Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
JPP 2018; 7(4): 3202-3211
Received: 11-05-2018
Accepted: 15-06-2018

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Agrimonia pilosa Ledeb: Phytochemistry, Ethnopharmacology, Pharmacology of an important traditional herbal medicine

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Abstract
Agrimonia pilosa Ledeb (Rosaceae, AP) has long been used as a widely herbal medicine in Asian countries for treatment of various diseases. AP contains many valuable secondary metabolites, such as flavonoids, triterpenoid, phenols and phenolic acids and has antioxidant, antibacterial, antiviral, anti-tumor, anti-diabetic properties and effects on alzheimer's disease. In the recently decades, a series of analytical methods have been developed to evaluate the quality of AP based on its bioactive components. This review aims to present an up-to-date and comprehensive overview of the ethnopharmacology, phytochemistry and pharmacology of AP, which should be useful for the greater development of AP, especially in the development of new drugs and therapeutics for various diseases.

Keywords: *Agrimonia pilosa* Ledeb; phytochemistry; pharmacology; flavonoids

1. Introduction
The species of the genus Agrimonia, belonging to the Rosaceae, has about a dozen species, which are perennial herbaceous flowering plants, mainly distributed in the temperate regions of Northern Hemisphere [1]. *Agrimonia pilosa* Ledeb (AP) commonly used in Chinese herbal medicine and widely distributed in most of China, is listed officially in the Chinese Pharmacopoeia [2]. This species has been studied because of its high value in traditional medicine. The results of modern pharmacological studies have revealed that AP could be used for the treatment of anti-tumor, antiviral, anti-microbial, anti-hyperglycemic, antioxidant [3,4]. So far, no studies on the toxicity of AP have been reported.
Recently, different classes of chemical compounds such as flavonoids and triperpenoids have been found in this plant. Among these isolated components, some single flavonoid compounds such as quercitrin, agriflavone, kaempferols, agripinols, apigenin are shown to have a variety of bioactivities *in vivo* or *in vitro*, and thereby are thought as the bioactive components of AP. Therefore, quality control base on these bioactive components to ensure the effects of AP materials and its related products is urgent and necessary. However, the quality control of AP in still not listed in many countries and other official pharmacopoeias. A number of studies have thus quantitative evaluation of AP
Aiming to provide beneficial information for modern uses and scientific studies of AP in the future, this review summarizes and evaluates the available phytochemical and bioactive properties of AP reported by the literature.

2. Botany and Ethnopharmacoloy
2.1 Botany
Taxonomic classification is Kingdom: Plantae; Subkingdom: Viridiplantae; Infrakingdom: Streptophyta; Division: Tracheophyta; Subdivision: Spermatophytina; Infradivision: Angiospermae; Class: Magnoliopsida; Superorder: Rosanae; Order: Rosales; Family: Rosaceae; Genus: Agrimonia; Species: *Agrimonia pilosa* Ledeb [5].
Agrimonia pilosa Ledeb is herb medicine with 30–120 cm tall. Rhizome short, usually tuberous, with many lateral roots and 1 to several underground buds. Stems have sparsely pilose and pubescent, or densely rigidly hairy (rarely sparsely hirsute) in lower part. Stipules green, falcate, rarely ovate or ovate-lanceolate, herbaceous, margin sharply serrate or lobed, rarely entire, apex acute or acuminate; petiole sparsely pilose or pubescent; leaf blade interrupted imparipinnate with (2 or) 3 or 4 pairs of leaflets, reduced to 3 leaflets on upper leaves; leaflets sessile or shortly petiolulate, obovate, obovate-elliptic, or obovate-lanceolate, 1.5–5 × 1–2.5 cm, abaxially appressed pilose on veins, or densely pubescent or tomentose-

pubescent between veins, rarely glabrescent, markedly or sparsely glandular punctate, adaxially pilose, or hirsute or hirtellous on veins, rarely glabrescent, base cuneate to broadly so, margin acutely to obtusely serrate, apex rounded to acute, rarely acuminate. Inflorescence terminal, spicate-racemose, branched or not; rachis pilose. Flowers 6–9 mm in diam.; pedicel 1–5 mm, pilose; bract usually 3-parted with segments linear; bracteoles in 1 pair, ovate, margin entire or lobed. Sepals 5, triangular-ovate. Petals are yellow and oblong. Stamens (5–) 8–15. Style filiform; stigma capitate. Fruiting hypanthium obovoid-conic, 7–8 × 3–4 mm including prickles, abaxially 10-ribbed, pilose, with a multiseriate crown of prickles; prickles erect when young, connivent at maturity. Flower and fruit from May–December

Thinned forests, forest margins, thickets, meadows, stream banks, roadsides; 100--3800 m. Throughout China [Bhutan, Northern India, Japan, Northern Laos, Korea, Mongolia, Myanmar, Nepal, Russia, Sikkim, Northern Thailand, Northern Vietnam; East Europe [6].

2.2. Ethnopharmacology

Agrimonia pilosa Ledeb has been used traditionally for treatment of abdominal pain, sore throat, headaches, bloody discharge, parasitic infections and eczema in Korean and other Asia countries since centuries [7]. It has also been used as an internal application for the treatment of various dermatological problems, such as healing wounds, diminishing wrinkles, pigmentation and atopic dermatitis [8]. The Japanese people widely used its root extract as a famous herbal medicine for cancer therapy. In addition, this plant is traditionally used to suppress diarrhoea, reduce gastric ulcers, relieve inflammation, improve eyesight, detoxify poison and increase the flow of urine in China [9]. Nowadays, The AP is routinely applied on the treatment of diseases, such as stomatitis, hepatitis, enteritis, hematischesis and nephritis caused by bacteria and virus infection. It has also been used as an anti-inflammatory agent in Bulgaria and Great Britain, as anti-parasitic in Korean medicine, as a hemostatic agent in China and Vietnam medicine [10].

