

Advance of the Chemical Components and Biological Activities of *Ajuga decumbens* Thunb





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Abstract

Ajuga decumbens Thunb is an annual herbaceous flowering plant, distributed in some parts of Asia. It is adequately used as folk medicines for the treatment different ailments. It contained important bioactive compounds (diterpenoids, iridoid glycosides, phytoecdysteroids, flavonoids and sesquiterpenoids) which made it to possess a wide spectrum of biological activities such as anti-cancer, antioxidant, Antifeedant, antibacterial, anti-inflammatory, antihyperlipidemic, anti-cholinesterase and cytotoxicity activities. This review gives an update about its phytochemicals and biological activities.

Keywords: *Ajuga decumbens* Thunb; Chemical components; Biological activities anization

Introduction

The genus *Ajuga*, belongs to the family of Labiatae, commonly known as “Bugleweed or Ground pine” [1] which distributed mainly in the temperate regions Europe, Asia and Africa [2] where most its species can be found, but only two of *Ajuga* species are available in southeastern Australia [3-4]. Pharmacological studies revealed that *Ajuga* possessed, have been used as anti-inflammatory agents, anti-cancer, astringent, anthelmintic, hypoglycemic, febrifuge diuretic, insecticidal properties and antifungal [5-11]. *Ajuga decumbens* is used as a folk medicine for the treatment of all kinds of ailment in ancient, most especially in China and Japan [12-15]. This review shows previous research on bioactive compounds of *A. decumbens* and biological activities of both the extracts and isolated compounds from this medicinal plant.

Distribution of *A. decumbens*

A. decumbens commonly found in stream sides, wet grassy slopes in Anhui, Fujian, Guangdong, Hainan, Hubei, Hunan, Jiangsu, Jiangxi, Qinghai, Sichuan, Taiwan, Yunnan, Zhejiang of China and some parts in Japan and Korea [16].

The Morphology of *Ajuga decumbens* Thunb

A. decumbens is an annual herbaceous flowering plant, which grow to 10-30 cm height with white villous on the young parts of the stem, numerous basal leaves longer than stem leaves, floral

leaves are bractlike and lanceolate, with funnel- shape calyx and corolla tubular, straight, basally slightly swollen. Flowering starts from March and lasts to the end of July. The fruiting season starts from May and continues till November [16].

Bioactive Compounds Isolated from *A. decumbens*

There are bioactive compounds isolated from *A. decumbens*, including diterpenoids, iridoid glycosides, triterpenoids, sesquiterpenoids, phytoecdysteroids, withanolides and other essential compounds, which are responsible for its effective biological activities.

Diterpenoids: *A. decumbens* is highly rich in diterpenoids as other *Ajuga* species, diterpenoids from *A. decumbens* are of two groups that are neoclerodane and abietane [11,17-18]. Eight diterpenoids were isolated from ethanol extract of *A. decumbens*, including *Ajugacumbins* A (1), *Ajugacumbins* B (2), *Ajugacumbins* C (3), *Ajugacumbins* D (4), *Ajugamarins* A2 (5), *Ajugamarins* G1(6), *Ajugamarins* H1(7) and *Ajugamarins* F4 (8) [19-20]. Min et al. also isolated *Ajugacumbins* E (9) and *Ajugacumbins* F (10) for the first time [21]. *Ajugacumbins* G (11) was isolated from *A. decumbens* [22]. Amano et al. isolated *Ajugatakasins* A (12), *Ajugatakasins* B (13), *Ajugaside* A (14), *Ajugapitin* (*Clerodendrin* D) (15) and Dihydroajugamarin (16) from the extract of *A. decumbens* [23].

Ajugacumbin H (17) was identified from the chloroform extracts of *A. decumbens* [24]. 15-*epi*-lupulin A (18), 6-*O*-deacetylajugamarin (19), *Ajugadecumbenins* A (20) and *Ajugadecumbenins* B (21) were discovered [25].

