

## Review Article

# Phytochemical and Biological Properties of *Ajuga decumbens* (Labiatae): A Review

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### Abstract

*Ajuga decumbens* Thunb is a member of Labiatae family and widespread in China, Korea and Japan. This plant possesses diverse pharmacological activities, such as anti-inflammatory, antitumor, antibacterial, antiviral, cytotoxic, as well as insecticidal activities. Several compounds have been isolated from *A. decumbens*, which display a wide spectrum of biological and pharmacological activities. Hence, it would be useful to review current literature for available pharmacological activities of the plant as well as its active ingredients.

**Keywords:** *Ajuga decumbens* Thunb, Anti-inflammatory, Antitumor, Antibacterial, Antiviral, Cytotoxic, Insecticidal, Diterpenes, Iridoids glycosides

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## INTRODUCTION

The genus *Ajuga* is widely spread throughout the temperate regions of Europe, Asia, Australia, North America, and Africa [1,2]; this group contains many medicinal plants such as *A. decumbens* Thunb., *A. bracteosa* Wall. ex Benth, *A. forrestii* Diels, *A. nipponensis* Makino, *A. ciliata*, etc. Studies have shown that *Ajuga* spp. are widely used for the treatment of hypertension, hyperglycemia, pneumonia, acute and chronic pharyngitis [3-6]. Additionally, *Ajuga* has been used in Iranian traditional medicine for the treatment of joint pain, gout, and jaundice [7]. All plants of *A. decumbens* have been utilized as a kind of folk medicine for a long time in China and Japan owing to their antibacterial, anti-inflammatory, antitumor and antiviral activities [8-11]. Many compounds whose structures have been characterized were isolated from *A.*

*decumbens*. Diterpenes and iridoid glycosides are the main bioactive compounds for the treatment of chronic pelvic inflammation and hysteromyoma [12,13]. It is urgent to understand the structure-activity relationships between the chemical constituents and biological activities of this plant with regard to its enormous social and economic implications. The primary objective of this review is to comprehensively report the various biological properties of *A. decumbens* as well as its main chemical constituents.

### Diterpenes

Previous investigations of *A. decumbens* indicate that its constituents can be classified into four categories, viz, diterpenes, iridoid glycosides, flavonoids and ecdysteroids. Among them, diterpenes and iridoid glycosides are predominant. Neo-clerodane diterpenes mostly

show insecticidal [14,15], antibacterial [16,17], antimalarial [18], and anticancer activities [19]. In 1989, eight compounds, named *Ajugacumbins A, B, C, D* (1 - 4), *Ajugamarins A2, G1, H1 and F4* (5 - 8), were isolated from the ethanol extract of *A. decumbens* [20,21]. After that, two new compounds, *ajugacumbins E, F* (9, 10), were isolated [22]. Similarly, Chen *et al* also obtained a new compound (11) from *A. decumbens* [23]. In late 20th and early 21st century, *Ajugatakasins A and B* (12, 13), *Ajugaside A* (14) were isolated from the extracts of *A. decumbens* [24,25]. In 2005, *ajugacumbin H* (15) was obtained from chloroform extracts of *A. decumbens* [26]. With the development of separation and analysis techniques, four new compounds were separated from the whole plants were: *15-epilupulin A* (16), *6-O-deacetylajugamarin* (17), and *ajugadecumbenins A and B* (18, 19) [27]. Sun *et al* isolated and characterized compounds 20-30 *Ajugamarin A1 Chlorhydrin* (20) from *A. decumbens* [28].

In addition the same year, they also isolated six new compounds and four well-known analogues, elucidated as (12S)-1 $\alpha$ ,19-epoxy-6 $\alpha$ ,18-diacetoxy-4 $\alpha$ ,12-dihydroxy-neoclerod-13-en-15,16-olide (21), (12s)-6 $\alpha$ ,19-diacetoxy-18-chloro-4 $\alpha$ -hydroxy-12-tigloyloxy-neo-clerod-13-en-15,16-olide (22), (12s,2''s)-6 $\alpha$ ,19-diacetoxy-18-chloro-4 $\alpha$ -hydroxy-12-(2-methylbutanoyloxy)-neo-clerod-13-en-15,16-olide (23), 6 $\alpha$ ,19-diacetoxy-4 $\alpha$ -hydroxy-1 $\beta$ -tigloyloxyneo-clerod-12-en-15-oic acid methyl ester-16-aldehyde (24), (12s)-18,19-diacetoxy-4 $\alpha$ ,6 $\alpha$ ,12-trihydroxy-1 $\beta$ -tigloyloxy-neo-clerod-13-en-15,16-olide (25), 4 $\alpha$ ,6 $\alpha$ -dihydroxy-18-(4'-methoxy-4'-oxobutyryloxy)-19-tigloyloxy-neo-clerod-13-en-15,16-olide (26), *Ajugaciliatin J* (27), *Ajuganipponin B* (28), *Ajugamarin A1*(29), *Ajugarin I* (30) [29-30].

In 2014, Lv *et al* reported a new compound *ajugacumbin J* (31) [31]. Besides, three clerodane diterpenoids and six abietane diterpenoids, including *dihydroclerodin* (32), *clerodinins C* (33), *clerodinins D* (34), *ajuforrestins A, Ajuforrestins B, Ajudecumins A-D* (35 - 38), were obtained from the aerial parts of *A. decumbens* [32]. The structures of these compounds are described in Table 1(a), Table 1(b); Fig 1(a)-1(e).