3. Phytochemistry

The chemical composition of AP has been studied during some recent decades due to the importance and availability of plant. The phytochemical studies on AP have resulted in the isolation of more than 50 compounds. As one of the important chemical composition, the flavonoids are the main compounds from this species. The isolated compounds (compounds 1- 54) are summarized in Table 1 and their chemical structure are presented in Figures from 1-8.

Table 1: Compounds in *Agrimonia Pilosa* Ledeb.

No.	Compounds	Classes	References
1	Quercetin	Flavonoid	[11]
2	Quercetin-3'-O-β-D-glucoside	Flavonoid	[12]
3	Isoquercitrin	Flavonoid	[1]
4	Quercitrin	Flavonoid	[11]
5	Kaempferol	Flavonoid	[13]
6	Kaempferol 3-O-α-L-rhamnopyranoside	Flavonoid	[14]
7	Kaempferol 3-O-β-D-glucopyranoside	Flavonoid	[14]
8	Kaempferol-7-O-β-D-glucoside	Flavonoid	[12]
9	Kaempferol-7-O-β-D-glucuronide	Flavonoid	[12]
10	Kaempferol-3-O-β-D-glucoside	Flavonoid	[12]
11	Kaempferol-3-O-glucoside	Flavonoid	[1]
12	Rutin	Flavonoid	[13]
13	Apigenin	Flavonoid	[13]
14	Apigenin-7-O- β-D-glucoside	Flavonoid	[12]
15	Apigenin-7-O- β-D-glucuronide	Flavonoid	[12]
16	Agriflavone	Flavonoid	[12]
17	Luteolin	Flavonoid	[10]
18	Luteolin-7-O-β-D-glucopyranoside	Flavonoid	[10]
19	Luteolin-7-O- β-D-glucoside	Flavonoid	[12]
20	Luteolin-7-O- β-D-glucuronide	Flavonoid	[12]
21	Luteolin-7-O- β-D-glucuronide methyl ester	Flavonoid	[12]
22	Luteolin-7-O- β-D-glucuronide butyl ester	Flavonoid	[12]
23	Luteolin-3'-O- β-D-glucoside	Favonoid	[12]
24	Hyperoside	Flavonoid	[13]
25	Tiliroside	Flavonoid	[10]
26	Vitexin	Flavonoid	[13]
27	Aromadendrin	Flavonoid	[15]
28	3-methoxy quercetin	Flavonoid	[11]
29	Tormentic acid	Triterpenoid	[13]
30	Maslinatic acid	Triterpenoid	[13]
31	Corosolic acid	Triterpenoid	[13]
32	Oleanolic acid	Triterpenoid	[13]
33	Agrimophol	Phenol	[10]
34	Agrimols A, B, C,D, E	Phenol	[16]
35	Esculetin	Coumarin	[17]
36	Esculin	Coumarin	[17]
37	Ubelliferone	Coumarin	[17]
38	Caffeic acid	Phenolic acid	[10]
39	Chlorogenic acid	Phenolic acid	[10]

40	Ellagic acid	Phenolic acid	[12]
41	Potentillin	Tannin	[10]
42	Agrimoniin	Tannin	[3]
43	Agritanin	Tannin	[12]
44	Takanechromone C	Phenolic glycoside	[1]
45	Agrimonolide 6-O-glucoside	Phenolic glycoside	[1]
46	Desmethylagrimonolide 6-O-β-D-glucopyranoside	Phenolic glycoside	[1]
47	(-)-aromadendrin 3-O-β-D-glucopyranoside	Phenolic glycoside	[1]
48	5,7-dihydroxy-2-propylchromone 7-O-β-D-glucopyranoside	Phenolic glycoside	[1]
49	Loliolide		[15]
50	Dihydro Dihydro Coniferyl alcohoh 9'-O-β-D-glucose.		[12]
51	Afzelin	Flavonol glycoside	[1]
52	Agripinol A		[18]
53	Agripinol B		[18]
54	Agripinol C		[18]

3.1 Flavonoids

Flavonoids are very common and important secondary metabolites in nature. So far, twenty eight flavonoids have been found in AP, including quercetin (1), Quercetin-3'-O-β-D-glucoside (2), Isoquercitrin (3), Quercitrin (4), Kaempferol (5), Kaempferol 3-O-α-L-rhamnopyranoside (6), Kaempferol 3-O-β-D-glucopyranoside (7), Kaempferol-7-O-β-D-glucoside (8), Kaempferol-7-O-β-D-glucuronide (9), Kaempferol-3-O-β-D-glucoside (10), Kaempferol-3-O-glucoside (11), Rutin (12), Apigenin (13), Apigenin-7-O- β-D-glucoside (14), Apigenin-7-O- β-D-glucuronide (15), Agriflavone (16), Luteolin (17), Luteolin- 7-O-β-D-glucopyranoside (18), Luteolin-7-O- β-D-glucoside (19), Luteolin-7-O- β-D-glucuronide (20), Luteolin-7-O- β-D-glucuronide methyl ester (21), Luteolin-7-O- β-D-glucuronide butyl ester (22), Luteolin-3'-O- β-D-glucoside (23), Hyperoside (24), Tiliroside (25), Vitexin (26), Aromadendrin (27), 3-methoxy quercetin (28) (Figure 1a and 1b).

