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<Review>

Ethnobotany, Phytochemistry, and Pharmacology of *Angelica decursiva* Fr. et Sav.

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Abstract – *Angelica decursiva* Fr. et Sav. (Umbelliferae) has traditionally been used to treat different diseases due to its antitussive, analgesic, and antipyretic activities. It is also a remedy for thick phlegm, asthma, and upper respiratory infections. Recently, the leaf of *A. decursiva* has been consumed as salad without showing any toxicity. This plant is a rich in different types of coumarin derivatives, including dihydroxanthyletin, psoralen, dihydropsoralen, hydroxycoumarin, and dihydropyran. Its crude extracts and pure constituents possess anti-inflammatory, anti-diabetic, anti-Alzheimer disease, anti-hypertension, anti-cancer, antioxidant, anthelmintic, preventing cerebral stroke, and neuroprotective activities. This valuable herb needs to be further studied and developed not only to treat these human diseases, but also to improve human health. This review provides an overview of current knowledge of *A. decursiva* metabolites and their biological activities to prioritize future studies.

Keywords – *Angelica decursiva*, Umbelliferae, Coumarins, Bioactivity studies, Anti-inflammatory activity

Introduction

The genus *Angelica* belongs to the family Apiaceae (*alt.* Umbelliferae), commonly known as parsley family. It comprises more than 90 species of medicinally important biennial or perennial herbs.[1-3] Many analytical techniques such as high-performance liquid chromatography (HPLC), Ultra high-pressure liquid chromatography (UPLC), gas chromatography (GC), and nuclear magnetic resonance spectroscopy (NMR) have been used to evaluate the quality and distinguish different species of *Angelica*.[4-7] According to traditional Chinese medicine (TCM), *Angelica decursiva* (*A. decursiva*) belongs to Plantae, Angiospermea Phylum, Dicotyledoneae Class. Umbelliflorae Order, Apiaceae Family, *Angelica* Genus.[8] It grows throughout Japan, China and Korea. It is mainly distributed in the hillside, grassland, or sparse forest. It is called 'Jahwajeonho' in Korean and 'Zi hua qian hu' in Chinese and Zenko in Japanese. It is widely employed in traditional medicine in Japan, China and Korea to cure diseases such as cough from pathogenic wind-heat and accumulation of phlegm and heat in lungs.[9] *A. decursiva* is also used in Korea as a salad without showing any toxicity.[10] The usage of roots of *A. decursiva* has a long history in China to clean heat, resolve summer heat, and stop bleeding. It is also officially listed in the Chinese pharmacopeia. Both *in vitro* and *in vivo* studies have indicated that *A. decursiva* exhibits a variety of pharmacological activities, including inhibition of airway inflammation, reducing allergic lung inflammation, therapy for ischemia-induced brain damage, anti-diabetic, anti-Alzheimer disease, anti-cancer, antioxidant, and neuroprotective activities.[11-20] This plant is rich source in different types of coumarin derivatives, including furanocoumarin, psoralen, dihydropsoralen, angelicin, dihydroangelicin, pyranocoumarin, dihydroxanthyletin, and dihydroseselin.[4-7,11,13,14,21-25] The available information on *A. decursiva* was collected using several different resources, including classic books on Chinese herbal medicine and a number of scientific databases, PubMed, SciFinder, the Web of Science and Science Direct.

This review herein summaries progress regarding chemical analysis of *A. decursiva* for the first time,

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primarily focusing on the development of phytochemistry, botanical aspects, ethnopharmacological, and pharmacological effects of *A. decursiva*. *A. decursiva* species is rich sources of different types of coumarin derivatives that exhibited number of biological activities and may be potentially impact human health. Unfortunately, *A. decursiva* has not been developed as a pharmaceutical agent. The main objective of this review a summary of the studies published to date on this promising plant, with a solid platform to design and conduct of clinical studies.

Botanical profile and taxonomy

The genus *Angelica* belongs to the family Apiaceae commonly known as parsley family. It comprises more than 90 species of medicinally important biennial or perennial herbs distributed widely in Asia, Europe, and North America.[1,2] About 20 species of *Angelica* genus have been found in Korea.[26] Among them, *A. decursiva* is a perennial herb growing up to 1.5 m. Photographs of *A. decursiva* are shown in Figure 1. It grows throughout Japan, China, and Korea. It is mainly distributed in the hillside, grassland, or sparse forest.[27] Its roots are conical with a few branches. They are 1 - 2 cm in diameter. Their appearance is brownish yellow to tan, with a strong odor.[28] Their roots and stems have long stalks. These stalks are 13 - 36 cm long. Their base is swelled into rounded purple leaf sheaths, clasped, and glabrous outside.[29] Their flowers are conical-shaped. Petals are obovate or elliptic-lanceolate. Fruits are oblong to ovate-oblong, 4 - 7 mm long, 3 - 5 mm wide, glabrous, and sulcate.[30] There are 1 - 3 oil pipes inside and 4-6 joint oil pipes. The ventral surface of the endosperm is slightly concave. These species are hermaphrodite (having both male and female organs). They are pollinated by insects. The plant is self-fertile. Light (sandy), medium (loamy), and heavy (clay) soils are suitable for its growth. Acid, neutral, and basic (alkaline) soils are all suitable for its growth. It can grow in semi-shade (light woodland) or no shade. It prefers moist soil. Its roots are called anterior which contains many active ingredients. They have been used as a remedy for fever, headache fever, bronchitis, cough fever, cough, heat stroke, chronic asthma breathing, and thick yellow phlegm.[9] They are also used for nerve pain and painkiller as a folk drug.

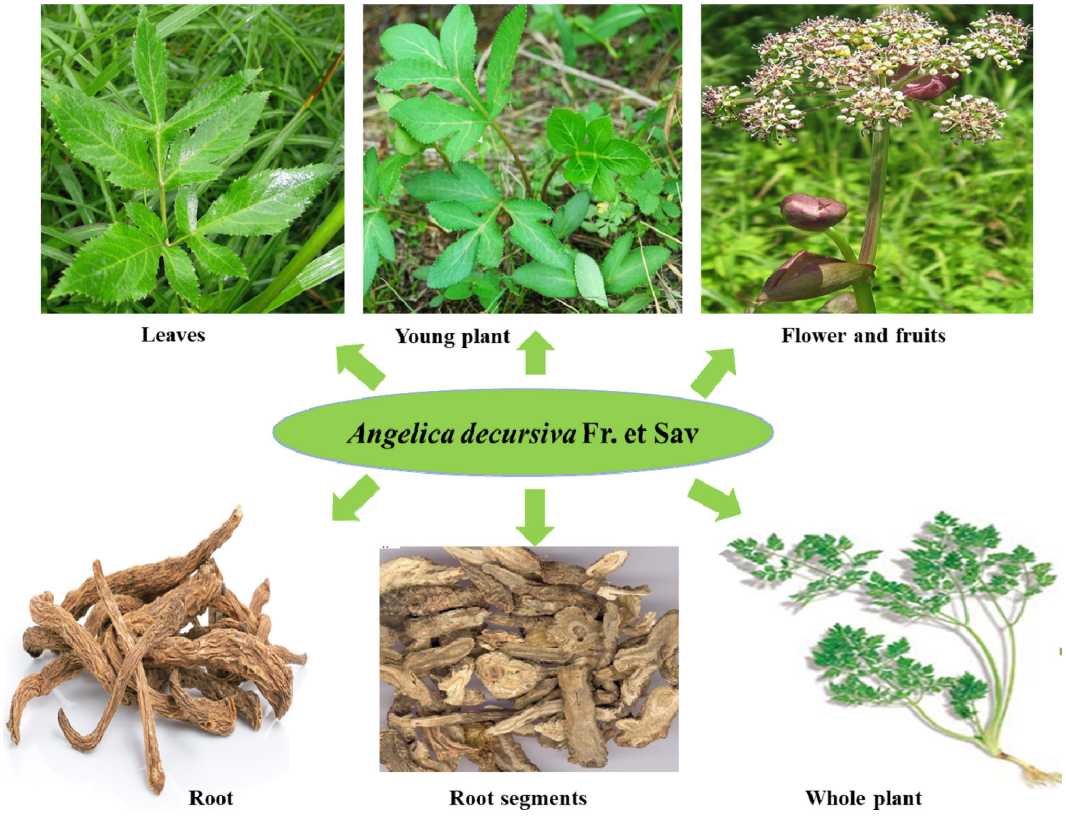

Fig. 1. Photograph of *A.decursiva*.

Traditional uses and ethnopharmacology

European folkloric reputation of the genus *Angelica* had a mythological belief that in the middle ages when Europe was almost destroyed by the plague, apparently an angel came to a monk and offered a herb that could cure the disease. Since then, this herb has a name called *Angelica*. Reports on traditional medicinal uses of *Angelica* species can be found in various ancient literature. The folklore of all North European countries depicts a common belief in their merits as a protection against contagion, for purifying blood, and for curing every conceivable ailment. In China, *A. decursiva* has been primarily used as traditional medicines to treat cough caused by pathogenic wind heat and accumulation of phlegm and heat in lungs.[9] Additionally, the root of *A. decursiva* (local name: Zi-Hue Qian-Hu) has been used to treat respiratory diseases and pulmonary hypertension.[5,11] Moreover, the usage of roots of *A. decursiva* has a long history in China to clean heat, resolve summer heat, and stop bleeding. It is also officially listed in the Chinese pharmacopeia. In Korea, the root of *A. decursiva*, local name Radix Peucedani (Qianhu), has been primarily used to dispel wind-heat, relieve cough, reduce sputum, treat cold and headache, dyspneal fullness and tightness in the chest, respiratory diseases, and pulmonary hypertension.[31] In Korean traditional medicines, it has been used as an antitussive, analgesic, antipyretic, and cough remedy.[11] *A. decursiva* is also used in Korea as a salad without toxicity.[10] In addition to medicinal preparations of *A. decursiva*, fairly large quantities are used in the confectionery and liquor industries. As a result, *A. decursiva* has now emerged as one of commercially important species.