### Iridoid glycosides

Iridoids are a class of secondary metabolites found in a wide variety of plants primarily served as a defense against herbivores or against infection by microorganisms [33]. The iridoids glycosides were firstly found by Takeda *et al*

obtained six iridoids glycosides from the MeOH extract of *A. decumbens*, elucidated as *Decumbeside A-D* (39 - 42), *reptoside* (43) and *8-Acetylharpagide* (44) [34]. Similarly, *Harpagide* (45) was isolated from *A. decumbens* [25]. The structures and physical states of these compounds are described in Table 1(b); Fig 1(e), Fig 1(f).

### Flavonoids

Flavonoids are another major group of compounds isolated from *A. decumbens*. Jin *et al* isolated *luteolin* (46) from the ethanol extract of *A. decumbens* [35]. In 2005, *5, 7-Dihydroxy-4'-methylflavone* (47) was obtained from the MeOH extract [36]. Other flavonoids, named *Apigenin* (48) and *Acacetin* (49), were isolated [28,32]. The structures and Physical states of these compounds are described in Table 1 (b); Fig 1(f).

### Ecdysteroids

Ecdysteroids are a group of chemically related polyhydroxylated steroids present in plants (phytoecdysteroids) and arthropods (zooecdysteroids). The phytoecdysteroids stimulate protein synthesis in plants and activate cell mitosis, and possibly act as plant growth regulators [37]. In 1970, *Ajugalactone* (50) was isolated from *A. decumbens* [38]. Up to 1999, eight ecdysteroids (51 - 58) were obtained from the flowering whole plant [39]. The structures of these compounds are described in Fig 1(f), Fig 1(g).

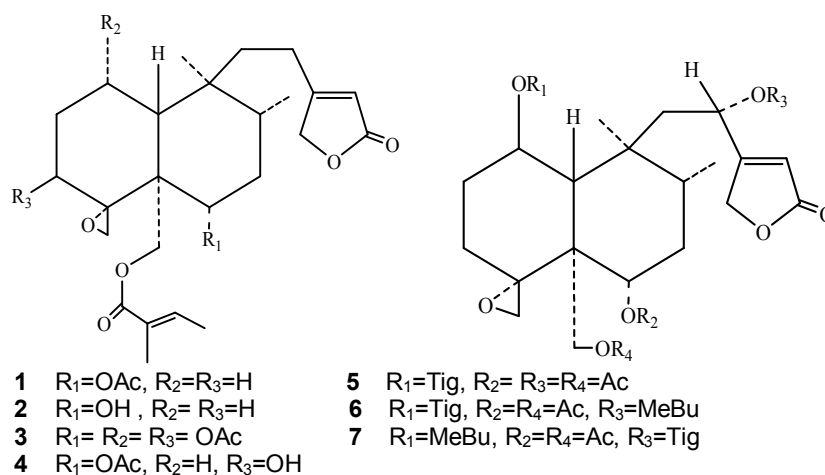
### Others compounds

Two known compounds (59 - 60), a new phenethyl alcohol glycoside (61) were isolated from *A. decumbens* [25]. In 1999, two compounds (62 - 63) were obtained and structurally characterized from the flowering whole plant of *A. decumbens* [39].

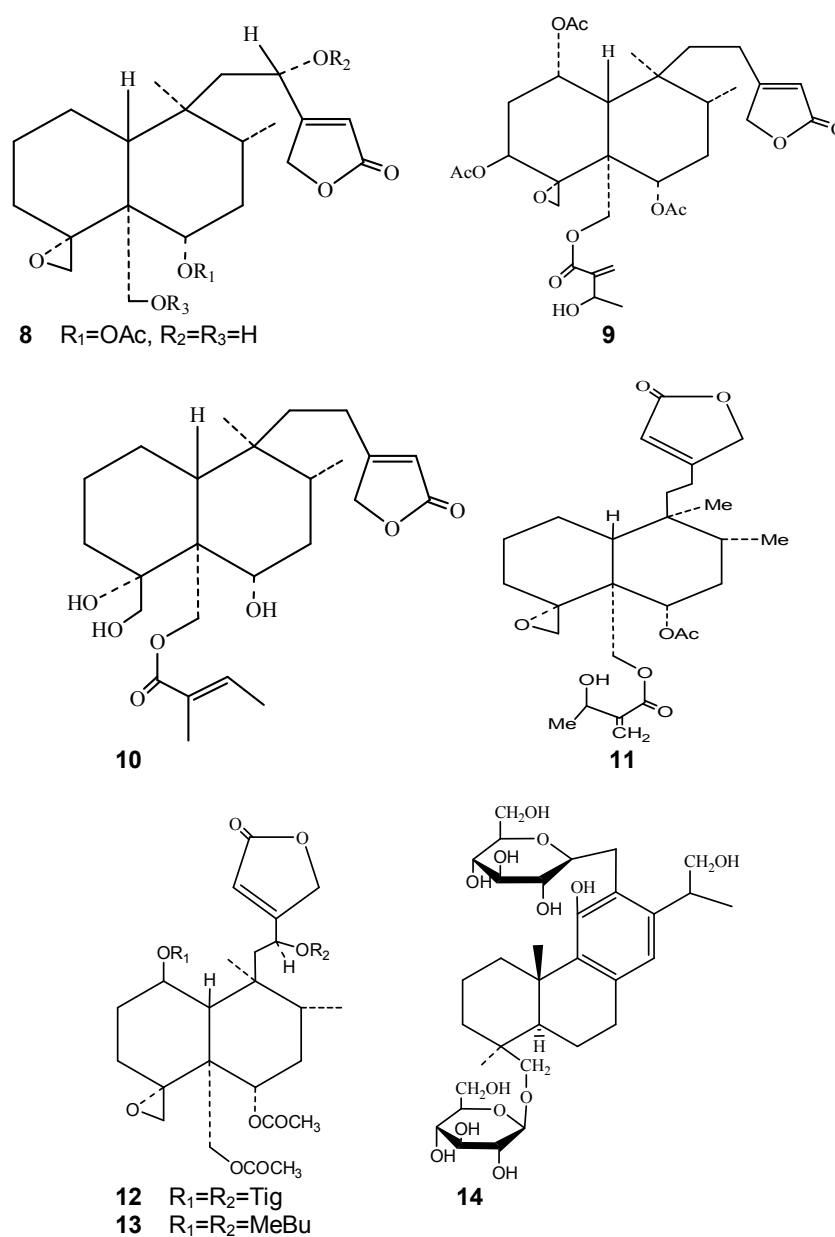
A few years later, four compounds, (6R,7E,9R)-9-hydroxy-4,7-megastigmadien-3-one (64), (3S,5R,6S,7E)-5,6-epoxy-3-hydroxy-7-megastigmen-9-one (65), (6E,9S)-9-hydroxy-4,6-megastigmadien-3-one (66), 6-hydroxy-4,7-megastigmadiene-3,9-dione (67) were identified by comparison of their NMR, optical rotation and MS data with those reported in the literature [32,40,41]. In the same year, five other compounds (68 - 72) were obtained from the methanol extract [28]. The structures of these compounds are stated in Fig 1(g) and Fig 1(h).