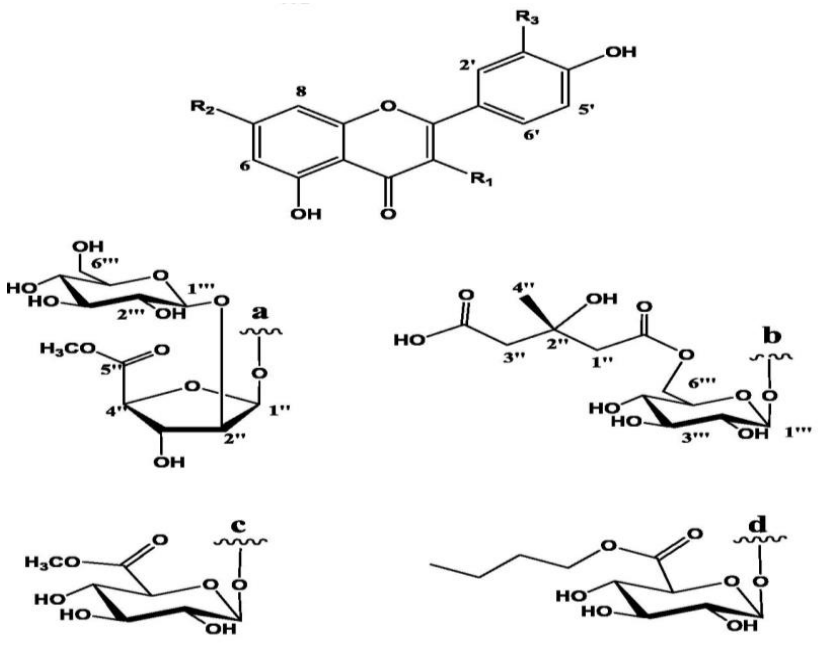


Fig 1a: Chemical structures of compounds 1-23 from AP *Note*: Rha= α-L-rhamnopyranosyl

No.	Compounds	R1	R2	R3
1	Quercetin	OH	OH	OH
2	Quercetin-3'-O-β-D-glucoside	OH	OH	O-Glucose
3	Isoquercitrin	O-Glucose	OH	OH
4	Quercitrin	O-Rha	OH	OH
5	Kaempferol	OH	OH	H
6	Kaempferol 3-O-α-L-rhamnopyranoside	O-Rha	OH	H
7	Kaempferol 3-O-β-D-glucopyranoside	O-Glucose	H	H
8	Kaempferol-7-O-β-D-glucoside	OH	O-Glucose	H
9	Kaempferol-7-O-β-D-glucuronide	OH	O-Glucuronic	H
10	Kaempferol-3-O-β-D-glucoside	O-Glucose	OH	H
11	Kaempferol-3-O-glucoside			
12	Rutin	O-Rha(1-6)Glucose	OH	OH
13	Apigenin	H	OH	H
14	Apigenin-7-O- β-D-glucoside	H	O-Glucose	H
15	Apigenin-7-O- β-D-glucuronide	H	O-Glucuronic	H

16	Agriflavone	H	a	H
17	Luteolin	H	OH	OH
18	Luteolin-7-O-β-D-glucopyranoside	H	O-	OH
19	Luteolin-7-O- β-D-glucoside	H	O-Glucose	OH
20	Luteolin-7-O- β-D-glucuronide	H	O-Glucuronic	OH
21	Luteolin-7-O- β-D-glucuronide methyl ester	H	c	OH
22	Luteolin-7-O- β-D-glucuronide butyl ester	H	d	OH
23	Luteolin-3'-O- β-D-glucoside	H	OH	O-Glucose