Ajugamarin A1 chlorhydrin (22) was isolated from the whole plant of *A. decumbens* [26]. Sun et al. also isolated ten neoclerodane diterpenoids, including 6 α ,19-diacetoxy-4 α -hydroxy-1 β -tigloyloxyneo-clerod-12-en-15-oic acid methyl ester-16-aldehyde (23), (12*s*)-18,19-diacetoxy-4 α ,6 α ,12-trihydroxy-1 β -tigloyloxy-neo-clerod-13-en-15,16-olide (24), (12*S*)-1 α ,19-epoxy-6 α ,18-diacetoxy-4 α ,12-dihydroxy-neoclerod-13-en-15,16-olide (25), (12*s*)-6 α ,19-diacetoxy-18-chloro-4 α -hydroxy-12-(2-methylbutanoyloxy)-neo-clerod-13-en-15,16-olide (27), 4 α ,6 α -dihydroxy-18-(4'-methoxy-4'-oxobutyryloxy)-19-tigloyloxy-neoclerod-13-en-15,16-olide (28), *Ajugaciliatin* J (29), *Ajuganipponin* B (30), *Ajugamarin* A1(31), *Ajugarin* I (32) [27-28]. Lv et al. reported *Ajugacumbin* J (33) as a new neo-clerodane diterpene [29]. Diglucopyranoside (34) and *Ajugaside* (14) were isolated from the whole plants of *A. decumbens* as a newly detected abietane [30]. Wang et al. isolated *Ajudecumin* A (35), *Ajudecumin* B (36), *Ajudecumin* C (37) and *Ajudecumin* D (38) as newly rearranged abietane hydroquinones, with *Ajuforrestin* A (39) and *Ajuforrestin* B (40) as known abietanes from the aerial parts of *A. decumbens* [18] (Figure 1).



Figure 1: Distribution of *A. decumbens*.

Iridoid Glycosides: Iridoid glycosides are other predominant compounds of *A. decumbens*, Iridoid glycosides in plant contribute to defense against external factors such as herbivores or infection by microorganisms. Takeda et al., isolated *Decumbeside* A (41), *Decumbeside* B (42), *Decumbeside* C (43), *Decumbeside* D (44), reptoside (45) and 8-*O*-Acetylharpagide (46) from Methanol extract of *A. decumbens* [31]. Three Iridoid glycosides were reported to be presence in *A. decumbens* out of seven compounds isolated and elucidated [30]. Wen et al., reported the contents of 8-*O*-acetylharpagide (46) and harpies (47) in *A. decumbens* by HPLC-ELSD [32] (Figure 2).

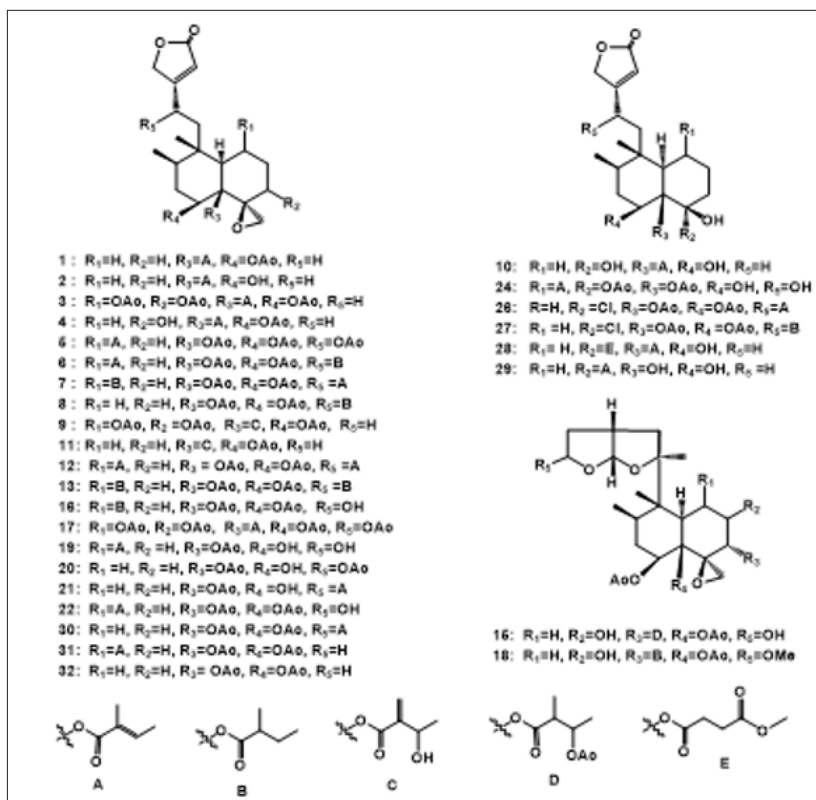


Figure 2.