**Table 1:** Compounds isolated from *A. decumbens* Thunb.

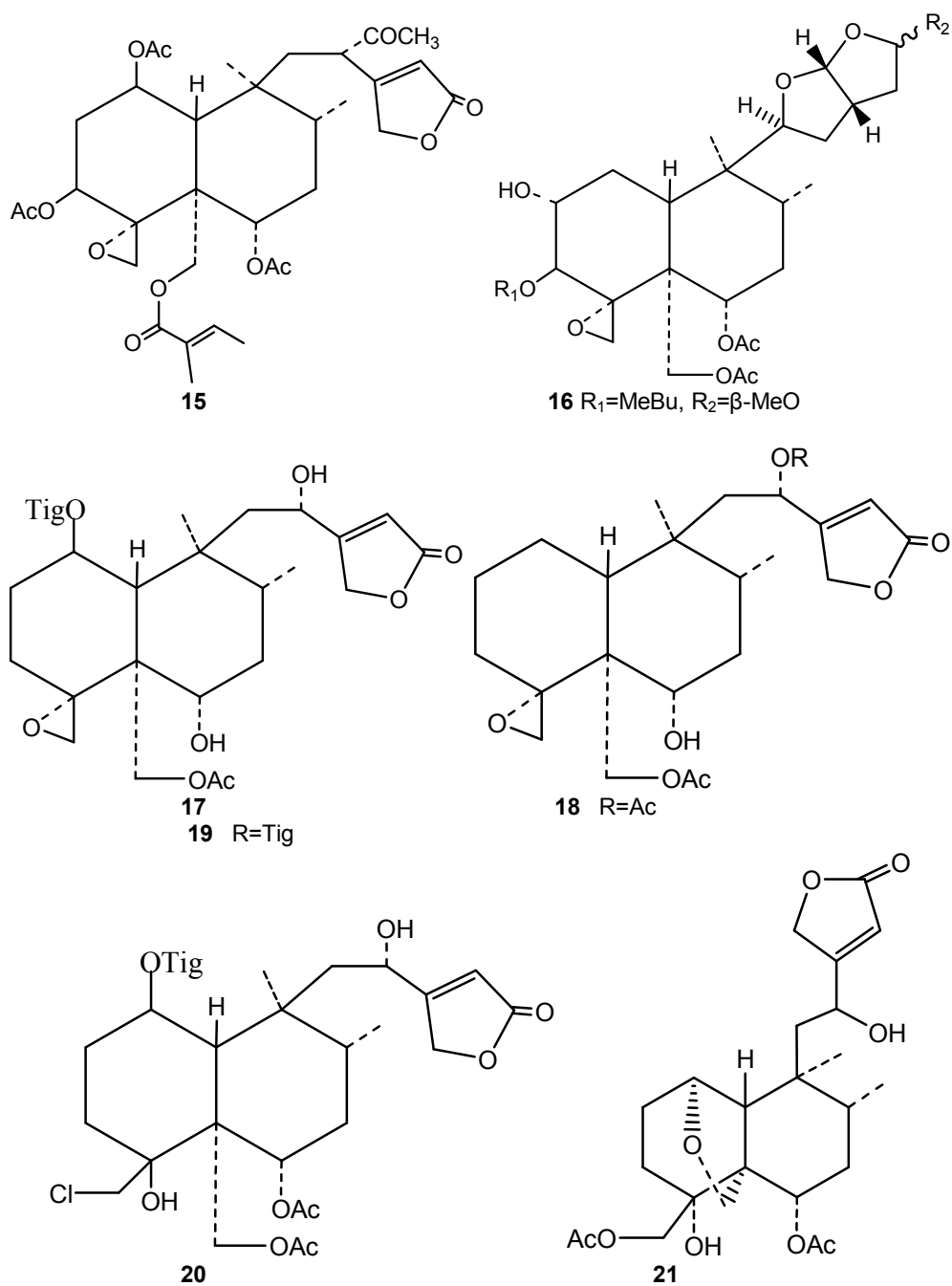
No.	Name	Physical state	Ref
1	<i>Ajugacumbins A</i>	Colorless crystal	[20]
2	<i>Ajugacumbins B</i>	Colorless crystal	[20]
3	<i>Ajugacumbins C</i>	Amorphous powder	[20]
4	<i>Ajugacumbins D</i>	Colorless crystals	[20]
5	<i>Ajugamarins A2</i>	Amorphous solid	[21]
6	<i>Ajugamarins G1</i>	Colorless crystal	[21]
7	<i>Ajugamarins H1</i>	Colorless needle	[21]
8	<i>Ajugamarins F4</i>	Colorless crystal	[21]
9	<i>Ajugacumbins E</i>	Colorless crystal	[22]
10	<i>Ajugacumbins F</i>	Colorless crystal	[22]
11	<i>Ajugacumbins G</i>	Colorless crystal	[23]
12	<i>Ajugatakasins A</i>	Colorless oil	[24]
13	<i>Ajugatakasins B</i>	Amorphous solid	[24]
14	<i>Ajugaside A</i>	Colorless crystal	[25]
15	<i>Ajugacumbins H</i>	Colorless crystal	[26]
16	<i>15-epilupulin A</i>	Colorless needle	[27]
17	<i>6-O-deacetylajugamarin</i>	Colorless needle	[27]
18	<i>Ajugadecumbenins A</i>	Colorless needle	[27]
19	<i>Ajugadecumbenins B</i>	Amorphous powder	[27]
20	<i>Ajugamarin A1 chlorhydrin</i>	Amorphous powder	[28]
21	<i>(12S)-1<math>\alpha</math>,19-epoxy-6<math>\alpha</math>,18-diacetoxy-4<math>\alpha</math>,12-dihydroxy-neo-clerod-13-en-15,16-olide</i>	Colorless flake	[29]
22	<i>(12S)-6<math>\alpha</math>,19-diacetoxy-18-chloro-4<math>\alpha</math>-hydroxy-12-tigloyloxy-neo-clerod-13-en-15,16-olide</i>	Colorless flake	[29]
23	<i>(12S,2''S)-6<math>\alpha</math>,19-diacetoxy-18-chloro-4<math>\alpha</math>-hydroxy-12-(2-methylbutanoyloxy)-neo-clerod-13-en-15,16-olide</i>	White powder	[29]