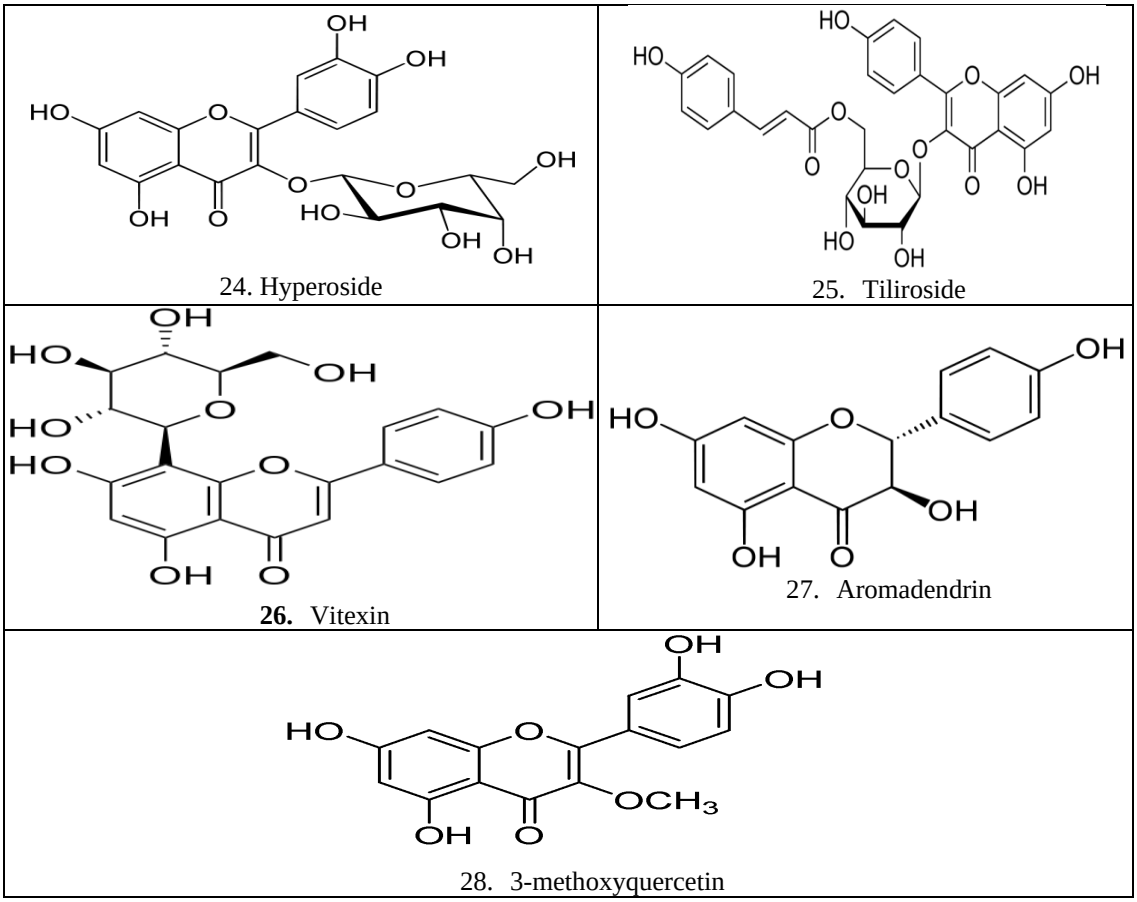
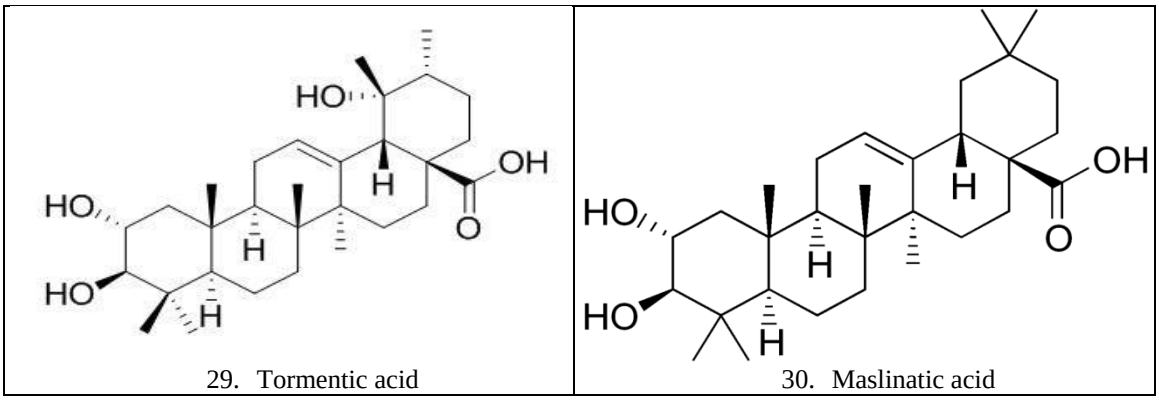
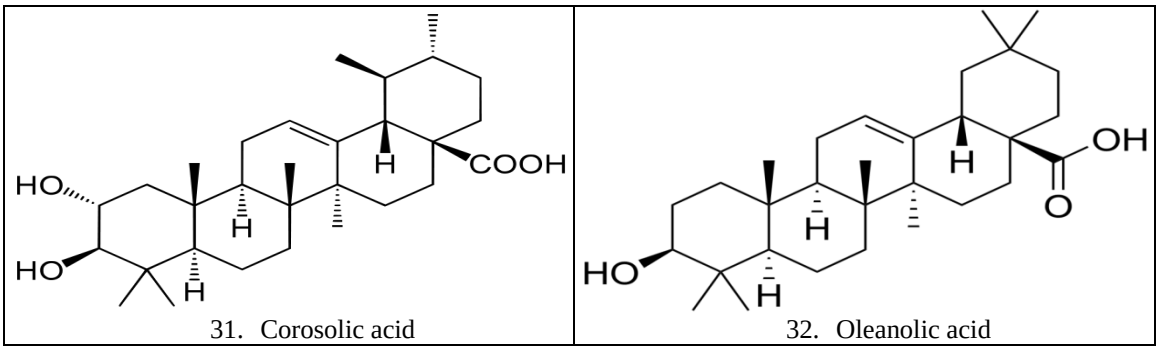


Fig 1b: Chemical structures of compounds 24-28 from AP

3.2 Triterpenoids

Tormentic acid (29), Maslinatic acid (30), Corosolic acid (31), Oleanolic acid (32) (Figure 2)





