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REVIEW

Angelica keiskei, an emerging medicinal herb with various bioactive constituents and biological activities

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Abstract *Angelica keiskei* (Miq.) Koidz. (Umbelliferae) has traditionally been used to treat dysuria, dyschezia, and dysgalactia as well as to restore vitality. Recently, the aerial parts of *A. keiskei* have been consumed as a health food. Various flavonoids, coumarins, phenolics, acetylenes, sesquiterpene, diterpene, and triterpenes were identified as the constituents of *A. keiskei*. The crude extracts and pure constituents were proven to inhibit tumor growth and ameliorate inflammation, obesity, diabetics, hypertension, and ulcer. The extract also showed anti-thrombotic, anti-oxidative, anti-hyperlipidemic, anti-viral, and anti-bacterial activities. This valuable herb needs to be further studied and developed not only to treat these human diseases but also to improve human health. Currently *A. keiskei* is commercialized as a health food and additives in health drinks. This article presents a comprehensive review of *A. keiskei* and its potential place in the improvement of human health.

Keywords *Angelica keiskei* · Umbelliferae · Chemical constituent · Biological activity

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Introduction

Angelica keiskei (Miq.) Koidz. is a hardy perennial, belonging to the family Umbelliferae. *A. keiskei* has traditionally been used as a diuretic, mild cathartic, tonic, and galactagogue (Kimura and Baba 2003). The herb is called 'Myeong-Il Yeob' in Korea and 'Ashitaba' in Japan, both literally meaning 'Tomorrow's Leaf' (Baba et al. 1998). Another common name for *A. keiskei* is 'Shin-Sun Cho', which means 'a precious herb used by God'. *A. keiskei* is mainly distributed in Asian countries including Korea and Japan (Park 2013). The aerial parts are mainly used as a source of green vegetable juice as a daily health food and the young leaves of the aerial parts are used by parboiling or deep-frying (Imai and Imai 2008). The aerial parts are also used in tea, flour, wine, and cosmetics (Bao 2014; Su 2014; Ku et al. 2014; Liu et al. 2014). This review paper summarizes botanical characteristics, phytochemical research, as well as biological studies on the extracts and pure constituents of *A. keiskei*. The extracts have been reported to have anti-inflammatory, anti-obesity, anti-oxidative, anti-coagulant, anti-tumor, anti-mutagenic, anti-diabetic, anti-bacterial, and hepato-protective activities. The biological activities of each pure compounds are also separately summarized in this review.

Botanical characteristics of *A. keiskei*

Angelica keiskei has glossy leaves and flowers from summer to fall. The leaves are harvested from spring to fall before they lose the gloss. A yellow exudate is squeezed out of the stems when the leaves are harvested (Imai and Imai 2008). This yellow color makes it easy to distinguish *A. keiskei* from *A. japonica*, an exudate of which shows a

nearly white color (Kimura et al. 2008). The characteristic botanical features of *A. keiskei* are described in Flora of Japan:

> *Rhizomes* thick and short, with few elongate roots. *Stems* stout, branched above, 80–120 cm long, glabrous. *Leaves* radical and lower cauline, usually evergreen, 2–3-ternate-pinnate, obtusely deltoid in outline, 20–60 cm. long, glabrous; leaflets rather thick, usually deeply 2–3 cleft of parted; segments usually ovate, 5–10 cm long, 3–6 cm wide, acute, toothed, with impressed veinlets on upper side; sheaths on the upper part elliptic, inflated. *Inflorescence* umbels rather numerous; peduncles in upper part; the inner side of rays and pedicels puberulent; rays 10–20; pedicels 20–40; bracteoles of involucel several, linear or slightly broaden at base, caudately elongate, slightly longer or shorter than pedicels; styles short, as long as stylopodium. *Fruit* oblong, glabrous, 6–8 mm long, flat; dorsal ribs short and rather thick; lateral ribs winged; vittae 1 in intervals, 4 on the commissure (Oi et al. 1965).