24	<i>6<math>\alpha</math>,19-diacetoxy-4<math>\alpha</math>-hydroxy-1<math>\beta</math>-tigloyloxyneo-clerod-12-en-15-oic acid methyl ester-16-aldehyde</i>	Colorless oil	[30]
25	<i>(12S)-18,19-diacetoxy-4<math>\alpha</math>,6<math>\alpha</math>,12-trihydroxy-1<math>\beta</math>-tigloyloxy-neo-clerod-13-en-15,16-olide</i>	White powder	[30]
26	<i>4<math>\alpha</math>,6<math>\alpha</math>-dihydroxy-18-(4'-methoxy-4'-oxobutyryloxy)-19-tigloyloxy-neo-clerod-13-en-15,16-olide</i>	White powder	[30]
27	<i>Ajugaciliatin J</i>	White powder	[30]
28	<i>Ajuganipponin B</i>	Needle crystal	[29]
29	<i>Ajugamarin A1</i>	Colorless crystal	[29]
30	<i>Ajugarin I</i>	Colorless crystal	[30]
31	<i>Ajugacumbin J</i>	Colorless oil	[31]
32	<i>Dihydroclerodin</i>	Amorphous powder	[32]
33	<i>Clerodinins C</i>	Amorphous powder	[32]
34	<i>Clerodinins D</i>	Amorphous powder	[32]
35	<i>Ajudecumins A</i>	Needle crystal	[32]
36	<i>Ajudecumins B</i>	Amorphous solid	[32]
37	<i>Ajudecumins C</i>	Amorphous solid	[32]
38	<i>Ajudecumins D</i>	Orange oil	[32]
39	<i>Decumbeside A</i>	Amorphous powder	[34]
40	<i>Decumbeside B</i>	Amorphous powder	[34]
41	<i>Decumbeside C</i>	Amorphous powder	[34]
42	<i>Decumbeside D</i>	Amorphous powder	[34]
43	<i>Reptoside</i>	Amorphous powder	[34]
44	<i>8-acetylharpagide</i>	Amorphous powder	[34]
45	<i>Harpagide</i>	Amorphous powder	[25]
46	Luteolin	Amorphous powder	[35]
47	5, 7-dihydroxy-4'-methylflavone	Needle crystal	[36]
48	Apigenin	Amorphous powder	[28]
49	Acacetin	Amorphous powder	[32]