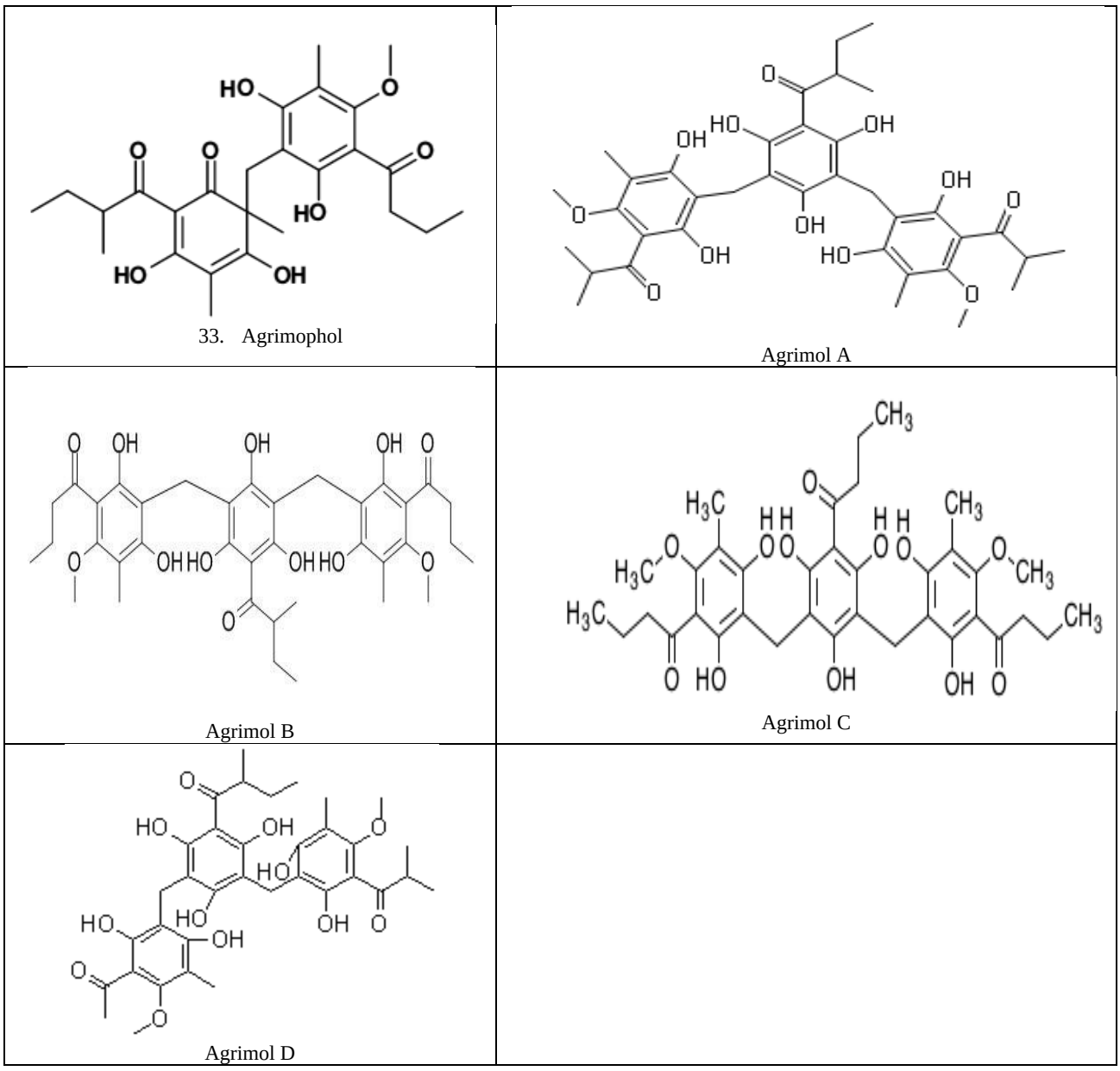
31. Corosolic acid

32. Oleanolic acid

Fig 2: Chemical structures of compounds 29-32 from AP

3.3 Phenols

Agrimophol (33), Agrimols A, B, C, D, E (34) (Figure 3)



33. Agrimophol

Agrimol A

Agrimol B

Agrimol C

Agrimol D

Fig 3: Chemical structures of compounds 33 and 34 from AP

3.4 Coumarins

Esculetin (35), Esculin (36), Umbelliferone (37) (Figure 4)

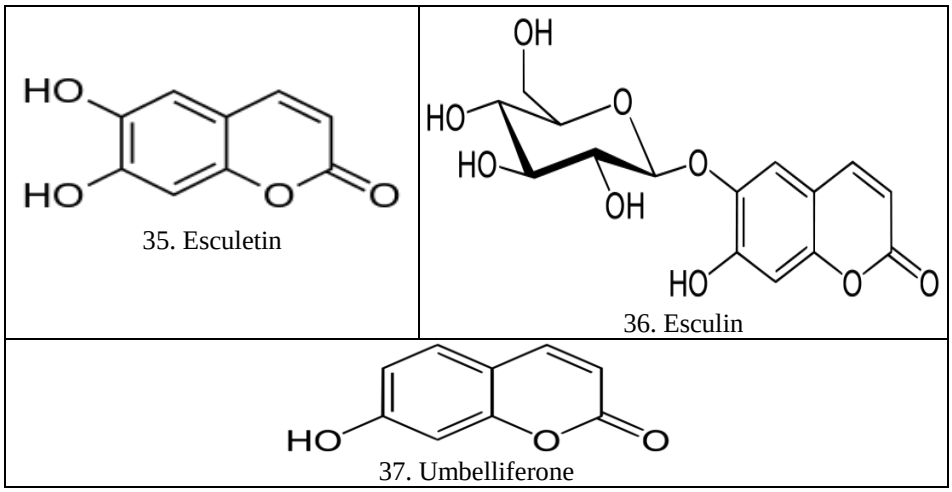


Fig 4: Chemical structures of compounds 35-37 from AP

3.5 Phenolic acids

Caffeic acid (38), Chlorogenic acid (39), Ellagic acid (40) (Figure 5)