Phytoecdysteroids: Phytoecdysteroids are plant-derived steroid-like compounds. Phytoecdysteroids are a class of triterpenoids that plants synthesize for protection against phytophagous (plant-eating) insects. Phytoecdysteroids were also present in *A. decumbens*. Cymserine (48) and Ecdysterone (49) are usually the most abundant phytoecdysteroids in the genus *Ajuga*, which were isolated from

the whole part of this medicinal plant [33]. Koreeda et al. reported the presence of Ajugalactone (50) from *A. decumbens* [34]. Eight phytoecdysteroids were also discovered from the plant [17]. Guo et al. isolated β -sitosterol 3-O- β -D-glucopyranoside (51) from the whole plant of *A. decumbens* [35] (Figure 3).

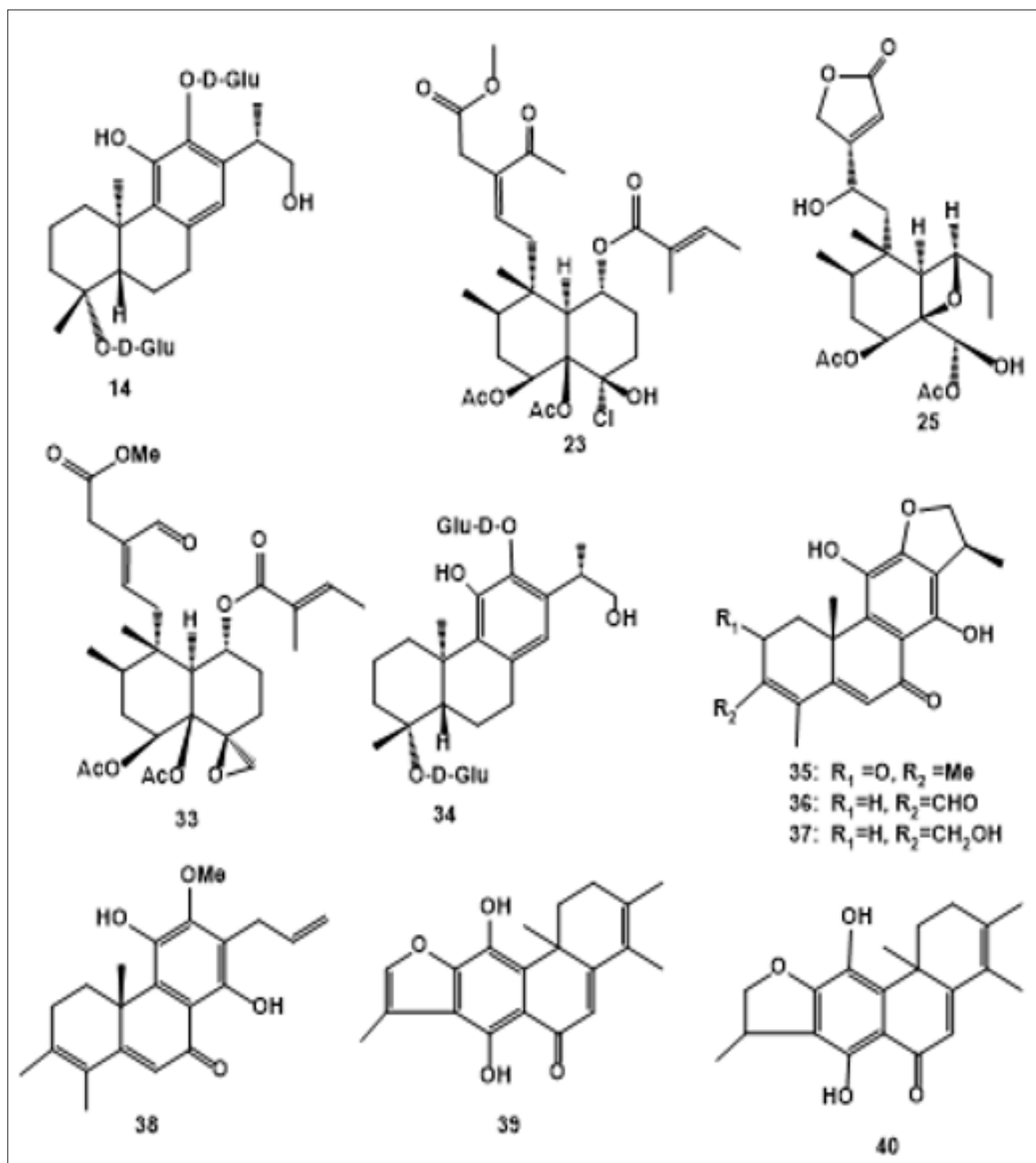


Figure 3.

Flavonoids: Studies have shown that various flavonoids are embedded in *A. decumbens*. Luteolin (52) was isolated from the ethanol extract of *A. decumbens* [36]. Guo et al. identified Dihydroxy-4-methyl flavone (53) from its methanol extract [35]. Api-

genin (54) was reported to be present in *A. decumbens* [26]. Acacetin (55) was obtained from the aerial parts of this medicinal plant [18] (Figure 4).

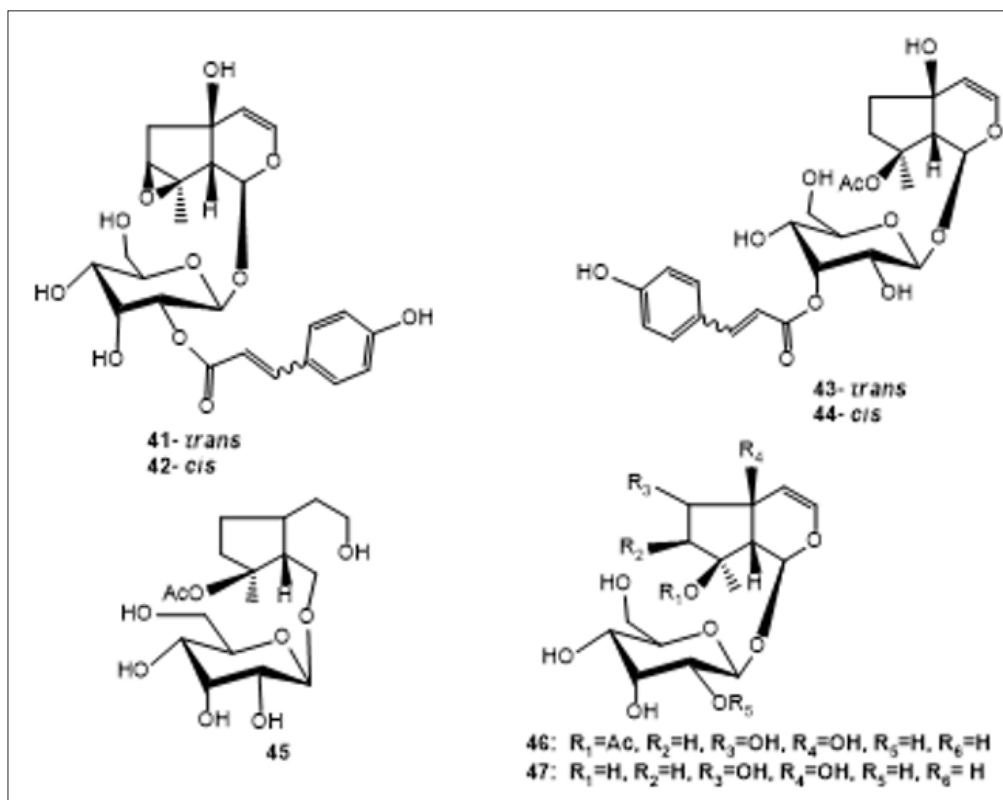


Figure 4.