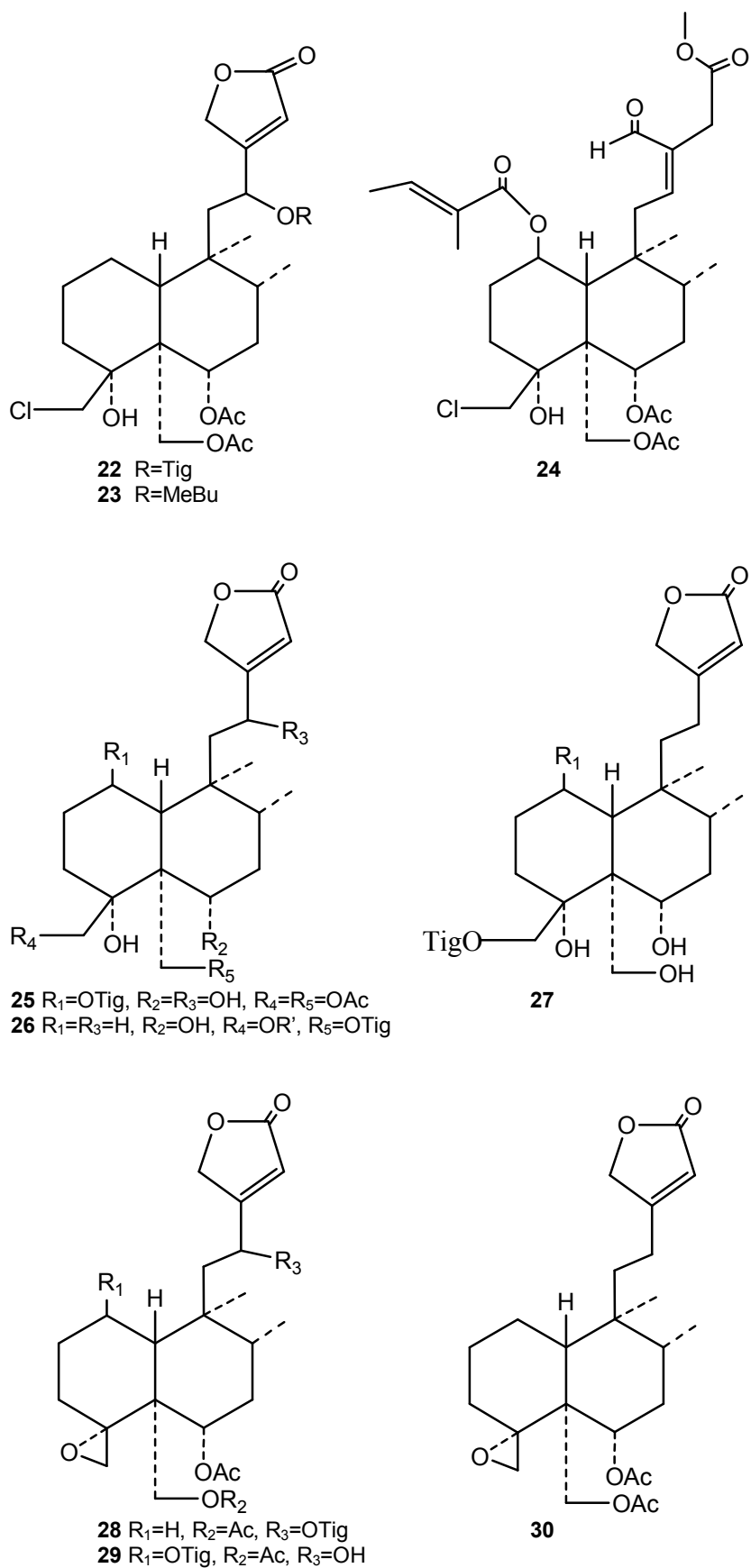
**Fig 1(a):** Structures of compounds from *A. decumbens* Thunb.



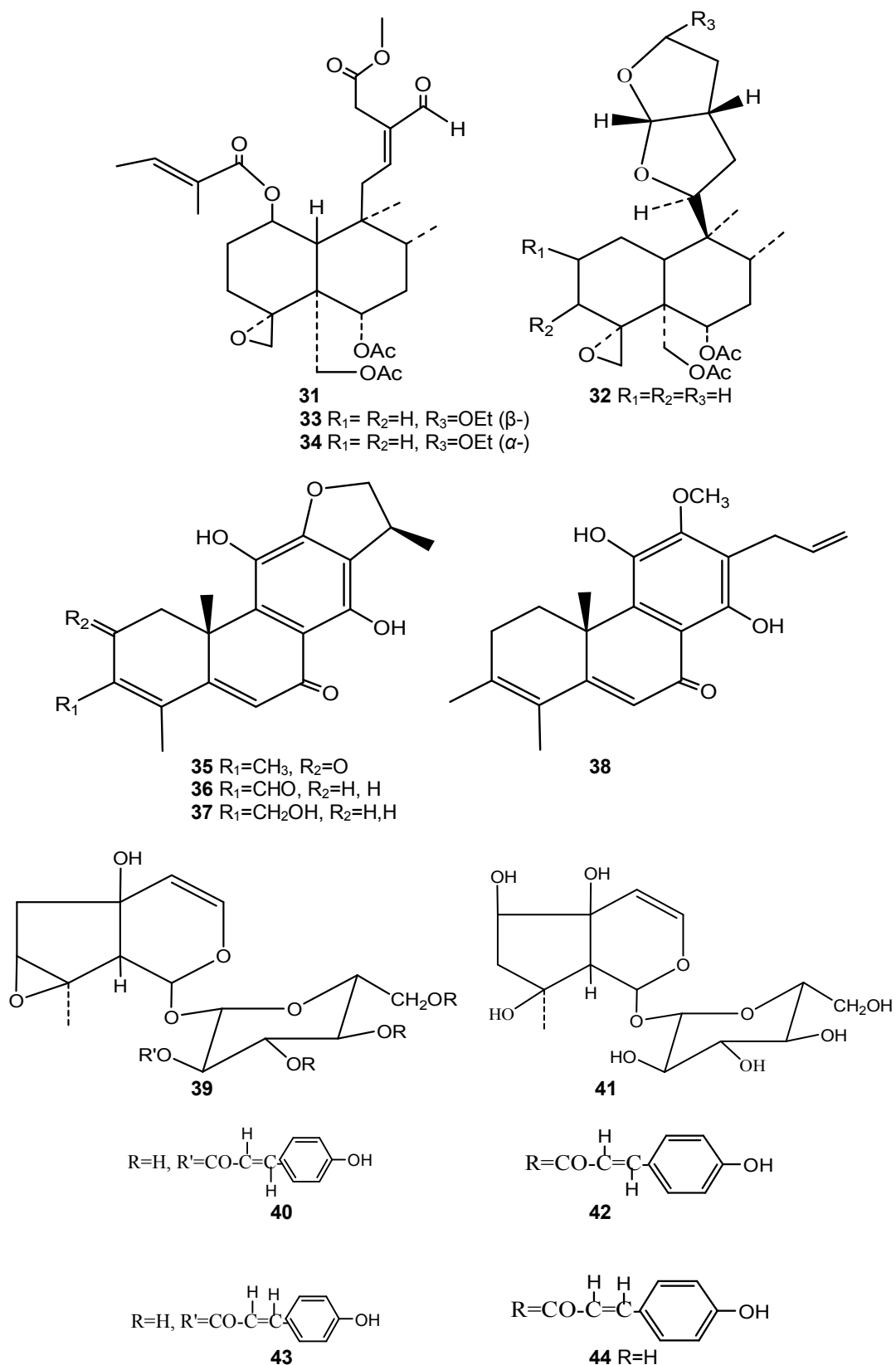
**Fig 1(b):** Structures of compounds from *A. decumbens* Thunb. (contd)