Phytochemistry

Several compounds have been isolated from *A. decursiva*, mainly different categories of coumarin derivatives and other constituents. They are listed in Table 1. Chemical structures of these main compounds are presented in Figures 2 ~ 7. Coumarins are among the most effective constituents present in *A. decursiva*. They are biologically active, possessing a wide range of pharmacological properties such as anti-diabetic, anti-Alzheimer disease, anti-cancer, antioxidant, anti-inflammatory, and neuroprotective activities. Coumarins are widely distributed in nature. They are found in all parts of plants. Coumarins

Table 1. Chemical compounds isolated from *Anelica decursiva*

Classification	No.	Chemical component	Source	Reference
Dihydroxanthyletin	**1**	Decursinol	Whole plant	14
	2	(+)-*trans*-decursidinol	Whole plant	13
	3	(-)-*cis*-decursidinol	Root	25
	4	4-Hydroxy Pd-C-III	Whole plant	13
	5	4'-Methoxy Pd-C-I	Whole plant	16
	6	Pd-C-I	Whole plant	13
	7	Pd-C-II	Whole plant	13
	8	Pd-C-III	Whole plant	13
	9	Pd-C-IV	Root	5
	10	Pd-C-V	Root	4
	11	Decursidine	Whole plant	13
	12	(+)-3′*S*-Decursinol	Root	25
	13	Decursin	Root	24
	14	AD-I	Root	24
	15	AD-II	Root	24
	16	(-)-Methoxydecursidinol	Root	25
	17	Alsaticol	Root	5
	18	Pd-D-V	Root	5
	19	Decursitin B	Root	24
	20	Decursitin C	Root	5
	21	Decursitin D	Root	24
	22	Decursitin F	Root	24

Table 1. continued

Classification	No.	Chemical component	Source	Reference
Dihydropsoralen	**23**	Nodakenin	Whole plant	11
	24	Nodakenetin	Whole plant	11
	25	Isorutarine	Whole plant	14
	26	Decuroside I	Root	4
	27	Decuroside II	Root	4
	28	Decuroside III	Root	4
	29	Decuroside IV	Root	22
	30	Decuroside V	Root	22
	31	Decuroside VI	Root	4
Psoralen	**32**	Imperatorin	Root	23
	33	Isoimperatorin	Root	24
	34	Bergapten	Root	24
	35	(+)-Oxypeucedanin hydrate	Root	25
	36	(+)-Oxypeucedanin	Root	25
	37	2'-Isopropyl psoralene	Whole plant	14
	38	Oreoselon	Root	6
	39	Deltoin	Root	23
	40	Columbianadin	Root	23
	41	Bakuchicin	Root	7
	42	Libanoridin	Root	7
	43	Edultin	Root	25
	44	Edulisin II	Whole plant	13
	45	Edulisin III	Root	25
Hydroxycoumarin	**46**	Umbelliferone	Whole plant	11
	47	Umbelliferone 6-carboxylic acid	Whole plant	11
	48	6-Formyl umbelliferone	Whole plant	18
	49	Umbelliprenin	Root	25
	50	Ostruthin	Root	5
	51	Ostenol	Root	7
	52	Suberosin	Root	7
	53	Scopoletin	Root	24
Dihydropyran	**54**	*Cis*-3′-acetyl-4′-angeloylkhellactone	Whole plant	14
	55	(3′*R*)-*O*-acetyl-(4′*S*)-*O* tigloylkhellactone	Whole plant	14
	56	Selinidin	Root	7
	57	Peujaponisinol A	Root	7
	58	Peujaponisinol B	Root	7
Others	**59**	β-Sitosterol	Root	24
	60	β-Sitosterol-β-D-glucoside	Root	24
	61	Crocatone	Root	7
	62	*Para*-hydroxy benzoic acid	Whole plant	14
	63	Vanillic acid	Whole plant	11
	64	Decursidate	Root	24

belong to the benzopyrone group, with a benzene ring connected to a pyrone moiety. Coumarin derivatives have been studied for their availability, low toxicity, relatively low expense, presence in the diet, and multiple bio-activities.[32] Dietary exposure to coumarin is quite significant than exposure to other compounds because they are widely found in Citrus fruits, vegetables, seeds, nuts, and higher plants. Previous phytochemical investiga-

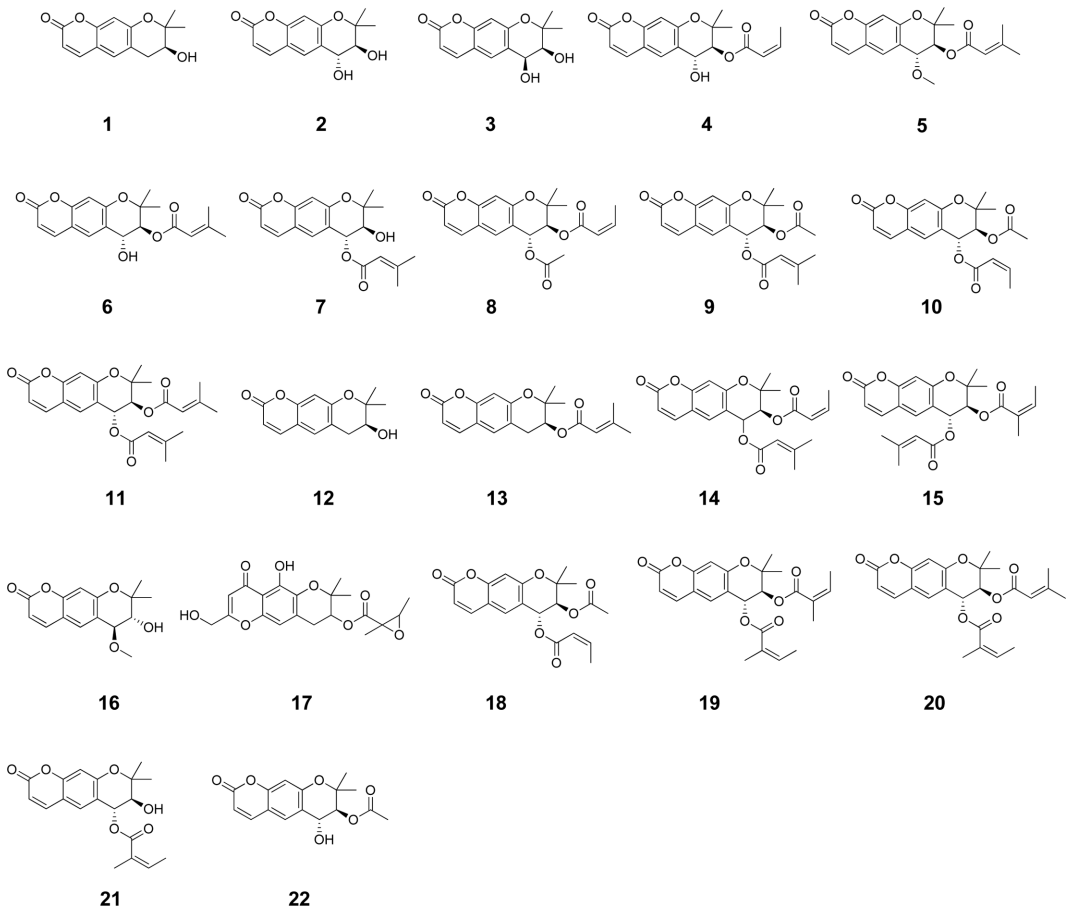

Fig. 2. Chemical structure of the major dihydroxanthyletin-type coumarins in *A.decursiva.*

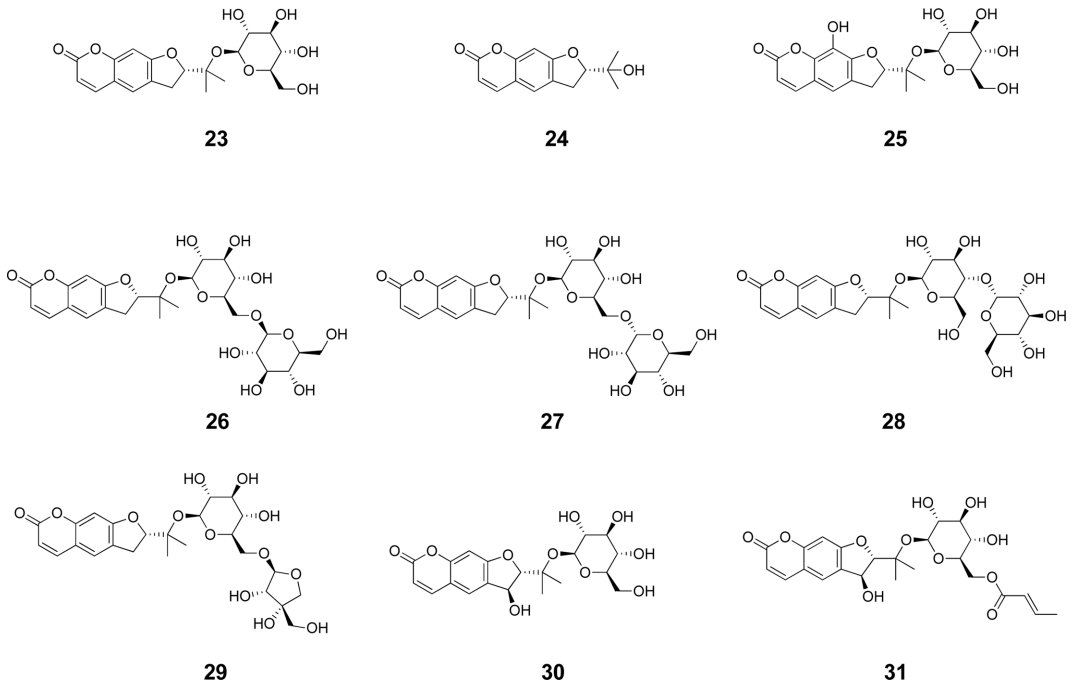

Fig. 3. Chemical structure of the dihydropsoralen-type coumarins in *A.decursiva.*