Sesquiterpenoids: Few of Sesquiterpenoids are reported, Glecholone (56), (6R,7E,9R)-9-Hydroxy-4,7-megastigmadien-3-one(57), (3S,5R,6S,7E)-5,6-Epoxy-3-hydroxy-7-megastigmen-9-one (58), (6E,9S)-9-Hydroxy-4,6-megastigmadien-3-one (59) and

6-Hydroxy-4,7-megastigmadiene-3,9-dione (60) were isolated from the aerial parts of *A. decumbens* [18]. Sun et al., Isolated Loliolide (61) from the whole plant of *A. decumbens* [26] (Figure 5).

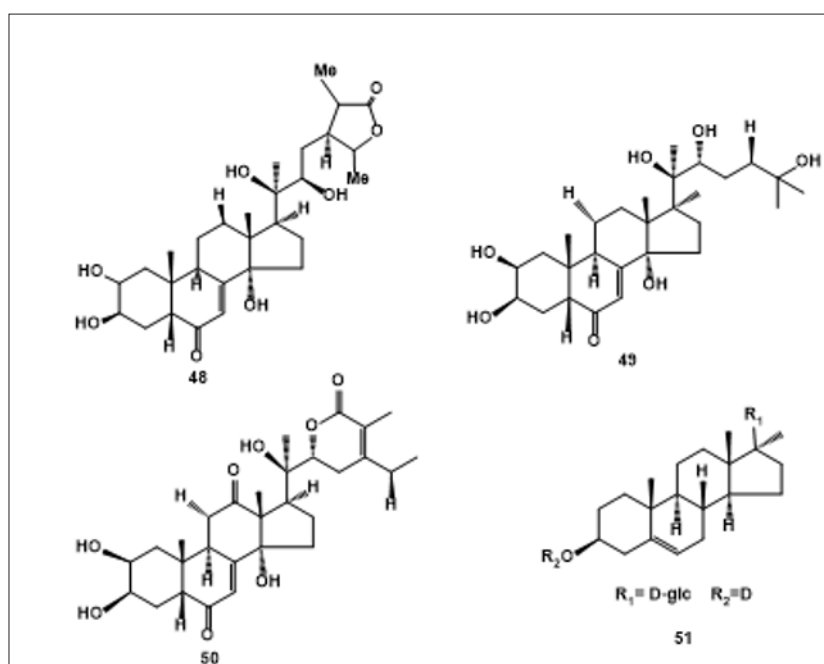


Figure 5.

Biological Activities

Anti-Cancer Activity: Takasaki et al. conducted in vitro inhibitory effects of the isolated compounds (*Ajugaside* A (14), Reptoside (45), 8-O-acetylharpagide (46), Harpagide (47), Galactosylmartynoside (62), Martynoside (63) and Darendoside B (64) on Activation of the Epstein-Barr virus transcription factor BZLF1 by 12-O-tetradecanoylphorbol-13-acetate induced phosphorylation were evaluated, the results revealed that 8-O-Acetylharpagide (46) displayed the strongest inhibitory effect on EBV activation induced by TPA [27-30]. 8-O-acetylharpagide (46) also displayed inhibitory effect on hepatic carcinogenesis using N-nitrosodiethylamine (DEN) as an initiator and phenol-barbital (PB) as a promoter [31-37]. Extracts of *A. decumbens* displayed anticancer and antimetastatic effects towards breast cancer through regulating the expression of MMPs and TIMPs [38]. Ajudecumin A

(35), Ajudecumin B (36) and Ajudecumin C (37) showed inhibitory effect on the proliferation of human breast cancer MCF-7 cells [18]. High and moderate dosage of total flavonoid of *A. decumbens* significantly lower the expression of serum Interleukin-1(IL-1) and Tumor necrosis factor alpha (TNF- α), When compared with control [39]. Water extracts of *A. decumbens* significantly inhibited the increase of HepG2 cells in a dose-dependent manner [40]. Wang et al., reported that *A. decumbens* combined with *Poria cocos* have the ability to inhibit breast cancer cell invasion by targeting the expression of Mitogen-activated protein kinase (MAPK) and Epithelial-Mesenchymal Transition [41]. Iridoid in *A. decumbens* was investigated on the metastasis of invasive breast cancer cells and its related mechanism. The result showed that *A. decumbens* inhibited breast cancer cell invasion by suppressing the MAPK/ERK pathway as well as reversing the EMT [42,43] (Figure 6).