Phytochemical investigations on *A. keiskei*

Previous phytochemical investigations on *A. keiskei* have led to the identification of over 100 compounds including various types of flavonoids (**1–31**, **41–56**), coumarins (**57–92**), phenolic (**96**), acetylenes (**98–102**), sesquiterpene (**103**), diterpene (**104**), and triterpenes (**105–106**). Structures of the reported constituents listed in Tables 1, 2 and 3 are shown in Fig. 1. In our recent study on the aerial parts of *A. keiskei*, eight constituents, 4,2′,4′-trihydroxy-3′-[(2*E*,5*E*)-7-methoxy-3,7-dimethyl-2,5-octadienyl]chalcone (**32**), (±)-4,2′,4′-trihydroxy-3′-[(2*E*)-6-hydroxy-7-methoxy-3,7-dimethyl-2-octenyl]chalcone (**33**), 4,2′,4′-trihydroxy-3′-[(2*E*)-3-methyl-5-(1,3-dioxolan-2-yl)-2-pentenyl] chalcone (**34**), 2′,3′-furano-4-hydroxy-4′-methoxychalcone (**35**), (±)-4-hydroxy-2′,3′-(2,3-dihydro-2-methoxyfurano)-4′-methoxychalcone (**36**), 3′-carboxymethyl-4,2′-dihydroxy-4′-methoxychalcone (**37**), (±)-4,2′,4′-trihydroxy-3′-[(3-hydroxy-2,2-dimethyl-6-methylenecyclohexyl)methyl] chalcone (**38**), and 2″-hydroxyangelichalcone (**39**) were isolated and reported as new compounds from an ethyl acetate extract along with eight known compounds, xanthoangelol (**1**), xanthoangelol F (**2**), 4-hydroxyderricin (**3**), xanthoangelol G (**6**), xanthoangelol D (**9**), xanthoangelol E (**10**), xanthoangelol H (**12**), (±)-4,2′,4′-trihydroxy-3′-[(6*E*)-2-hydroxy-7-methyl-3-methylene-6-octenyl]chalcone (**27**), artocarmitin A (**40**), (+)-*cis*-(3′*R*,4′*R*)-methylkhellactone (**93**), (-)-*trans*-(3′*R*,4′*S*)-methylkhellactone (**94**), 3,4-dihydroxanthotoxin (**95**), and (*Z*)-*p*-coumaryl alcohol (**97**) (Kil et al. 2015a, 2016). In particular, xanthoangelol (**1**) and 4-hydroderricin (**3**) were isolated in bulk (**1**: 5 g, **2**: 1.8 g), which supported that the two chalcones are the predominant constituents in this herb. As a part of our research on the aerial parts of *A. keiskei*, an effective method was developed to prepare two chalcones from the crude extract using high-speed counter-current chromatography (two-phase solvent system: *n*-hexane–ethyl acetate–methanol–water 9:5:9:4, revolution rate: 800 rpm, flow rate: 1.5 mL/min) (Kil et al. 2015b).

Biological activities of extracts

Anti-inflammatory activity

An *n*-hexane fraction from an ethanol extract of the aerial parts of *A. keiskei* showed inhibitory effects on production of lipopolysaccharide (LPS)-induced nitric oxide (NO) and prostaglandin E_2 (PGE_2) by downregulating inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2) protein and mRNA (Lee et al. 2010). An ethyl acetate fraction also inhibited production of NO in LPS-activated RAW 264.7 cells (Chang et al. 2014).

Anti-obesity activity

In a study in mice, an ethyl acetate extract was reported to prevent high-fat diet induced adiposity by modulating lipid metabolism through increasing phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) in adipose tissue and liver (Zhang et al. 2015). A patent has been filed on the anti-obesity activity of the ethanol extract of the aerial parts of *A. keiskei* in mice (Lee et al. 2012a).

Anti-hyperlipidemic activity

Dietary *A. keiskei* as an ethyl acetate extract from yellow exudates produced elevation of serum high-density lipoprotein (HDL) levels containing apolipoprotein A1 (ApoA1) and ApoE and reduction of liver triglyceride (TG) levels with decreased mRNA expression of hepatic Acyl-coenzyme A (CoA) synthetase in stroke-prone spontaneously hypertensive rats (SHRSP) (Ogawa et al. 2003). An ethyl acetate fraction from a methanol extract showed inhibitory effects against 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase, a crucial and rate limiting enzyme in biosynthesis of cholesterol (Park et al. 1997b). The impact of *A. keiskei* was examined in rats fed a high fat diet, and it was shown that liver weight was decreased and gene expression of the anti-oxidant enzymes, catalase and glutathione-*s*-reductase, in the liver was increased (Kim et al. 2012). In addition, treatment of the ethanol extract