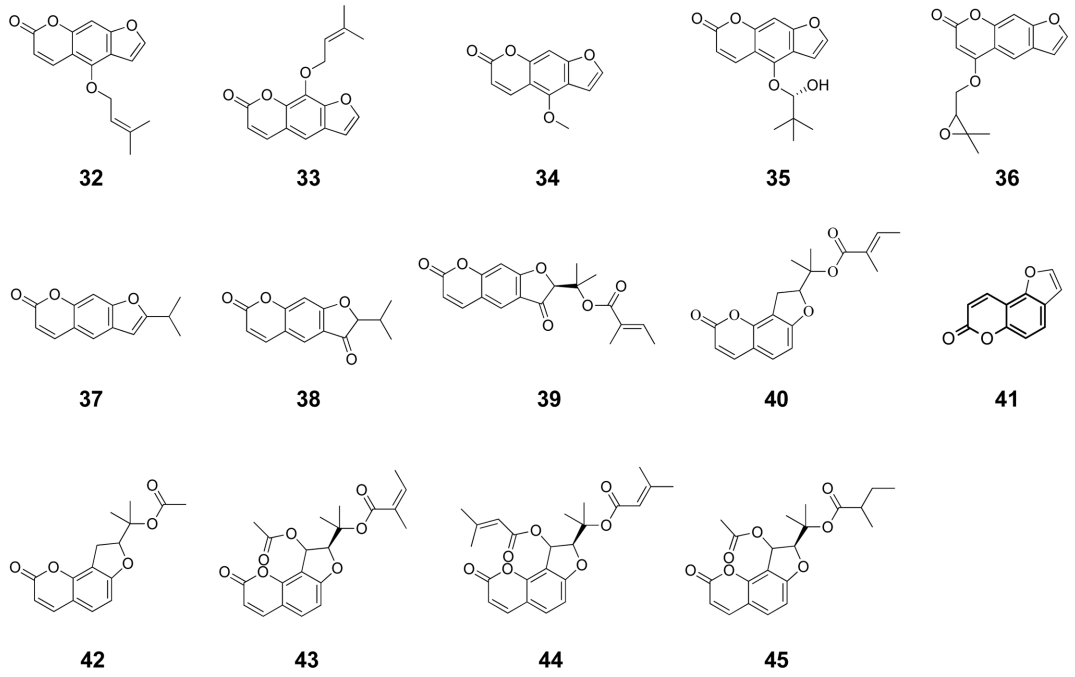

Fig. 4. Chemical structure of the psoralen-type coumarins in *A.decursiva.*

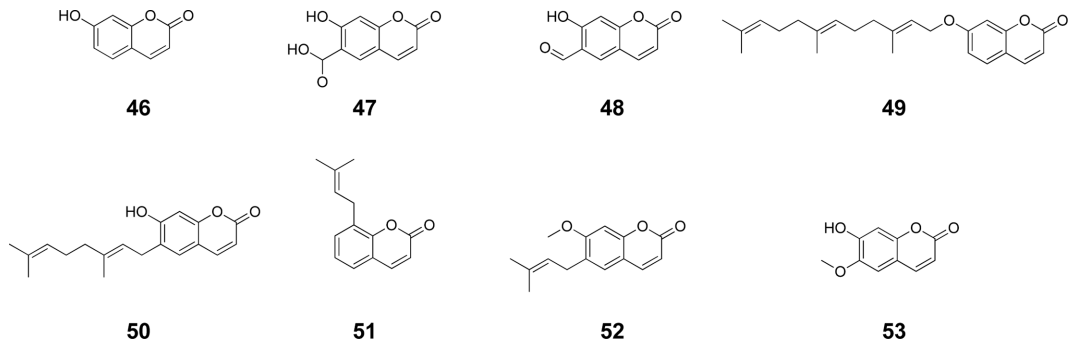

Fig. 5. Chemical structure of the hydroxycoumarins in *A.decursiva.*

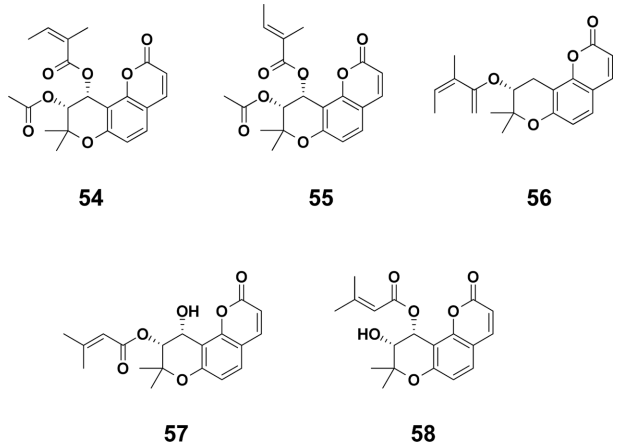

Fig. 6. Chemical structure of the dihydropyran-type coumarins in *A.decursiva.*

tions on *A. decursiva* have led to the identification of over 64 compounds, including coumarins **1 - 58** and others (**59 - 64**). Analysis of the whole *A. decursiva* plant has shown the presence of various compounds, including decursinol (**1**), 4-hydroxy Pd-C-III (**4**), 4'-methoxy Pd-C-I (**5**), Pd-C-I (**6**), Pd-C-II (**7**), Pd-C-III (**8**), decursidine (**11**), nodakenin (**23**), nodakenetin (**24**), isorutarine (**25**), (+)-*trans*-decursidinol (**2**), 2'-isopropyl psoralene (**37**), edulisin II (**44**), umbelliferone (**46**), umbelliferone 6-carboxylic acid (**47**), 6-formyl umbelliferone (**48**), *cis*-3′-acetyl-4′-angeloylkhellactone (**54**), (3′*R*)-*O*-acetyl-(4′*S*)-*O* tigloyl-khellactone (**55**), *para*-hydroxy benzoic acid (**62**), and vanillic acid (**63**).[11,13,14,16] Roots of *A. decursiva* contain (-)-*cis*-decursidinol (**3**), Pd-C-IV (**9**), Pd-C-V (**10**), (+)-3′*S*-decursinol (**12**), decursin (**13**), AD-I (**14**), AD-II (**15**), (-)-

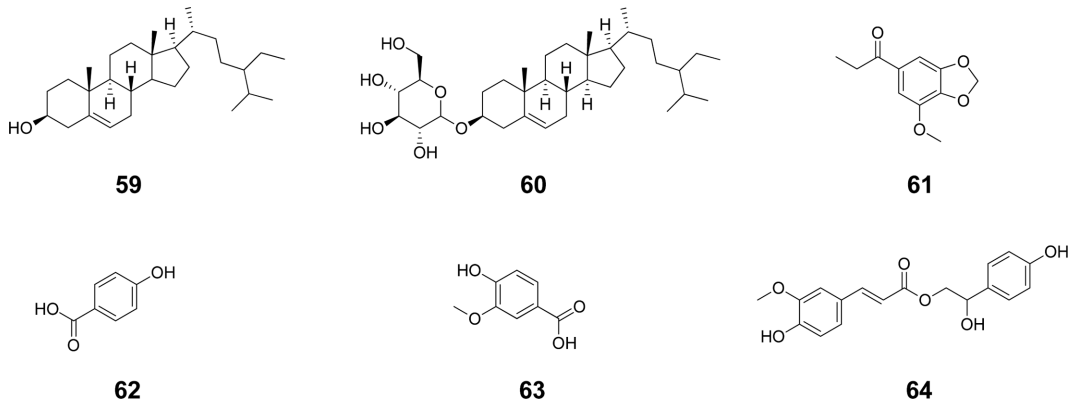

Fig. 7. Chemical structure of the other constituent in *A.decursiva.*

methoxydecursidinol (**16**), alsaticol (**17**), Pd-D-V (**18**), decursitin B (**19**), decursitin C (**20**), decursitin D (**21**), decursitin F (**22**), decuroside I (**26**), decuroside II (**27**), decuroside III (**28**), decuroside IV (**29**), decuroside V (**30**), decuroside VI (**31**), imperatorin (**32**), isoimperatorin (**33**), bergapten (**34**), (+)-oxypeucedanin hydrate (**35**), (+)-oxypeucedanin (**36**), oreoselon (**38**), deltoin (**39**), columbianadin (**40**), bakuchicin (**41**), libanoridin (**42**), edultin (**43**), edulisin III (**45**), umbelliprenin (**49**), ostruthin (**50**), ostenol (**51**), suberosin (**52**), scopoletin (**53**), selinidin (**56**), peujaponisinol A (**57**), peujaponisinol B (**58**), β-sitosterol (**59**), β-sitosterol-β-D-glucoside (**60**), crocatone (**61**), and decursidate (**64**).[4-7,22-25]

Biological and pharmacological activities

Numerous studies have investigated pharmacological activities of various *A. decursiva* extracts. Table 2 summarizes its pharmacological features that have been observed, including antidiabetic, anti-inflammatory, anticancer, antioxidant, anti-hypertension, prevention of cerebral stroke, anti-Alzheimer's disease, and anthelmintic properties. Coumarins isolated from *A. decursiva* are structurally diverse. They exhibit multiple pharmacological properties, suggesting that these compounds contribute to therapeutic effects of *A. decursiva* (Table 3).

