aureus*, and *Trichophyton rubrum*. Furthermore, it is reported that (+)-lyoniresinol-3α-*O*-β-D-glucopyranoside (**37**) has excellent potential as a leading compound for the development of antibiotic agents (Lee et al., 2005).

In a short conclusion of this part, there are many studies on the antimicrobial activity of *A. flava*, but there are few studies on *A. gusanlung* and *A. tympanopoda*. In the study of *A. flava*, berberine (**1**) is the main active component, and its mechanism may be the inhibition of protein and cell wall synthesis.

4.2. Anti-inflammatory activity

It is reported that *A. gusanlung* has anti-inflammatory activity (Chinese Pharmacopoeia, 1977). Hu (Hu et al., 2013) *et al* used various inflammatory models including ear swelling induced by xylene in mice, paw edema induced by carrageenan and cotton pellet granuloma in rats. The results

Table 3 The ^{13}C NMR data of some alkaloids.

Positions	**1** [a] (Yu et al., 2014)	**2** [a] (Yu et al., 2014)	**3** [a] (Yu et al., 2014)	**4** [a] (Yu et al., 2014)	**6**[b,c] (Grycová et al., 2007)	**8** [a] (Yu et al., 2014)	**9**[c] (Blanchfield et al., 2003)	**10**[b] (Zhang and Chen, 1991)	**12** [a] (Yu et al., 2014)
1	105.4	106.4	115.5	104.7	114.9	108.7	108.5	106.1	106.5
1a	120.4	122.0	119.8	121.9	121.4	128.4	129.5	129.3	131.0
2	147.6	150.0	148.9	148.9	143.7	147.1	147.4	145.9	146.5
3	149.7	152.1	149.9	149.7	150.4	147.5	147.3	147.7	146.6
4	108.4	109.4	112.5	110.5	109.4	110.8	111.2	107.8	108.5
4a	130.6	131.6	130.3	132.6	133.6	128.4	126.6	129.1	128.7
5	26.4	28.3	26.8	27.3	26.3	29.2	28.9	29.0	29.0
6	55.2	57.1	57.2	56.6	55.6	51.3	51.3	37.8	39.2
8	145.4	145.2	145.3	145.3	144.8	54.0	53.8	161.4	162.4
8a	121.4	124.4	135.0	120.1	117.4	128.4	127.6	122.3	125.9
9	143.6	143.2	151.7	153.7	148.0	145.0	144.9	149.7	153.3
10	150.4	150.8	144.6	144.6	149.9	146.0	150.1	145.7	150.1
11	126.7	132.4	123.8	126.9	126.5	111.1	110.8	118.9	115.8
12	123.5	124.7	123.0	124.4	123.3	123.8	123.7	122.1	121.5
12a	132.9	135.3	122.9	126.9	128.2	134.8	128.5	128.2	128.9
13	120.2	121.7	121.5	121.5	119.8	38.2	36.1	37.7	38.2
13a	137.4	139.4	139.4	138.4	138.3	63.0	59.1	54.4	55.5
2-OCH_3			56.5	57.2		55.5	55.9		
3-OCH_3				57.3		55.6	55.7		
9-OCH_3	62.0	62.4	62.2	63.0	56.9	60.0	60.0		56.2
10-OCH_3	57.1			57.3	61.8	56.0	55.6	60.5	61.5
–OCH_2O	102.1	103.6			56.3			100.5	101.5
N-CH_3						18.2			

[a] Recorded in CD_3OD.
[b] inDMSO-d_6.
[c] in $CDCl_3$.