Table 1 The reported biological activities of xanthoangelol (**1**)

Part[a]	Biological activity	Reference(s)
RT	First isolation from the part	Kozawa et al. (1977)
RT	Anti-ulcer activity: gastric H^+–K^+ ATPase	Murakami et al. (1990)
RT	Anti-bacterial activity: gram-positive bacteria	Inamori et al. (1991)
Syn	Anti-bacterial activity: gram-positive bacteria	Sugamoto et al. (2011)
RT	Anti-tumor-promoter activity: TPA-stimulated ^{32}Pi-incorporation, Ca^+-calmodulin system	Okuyama et al. (1991)
EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2003)
RT	Anti-tumor and anti-metastatic activities: DNA synthesis, tumor-induced neovascularization, binding of VEGF to HUVECs	Kimura and Baba (2003)
EXD	Anti-tumor activity: apoptosis (caspase-3) in human neuroblastoma (IMR-32), leukemia (Jurkat) cells	Tabata et al. (2005)
EXD	Anti-tumor activity: apoptosis (caspase-9, cytochrome c), ROS, DJ-1 protein in human neuroblastoma (IMR-32) cells	Motani et al. 2008)
EXD, ST	Cytotoxicities: human neuroblastoma cells (LA-N-1, NB-39: drug-resistant; IMR-32, SK-N-SH: drug-sensitive)	Motani et al. (2008), Nishimura et al. (2007)
ST	Anti-tumor activity: apoptosis (DNA fragmentation) in human stomach cancer (KATO III) cells	Takaoka et al. (2008)
AP	Anti-diabetic activity: insulin-like activity	Enoki et al. (2007)
RT	Anti-diabetic activity: GLUT4 translocation	Kawabata et al. (2011)
AP	Anti-diabetic activity: α-glucosidase	Luo et al. (2012)
ST	Anti-diabetic activity: PTP1B	Li et al. (2015)
RT	Anti-hypertensive activity: vasoconstriction in rat aortic rings	Matsuura et al. (2001)
RT	Preventive effect against metabolic syndrome: adiponectin production	Ohnogi et al. (2012b)
RT	Preventive effect against metabolic syndrome: adipocytes differentiation (AMPK, MAPK pathways; C/EBPs, PPARγ)	Zhang et al. (2013)
EXD	Anti-inflammatory activity (details in the patent)	Akihisa et al. (2007)
RT	Anti-inflammatory activity: NO, TNF-α, iNOS, COX-2, AP-1	Yasuda et al. (2014)
LF	Anti-inflammatory activity: IL-6 in TNF-α-stimulated osteosarcoma cells	Shin et al. (2011)
AP	Anti-oxidative activity: NQO1 induction, DPPH radical scavenging	Luo et al. (2012)
ST	Anti-oxidative activity: XO	Kim et al. (2014)
ST	Anti-thrombotic activity: PAI-1	Ohkura et al. (2011)
RT	Anti-thrombotic activity: platelet aggregation (induced by collagen, platelet-activating factor, phorbol 12-myristate 13-acetate, not thrombin)	Son et al. (2014)
ST	Whitening activity: melanin formation in B16 melanoma cells	Arung et al. (2012)
AP	Anti-depressant activity: MAO (nonselective), DBH	Kim et al. (2013)
WP	Anti-viral activity: SARS-CoV (viral proteases: $3CL^{pro}$, PL^{pro})	Park et al. (2015)

[a] Plant part code: *WP* whole plant, *RT* root, *AP* aerial part (including stem and leaf), *ST* stem, *LF* leaf, *EXD* exudate; other source code: *Syn* synthetic

reduced increased levels of serum insulin and triglycerides in rats after drinking fructose. The ethanol extract enhanced expression of genes related to fatty acid β-oxidation and HDL production, acyl-CoA oxidase 1 (ACO1), medium-chain acyl-CoA dehydrogenase (MCAD), ATP-binding membrane cassette transporter A1 (ABCA1), and ApoA1 genes in the fructose fed rats (Ohnogi et al. 2012a).