Anti-inflammatory activity – The root of *A. decursiva* has been frequently used in traditional medicine as anti-inflammatory, antitussive, and analgesic agents and expectorant, especially for treating cough, asthma, bronchitis, and upper respiratory tract infections. Nitric oxide (NO) is a mutagen that affects microbial and mammalian cells due to the production of free radical. The 70% EtOH extract from root of *A. decursiva* and ethyl acetate (EtOAc), dichloromethane (CH_2Cl_2), and *n*-butanol (*n*-BuOH) fractions from an MeOH extract of the whole plant of *A. decursiva* have shown inhibitory effects on lipopolysaccharide (LPS)-induced NO production in MH-S and RAW 264.7 cells, respectively.[11,12] Interleukin 6 (IL-6) is a pro-inflammatory cytokine that has pathological effect on chronic inflammation. Pretreatment with aqueous (H_2O) or 70% EtOH root extract of *A. decursiva* can inhibit IL-6 production in a dose-dependent (50 - 200 μg/ml) manner in IL-1β treated A549 cells.[12] Additionally, 70% EtOH and H_2O root extract can reduce cell number in the bronchoalveolar lavage fluid (BALF) of LPS-induced acute lung injury in mice.[12] Another *in vivo* study has shown that 70% EtOH extract can markedly reduce mucus production, inhibit eosinophils, neutrophils, macrophages, lymphocytes, and type 2 cytokines (IL-4, IL-5, IL-13, and eotaxin-3), histamine secretion, and IgE levels, It can also down-regulate Th2 (T helper) cells activation and diminish activated CD4 T cell and GATA-3 levels in the lung.[17] Three major coumarins (nodakenin, umbelliferone, and nodakenetin) from *A. decursiva* inhibited NO and IL-6 production.[11,12] Nodakenin is a major coumarin glycoside from *A. decursiva*. Effect of nodakenin in suppressing airway inflammation, hyperresponsiveness, and remodeling in a murine model of chronic asthma has been investigated.[33] Pre-treatment with nodakenin (20 mg/kg) markedly inhibited airway inflammation, hyper-responsiveness, and remodeling. It improved subepithelial fibrosis, smooth muscle hypertrophy, and goblet cell hyperplasia. It also decreased levels of interleukin (IL)-4, IL-5, IL-13, and matrix metalloproteinase-2/-9 in bronchoalveolar lavage fluid as well as serum level of OVA-specific IgE. In addition, NF-κB DNA-binding activity in lung tissues was decreased by nodakenin treatment.[33] As a rare hydroxycoumarin, umbelliferone 6-carboxylic acid could inhibit NO, reactive oxygen species (ROS), iNOS, cyclooxygenase-2 (COX-2), and NF-κB activity.[34] It also reduced TNF-α

Table 2. Pharmacological activities of *Angelica decursiva* extracts

Pharmacological activity	Part of plant	Type of extract	*In vivo* / *in vitro*	Model	Administration (*in vivo*)	Dose range	Active concentration	Reference
Anti-inflammatory activity	Root	70% EtOH ext.	*In vitro*	(a) Inhibits NO production and iNOS expression in a dose-dependent manner in MH-S cells	-	50-300 μg/mL	(a) Reduced NO and iNOS level at 300 μg/mL	12
				(b) Inhibit IL-6 production in a dose-dependent manner in IL-1β treated A549 cells		50-200 μg/mL	(b) Significantly reduced IL-6 production at 100 μg/mL	
			In vivo	Reduced the cell numbers in the BALF, LPS-induced acute lung injury in mice	Oral	100–400 mg/kg	Inhibit cells number 53.2% at a dose of 400 mg/kg	12
	Root	H_2O ext.	*In vitro*	Inhibit IL-6 production in a dose-dependent manner in IL-1β treated A549 cells	-	50-200 μg/mL	Significantly reduced IL-6 production at 200 μg/mL	12
			In vivo	Reduced the cell numbers in the BALF, LPS-induced acute lung injury in mice	Oral	100–400 mg/kg	Inhibit cells number 44.5% at a dose of 400 mg/kg	12
	Whole plants	90% MeOH ext.	*In vitro*	Inhibit NO production of LPS-stimulated in RAW 264.7 cells	-	5 μg/mL	Significantly inhibit NO production at 5 μg/mL	13
	Whole plants	MeOH ext. EtOAc fr. CH_2Cl_2 fr. *n*-BuOH fr. H_2O fr.	*In vitro*	Inhibit NO production of LPS-stimulated in RAW 264.7 cells	-	10-200 μg/mL	MeOH, EtOAc, CH_2Cl_2 and *n*-BuOH fr, exhibited greatest inhibitory activity against NO production with IC_{50} ranges 1.29-4.22 μg/mL.	11
	Root	70% EtOH ext.	*In vivo*	Markedly attenuated mucus production of airway epithelium in lung tissue in mice	Oral	200 mg/kg	Reduced mucus production at 200 mg/kg	17
				Inhibits eosinophils, neutrophils, macrophages, and lymphocytes cells in OVA-challenged mice	Oral	200 mg/kg	Markedly reduced eosinophils level at 200 mg/kg	
				Inhibits type 2 cytokines (IL-4,5,13 and eotaxin-3) levels in BALF.	Oral	200 mg/kg	Reduced cytokines levels at 200 mg/kg	
				Decreased histamine secretion in BALF and OVA-specific IgE levels in serum	Oral	200 mg/kg	200 mg/kg	
				Inhibited Th2-related cytokine production by down-regulating Th2 cell activation in OVA-induced allergic lung inflammation mice	Oral	200 mg/kg	200 mg/kg	
				Diminished activated CD4 T cell (CD4+CD25+ cell) and GATA-3 level in the lung	Oral	200 mg/kg	200 mg/kg	
			In vitro	Reduced Th2 cell activation in vitro primary cell	-	200, 400 μg/mL	400 μg/mL	17

Table 2. continued

Pharmacological activity	Part of plant	Type of extract	*In vivo* / *in vitro*	Model	Administration (*in vivo*)	Dose range	Active concentration	Reference
Anti-Alzheimer disease activity	Whole plants	MeOH ext. EtOAc fr. CH_2Cl_2 fr. *n*-BuOH fr. H_2O fr.	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity (c) β-secretase inhibitory activity	-	(a) 0.5-100 μg/ml (b) 0.4-100 μg/ml (c) 2.5-162.5 μg/ml	(a) IC_{50}= 2.59~16.58 μg/ml (b) IC_{50}= 0.42~15.63 μg/ml (c) IC_{50}= 9.1~35.56 μg/ml	14
Anti-diabetic activity	Whole plants	MeOH ext. EtOAc fr. CH_2Cl_2 fr. *n*-BuOH fr. H_2O fr.	*In vitro*	Inhibitory activity against PTP1B, α-glucosidase and RLAR	-	0.5-200 μg/ml for PTP1B, 12.5 -400 μg/ml for α-glucosidase 5-250 μg/ml for RLAR	EtOAc fr. (IC_{50} = 9.51, 86.08 and 12.66 μg/ml) exhibited greatest inhibitory activity against PTP1B, α-glucosidase and RLAR respectively.	14
Antioxidant activity	Whole plants	MeOH ext. EtOAc fr. CH_2Cl_2 fr. *n*-BuOH fr. H_2O fr.	*In vitro*	(a) Scavenges DPPH radicals (b) Scavenges ABTS radicals (c) Scavenges $ONOO^-$ radicals	-	(a) 25-1600 μg/ml (b) 0.8-100 μg/mL (c) 0.08-50 μg/mL	(a) IC_{50}= 45.50 μg/mL (b) IC_{50}=15.20 μg/mL (c) IC_{50}= 1.58 μg/mL	11
Anticancer activity	Root	95% EtOH ext.	*In vitro*	(a) Cytotoxicity against in KB cells (b) Increased cellular apoptosis and reduced cell proliferation in KB cells (c) Decreased the expression of procaspase-7 and -9 in the KB cells (d) Activation of caspase-7 in KB cells	-	(a) 0.01-30 μg/m1 (b) 0.3 μg/m1 (c) 0.3 μg/m1 (d) 0.3 μg/m1	(a) IC_{50}= 0.21 μg/mL (b) 0.3 μg/m1 (c) 0.3 μg/m1 (d) 0.3 μg/m1	42
			In vitro	(a) Cytotoxicity against in C6 rat glioma cells (b) Increased cellular apoptosis and reduced cell proliferation in C6 cells (c) Decreased the expression of procaspase-3, -7, and -9 in the C6 cells (d) Activation of caspase 3/-7 in C6 cells	-	(a) 0.01-300 μg/m1 (b) 1 μg/m1 (c) 1 μg/m1 (d) 1 μg/m1	(a) IC_{50}= 0.19 μg/mL (b)1 μg/m1 (c) 1 μg/m1 (d) 1 μg/m1	40
			In vitro	(a) Cytotoxicity against in FaDu cells (b) Increased cellular apoptosis and reduced cell proliferation in FaDu cells (c) Decreased the expression of procaspase-3, -7, and -9 in the FaDu cells (d) Activation of caspase 3/-7 in FaDu cells	-	(a) 0.01-10 μg/m1 (b) 1 μg/m1 (c) 1 μg/m1 (d) 1 μg/m1	(a) IC_{50}= 0.23 μg/mL (b)1 μg/m1 (c) 1 μg/m1 (d) 1 μg/m1	41
			In vitro	(a) Cytotoxicity against Saos2 human osteogenic sarcoma cells (b) Increased cellular apoptosis and reduced cell proliferation in Saos2 cells (c) Decreased the expression of procaspase-3 and -7 in the Saos2 cells (d) Activation of caspase-3 and 7 in Saos2 cells	-	(a) 0.01-30 μg/m1 (b) 0.3 μg/m1 (c) 0.3 μg/m1 (d) 0.3 μg/m1	(a) IC_{50}= 1.4 μg/ml (b) 0.3 μg/m1 (c) 0.3 μg/m1 (d) 0.3 μg/m1	8
	Root	MeOH ext. EtOAc fr. He fr. Ac fr. H_2O fr.	*In vitro*	Cytotoxicity against HeLa cells	-	0.01-50 μg/m1	EtOAc and He fr. (100% inhibition) exhibited greatest inhibitory activity in HeLa cells	45