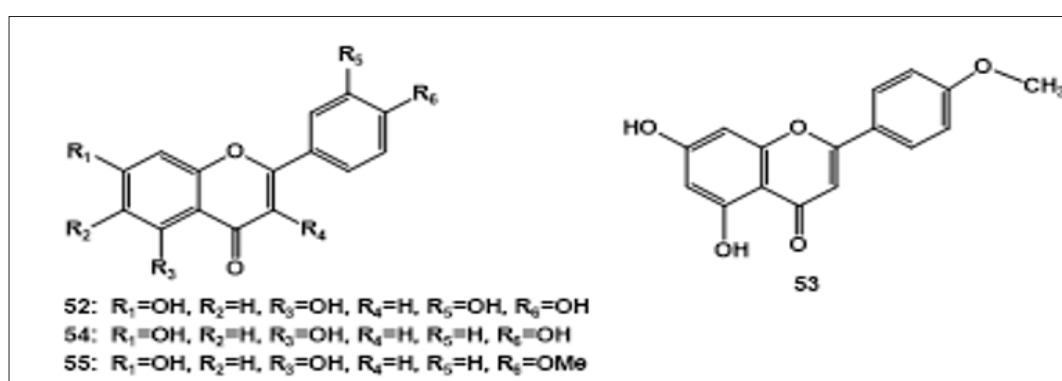


Figure 6.

Antifeedant Activity: Ajugapitin (15) which is also known as Clerodendrin D was discovered from the leaves of *A. decumbens* as a feeding stimulant for *Athalia rosae ruficornis* [23]. Min et al. isolated four Diterpenoids (Ajugacumbins A, B, C and D) from the ethanol extract of *A. decumbens*, these isolated compounds displayed

inhibition against the growth of insects [19]. Ajugacumbins E (9) and Ajugacumbins F (10) from *A. decumbens* showed insecticidal activities [21]. Ajugacumbins G (11) from this plant also exhibited growth-inhibitory activities against insects [22] (Figure 7).

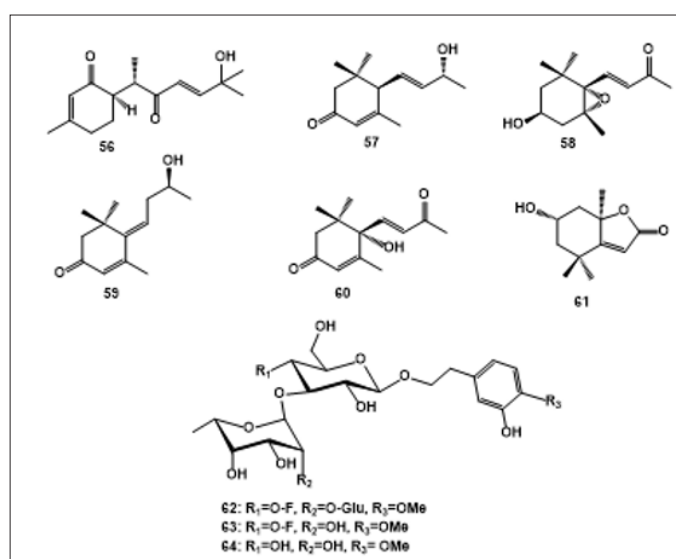


Figure 7.

Anti-Inflammatory Activity: Ajugacumbin J (33) and Ajugacumbin D (4) isolated from the whole plant medicinal plant exhibited inhibitory activities of lipopolysaccharide-induced nitric oxide production in RAW 264.7 macrophages with IC50 s of 46.2 and 35.9mM, respectively [29]. Ono et al. examined the effects of ethanolic extracts of *A. decumbens* on nitric oxide (NO) production, expression of inducible nitric oxide synthase (iNOS), osteoblast and osteoclast activities. The results showed that ethanolic extracts inhibited expression of iNOS which caused concentration dependent inhibition of NO production, prevented brittle bones in ovariectomized mice and swelling of the left hind ankle in adjuvant induced arthritic rats [14] (Table 1).