indicated that *A. gusanlung* had effect on acute and chronic inflammatory. Jiang (Yu et al., 2011) *et al* found that the anti-inflammatory effects of *N-trans*-feruloyltyramine (**34**) might be attributed to downregulation of COX-2 (Cyclooxygenase-2) and iNOS (Inducible Nitric Oxide Synthase) *via* suppression of AP-1 (Activator Protein-1) and the JNK (c-JunN-terminalkinase) signaling pathway in RAW 264.7 macrophages (Mouse Monocyte Macrophage Leukemia Cells). Levita (Levita et al., 2018) *et al* thought that phytoconstituents in *A. flava* fit the pharmacophore features generated from AT2 (PDB code: 3E7G) or SEITU (PDB code: 4NOS) complex with iNOS, therefore, they might be potential as iNOS inhibitors. Besides, dihydroberberine (**28**) was proved to be one of the anti-inflammatory ingredients and the anti-inflammatory mechanism might be associated with dual modulation of NF-κB (Nuclear Transcription Factor-κB) and MAPK (Mitogen-activated Protein Kinase) signaling pathways and regulation of inflammatory mediators (Tan et al., 2019). Futhermore, Singh (Singh et al., 2010) *et al* found that berberine (**1**) has anti-inflammatory activity. In additiion, Choi (Choi et al., 2009) *et al* found that the anti-inflammatory effect of berberine (**1**) is not mediated by the inhibition of leptin signal transduction. Moreover, they have also found that berberine (**1**) can down-regulate the NF-κB signaling pathway.

In general, there are few studies on the anti-inflammatory activities of *A. flava* and *A. gusanlung*, only the mechanism of action of *N-trans*-feruloyltyramine (**34**) isolated from *A. gusanlung* is clear, and the mechanism of action of other compounds still needs further study.

4.3. Antimalarial activity

It is also reported that *A. flava* has antimalarial activity (Kaur et al., 2009; Lovin et al., 2012). The active components are protoberberine alkaloids such as berberine (**1**), jatrorrhizine (**3**), palmatine (**4**) and columbamine (**6**), which possess strong antiplasmodial activity (Iwasa et al., 1998) and inhibit *Plasmodium falciparum* telomerase activity (Sriwilaijareon et al., 2002). Besides, berberine (**1**) in combination with pyrimethamine, demonstrated the best parasite clearance when compared with treatment using a combination of pyrimethamine and tetracycline or pyrimethamine and cotrimoxazole in patients with chloroquine-resistant malaria (Sheng et al., 1997).

At present, malaria is a major global public health problem and is responsible for the death of over one million people annually, with more than 90% of cases found in sub-Saharan Africa. The increasing global spread of drug resistance to most of the available and affordable antimalarial drugs is a major concern and requires innovative strategies to combat. *A. flava* is expected to play a key role in the treatment of malaria.

4.4. Antidiabetic activity

It is reported that the ethyl acetate and hexane extracts of *A. flava* leaves possessed the potential antidiabetic activity which was comparable that of the standard acarbose. And the ethyl acetate extract possesessed the most potential antidiabetic effect because it has a high inhibitory activity on α-amylase

Table 4 The ^{13}C NMR data of some alkaloids.