Table 2. continued

Pharmacological activity	Part of plant	Type of extract	*In vivo* / *in vitro*	Model	Administration (*in vivo*)	Dose range	Active concentration	Reference
Anthelmintic activity	Root	MeOH ext. EtOAc fr. Chloroform fr *n*-BuOH fr. H_2O fr.	*In vivo*	Anthelmintic efficacy against *Dactylogyrus intermedius*	Intraperitoneal injection	125-1000 mg/mL	Chloroform fr. (EC_{50}=240. 4mg/l; EC_{90}= 433.9 mg/l) exhibited greatest inhibitory activity against *D.intermedius*	48
Anti-hypertension activity	Root	70% EtOH ext.	*In vivo*	(a) Showed vasorelaxant effects on PE (or KCl)-induced contraction (b) Showed relaxation effects in endothelium-intact and endothelium-denuded aortic rings (c) Showed vasorelaxant effect on aortic rings preincubated with TEA, glibenclamide and 4-AP (d) Inhibition of extracellular Ca^{2+}	Intraperitoneal injection	(a) 25-800 µg/m1 (b) 25-800 µg/m1 (c) 25-200 µg/m1 (d) 100-400 µg/m1	(a) high relaxant effect 94.3% at 800 µg/m1 (b) High relaxant effects on PE/KCl-induced 95.5 and 96.9% at 800 µg/m1 (c) active at 200 µg/ml (d) active at 400 µg/ml	50
Prevention of cerebral stroke	Root	MeOH ext.	*In vivo*	(a) Significantly decreased infarct lesions in C57BL/6 mice (b) Suppressed the iNOS expression level (c) Decreased the ROS, and MDA levels (d) Inhibits cytokines IL-1β and TNF-α	Oral	(a) 20-200 mg/kg (b) 20-200 mg/kg (c) 20-200 mg/kg (d) 20-200 mg/kg	(a) 60, 200 mg/kg (b) 20, 60, 200 mg/kg (c) 200 mg/kg (d) 200 mg/kg for IL-1β and 60, 200 mg/kg for TNF-α	51

Table 3. Major Phytochemicals in *Angelica decursiva* and their pharmacological activities

Compounds	Biological activity	*in vivo* / *in vitro*	Model	Administration (*in vivo*)	Dose range	Active concentration	Reference
Nodakenin	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity (c) β-secretase inhibitory activity	-	(a) 0-100 μM (b) 0-100 μM (c) 12.5-250 μM	(a) IC_{50}=33.67 μM (b) IC_{50}=54.6 μM (c) IC_{50}=147.7 μM	14
		In vivo	(a) Showed memory-enhancing activity by passive avoidance task (b) Enhance the proliferation and survival of newborn cells in DG region (c) Increases the number of immature neurons in the hippocampal DG region (d) Significantly increased the phosphorylation level of Akt or GSK-3β expression	Oral	(a) 0.3-1 mg/kg (b) 0.3-1 mg/kg (c) 0.3-1 mg/kg (d) 1.0 mg/kg	(a) 1.0 mg/kg (b) 1.0 mg/kg (c) 1.0 mg/kg (d) 1.0 mg/kg	47
	Anti-inflammatory activity	*In vitro*	Inhibit NO production of LPS-stimulated in RAW 264.7 cells	-	31.25-500 μg/mL	Inhibition of NO, 20.72% at 125 μg/mL	11
		In vitro	Inhibit IL-6 production of IL-1β treated in A549 cells	-	10-100 μM	Inhibition of IL-6, 19.34% at 100 μM	12
	Prevention of asthma airway inflammation	*In vivo*	(a) Significantly reduced airway hyper-responsiveness in BALB/c mice (b) Reduced the leucocyte cells and inhibited intra-alveolar exudation, bronchi and interstitial edema in airway (c) Showed improvement in subepithelial fibrosis, smooth muscle hypertrophy, and goblet cell hyperplasia (d) Decreased the levels of IL-4, IL-5, IL-13, MMP-2 and MMP-9 in BALF (e) Reduced the gelatinolytic activities of pro-MMP-2, MMP-2, and pro-MMP-9 (f) Suppressed NF-κB DNA-binding activity in lung tissues	Intravenously	(a) 5-20 mg/kg (b) 5-20 mg/kg (c) 5-20 mg/kg (d) 5-20 mg/kg (e) 5-20 mg/kg (f) 5-20 mg/kg	(a) 20 mg/kg (b) 20 mg/kg (c) 20 mg/kg (d) 20 mg/kg (e) 20 mg/kg (f) 20 mg/kg	33
Nodakenetin	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity (c) β-secretase inhibitory activity	-	(a) 0-100 μM (b) 0-100 μM (c) 12.5-250 μM	(a) IC_{50}= 46.19 μM (b) IC_{50}= 46.07 μM (c) IC_{50}=153.46 μM	14
	Anti-diabetic activity	*In vitro*	(a) PTP1B inhibitory activity (b) α-glucosidase inhibitory activity (c) RLAR inhibitory activity	-	(a) 0-100 μM (b) 0-250 μM (c) 2.5-100 μM	(a) IC_{50}= 409.98 μM (b) IC_{50}= 720.29 μM (c) IC_{50}= 266.29 μM	14
	Anti-inflammatory activity	*In vitro*	Inhibit IL-6 production of IL-1β treated in A549 cells	-	10-100 μM	Inhibition of IL-6, 37% at 100 μM	12
		In vitro	Inhibit NO production of LPS-stimulated in RAW 264.7 cells	-	31.25-500μg/mL	Inhibition of NO, 43.12% at 250 μg/mL	11

Table 3. continued

Compounds	Biological activity	*in vivo* / *in vitro*	Model	Administration (*in vivo*)	Dose range	Active concentration	Reference
Umbelliferone	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity (c) β-secretase inhibitory activity	-	4.0-100 μM	(a) IC_{50}= 145.19 μM (b) IC_{50}= 105.28 μM (c) IC_{50}=143.1 μM	15
	Anti-diabetic activity	*In vitro*	(a) PTP1B inhibitory activity (b) α-glucosidase inhibitory activity (c) RLAR inhibitory activity	-	(a) 0-100 μM (b) 0-250 μM (c) 2.5-100 μM	(a) IC_{50}= 277.82 μM (b) IC_{50}= 629.87 μM (c) IC_{50}= 265.09 μM	14
	Anti-inflammatory activity	*In vitro*	Inhibit NO production of LPS-stimulated in RAW 264.7 cells	-	31.25-500 μg/ml	Inhibition of NO, 46.10% at 500 μg/mL	11
		In vitro	Inhibit IL-6 production of IL-1β treated in A549 cells	-	10-100 μM	Inhibition of IL-6, 37.6% at 100 μM	12
		In vitro	Inhibit MUC5AC mucin gene expression and production provoked by growth factor EGF, PMA and cytokine TNF-α	-	1-100 μM	100 μM	17
	Anti-oxidant activity	*In vitro*	$ONOO^-$ scavenging activity	-	1-200 μg/mL	IC_{50}= 36.28 μg/mL	11
Umbelliferone 6-carboxylic acid	Anti-inflammatory activity	*In vitro*	(a) Inhibit NO production and ROS generation in RAW 264.7 cells (b) Reduced TNF-α and PGE2 production (c) Inhibition of iNOS, COX-2 and NF-κB expression level	-	(a) 31-250 μg/ml (b) 50-200 μg/ml (c) 50-200 μg/ml	(a) 250 μg/ml (b) 100, 200 μg/ml (c) 200 μg/ml	34
		In vivo	Inhibit carrageenan-induced mouse paw edema	Oral	25, 50 mg/kg	50 mg/kg	
	Anti-diabetic activity	*In vitro*	(a) PTP1B inhibitory activity (b) α-glucosidase inhibitory activity	-	(a) 0.8-20 μM (b) 62.5-250 μM	(a) 7.98 μM (b) IC_{50}= 172.10 μM	16
	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity (c) β-secretase inhibitory activity	-	(a) 0-100 μM (b) 0-100 μM (c) 0.1-10 μM	(a) IC_{50}= 104.12 μM (b) IC_{50}= 27.19 μM (c) IC_{50}= 0.34 μM	15
	Antioxidant activity	*In vitro*	(a) ABTS radical scavenging activity (b) DPPH radical scavenging activity (c) $ONOO^-$ scavenging assay (d) $ONOO^-$-mediated tyrosine nitration inhibition	-	(a) 0.8-100 μg/ml (b)0.8-800 μg/ml (c) 0.2-50 μg/ml (d) 12.5-100 μM	(a) IC_{50}= 11.20 μg/ml (b) IC_{50}= 681.86 μg/ml (c) IC_{50}= 8.04 μg/ml (d) 100 μM	11 16
6-Formyl umbelliferone	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity (c) β-secretase inhibitory activity	-	(a) 5-250 μM (b) 5-250 μM (c) 0.4-10 μM	(a) IC_{50}= 16.70 μM (b) IC_{50}= 27.90 μM (c) IC_{50}= 1.31 μM	18
	Antioxidant activity	*In vitro*	$ONOO^-$-mediated tyrosine nitration inhibition	-	12.5-100 μM	100 μM	18
2'-Isopropyl psoralene	Anti-diabetic activity	*In vitro*	(a) PTP1B inhibitory activity (b) α-glucosidase inhibitory activity	-	(a) 4-100 μM (b) 62.5-250 μM	(a) IC_{50}= 10.78 μM (b) IC_{50}= 85.82 μM	16
	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activiy	-	(a) 20-200 μM (b) 20-200 μM	(a) IC_{50}= 173.89 μM (b) IC_{50}= 179.22 μM	15
	Antioxidant activity	*In vitro*	$ONOO^-$-mediated tyrosine nitration inhibition	-	12.5-100 μM	100 μM	16