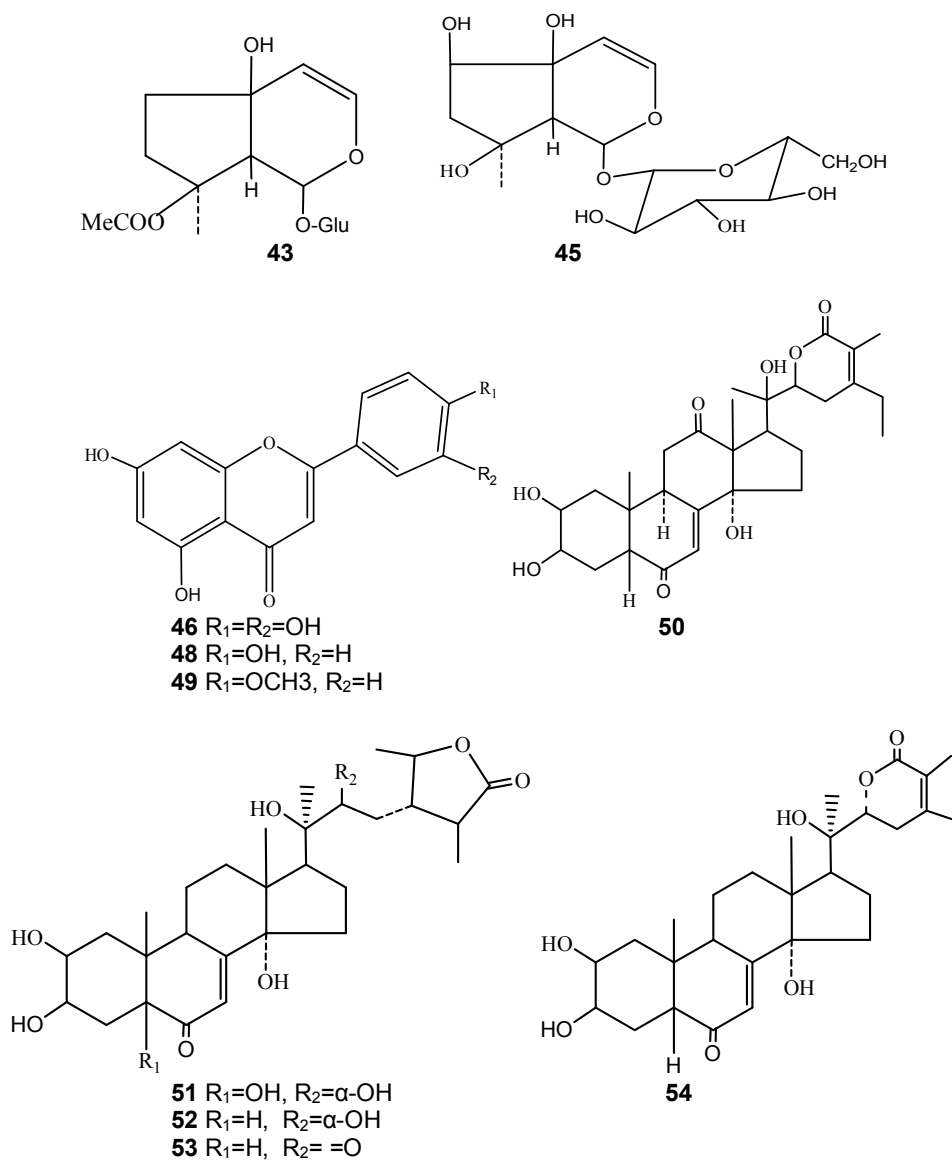
**Fig 1(c):** Structures of compounds from *A. decumbens* Thunb. (contd)