Positions	**13**[c] (Zhang et al., 1995)	**14** [a] (Yu et al., 2014)	**17** [a] (Yu et al., 2014)	**20**[c] (Zhang et al., 1995)	**21** [a] (Yu et al., 2014)	**23** [a] (Yu et al., 2014)	**26** [a] (Yu et al., 2014)	**27** [a] (Yu et al., 2014)
1	107.3	119.7	104.9	104.0	121.8	114.5	106.7	109.5
1a	126.5	128.0	135.9	122.1	135.4	125.8	131.0	130.7
2	135.0	156.7	148.1	141.6	147.9	147.5	144.1	148.0
3	147.0	122.5	148.8	146.4	148.9	150.1	144.0	147.9
4	107.5	116.1	109.6	107.1	118.8	113.3	110.8	111.5
4a	126.5	131.0	129.8	109.6	138.1	120.3	127.8	127.8
5	29.7	36.8	29.8	28.4	31.8	24.3	29.2	29.8
6	42.0	40.2	38.8	39.1	39.5	53.3	51.5	39.2
8	162.0	167.0	160.3	164.0	168.6	65.1	53.0	162.7
8a	117.3	116.0	126.4	129.9	132.6	118.0	125.9	123.0
9	128.7	130.3	153.0	149.0	156.2	114.1	145.0	153.4
10	127.9	149.0	149.6	147.5	153.4	146.7	143.0	150.7
11	127.1	130.3	109.7	114.9	110.7	147.8	111.3	115.5
12	126.8	116.0	124.6	120.0	109.6	115.8	121.7	120.6
12a	124.6	148.6	134.0	128.9	124.5	122.0	127.1	127.3
13	33.5	140.7	103.6	103.6	203.9	35.4	36.2	38.0
13a	49.4	111.6	119.7	133.6	103.9	67.6	59.0	54.5
2-OCH_3								56.2
3-OCH_3						56.7		56.2
9-OCH_3			60.9		62.8		55.1	61.5
10-OCH_3			56.2	56.7	57.5			56.2
–OCH_2O	100.9		102.3	100.6	92.2		101.3	
–$COOCH_3$		56.5						
–CH_3						50.7		

[b]inDMSO-d_6.
[a] Recorded in CD_3OD.
[c] in $CDCl_3$.

and α-glucosidase (Wahyudi et al., 2016). In addition, It is reported that dihydroberberine (**28**) possessed the antidiabetic effect (Turner et al., 2008). Furthermore, Pan (Pan et al., 2003) *et al* found that the anti-hyperglycaemic activity of berberine (**1**) was at least partly due to its ability to inhibit α-glucosidase and decrease glucose transport through the intestinal epithelium. Besides, Chang (Chang, 2017) found that berberine (**1**) has shown promise as an anti-hyperglycaemic, anti-hyperlipidaemic agent against type 2 diabetes.

In our opinion, we can further isolate the *A. flava* to identify its antidiabetic ingredients and further study its mechanism.

Table 5 The ^{13}C NMR data of *N-trans*-feruloyltyramine.

Positions	**34** [a] (Jiang et al., 2015)
1	131.5
2	131.0
3	116.5
4	157.1
5	116.5
6	131.0
7	36.0
8	42.7
1′	128.5
2′	111.8
3′	149.5
4′	150.0
5′	116.7
6′	123.4
7′	142.4
8′	118.9
9′	169.4
3′–OCH_3	56.6

[a] Recorded in CD_3OD.

4.5. Antibabesial activity

Subeki (Subeki et al., 2005) *et al* tested the compounds isolated from *A. flava* for antibabesial activity against *babesia gibsoni* in culture. Among them, berberine (**1**), jatrorrhizine (**3**), palmatine (**4**) and dihydroberberine (**28**) showed significant inhibitions at concentrations from 100 to 1.0 μg/ml, while 20-hydroxyecdysone (**63**) at a concentration of 100 μg/ml. In addition, Subeki (Subeki et al., 2004) *et al* reported that the extract of *A. flava* displayed very high antibabesial activity with IC_{50} (Half Maximal Inhibitory Concentration) of 5.3 μg/ml.

In our view, *A. flava* has a good inhibitory effect against *babesia gibsoni*, the range of action is clear, and its mechanism needs further study.

4.6. Antioxidant activity

Keawpwadub (Niwat et al., 2005) *et al* reported that methanol extract of *A. flava* exhibited moderate antioxidant activity. In addition, phenolic extract of *A. flava* leaves possessed the potential antioxidant activity which is comparable that of the standard vitamin C. Furthermore, the methanol extract exhibited the strongest DPPH radical scavenging ability and hydro-

Table 6 The ^{13}C NMR data of phenylpropanoids.