Table 3. continued

Compounds	Biological activity	*in vivo* / *in vitro*	Model	Administration (*in vivo*)	Dose range	Active concentration	Reference
4'-Methoxy Pd-C-I	Anti-diabetic activity	*In vitro*	(a) PTP1B inhibitory activity (b) α-glucosidase inhibitory activity (c) HRAR inhibitory activity (d) AGE inhibitory activity	-	(a) 4-100 μM (b) 62.5-250 μM (c) 0.5-10 μM (d) 2-50 μM	(a) IC_{50}= 6.62 μM (b) IC_{50}= 89.19 μM (c) IC_{50}= 5.88 μM (d) IC_{50}= 4.01 μM	16 19
	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity (c) β-secretase inhibitory activity	-	(a) 0.8-20 μM (b) 5-100 μM (c) 4-100 μM	(a) IC_{50}= 2.90 μM (b) IC_{50}= 8.86 μM (c) IC_{50}= 17.34 μM	20
	Antioxidant activity	*In vitro*	$ONOO^-$-mediated tyrosine nitration inhibition	-	12.5-50 μM	50 μM	16
Decursidine	Anti-inflammatory activity	*In vitro*	(a) Inhibit NO production in RAW 264.7 cells (b) Inhibits iNOS and COX-2 expression levels (c) Inhibit TNF-α production in RAW 264.7 cells	-	3-12 μM	(a) IC_{50}= 4.08 μM (b) 12 μM (c) 6, 12 μM	13
	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity (c) β-secretase inhibitory activity	-	(a) 2-100 μM (b) 5-100 μM (c) 4-50 μM	(a) IC_{50}= 3.47 μM (b) IC_{50}= 9.37 μM (c) IC_{50}= 1.99 μM	20
	Anti-diabetic activity	*In vitro*	(a) PTP1B inhibitory activity (b) α-glucosidase inhibitory activity (c) HRAR inhibitory activity (d) AGE inhibitory activity	-	(a) 4-100 μM (b) 62.5-250 μM (c) 0.5-10 μM (d) 2-50 μM	(a) IC_{50}= 11.22 μM (b) IC_{50}= 79.09 μM (c) IC_{50}= 6.01 μM (d) IC_{50}= 0.41 μM	15 20
	Anaphylactic activity	*In vitro*	Reduction of ^{45}Ca uptake induced by concanavalin A into rat mast cells	-	500 μM	4.75 cpm×10^{-4}/10^6 cells	49
	Antioxidant activity	*In vitro*	$ONOO^-$-mediated tyrosine nitration inhibition	-	12.5-50 μM	50 μM	16
4-Hydroxy Pd-C-III	Anti-diabetic activity	*In vitro*	(a) PTP1B inhibitory activity (b) α-glucosidase inhibitory activity (c) HRAR inhibitory activity (d) AGE inhibitory activity	-	(a) 0.8-20 μM (b) 62.5-250 μM (c) 0.1-2.5 μM (d) 2-50 μM	(a) IC_{50}= 5.39 μM (b) IC_{50}= 77.30 μM (c) IC_{50}= 2.56 μM (d) IC_{50}= 5.56 μM	16 19
	Anti-inflammatory activity	*In vitro*	(a) Inhibit NO production in RAW 264.7 cells (b) Inhibits iNOS and COX-2 expression levels (c) Inhibit TNF-α production in RAW 264.7 cells	-	10-40 μM	(a) IC_{50}= 26 μM (b) 40 μM (c) 40 μM	13
	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity (c) β-secretase inhibitory activity	-	(a) 0.8-20 μM (b) 5-100 μM (c) 4-50 μM	(a) IC_{50}= 1.09 μM (b) IC_{50}= 5.78 μM (c) IC_{50}= 4.65 μM	20
	Antioxidant activity	*In vitro*	$ONOO^-$-mediated tyrosine nitration inhibition	-	12.5-50 μM	50 μM	16
Pd-C-I	Anti-inflammatory activity	*In vitro*	(a) Inhibit NO production in RAW 264.7 cells (b) Inhibit iNOS expression levels (c) Inhibit TNF-α production in RAW 264.7 cells	-	10-40 μM	(a) IC_{50}= 31.83 μM (b) 40 μM (c) 40 μM	13
	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity (c) β-secretase inhibitory activity	-	(a) 0.8-20 μM (b) 4-100 μM (c) 4-100 μM	(a) IC_{50}= 1.84 μM (b) IC_{50}= 7.34 μM (c) IC_{50}= 7.34 μM	20
	Anti-diabetic activity	*In vitro*	(a) HRAR inhibitory activity (b) AGE inhibitory activity	-	(a) 0.5-10 μM (b) 2-50 μM	(a) IC_{50}= 3.43 μM (b) IC_{50}= 2.31 μM	19

Table 3. continued

Compounds	Biological activity	*in vivo* / *in vitro*	Model	Administration (*in vivo*)	Dose range	Active concentration	Reference
Pd-C-II	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity (c) β-secretase inhibitory activity	-	(a) 2-100 μM (b) 4-100 μM (c) 4-100 μM	(a) IC_{50}= 4.01 μM (b) IC_{50}= 13.91 μM (c) IC_{50}= 14.56 μM	20
	Anti-diabetic activity	*In vitro*	(a) HRAR inhibitory activity (b) AGE inhibitory activity	-	(a) 0.5-10 μM (b) 2-50 μM	(a) IC_{50}= 3.81 μM (b) IC_{50}= 3.16 μM	19
	Anti-inflammatory activity	*In vitro*	(a) Inhibit NO production in RAW 264.7 cells (b) Inhibit iNOS expression levels (c) Inhibit TNF-α production in RAW 264.7 cells	-	20-80 μM	(a) IC_{50}= 62.70 μM (b) 80 μM (c) 40, 80 μM	13
Pd-C-III	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity (c) β-secretase inhibitory activity	-	(a) 0.8-20 μM (b) 4-100 μM (c) 1-10 μM	(a) IC_{50}= 3.71 μM (b) IC_{50}= 9.18 μM (c) IC_{50}= 2.56 μM	20
	Anti-inflammatory activity	*In vitro*	(a) Inhibit NO production in RAW 264.7 cells (b) Inhibits iNOS and COX-2 expression levels (c) Inhibit TNF-α production in RAW 264.7 cells	-	15-60 μM	(a) IC_{50}= 15.60 μM (b) 60 μM (c) 60 μM	13
	Anti-diabetic activity	*In vitro*	(a) HRAR inhibitory activity (b) AGE inhibitory activity	-	(a) 0.5-10 μM (b) 0.1-5 μM	(a) IC_{50}= 21.3 μM (b) IC_{50}= 0.77 μM	19
Columbianadin	Anti-inflammatory activity	*In vitro*	(a) Inhibit NO production of LPS-stimulated in MH-S cells (b) Inhibit IL-6 production of IL-1β treated in A549 cells (c) Inhibit iNOS expression level in MH-S cells	-	10-50 μM	50,100 μM	12
		In vivo	(a) Reduced the cell numbers in the BALF, LPS-induced acute lung injury in mice (b) Reduced the cell numbers in the BALF, LPS-induced in alveolar macrophage, dendritic cell, neutrophil, and interstitial macrophage	Oral	20-60 mg/kg 20-60 mg/kg	20,60 mg/kg 20,60 mg/kg	12
		In vitro	(a) Inhibited the expression of MUC5AC mucin gene induced by EGF or PMA in NCI-H292 cells (b) Inhibited the production of MUC5AC mucin protein induced by PMA in NCI-H292 cells	-	1-100 μM	100 μM	17
	Anti-cancer activity	*In vitro*	(a) Cytotoxicity against in HCT116 cells (b) Increased the sub-G1 phage of cells (c) Promoted the expressions of cleaved caspase-9, 3, Bax, P53 and down-regulated of Bcl-2, Bim and BH3 levels (d) Increases Annexin V+/PI+ biomarker of apoptosis and V-/PI+ of necroptosis in HCT-116 cells (e) Suppressed cleaved caspase-8 and up-regulated RIP-3, and activation of PARP and cleaved PARP levels (f) Increased the intracellular ROS level (g) Suppressed of catalase and SOD-1 and activated SOD-2 and GPx-1 expressions level	-	(a) 12.5-50 μM (b) 0-50 μM (c) 12.5-50 μM (d) 12.5-50 μM (e)12.5-50 μM (f)12.5-50 μM (g)12.5-50 μM	(a) IC_{50}= 32.4 μM (b) 50 μM (c) 25 μM (d) 25, 50 μM (e) 50 μM (f) 50 μM (g) 50 μM	46
(+)-*trans*-decursidinol	Anti-diabetic activity	*In vitro*	(a) HRAR inhibitory activity (b) AGE inhibitory activity	-	(a) 0.1-2 μM (b) 2-50 μM	(a) IC_{50}= 1.03 μM (b) IC_{50}= 1.33 μM	19