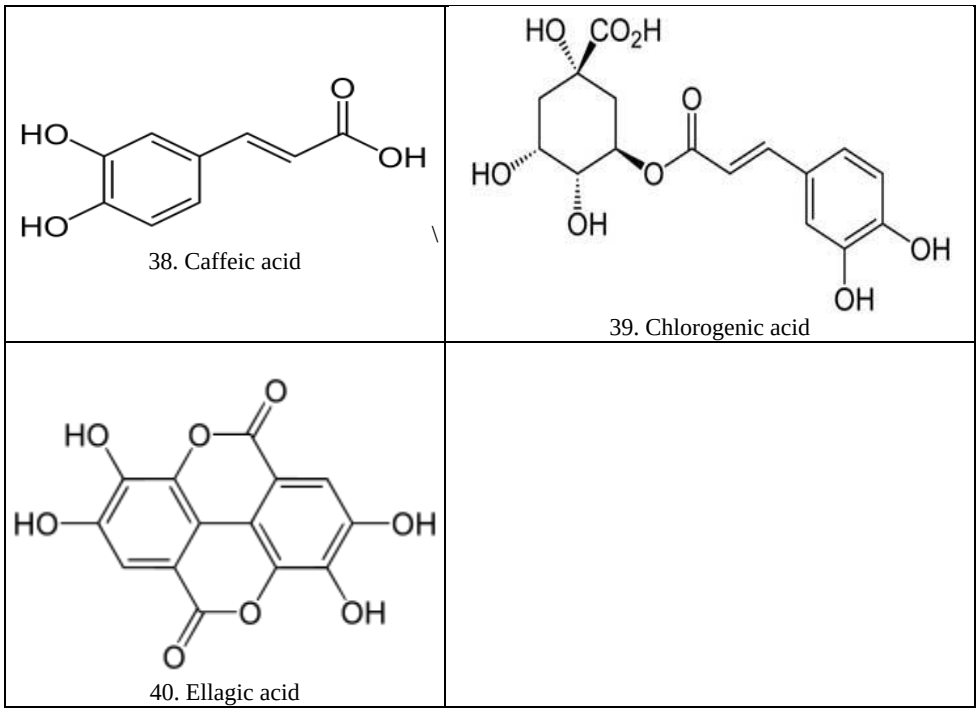
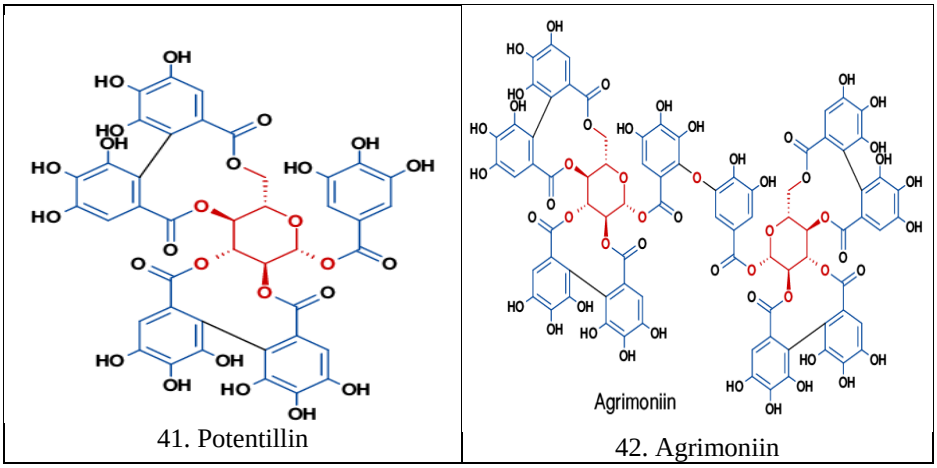
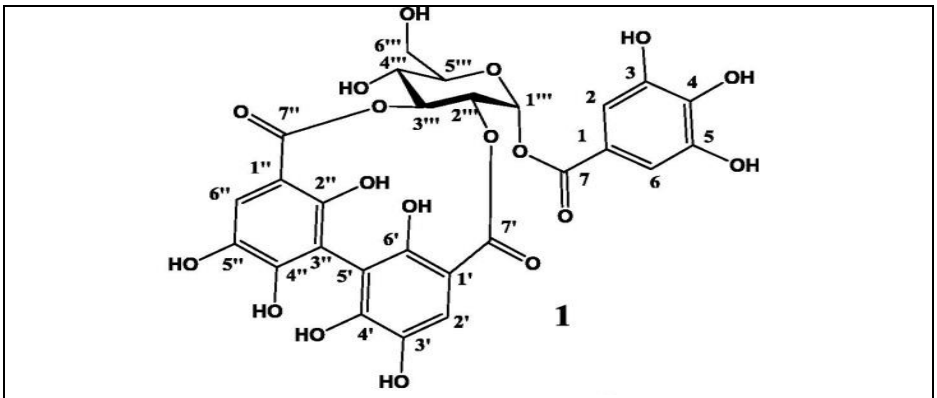


Fig 5: Chemical structures of compounds 38-40 from AP

3.6 Tannins

Potentillin (41), Agrimoniin (42), Agritanin (43) (Figure 6)



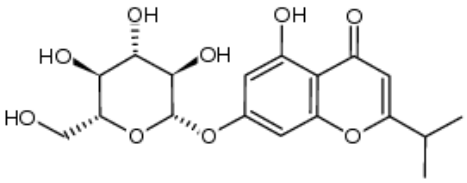


43. Agritanin

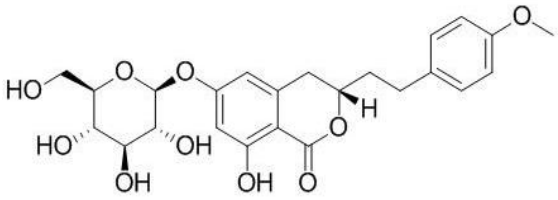
Fig 6: Chemical structures of compounds 41-43 from AP

3.7 Phenolic glycosides

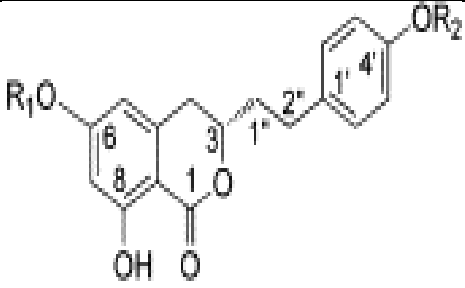
Takanechromone C (44), Agrimonolide- 6-O-glucoside (45), Desmethylagrimonolide 6-O-β-D-glucopyranoside (46), (-)-aromadendrin 3-O-β-D-glucopyranoside (47), 5,7-dihydroxy-2-propylchromone 7-O-β-D-glucopyranoside (48) (Figure 7)