Positions	**37**[a] (Ohashi et al., 1994)	**38** [a] (Ohashi et al., 1994)
1	33.8	33.9
2	40.7	41.3
3	46.7	46.6
4	42.8	43.3
5	147.7	147.6
6	139.0	139.5
7	148.7	148.7
8	108.0	107.8
9	130.3	130.2
10	126.5	126.3
1′	134.6	134.6
2′,6′	107.1	107.1
3′,5′	149.1	149.0
4′	139.4	138.9
2α	66.4	66.2
3α	71.6	72.0
5-OCH_3	60.3	60.1
7-OCH_3	56.7	56.6
3′,5′–OCH_3	57.0	56.9
1″	104.9	104.3
2″	75.3	75.1
3″	78.3	78.2
4″	71.8	71.6
5″	78.0	78.0
6″	62.9	62.7

[a] Recorded in CD_3OD.

xyl radical scavenging ability. Moreover, the ethyl acetate extract exhibited the strongest superoxide anion radical scavenging ability (Wahyudi et al., 2016). Besides, Singh (Singh et al., 2010) *et al* found that berberine (**1**) has antioxidant activity.

In our opinion, we can further isolate the *A. flava* to identify its antioxidant ingredients and further study its mechanism.

4.7. Antitumor activity

Several secondary metabolites of *A. flava* showed antiproliferative activity towards cancer cells (Pratama, 2016). Moreover, berberine (**1**) was also found to have antiproliferative activities against human cervix HeLa adenocarcinoma, human lung A549 adenocarcinoma, murine colon 26-L5 carcinoma, murine LLC (Lewis lung carcinoma), and murine B16-BL6 melanoma cells (Ueda et al., 2002). In addition, an experiment using berberine (**1**) to treat $HepG_2$ (Hcuman Hepatoellular Carcinomas) cells indicated that the viability was increased to more than 90% after treatment and the secretion of alpha-fetoprotein by $HepG_2$ cells was also inhibited by berberine (**1**) (Watthanachaiyingcharoen et al., 2010; Sun et al., 2009). Singh (Singh et al., 2010) *et al* found that berberine (**1**) has antitumor activity. And Ho (Ho et al., 2009) *et al found that* berberine (**1**) induced apoptosis via promoting the expression of Caspase-8, −9 and −3, apoptosis-inducing factor and endonuclease G in SCC-4 human tongue squamous carcinoma cancer cells. Futhermore, chloroform extracts of *A. flava* showed pronounced cytotoxic activity against brine shrimp

Table 7 The ^{13}C NMR data of gusanlungionosides.

Positions	**44** [a] (Yu et al., 2011)	**56** [a] (Yu et al., 2011)	**57** [a] (Yu et al., 2011)	**58** [a] (Yu et al., 2011)
1	37.4	37.3	37.6	37.5
2	48.6	48.6	48.3	48.3
3	202.2	202.2	202.6	202.6
4	126.3	126.4	125.7	125.6
5	166.2	166.0	170.2	170.2
6	57.0	56.9	52.7	52.6
7	128.9	129.0	27.3	26.9
8	138.6	138.4	38.3	38.0
9	76.6	76.9	75.3	75.1
10	21.2	21.2	20.0	20.0
11	27.6	27.8	27.8	27.8
12	28.2	28.3	29.2	29.3
13	24.2	24.0	25.3	25.2
1′	100.9	101.0	100.5	100.5
2′	78.8	78.9	78.6	78.5
3′	79.6	79.7	79.8	79.8
4′	71.9	71.9	72.2	72.2
5′	78.0	78.0	77.9	78.0
6′	62.9	62.9	63.2	63.1
1″	102.1	102.2	102.1	102.0
2″	72.5	72.5	72.5	72.5
3″	72.4	72.4	72.5	72.4
4″	74.1	74.1	74.2	74.1
5″	69.9	69.9	69.8	69.8
6″	18.3	18.3	18.3	18.3

[a] RecordedinCD_3OD.

Table 8 The ^{13}C NMR data of terpenoids.