Table 3. continued

Compounds	Biological activity	*in vivo* / *in vitro*	Model	Administration (*in vivo*)	Dose range	Active concentration	Reference
Decursinol	Anti-diabetic activity	*In vitro*	(a) PTP1B inhibitory activity (b) α-glucosidase inhibitory activity	-	(a) 4-100 μM (b) 31.5-125 μM	(a) IC_{50}= 58.90 μM (b) IC_{50}= 65.29 μM	16
	Antioxidant activity	*In vitro*	$ONOO^-$-mediated tyrosine nitration inhibition	-	25-100 μM	100 μM	16
Edulisin II	Anti-inflammatory activity	*In vitro*	(a) Inhibit NO production in RAW 264.7 cells (b) Inhibits iNOS and COX-2 expression levels (c) Inhibit TNF-α production in RAW 264.7 cells	-	1-4 μM	(a) IC_{50}= 2.50 μM (b) 2,4 μM (c) 2,4 μM	13
Isorutarine	Anti-diabetic activity	*In vitro*	(a) PTP1B inhibitory activity (b) RLAR inhibitory activity	-	(a) 4-100 μM (b) 10-250 μM	(a) IC_{50}= 80.09 μM (b) IC_{50}= 121.99 μM	14
	Anti-Alzheimer's treat	*In vitro*	Acetylcholinesterase inhibitory activity	-	(a) 4-100 μM	(a) IC_{50}= 28.72 μM	14
Parahydroxybenzoic acid	Anti-diabetic activity	*In vitro*	(a) PTP1B inhibitory activity (b) α-glucosidase inhibitory activity (c) RLAR inhibitory activity	-	(a) 20-250 μM (b) 62.5-500 μM (c) 12.5-250 μM	(a) IC_{50}= 214.83 μM (b) IC_{50}= 982.39 μM (c) IC_{50}= 290.29 μM	14
	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity	-	(a) 4-100 μM (b) 4-100 μM	(a) IC_{50}= 17.10 μM (b) IC_{50}= 54.99 μM	14
3′(*R*)-*O*-Acetyl-4′(*S*)-*O*-tigloylkhellactone	Anti-diabetic activity	*In vitro*	(a) PTP1B inhibitory activity (b) α-glucosidase inhibitory activity (c) RLAR inhibitory activity	-	(a) 4-100 μM (b) 31.5-125 μM (c) 12.5-250 μM	(a) IC_{50}= 106.21 μM (b) IC_{50}= 93.39 μM (c) IC_{50}= 165.39 μM	14
	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity (c) β-secretase inhibitory activity	-	(a) 0.8-100 μM (b) 4-100 μM (c) 2.5-62.5 μM	(a) IC_{50}= 11.02 μM (b) IC_{50}= 89.92 μM (c) IC_{50}= 22.69 μM	14
Cis-3′-acetyl-4′-angeloylkhellactone	Anti-diabetic activity	*In vitro*	(a) PTP1B inhibitory activity (b) α-glucosidase inhibitory activity (c) RLAR inhibitory activity	-	(a) 4-100 μM (b) 31.5-250 μM (c) 12.5-125 μM	(a) IC_{50}= 86.95 μM (b) IC_{50}= 264.26 μM (c) IC_{50}= 107.89 μM	14
	Anti-Alzheimer's treat	*In vitro*	(a) Acetylcholinesterase inhibitory activity (b) Butyrylcholinesterase inhibitory activity (c) β-secretase inhibitory activity	-	(a) 0.8-20 μM (b) 4-100 μM (c) 2.5-62.5 μM	(a) IC_{50}= 6.44 μM (b) IC_{50}= 106.7 μM (c) IC_{50}= 21.69 μM	14
Vanilic acid	Anti-oxidant activity	*In vitro*	(a) DPPH scavenging activity (b) ABTS scavenging activity (c) Inhibit NO production	-	(a) 20-250 μg/ml (b) 0.4-20 μg/ml (c)31.2-500 μg/ml	(a) IC_{50}= 725.79 μg/ml (b) IC_{50}= 1.39 μg/ml (c) IC_{50}= 23.38 μg/ml	11

and PGE2 production and dose-dependently (25, 50 mg/kg) inhibited carrageenan-induced mouse paw edema.[34] Columbianadin, a psoralen type coumarin from *A. decursiva*, exhibits potent anti-inflammatory activity through inhibition of NO, IL-6, and iNOS expression level in MH-S cells. In *in vivo* study, columbianadin at concentrations of 20 - 60 mg/kg also decreased cell numbers in BALF and LPS-induced alveolar macrophage, dendritic cell, neutrophil, and interstitial macrophage.[12] Recently, Ishita et al. (2015) have investigated the anti-inflammatory activity of different dihydroxanthyletin-type coumarins.[13] Among them, decursidin, Pd-C-I, Pd-C-II, Pd-C-III, and 4-hydroxy Pd-C-III can inhibit NO and TNF-α production and expression levels of iNOS and COX-2. Edulisin II also inhibited NO and TNF-α production and expression levels of iNOS and COX-2 in RAW 264.7 cells.[13]

Antioxidant activity – Natural products are highly promising sources of antioxidants. A wide range of bioactive constituents of plants has antioxidant activities. Based on various assay methods and activity indices, antioxidant activities and nutraceutical and therapeutic effects of traditional Chinese medicines as well as mechanisms underlying such activities and effects have been investigated.[35] Generation of free radicals can result in damage to the cellular machinery. Whole plants of MeOH extract and EtOAc, CH_2Cl_2, *n*-BuOH, and H_2O fractions of *A. decursiva* have exhibited 1,1-diphenyl-2-picrylhydrazyl (DPPH), 2,2'-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS), and peroxynitrite ($ONOO^-$) scavenging activities.[11] Among these tested fractions, EtOA fraction was found as the most active one, with IC_{50} value of 45.50 μg/ml for DPPH, 15.20 μg/ml for ABTS, and 1.58 μg/ml for $ONOO^-$ assays.[11] Coumarin umbelliferone 6-carboxylic acid exhibits potent antioxidant activity by scavenging DPPH (IC_{50} = 681.86 μg/ml), ABTS (IC_{50} = 11.20 μg/ml), and $ONOO^-$ (IC_{50} = 8.04 μg/ml). It also dose-dependently (12.5 - 100 μM) inhibited $ONOO^-$ -mediated tyrosine nitration.[16] Vanilic acid, a phenolic compound, also possesses antioxidant activity by scavenging DPPH (IC_{50} = 725.79 μg/ml) and ABTS (IC_{50} = 1.39 μg/ml).[11] It can also inhibit NO production, with IC_{50} value of 23.38 μg/ml.[11] Coumarins 4-hydroxy Pd-C-III, 4'-methoxy Pd-C-I, decursidine, decursinol, and 2'-isopropyl psoralene can also inhibit $ONOO^-$-mediated tyrosine nitration in a dose-dependent manner at concentrations ranging from 12.5 μM to 100 μM.[16]

Antidiabetic activity – Protein tyrosine phosphatase 1B (PTP1B) and α-glucosidase are two key enzymes that are effective in treating diabetes mellitus (DM). PTP1B can negatively regulate insulin signaling pathway. It is a promising target for the treatment of type II DM.[36] MeOH extract of *A. decursiva* whole plant has inhibitory activities against PTP1B and α-glucosidase. Out of 12 coumarins from this extract, decursinol, 4-hydroxy Pd-C-III, 4'-methoxy Pd-C-I, decursidine, 2'-isopropyl psoralene, and umbelliferone 6-carboxylic acid exhibited the highest inhibitory activities against PTP1B, with IC_{50} values of 5.39 - 58.90 μM.[14,16] Kinetic studies revealed that coumarins, 4-hydroxy Pd-C-III, umbelliferone 6-carboxylic acid, and 2'-isopropyl psoralene were competitive inhibitors against PTP1B. They showed tight binding with the active site of PTP1B by hydrogen bond interactions.[16] Moreover, α-glucosidases can aid in carbohydrate digestion and glucose release. Increased activity of these enzymes can lead to hyperglycemia and development of type II diabetes. Currently, α-glucosidase inhibitors can suppress the onset of this disorder. Several coumarins such as decursinol, 4-hydroxy Pd-C-III, 4'-methoxy Pd-C-I, decursidine, 2'-isopropyl psoralene, and (3′*R*)-*O*-acetyl-(4′*S*)-*O* tigloylkhellactone have α-glucosidase inhibitory activity, with IC_{50} values below 93 μM when 4-nitrophenyl-alpha-D-glucopyranoside is used as the substrate. Such IC_{50} values are considerably lower than the IC_{50} value (201 μM) of acarbose as a control drug.[14,16] Kinetic studies have revealed that coumarins decursinol, 4-hydroxy Pd-C-III, 4'-methoxy Pd-C-I, decursidine, and 2'-isopropyl psoralene show different modes of inhibition against α-glucosidase.[16]