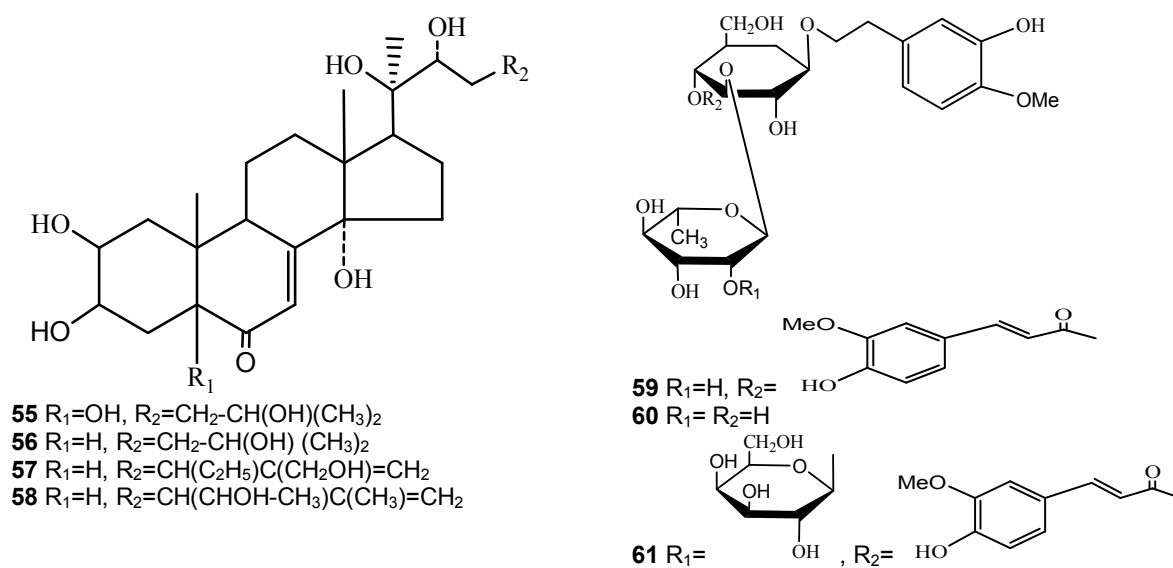
**Fig 1(d):** Structures of compounds from *A. decumbens* Thunb. (cont'd)



**Fig 1(e):** Structures of compounds from *A. decumbens* Thunb. (contd)



**Fig 1(f):** Structures of compounds from *A. decumbens* Thunb. (contd)



**Fig 1(g):** Structures of compounds from *A. decumbens* Thunb. (contd)



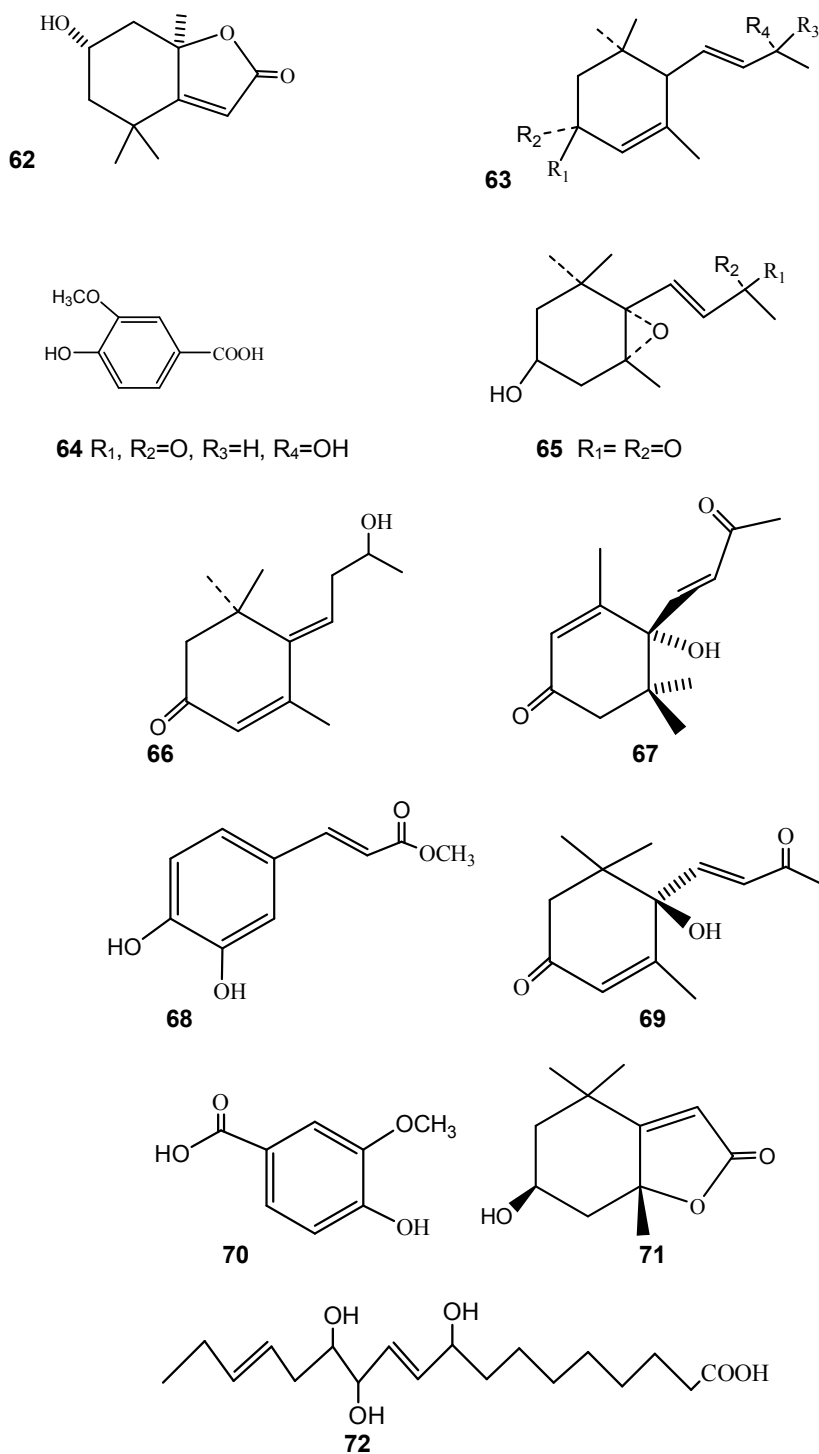


Fig 1(h): Structures of compounds from *A. decumbens* Thunb. (contd)

## BIOLOGICAL PROPERTIES

Various extracts or purified compounds from *A. decumbens* exhibit diverse biological characteristics, which are anti-inflammatory, antitumor, antibacterial, antiviral, cytotoxic, as well as insecticidal activities. Herein, we describe the biological activities as well as its active extracts or compounds.