Positions	**45**[b] (Kunii et al., 1985)	**46**[b] (Kunii et al., 1985)	**47**[b] (Kunii et al., 1985)	**48**[b] (Kunii et al., 1985)	**49**[b] (Kunii et al., 1985)	**50**[b] (Kunii et al., 1985)	**51**[b] (Kunii et al., 1985)	**52**[c] (Suzuki et al,. 2011)
1	73.8	73.5	69.7	69.9	28.6	72.9	69.2	23.7
2	130.6	131.0	49.5	49.4	62.5	131.2	49.1	52.8
3	137.0	135.9	51.6	51.1	139.3	135.0	50.5	57.2
4	80.3	81.9	80.0	82.0	138.7	82.8	82.7	80.5
5	35.6	35.6	35.2	35.2	36.0	35.5	34.8	36.7
6	31.1	71.1	31.2	70.2	43.9	70.0	69.3	25.8
7	142.1	146.6	142.1	145.8	19.7	28.2	27.3	15.9
8	134.3	132.1	133.3	131.1	47.0	44.3	43.1	40.9
9	42.4	46.5	44.8	48.7	36.9	40.2	43.4	43.0
10	55.9	57.3	54.0	55.1	54.2	57.5	55.5	48.8
11	42.1	41.8	42.0	42.0	34.8	43.7	43.2	47.2
12	69.7	69.9	70.6	71.0	69.4	71.9	71.3	70.0
13	125.0	124.8	125.0	124.8	124.6	125.4	125.2	123.9
14	109.1	109.1	109.1	109.0	109.2	109.5	109.1	108.5
15	140.4	140.5	140.4	140.4	140.1	140.7	140.4	143.7
16	143.8	143.8	143.9	143.9	143.8	144.1	143.8	139.6
17	163.2	162.4	163.2	168.4	168.0	172.4	171.4	174.0
18	26.4	20.8	25.0	21.3	33.2	18.1	17.2	28.9
19	20.4	19.4	20.7	18.4	22.7	18.6	18.4	23.4
20	174.6	174.2	171.5	171.1	174.2	174.9	171.7	174.0
4-OCH_3					51.5			
–$COOCH_3$								53.2

[a]Recorded in CD_3OD.
[b] In DMSO d_6.
[c] In $CDCl_3$.

and MCF-7 cells with LC_{50} (lethal concentration 50) and IC_{50} values of 210–278 and 8–12 μg/ml, respectively. And berberine (**1**), palmatine (**4**), and jatrorrhizine (**3**) isolated from *A. flava* showed cytotoxic activity against MCF-7 (Michigan Cancer Foundation-7) cells (Niwat et al., 2005). Gusanlung E (**23**) showed weak cytotoxicity against cancer cell line SGC 7901 with IC_{50} value of 85.1 μM (Yu et al., 2014). It is reported that protoberberine alkaloids are highly effective as cytotoxic and antileukemic agents against human fibroblast and promyelocytic leukemic cells (Kuo et al., 1995; Orfila et al., 2000).

Cancer is one of the major causes of death in developed countries, together with cardiac and cerebrovascular diseases (World Health Organization, 1998). Cancer is clinically treated by surgery, radiotherapy and chemotherapy. After surgical ablation of progressive cancer, however, metastasized tumor cells continue to progress, and this is one of the causes making cancer treatment difficult (Fidler and Kripke, 1977). Thus, more effective anticancer drugs with high selectivity against only malignant cells and with ability to repress tumor metastasis are desired, as candidates for such drugs, *A. flava* and *A. gusanlung* may become as the key drugs.

4.8. Cardiotonic and antihypertensive activities

Ethanol extract of *A. flava* exhibited cardiotonic activity on turtle heart (perfusion) and hypotensive activity in dog (Keawpradub et al., 2005; Estrada et al., 1963). In addition, berberine (**1**) has been reported that it reduced heart disease or NAFLD (non alcholic fatty liver disease). It has a role in heart steatosis recovery, lipid metabolism disturbance, inflammation relieve, and insulin resistance (Singh et al., 2010; Pramono et al., 2019; Xing et al., 2011).