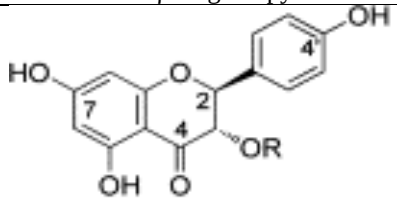
44. Takanechromone C



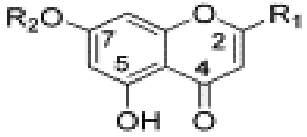
45. Agrimonolide- 6-O-glucoside



46. Desmethylagrimonolide 6-O-β-D-glucopyranoside. R1=Glucose, R2=H



47. (-)-aromadendrin 3-O-β-D-glucopyranoside. R=Glucose



48. 5,7-dihydroxy-2-propylchromone 7-O-β-D-glucopyranoside; R1=propyl, R2=Glucose

Fig 7: Chemical structures of compounds 44-48 from AP

3.8 Other compounds

Loliolide (49), Dihydro Dihydro Coniferyl alcohoh 9'-O-β-D-glucose (50), Afzelin (51), Agripinol A (52), Agripinol B (53) and Agripinol C (54) (Figure 8)

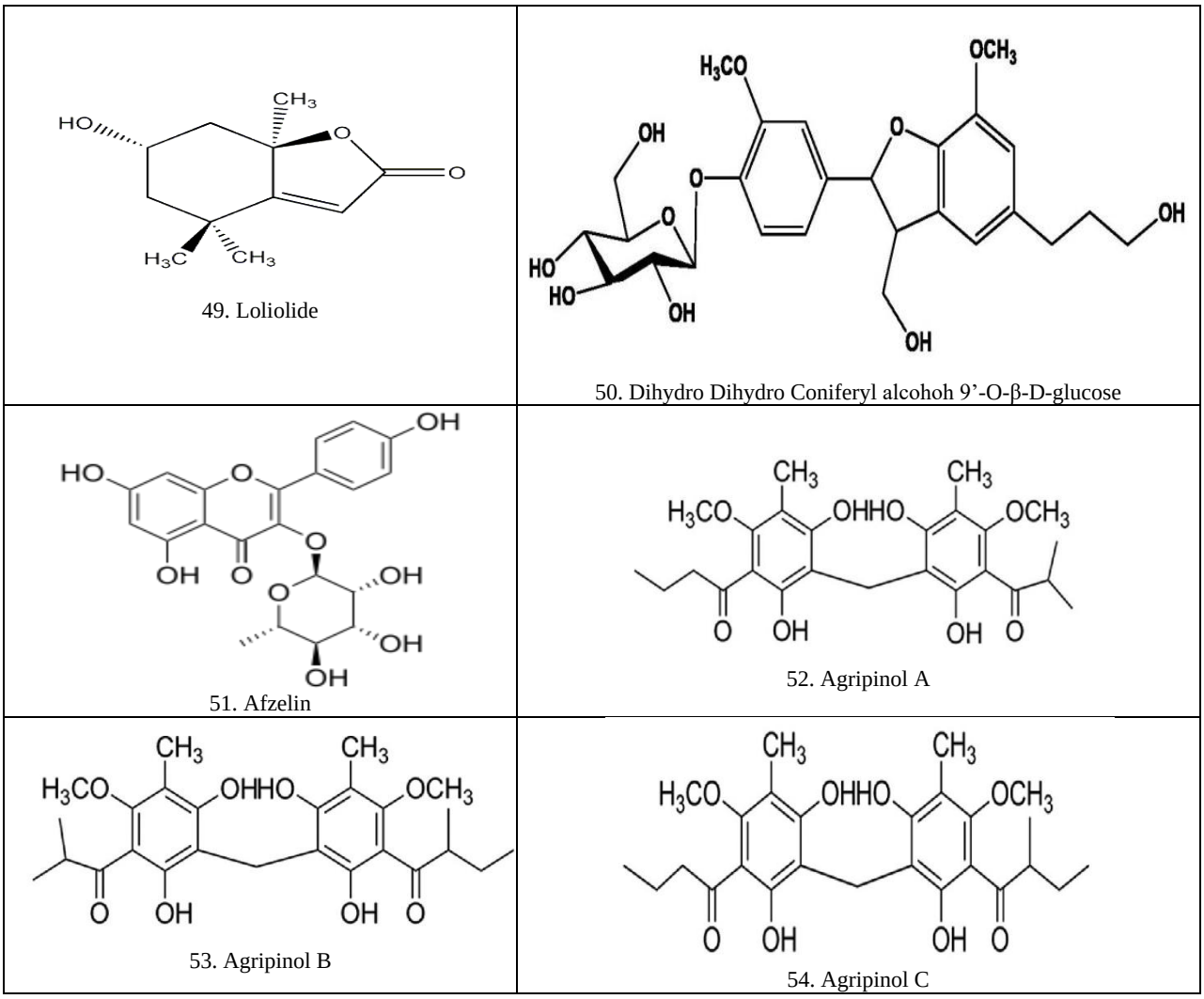


Fig 8: Chemical structures of compounds 49-54 from AP

4. Pharmacology

4.1 Antioxidant activity

The antioxidant effect of AP is one of the most prominent effects because of its responsibility for many of the other activities. Many researches demonstrated antioxidant activity of AP. Its alcoholic extract has shown obvious antioxidant activity by DPPH scavenging, ABTS radical scavenging with values of IC = 7.99±0.25 µg/mL; 5.88±0.25 µg/mL, respectively [2]. The EC50 values of the flavonoid compounds on DPPH radical, hydroxyl radical and ABTS radical scavenging activities are 7.7 µg/ ml, 3.6 µg/ ml and 5.9 µg/ ml, respectively [13]. Chen and Kang, 2014 also researched antioxidant activities of AP from its different fractions and results showed that the DPPH scavenging activity of AP is arrange in the following descending order: Methanol>EtOAc>BuOH>n-hexane [19].