Anti-oxidative activity

The alcohol extracts of *A. keiskei* were evaluated for their scavenging capability against superoxide anion and 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radicals, and resulted in decreases of free radical formations. The scavenging effects of the leaves extract were greater than those of the stems extract (Qin et al. 2014; Guo et al. 2013).

Anti-thrombotic activity

Exudates of *A. keiskei* resulted in anti-coagulation by inhibiting elevated plasma plasminogen activator inhibitor 1 (PAI-1) under inflammatory conditions induced by LPS (Ohkura et al. 2011). A methanol extract of its roots showed anti-platelet activity when evaluated in a washed rabbit platelets model system (Son et al. 2014).

Table 2 The reported biological activities of 4-hydroxyderricin (**3**)

Part[a]	Biological activity	Reference(s)
RT	First isolation from the part	Kozawa et al. (1977)
RT	Anti-ulcer activity: gastric H^+–K^+ ATPase	Murakami et al. (1990)
RT	Anti-bacterial activity: gram-positive bacteria	Inamori et al. (1991)
Syn	Anti-bacterial activity: gram-positive bacteria	Sugamoto et al. (2011)
Syn	Anti-bacterial activity: *S. aureus* seryl-tRNA synthetase	Battenberg et al. (2013)
RT	Anti-tumor-promoter activity: TPA-stimulated ^{32}Pi-incorporation, Ca^+-calmodulin system	Okuyama et al. (1991)
EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2003)
ST	Anti-tumor activity: apoptosis (DNA fragmentation) in human stomach cancer (KATO III) cells	Takaoka et al. (2008)
RT	Anti-tumor and anti-metastatic activities: DNA synthesis, tumor-induced neovascularization, lymphocytes, $CD4^+$, $CD8^+$, NK-T cells	Kimura et al. (2004)
RT	Anti-tumor activity: apoptosis (DNA topoisomerase, procasparases-3, -8, -9 in human leukemia (HL60) cells	Akihisa et al. (2011)
	Cytotoxicities: human leukemia (HL60), melanoma (CRL1579), lung cancer (A549), stomach cancer (AZ521) cells	
ST	Cytotoxicities: human neuroblastoma cells (IMR-32, NB-39)	Nishimura et al. (2007)
RT	Anti-hypertensive activity: vasoconstriction in rat aortic rings	Matsuura et al. (2001)
ST	Anti-hypertensive activity: systolic blood pressure in SHRSP	Ogawa et al. (2005b)
	Anti-hyperlipidemic activity: serum VLDL (microsomal TG transfer-protein), hepatic TG (differentiation factor 1, fatty acid synthase) levels in SHRSP	
AP	Anti-diabetic activity: insulin-like activity	Enoki et al. (2007)
RT	Anti-diabetic activity: chronic ingestion on borderline mild hyperglycemia (adiponectin)	Ohnogi et al. (2007)
RT	Anti-diabetic activity: GLUT4 translocation	Kawabata et al. (2011)
AP	Anti-diabetic activity: α-glucosidase	Luo et al. (2012)
ST	Anti-diabetic activity: PTP1B	Li et al. (2015)
EXD	Anti-inflammatory activity (details in the patent)	Akihisa et al. (2007)
LF	Anti-inflammatory activity: IL-6 in TNF-α-stimulated osteosarcoma cells	Shin et al. (2011)
RT, AP	Anti-inflammatory activity: NO, TNF-α, iNOS, COX-2, AP-1	Yasuda et al. (2014), Chang et al. (2014)
AP	Anti-inflammatory activity: I-κB degradation, NF-κB nuclear translocation	Chang et al. (2014)
RT	Anti-thrombotic activity: platelet aggregation (induced by collagen, platelet-activating factor, phorbol 12-myristate 13-acetate, not thrombin)	Son et al. (2014)
LF	Anti-viral activity: influenza virus neuraminidase	Park et al. (2011)
WP	Anti-viral activity: SARS-CoV (viral proteases: $3CL^{pro}$, PL^{pro})	Park et al. (2015)
RT	Preventive effect against metabolic syndrome: adiponectin production	Ohnogi et al. (2012b)
RT	Preventive effect against metabolic syndrome: adipocytes differentiation (AMPK, MAPK pathways; C/EBPs, PPARγ)	Zhang et al. (2013)
AP	Anti-oxidative activity: NQO1 induction	Luo et al. (2012)
WP	Anti-oxidative activity: XO	Kim et al. (2014)
ST	Whitening activity: melanin formation in B16 melanoma cells	Arung et al. (2012)
AP	Anti-depressant activity: inhibition of MAO-B (selective), DBH	Kim et al. (2013)