4.9. Neuraminidase inhibitive activity

A. flava contains many secondary metabolites which potentially have effects as neuraminidase inhibitor (Mohammad et al., 2017), and some literatures have reported that fibleucin (**45**) could be considered as neuraminidase inhibitor and should be potential to be developed as antiinfluenza particularly to H5N1 (Influenza A Virus Subtype H5N1) with oseltamivir resistance (Mohammad et al., 2017; Shen et al., 2015).

At present, only molecular docking technology is used to preliminarily infer that fibleucin (**45**) is a neuraminidase inhibitor and the mechanism of action and the property of patent medicine need to be further studied.

4.10. Tyrosinase inhibitive activity

Gusanlungionosides A-D (**56~59**) exhibited strong inhibitory effects not only on the mushroom tyrosinase activity *in vitro* but also on melanogenesis in cells (Yu et al., 2011). And it is reported that melanogenesis was inhibited by *N-trans*-feruloyltyramine (**34**) in a dose-dependent manner (Efdi et al., 2007).

In our opinion, we can further study the mechanisms of gusanlungionosides A-D (**56~59**) as tyrosinase inhibitors.

4.11. Other activities

Studies have shown that by means of hot-plate test and peripheral analgesia model of the acetic acid injection in mice, Hu (Hu et al., 2013) *et al* found that *A. gusanlung* had analgesic effect on the central nervous system, but its peripheral anal-

Table 9 Pharmacological activities of genus *A*.

Biological activity	Object of study	Bioactive compound	Study model and mechanism	Refs.
Antimicrobial activity	*A. flava*, stem, water extract	–	*Candida albicans*: inhibition zone 16.65 ± 4.52 mm, MIC value 10 mg/ml, MBC value 40 mg/ml; *Trichophyton mentagrophytes*: inhibition zone 6.55 ± 0.05 mm, MIC value 10 mg/ml, MBC value 50 mg/ml	Setyowati et al., 2014
	A. flava, leaf, 96% methanol extract	–	*Pseudomonas fluorescens*: MIC value concentration of 1.5%, inhibition zone 7.18 mm; MBC value concentration of 3.5%, inhibition zone 14.17 mm	Maryani et al., 2018
	A. flava, stem, water extract	–	Inhibition zone: *Salmonella typhii* 19.35 mm, *Staphylococcus aureus* 16.98 mm, *Trichophyton rubrum* 19.78 mm, respectively at application level of 2% (v/v)	Hesty et al., 2015
	A. flava	berberine (**1**)	Molecular docking (inhibition of protein and cell wall synthesis)	Pratama et al, 2018
	A. flava, chloroform extract	–	*Aeromonas hydrophila*: widest preventive zone 17.25 mm	Maryani et al., 2013
	A. flava, oneendophytic filamentous fungus	pachybasin (**64**)	*Escherichia coli*, *Bacillus subtilis*, *Micrococcus luteus*, *Candida albicans*, *Saccharomyces cerevisiae*, *Aspergillus niger*, *Aspergillus flavus* with MIC values of 64.0 μg/ml, *Staphylococcus aureus*: MIC 32.0 μg/ml, *Fusarium oxysporum*: MIC 16.0 μg/ml	Wulansari et al., 2014
	A. flava, root, 80% ethanol extract	–	*Staphylococcus aureus*, *Bacillus cereus*	Soonthornchareonnon et al., 2012
	A. flava, root, acetone and methanol extract	2*β*, 3α-dihydroxy-2,3,7,8α-tetrahydropenianthic acid-2,17-lactone (**54**)	*Trametes versicolor*, *Fomitopsis palustris*	Suzuki, et al., 2011
Anti-inflammatory activity	*A. gusanlung*, rhizome, 70% ethanol extract	–	Ear swelling induced by xylene in mice, paw edema induced by carrageenan and cotton pellet granuloma in rats	Hu et al., 2013
	A. gusanlung, stem, methanol extract	*N-trans*-feruloyltyramine (**34**)	Downregulation of COX-2 and iNOS *via* suppression of AP-1 and the JNK signaling pathway in RAW 264.7 macrophages	Jiang et al., 2015
	A. flava	berberine (**1**), thalifendine (**2**), jatrorrhizine (**3**), palmatine (**4**), columbamine (**6**), dehydrocorydalmine (**7**), dihydroberberine (28), limacine (31), pycnarrhine (**32**), fibraurin (**48**), 20-hydroxyecdysone (**63**)	Molecular docking (iNOS inhibitors)	Levita et al., 2018
Antimalarial activity	*A. flava*	–	Antiplasmodial activities IC_{50} = 0.4– 8.6 μg/ml	Kaur et al., 2009
	A. flava	berberine (**1**)	*Plasmodium falciparum*: dose-dependent range 30–300 μM	Sriwilaijareon et al., 2002
Antidiabetic activity	*A. flava*, leaf, hexane and ethyl acetate extract	–	α-amylase and α-glucosidase inhibition assays	Wahyudi et al., 2016