4.2 Anti-Cancerous activity

As a result, the anti-cancerous effect is a noticeable bioactivity for AP reported in some recent years. The anti-tumor potentials of AP extracts were studied. The *Agrimonia pilosa* Ledeb ethanol extract (APE) induced apoptotic cell death in the human hepatocellular carcinoma HepG2 cells. Growth inhibition was associated with increased caspase activity and sub-G1 apoptotic fractions. APE stimulated the apoptotic factors including bcl-2, bcl-xl, mcl-1, XIAP, BID, BIK, caspase-3, caspase-9 and PARP in this cell line [20]. Miyamoto *et al*., 1985 reported that Agrimoniin compound is the main antitumor active constituent of AP. AP-M significantly prolonged the life span of S180-, Meth-A fibrosarcoma- and MM-2 mammary carcinoma-bearing mice by intraperitoneal (i.p.) pre- or postmedication. AP-M also inhibited the growth of S-180 solid type tumor [21]. On the other hand, the prolongation of life span induced by AP-M on S-180 ascites type tumor-bearing mice was markedly minimized or abolished by the pretreatment of cyclophosphamide. AP-M showed considerably strong cytotoxicity on MM-2 cells *in vitro* [22]. The APP, A homogenous polysaccharide (APP) isolated from the dried aerial parts of Agrimonia pilosa, significantly inhibited cell viability in a concentration dependent manner via induction of apoptotic death in human osteosarcoma U-2 OS cells [23].

4.3 Antiviral activity

Li *et al*., 2004 [24] reported that *Agrimonia pilosa* Ledeb showed anti-HSV-1 activity which was possibly contributed by its polyphenolic compounds. The ethanol extract of AP was shown to be high effective against all three subtypes of human influenza viruses including H1N1 and H3N2 influenza A subtypes and influenza B virus. The influenza A virus inhibitory capacity (IC50 of 14-23 µg/ ml) was tested by the plaque reduction assay on MDCK cells. The extract also displayed a virucidal effect at concentration of 160-570 ng/ml against influenza A and B viruses. Besides, the extract also showed a strong inhibitory effect *in ovo* on the H9N2 avian

influenza virus at a concentration of 280 ng/ml as tested in embryonated checken eggs [25].

4.4 Anti-nociception activity
The antinociceptive property of AP extract was examined in male ICR mice. AP extract administered orally (200 mg/kg) exhibited an antinociceptive effect as measured by the tail-flick and hot-plate tests. Intraperitoneal pretreatment with yohimbine (α2-adrenergic receptor antagonist) attenuated antinociceptive effect induced by AP extract in writhing test [7].

4.5 Anti-inflammatory activity
The effects of AP extracts on the expression of inflammation realated genes such as the inducible nitric oxide synthase (iNOS) in macrophage cell line, RAW 264.7 cells. The n-butanol fraction exhibited the most powerful inhibitory ability against nitric oxide (NO) production in lipopolysaccharide (LPS)-induced RAW 264.7 cells without affecting cell viability [26]. AP attenuated the production of inflammatory mediators such as NO, PGE2 and pro-inflammatory cytokines in LPS-induced RAW 264.7 cells [4]. Taira *et al*., 2008 [15] reported that three flavonoids (aromadendrin, dihyrokaempferol 3-O-β-D-glucoside and quercitrin) were remarkably high in NO scavenging activity. Agrimonolide from *Agrimonia pilosa* showed a strong anti-inflammatory activity. The pre-treatment with agrimonolide significantly reduced the levels of pro-inflammatory cy- tokines (IL-1 β, IL-6, and TNF- α), as well as attenuated the expression of iNOS and COX-2 in LPS- stimulated macrophages. Furthermore, agrimonolide inhibited the activation of JNK and p38 MAPKs and decreased the activation of JAK-STAT and NF- κB in LPS-stimulated macrophages [27].

4.6 α-glucosidase inhibition activity
The α-glucosidase inhibition activity was evalued by Liu *et al*. 2014 [13] that the flavonoid compound and triterpenoid compound have strong α-glucosidase inhibitory activities with IC50 of 8.72 μg/ml and 3.67 μg/ml, respectively.

4.7 Acetylcholinesterase (AchE) inhibition activity
Jung and Park, 2007 [11] researched acetylcholinesterase (AchE) inhibition capacity of four flavonol compounds including tiliroside, 3- methoxy quercetin, quercitrin and quercetin isolated from *Agrimonia pilosa* Ledeb. Results revealed these compounds inhibited AchE activity in a dose dependent manner and IC50 of values is from 19.8 to 66.9 μM. AP containing many flavanonol glucosides have AchE inhibitory activity effect, with values ranging from 76.59 ± 1.16 to 97.53 ± 1.64 mM [28].

5. Conclusion
Pharmacological studies on flavonoids and triterpenoids have been performed *in vitro*, while pharmacological studies on other main bioactive components *in vivo* in animals rare. Though several pharmacological mechanisms related to biological activity have already been explained, the comprehensive pharmacological mechanisms of *Agrimonia pilosa* Ledeb need to be elucidated. Based on phytochemical and pharmacological research, the flavonoids responsible for the good anti-tumor, acetylcholinesterase inhibition and anti-viral activities were selected as chemical markers to evaluate the quality of AP and its products. However, pharmacokinetics studies on the main components, especially the bioactive components are still largely lacking, therefore firm evidence for further clinical application is necessary in order to assess the therapeutic potential of AP and its pharmaceutical commodities.

6. Acknowledgments
We would like to thank national Pingtung University of science and technology, Taiwan scholarship, food science department and Chinese herb medicine laboratory in our university.

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