## Anti-inflammatory activities

Several studies investigated that the whole plant of *A. decumbens* possessed the anti-inflammatory effects described in the famous pharmacy book of China, Dictionary of Chinese Materia Medica [42-43]. The inhibitory activities on LPS - induced NO production of diterpenes were evaluated, compounds (22-26, 28) showed inhibitory effects, indicating these substances

were expected to be useful as effective potential anti-inflammatory agents [29,30]. Similarly, *Ajugacumbin J* (31) and *ajugacumbin D* (4) exhibited the inhibitory activities of LPS-induced NO production in RAW 264.7 macrophages with an IC<sub>50</sub> value of 46.2 and 35.9 mM, respectively [31]. The ethanol extracts of *A. decumbens* extracts (KE) improved the balance of bone resorption and bone formation, showing anti-inflammatory effects. The results exhibited that KE were beneficial for sufferers of bone and joint disease [44]. Total flavonoids of *A. decumbens* (TFA) had a therapeutic effect on chronic serum sickness glomerulonephritis (CSS-GN) rats by increasing SOD activity, lowering MDA and inhibiting lipid peroxidation [45].

### Antitumor activities

The inhibitory effects of these compounds (14, 43-45, 59-61) on EBV activation induced by TPA were examined via a primary screening for anti-tumor activity, and the results showed that 8-*Acetylharpagide* (44).

exhibited the strongest inhibitory effect on EBV activation [25]. In addition, compound 44 exhibited an anti-proliferative effect on mouse hepatic tumor using N-nitrosodiethylamine (DEN) as an initiator and phenobarbital (PB) as a promoter [46]. Takasaki et al also found that compounds 44 and 52 had potent antitumor-promoting activities on mouse skin *in vivo* two-stage carcinogenesis procedure. Furthermore, compound 44 also exhibited potent chemopreventive activity in a mouse pulmonary tumor model [39]. Compounds 35 - 37 exhibited moderate inhibitory activity on the proliferation of human breast cancer MCF-7 cells [32]. *A. decumbens* extracts showed anticancer and antimetastatic effects towards breast cancer through regulating the expression of MMPs and TIMPs [47]. Additionally, *A. decumbens* extracts exhibited an anti-proliferative effect on lung

cancer A-549, liver cancer SMMC-7721 and Sarcoma S18 [48,49]. What is more, water extracts of *A. decumbens* significantly inhibited the proliferation of HepG2 cells in a dose-dependent manner [50].

### Antibacterial activities

*A. decumbens* extracts exhibited significantly antibacterial effect by inhibiting the growth of *S. aureus*, *S. epidermidis*, *K. pneumonia*, *E. coli* and *P. aeruginosa* [51]. Besides, through the analysis of antibacterial activity *in vivo* and *in vitro*, water extracts of *A. decumbens* also possessed antibacterial activities against *Streptococci* [52].

### Antivirus activities

Ma et al found that the whole plant of *A. decumbens* showed potent antiviral activities against respiratory syncytial virus (RSV) with an IC<sub>50</sub> value of 131.6 µg/ml [53]. In addition, *A. decumbens* water extracts could inhibit infectious bronchitis virus (IBV) *in vitro* with the concentration of 750 - 1500 mg/ml [54].

### Cytotoxicity

*Myrotheciumone A* isolated from *A. decumbens* was found to exert cytotoxicity via induction of apoptosis in cancer cell lines [55].

### Insecticidal activities

Min et al reported that these compounds (1-4, 9-10) from the ethanol extract of *A. decumbens* displayed growth-inhibitory properties against insects [20,22]. Similarly, compound 11 also exhibited significant insecticidal activities [23].

The active extracts/compounds of *A. decumbens* and their mechanisms of action are provided in Table 2.

**Table 2:** The active extracts or compounds together with their bioactivities

Biological property	Mechanism of action	Extract/Compound no.
Anti-inflammatory effect	iNOS Lipid peroxidation	22, 23, 24, 25, 26, 28, 31 Total flavonoids
Antitumor effect	EBV human breast cancer lung cancer, liver cancer HepG2 cells	14, 43, 44, 45, 59, 60, 61 35, 36, 37 Water extract
Antibacterial effect	Bacterium	Water extract
Antivirus effect	RSV IBV	Water extract
Cytotoxicity	Tumor cell lines	<i>Myrotheciumone A</i>
Insecticidal effect	insect antifeedant	1, 2, 3, 4, 9, 10, 11

## CONCLUSION

The chemical composition of *A. decumbens* (Labiateae) includes diterpenes, iridoids glycosides, flavonoids, ecdysteroids, and phenethyl alcohol glycoside. A variety of biological properties recorded for *A. decumbens* extracts and chemical compounds indicate that they are of medicinal value. Limited efforts have, however, been made to determine the pharmacokinetics and mechanisms of action of the individual compounds of the plant. The therapeutic potentials of the new chemical compounds from the plant needs to be explored in detail.

## ACKNOWLEDGEMENT

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