Table 9 (*continued*)

Biological activity	Object of study	Bioactive compound	Study model and mechanism	Refs.
Antibabesial activity	*A. flava*, stem, water extract	berberine (**1**), jatrorrhizine (**3**), palmatine (**4**) and dihydroberberine (**28**)20-hydroxyecdysone (**63**)	Against *babesia gibsoni* in cultureberberine (**1**), jatrorrhizine (**3**), palmatine (**4**) and dihydroberberine (**28**) inhibition concentration: 100–1.0 μg/ml, 20-hydroxyecdysone (**63**)**:** 100 μg/ml	Subeki et al., 2005
	A. flava, water extract	–	IC_{50} values: 5.3–49.3 μg/ml	Subeki et al., 2004
Antioxidant activity	*A. flava*, stem, methanol extract	–	DPPH, EC_{50} values 25–55 μg/ml	Niwat et al., 2005
	A. flava, leaf, hexane, ethyl acetate and methanol extract	–	Methanol extract: highest scavenging activity on superoxide and hydroxyl radical. ethyl acetate extract: highest scavenging activity on DPPH radical	Wahyudi et al., 2016
Antitumor activity	*A. flava*	berberine (**1**)	Molecular docking (EGFR inhibitor especially EGFR-2)	Pratama, 2016
	A. flava, stem, chloroform extract	berberine (**1**), jatrorrhizine (**3**), palmatine (**4**)	Cytotoxic activity against brine shrimp and MCF-7 cells Chloroform extracts: LC_{50} values: 210–278 μg/ml, IC_{50} values: 8–12 μg/ml, berberine (**1**), jatrorrhizine (**3**), palmatine (**4**): LC_{50} values on brine shrimp 37–206 μg/ml; IC_{50} values against MCF-7 cells 1–4 μg/ml	Niwat et al., 2005
	A. gusanlung, stem, methanol extract	gusanlung E (**23**)	Cancer cell line SGC 7901: IC_{50} value, 85.1 μM	Yu et al., 2014
Cardiotonic and antihypertensive activities	*A. flava*, ethanol extract	–	Exhibited cardiotonic activity on turtle heart (perfusion) and hypotensive activity in dog	Niwat et al.,2005, Estrada et al., 1963
Neuraminidase inhibitive activity	*A. flava*	fibleucin (**45**)	Antiinfluenza particularly to H5N1 with oseltamivir resistance	Mohammad et al., 2017
Tyrosinase inhibitive activity	*A. gusanlung*, stem, methanol extract	gusanlungionosides A-D (**56~59**)	On the mushroom tyrosinase activity *in vitro* but also on melanogenesis in cells	Yu et al., 2011
Analgesic effect	*A. gusanlung*, 70% ethanol extract	–	Hot-plate test and peripheral analgesia model of the acetic acid injection in mice	Hu et al., 2013
Antipyretic effect	*A. gusanlung*, 70% ethanol extract	–	Rat fever model induced by yeast	Hu et al., 2013
Antitussive effect	*A. gusanlung*, 70% ethanol extract	–	Sequential method	Hu et al., 2013
Expectorant action	*A. gusanlung*, 70% ethanol extract	–	Tracheal excretion of phenol red	Hu et al., 2013
Antidiarrheal function	*A. gusanlung*, 70% ethanol extract	–	Observed on normal intestinal propulsion of mouse model of diarrhea induced by decoction of *Sennae Folium*	Hu et al., 2013
Antidepressant activity	*A. flava*, stem, water extract	–	312 mg/kg BW on white mice balb-c strain in terms of immobility time in the forced swim test method	Tiara et al., 2015