[a] Plant part code: *WP* whole plant, *RT* root, *AP* aerial part (including stem and leaf), *ST* stem, *LF* leaf, *EXD* exudate; other source code: *Syn* synthetic

Anti-tumor and anti-mutagenic activity

The extracts induced apoptotic cell death in various human cancer cell lines including breast cancer (MDA-MB-231) (Jeong and Kang 2011), leukemia (HL60), melanoma (CRL1579), lung cancer (A549), stomach cancer (AZ521) (Akihisa et al. 2011), prostate cancer (LNCaP) (Lee et al. 2014). In these cancer cell lines studies, increasing expression level of the proapoptotic gene, Caspase-3, and apoptotic inducer gene, B cell lymphoma 2 (Bcl-2), and decreasing expression level of the apoptotic suppressor gene, Bcl-2 associated x (Bax), were presented as the mechanism of action of anti-cancer effects of *A. keiskei* (Jeong and Kang 2011). The methanol extract showed an anti-mutagenic activity against aflatoxin B1 (AFB1), *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine,

Table 3 Constituents from *A. keiskei* and their reported biological activities

Compound class/name	Part[a]	Biological activity	Reference(s)
Flavonoids			
Chalcones			
Xanthoangelol F (**2**)	RT	First isolation from the part	Nakata et al. (1999)
	RT	Anti-hypertensive activity: phenylephrine-induced vasoconstriction in rat aortic rings	Matsuura et al. (2001)
	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2003)
		Anti-tumor-initiator activity: NOR 1	
	EXD	Anti-inflammatory activity (details in the patent)	Akihisa et al. (2007)
	ST	Cytotoxicities: human neuroblastoma (IMR-32, NB-39)	Nishimura et al. (2007)
	Syn	Anti-bacterial activity: Gram-positive bacteria	Sugamoto et al. (2011)
	AP	Anti-viral activity: influenza virus neuraminidase	Park et al. (2011)
	WP	Anti-viral activity: SARS-CoV ($3CL^{pro}$, PL^{pro})	Park et al. (2015)
	WP	Anti-oxidative activity: XO	Kim et al. (2014)
	ST	Anti-diabetic activity: PTP1B	Li et al. (2015)
Isobavachalcone (**4**)	RT	First isolation from the part	Nakata et al. (1999)
	EXD	Anti-tumor-promoter activity: EBV-EA by TPA, *in vivo*	Akihisa et al. (2003)
		Two-stage mouse skin carcinogenesis test	Akihisa et al. (2006)
		Anti-tumor-initiator activity: NOR 1	
	ST	Anti-tumor activity: apoptosis (procaspase-3, -9, Bax) in human neuroblastoma cells (IMR-32, NB-39)	Nishimura et al. (2007)
	EXD	Anti-inflammatory activity (details in the patent)	Akihisa et al. (2007)
	Com	Anti-inflammatory activity: iNOS	Shin et al. (2013)
	Syn	Anti-bacterial activity: Gram-positive bacteria	Sugamoto et al. (2011)
	AP	Anti-oxidative activity: NQO1 induction, DPPH radical scavenging	Luo et al. (2012)
	WP	Anti-oxidative activity: XO	Kim et al. (2014)
	AP	Anti-diabetic activity: α-glucosidase	Luo et al. (2012)
	WP	Anti-viral activity: SARS-CoV ($3CL^{pro}$, PL^{pro})	Park et al. (2015)
Xanthoangelol B (**5**)	RT	First isolation from the part	Baba et al. (1990b)
	RT	Anti-hypertensive activity: phenylephrine-induced vasoconstriction in rat aortic rings	Matsuura et al. (2001)
	RT	Anti-allergic activity: compound 48/80-induced histamine release	Nakata and Baba (2001)
	ST	Anti-oxidative activity: superoxide-scavenging	Aoki et al. (2008)
	WP	Anti-oxidative activity: XO	Kim et al. (2014)
	LF	Anti-inflammatory activity: IL-6 in TNF-α-stimulated osteosarcoma cells	Shin et al. (2011)
	AP	Anti-inflammatory activity: NO, iNOS, COX-2 (IκB degradation, NF-κB nuclear translocation)	Chang et al. (2014)
	AP	Anti-viral activity: influenza virus neuraminidase	Park et al. (2011)
	ST	Anti-thrombotic activity: TNFα-induced PAI-1	Ohkura et al. (2011)
	WP	Anti-viral activity: SARS-CoV ($3CL^{pro}$, PL^{pro})	Park et al. (2015)
Xanthoangelol G (**6**)	RT	First isolation from the part	Nakata et al. (1999)
	AP	Anti-viral activity: influenza virus neuraminidase	Park et al. (2011)
	WP	Anti-viral activity: SARS-CoV ($3CL^{pro}$, PL^{pro})	Park et al. (2015)
4,2′-Dihydroxy-3′-[(2*E*)-6-hydroperoxy-3-methyl-7-methylene-2-octenyl]-4′-methoxy chalcone (**7**)	RT	Preventive effect against metabolic syndrome: adiponectin production	Ohnogi et al. (2012b)