Hyperglycemia is considered a vital initiator of several complications associated with diabetes by activating various metabolic pathways such as polyol pathway and formation of advanced glycation end products (AGE).[37] Thus, inhibiting aldose reductase (AR) and AGE formation has been used as a therapeutic strategy for diabetic complications.[38,39] Several coumarins derivatives including 4-hydroxy Pd-C-III, 4'-methoxy Pd-C-I, decursidine, (+)-*trans*-decursidinol, Pd-C-I, Pd-C-II, and Pd-C-III show potent human recombinant aldose reductase (HRAR) and AGE inhibitory activities, with IC_{50} values of 1.03 – 21.31 μM against HRAR and 0.41 – 5.56 μM against AGE.[19] Kinetic studies have revealed that coumarins 4-hydroxy Pd-C-III, Pd-C-I, Pd-C-II, and (+)-*trans*-decursidinol are competitive inhibitors against HRAR. Molecular analysis has shown that these coumarins have high affinity and tight binding capacities for the HRAR active site.[19] Ali et al. (2015) have also investigated inhibitory activities of serval coumarins and their derivatives against rat lens aldose reductase (RLAR) and found that their IC_{50} values range from 107.89 μM to

266.39 μM.[14]

Anticancer activity – *A. decursiva* root extract possesses anticancer activity *in vitro* by inhibiting cell proliferation and inducing apoptosis.[8,40-42] It has been shown that 95% EtOH extract of *A. decursiva* root can induce apoptosis of various cancer cells, including C6 rat glioma cells[40], FaDu human head and neck squamous cell carcinoma cells[41], Saos2 human osteogenic sarcoma cells[8], and human oral cancer cell line KB.[42] Procaspase-9 activated via a mitochondrial pathway can subsequently activate other executioner caspases such as caspases-3, -6, and -7.[40] These caspases also play an important role in the initiation and execution of apoptosis induced by various stimuli.[43,44] Cho et al. (2009) have reported that *A. decursiva* extract possesses cytotoxic (IC_{50} = 0.19 μg/mL) activity by inducing cell death in a concentration- (0.01 - 300 μg/m1) and time-dependent (1 - 3 days) manner and upregulating expression levels of proteolytic caspase genes such as caspase-3, -7, -9.[40] In another study, Shin et al. (2010) have found that 95% EtOH extract of *A. decursiva* has anti-cancer activity in FaDu human head and neck squamous cell carcinoma cells by inducing cell death (IC_{50} = 0.23 μg/mL) in a concentration- (0.01 - 10 μg/m1) and time-dependent (1 - 3 days) manner.[41] It also increased expression levels of proteolytic genes of caspase-3, -7, and -9.[41] Moreover, ethanol extract of *A. decursiva* root can suppress growth of Saos2 human osteogenic sarcoma cells and induce apoptotic cell death (IC_{50} = 1.4 μg/ml) in a concentration (0.01-10 μg/m1)-dependent manner.[8] Furthermore, proteolytic processing and activities of caspase-3 and -7 in Saos2 cells are increased by treatment with *A. decursiva* extract.[8] Additionally, ethanol extract of *A. decursiva* root possesses cytotoxic (IC_{50} = 0.21 μg/mL) activity and induces cell death of human oral cancer cell line KB.[42] Treatment of KB cells with extract of *A. decursiva* induced apoptotic cell death in both dose- and time-dependent manner. It also decreased levels of procaspase-7 and -9 and activation of caspase-7.[42] MeOH extract of *A. decursiva* and its different fractions also exhibit cytotoxic activity against HeLa cells.[45] Columbianadin as a coumarin also possesses anticancer activity by inhibiting cell proliferation and inducing apoptosis and necroptosis of HCT116 colon cancer cells.[46] Columbianadin exhibited cytotoxic activity (IC_{50} = 32.4 μM), increased sub-G1 phase and expression levels of caspases-9, caspase-3, Bax, and p53, and down-regulated expression levels of Bcl-2, Bim, and BH3 in HTC116 cells. In addition, pretreatment with columbianadin at concentration of 50 μM increased apoptosis (annexin V+/PI+) and necroptosis (annexin V-/PI+). In addition, columbianadin suppressed cleaved caspase-8 but increased levels of RIP-3, activated PARP, and cleaved PARP in a concentration (12.5 - 50 μM) dependent manner. Furthermore, columbianadin induced the accumulation of ROS and imbalance of intracellular antioxidant enzymes such as SOD-1, SOD-2, catalase, and GPx-1.[46]

Anti–Alzheimer's disease activity – Acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and β-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) are three key enzymes that are effective in treating Alzheimer's disease (AD). MeOH extract of whole plant of *A. decursiva* and its solvent-soluble fractions have been tested for their AChE and BChE inhibitory activities using Elman's method. Butanol and ethyl acetate fractions at a final concentration of 100 μg/mL significantly inhibited AChE activity, with IC_{50} values of 6.01 ± 0.09 and 9.67 ± 0.73 μg/mL, respectively. Butanol (IC_{50} = 0.42 ± 0.01 μg/mL), dichloromethane (IC_{50} = 2.35 ± 0.74 μg/mL), and ethyl acetate (IC_{50} = 5.47 ± 0.38 μg/mL) fractions also exhibited potent inhibitory activities against BChE. Furthermore, butanol fraction (IC_{50} = 9.1 ± 0.46 μg/mL) significantly inhibited β-secretase (BACE1) activity.[14] Nodakenin, the major coumarin from *A. decursiva*, showed significant inhibitory activities against AChE, BChE, and BACE1, with IC_{50} values of 33.67, 54.6, and 147.7 μM, respectively.[14] Additionally, nodakenin (1.0 mg/kg) improved memory impairment, enhanced proliferation and survival of newborn immature neuronal cells, and significantly increased phosphorylation level of Akt and expression level of GSK-3β.[47] In addition, coumarins umbelliferone 6-carboxylic acid, 6-formyl umbelliferone, 4'-methoxy Pd-C-I, decursidine, 4-hydroxy Pd-C-III, Pd-C-I, Pd-C-II, and Pd-C-III that displayed strong anti-AD activities by inhibiting AChE, BChE, and BACE1 enzymes were isolated from this plant.[14-16] Moreover, nodakenetin, umbelliferone, 3′(*R*)-*O*-acetyl-4′(*S*)-*O*-tigloylkhellactone, 2'-isopropyl psoralene, para-hydroxybenzoic acid, isorutarine, and *cis*-3′-acetyl-4′-angeloylkhellactone exhibited significant anti-AD activities by inhibiting AChE and BChE.[14,15]

Other activities – MeOH extract of *A. decursiva* root and its EtOA, chloroform, *n*-BuOH, and H_2O fractions exhibited anti-parasitic effects for the control of *Dyschirius intermedius*.[48] Especially, its chloroform fraction (100 - 350 mg/L) exhibited the highest inhibitory activity against *D. intermedius* (EC_{50} = 240.4 mg/l; EC_{90} = 433.9 mg/l). Coumarin decursidine also displayed anaphylactic activity by decreasing ^{45}Ca uptake induced by concanavalin A into rat mast cells.[49] It has been reported that 70% ethanol extract (25 - 800 μg/m1) of *A. decursiva* dried root possesses vasorelaxant effects on phenylephrine and KCl *in vivo*.[50]

The vasorelaxant effect of the extract was inhibited by pre-treatment (25 - 200 μg/m1) with glibenclamide, an ATP-sensitive K^+ channel blocker. Furthermore, the extract of *A. decursiva* concentration-dependently (100 - 400 μg/m1) inhibited Ca^{2+} supplementation-induced vasoconstriction of aortic rings pretreated with phenylephrine or KCl in the presence of Ca^{2+}.[50] Recently, MeOH extract of *A. decursiva* root has been investigated for its potential to prevent or treat cerebral stroke.[51] *In vivo* study showed that the extract (at concentrations of 60 mg/kg) significantly decreased infract lesions in C57BL/6 mice. Additionally, pretreatment with the extract at 200 mg/kg effectively suppressed expression levels of iNOS, reactive oxygen species (ROS), and malondialdehyde (MDA) and pro-inflammatory cytokines such as IL-1β and TNF-α in brain tissues of mice with MCAO-induced brain injury.[51]

Conclusion and perspectives

As presented in this review, pharmacological studies on *A. decursiva* and its putative active compounds, especially coumarins, support that several biological activities of *A. decursiva* can potentially impact human health. Coumarins can be effectively isolated and purified from *A. decursiva* root and its whole plant with various extraction analytical methods, mainly separation-based methods using TLC, HPLC, high-speed counter-current chromatography (HSCCC), and column chromatography (silica gel, reverse-phase, and Sephadex). Coumarins derived from *A. decursiva* have a wide range of crucial bioactivities, including anti-inflammatory, anti-diabetic, anti-Alzheimer's disease, anti-hypertension, anti-cancer, antioxidant, anthelmintic, prevention of cerebral stroke, and neuroprotective activities. Despite these reported biological activities of *A. decursiva* and coumarins derivatives, *in vivo* studies in animals and clinical studies must be conducted to understand effects of coumarins metabolites on human health because effects of these coumarins on human tissues and cells measured by *in vitro* do not accurately recapitulate their actual *in vivo* effects. Thus, there are still opportunities and challenges for research of coumarins. The number of modern studies on bioactive coumarins is increasing in biomedicine, suggesting that these compounds might have great medical significance in the future. This review presents a summary of studies published to date on this promising plant.

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