gesic effect was greater. And they used in rat fever model induced by yeast observed antipyretic effect and its effect was obvious, the greater of the dosage was, the longer the effect lasted. Besides, Hu (Hu et al., 2013) *et al* used sequential method tested antitussive effect in mice, and the result was that *A. gusanlung* H. S. Lo could prolonged the latency of cough (Hu et al., 2013; Liu et al., 2009). Futhermore, the expectorant action was evaluated by tracheal excretion of phenol red, and the result showed that *A. gusanlung* H. S. Lo obviously increased the tracheal excretion of phenol red (Hu et al.,

2013). Additionally, the antidiarrheal function was observed on normal intestinal propulsion of mouse model of diarrhea induced by decoction of *Sennae Folium* (Hu et al., 2013). And it is reported that berberine (**1**) and palmatine (**4**) have common antidiarrheal effects. However, the antidiarrhoeal mechanisms are different. Berberine (**1**) blocked basolateral K^+ (Potassium ion) channels, while palmatine (**4**) inhibited on both Ca^{2+}-activated (Calcium Ion-activated) and Camp-activated pathways (Taylor et al., 1999; Wu et al., 2008; Mcnamara et al., 1999; Albano et al., 2005). Even more impressively, antidepressant effect of *A. flava* has also been reported (Tiara et al., 2015). And Singh (Singh et al., 2010) *et al* found that berberine (**1**) has antidepressant activity.

5. Conclusion

In this review, we reported the phytochemical progress including all the isolated from the genus *A*., and their pharmacological activities together with the ^{13}C NMR spectral data of the main biologically active compounds. Compounds isolated from the genus *A*. including alkaloids, phenylpropanoids, terpenoids, glycosides and some other components, and alkaloids are the main compounds found in this genus. Meanwhile, we have summarized a wide range of biological properties, such as antimicrobial, anti-inflammatory, antimalarial, antidiabetic, antibabesial, antioxidant, antitumor, cardiotonic and antihypertensive activities, *et al*. At present, there are relatively few studies on the genus *A*., especially for *A. tympanopoda*, and the related mechanism of *A. flava* is still the focus in the future's research, while the most research on *A. gusanlung* is still the chemical separation.

Although there are only three species in this genus, the chemical composition of this genus is rich and diverse, and mainly contains alkaloids with a variety of activities. The pharmacological activity and mechanism of action of its main components are still very superficial. Therefore, the further study of the chemical constituents of the genus and the bioactivity of the isolated compounds still needs the attention and efforts of medical researchers. Consequently, we hope this review will provide a reference for further investigation and application of the genus *A*.

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.

Acknowledgements

This work was supported by the National Key R&D Program of China, Synthetic Biology Research (No. 2019YFA0905300) and the National Natural Science Foundation of China (No. 82074276).

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