Table 3 continued

Compound class/name	Part[a]	Biological activity	Reference(s)
Xanthoangelol C (**8**)	RT		Baba et al. (1990b)
	RT	Anti-allergic activity: compound 48/80-induced histamine	Nakata and Baba (2001)
Xanthoangelol D (**9**)	RT	First isolation from the part	Baba et al. (1990b)
	RT	Anti-inflammatory activity: TNF-α induced ET-1 (NF-κB)	Sugii et al. (2005)
	AP	Anti-viral activity: influenza virus neuraminidase	Park et al. (2011)
	ST	Anti-thrombotic activity: TNFα-induced PAI-1	Ohkura et al. (2011)
	WP	Anti-viral activity: SARS-CoV ($3CL^{pro}$, PL^{pro})	Park et al. (2015)
	ST	Anti-diabetic activity: PTP1B	Li et al. (2015)
Xanthoangelol E (**10**)	RT	First isolation from the part	Baba et al. (1990b)
	RT	Anti-ulcer activity (details in the patent)	Murakami et al. (1992)
	RT	Anti-thrombotic activity: arachidonic acid metabolism in platelets	Fujita et al. (1992)
	RT	Anti-hypertensive activity: phenylephrine-induced vasoconstriction in rat aortic rings	Matsuura et al. (2001)
	RT	Anti-allergic activity: compound 48/80-induced histamine	Nakata and Baba (2001)
	LF	First isolation from the part	Shin et al. (2011)
	AP	Anti-inflammatory activity: NO, iNOS, COX-2 (IκB degradation, NF-κB nuclear translocation)	Chang et al. (2014)
	WP	Anti-viral activity: SARS-CoV ($3CL^{pro}$, PL^{pro})	Park et al. (2015)
	ST	Anti-diabetic activity: PTP1B	Li et al. (2015)
Ashitaba-chalcone (**11**)	RT	Anti-tumor-promoter activity: TPA-stimulated ^{32}Pi-incorporation	Okuyama et al. (1991)
Xanthoangelol H (**12**)	RT	First isolation from the part	Nakata et al. (1999)
	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2003)
	ST	Cytotoxicities: human neuroblastoma (IMR-32, NB-39)	Nishimura et al. (2007)
	ST	Whitening activity: melanin formation in melanoma cells	Arung et al. (2012)
Deoxyxanthoangelol H (**13**)	EXD	First isolation from the part	Akihisa et al. (2006)
	EXD	Anti-inflammatory activity (details in the patent)	Akihisa et al. (2007)
	ST	Whitening activity: melanin formation in melanoma cells	Arung et al. (2012)
Xanthoangelol I (**14**)	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2006)
		Anti-tumor-initiator activity: NOR 1	
	ST	Cytotoxicities: human neuroblastoma (IMR-32, NB-39)	Nishimura et al. (2007)
2″-Hydroxy-xanthoangelol I (**15**)	RT	Protective effect on nerve cells (details in the patent)	Onogi et al. (2004)
	RT	Preventive effect against metabolic syndrome: adiponectin	Ohnogi et al. (2012b)
Xanthoangelol J (**16**)	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2006)
		Anti-tumor-initiator activity: NOR 1	
Xanthoangelol K (**17**)	ST	Anti-diabetic activity: PTP1B	Li et al. (2015)
Xanthoangelol L (**18**)	ST	First isolation from the part	Li et al. (2015)
Jejuchalcone D (**19**)	ST	First isolation from the part	Li et al. (2015)
Xanthoangelol M (**20**)	ST	Anti-diabetic activity: PTP1B	Li et al. (2015)
4-Hydroxy-2′,3′-(2,3-dihydro-2-hydroxy isopropylfurano)-4′-methoxychalcone (**21**)	RT	Preventive effect against metabolic syndrome: adiponectin production	Ohnogi et al. (2012b)
Jejuchalcone E (**22**)	ST	First isolation from the part	Li et al. (2015)
Dorsmannin A (**23**)	EXD	First isolation from the part	Akihisa et al. (2006)