Table 1: Scientific Classification of *Ajuga decumbens* [16].

Kingdom	Plantae
Phylum	<i>Tracheophyta</i>
Class	<i>Magnoliopsida</i>
Order	<i>Lamiales</i>
Family	<i>Lamiaceae</i>
Genus	<i>Ajuga</i>
Species	<i>Decumbens</i>

Anti-hyperlipidemic Effect: Xiaoming et al. reported that both the water and alcohol extracts of *A. decumbens* significantly showed reduction in the lipid levels in the blood, by administering the extracts on hyperlipemia mouse model [44].

Antivirus Activity: Takasaki et al. reported that 8-acetylharpagide (46) among other compounds isolated from the whole plant of *A. decumbens* showed the strongest inhibitory effect on Epstein-Barr virus activation induced by 12-O-tetradecanoylphorbol-13-acetate [30]. Water extract of *A. decumbens* at the range of 750-1500 mg/ml concentrations exhibited in vitro inhibition on infectious Bronchitis virus [45]. Extract from the whole plant of *A. decumbens* possessed potent antiviral activities against respiratory syncytial virus (RSV) with IC50 of 131.6 µg/ml [46].

Antibacterial Activity: All doses of the extract of *A. decumbens* inhibited the growth *Staphylococcus aureus*, *S. epidermis*, *Klebsiella pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa*, but low dose was not as effective as Reyanning which a control was [47]. Water extract of *A. decumbens* possessed antibacterial activities against *Streptococci*, when analyzed its antibacterial activity *in vivo* and *in vitro* [48].

Cytotoxicity: Isolated diterpenoids from *A. decumbens* such as Ajudecumin A (35), Ajudecumin B(36), Ajudecumin C (37) and Ajudecumin D (38) were tested in vitro inhibition of cell proliferation. The results showed that Ajudecumin A (35) and Ajudecumin C (37) exhibited moderate cytotoxic activities against MCF-7 cell lines with IC50 values of 19.4 and 12.5 µM, respectively [18]. Myrotheciumone A isolated from endophytic fungus of *A. decumbens* exhibited in vitro cytotoxicity and apoptotic activity [49].

Anti-cholinesterase Activity: Xu et al. reported that ethylacetate extract of *A. decumbens* showed high inhibition to

acetylcholinesterase with IC50 of 0.0997mg/mL, it was concluded that the inhibition was possibly due to the flavonoids, which exist as the main chemical composition in *A. decumbens* [50].

Antioxidant Activity: *decumbens* showed the therapeutic effects on Mesangial Proliferative Glomerulonephritis (MsPGN) in rats, by reducing the urinary protein in the rats when it was compared with Tripterygium Wilfordii Polyglycosidium (TWP) group [51]. Nan also reported that total flavonoids of *A. decumbens* reduced the damage of free radicals by increasing Superoxide dismutase (SOD), lowering malondialdehyde (MDA) and inhibition of lipid peroxidation of the induced chronic serum sickness glomerulonephritis rats [52].

Conclusion and Future Perspectives

A. decumbens is extensively used as traditional medicine for curing different ailments. Previous studies showed that both the isolated compounds and extracts possessed a wide spectrum of biological activities, such as anti-cancer, antioxidant, antifeedant, antibacterial, anti-inflammatory, antihyperlipidemic, anti-cholinesterase and cytotoxicity activities. All these pharmacodynamic basis supported the use of *A. decumbens* as traditional medicines. However, although some structures of compounds were isolated and the relevant biological activities were tested, more compounds can be discovered and the medicinal values also need to be examined, such as analgesic, anthelmintic, cardioprotective and hypoglycaemic effects. *In vivo* experiments and toxicity of isolated bioactive compound and extracts should be overemphasized in order to be saved from consumptions. Researchers should focus on identification and quantification the bioactive compounds responsible for each biological activity that *A. decumbens* displays. There should adequate studies on elucidation of the molecular mechanisms underlying the activity of these bioactive compounds, which can lead to use of this plant extracts for drug development.

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