Table 3 continued

Compound class/name	Part[a]	Biological activity	Reference(s)
Xanthokeismin A (**24**)	ST	Anti-oxidative activity: superoxide-scavenging	Aoki et al. (2008)
	AP	Anti-inflammatory activity: NO, iNOS, COX-2 (IκB degradation, NF-κB nuclear translocation)	Chang et al. (2014)
Xanthokeismin B (**25**)	ST	Anti-oxidative activity: superoxide-scavenging	Aoki et al. (2008)
Xanthokeismin C (**26**)	ST	Anti-oxidative activity: superoxide-scavenging	Aoki et al. (2008)
4,2′,4′-Trihydroxy-3′-[(6*E*)-2-hydroxy-7-methyl-3-methylene-6-octenyl]chalcone (**27**)	LF	Anti-inflammatory activity: IL-6 in TNF-α-stimulated osteosarcoma cells	Shin et al. (2011)
	AP		Kil et al. (2015a)
		Protective activity on damaged normal cells: HSPs	
Xanthokeistal A (**28**)	AP	Anti-viral activity: influenza virus neuraminidase	Park et al. (2011)
	WP	Anti-viral activity: SARS-CoV ($3CL^{pro}$, PL^{pro})	Park et al. (2015)
4,2′4′-Trihydroxy-3′-[(2*E*)-6,7-dihydroxy-3,7-dimethyl-2-octenyl] chalcone (**29**)	RT	First isolation from the part	Ohnogi et al. (2012b)
	AP	First isolation from the part	Luo et al. (2012)
4,2′-Dihydroxy-3′,4′-{2,3-dihydro-2-[(4*E*)-1-hydroxy-1,5-dimethyl-4-hexenyl]furano} chalcone (**30**)	RT	Preventive effect against metabolic syndrome: adiponectin production	Ohnogi et al. (2012b)
Angelichalcone (**31**)	RT	Protective effect on nerve cells (details in the patent)	Onogi et al. (2004)
	RT	Osteogenesis promotive activity (details in the patent)	Ohnogi et al. (2004)
4,2′,4′-Trihydroxy-3′-[(2*E*,5*E*)-7-methoxy-3,7-dimethyl-2,5-octadienyl] chalcone (**32**)	AP	First isolation from the part	Kil et al. (2015a)
(±)-4,2′,4′-Trihydroxy-3′-[(2*E*)-6-hydroxy-7-methoxy-3,7-dimethyl-2-octenyl]chalcone (**33**)	AP	First isolation from the part	Kil et al. (2015a)
4,2′,4′-Trihydroxy-3′-[(2*E*)-3-methyl-5-(1,3-dioxolan-2-yl)-2-pentenyl]chalcone (**34**)	AP	First isolation from the part	Kil et al. (2015a)
2′,3′-Furano-4-hydroxy-4′-methoxychalcone (**35**)	AP	First isolation from the part	Kil et al. (2015a)
(±)-4-Hydroxy-2′,3′-(2,3-dihydro-2-methoxyfurano)-4′-methoxychalcone (**36**)	AP	First isolation from the part	Kil et al. (2015a)
3′-Carboxymethyl- 4,2′-dihydroxy-4′-methoxy chalcone (**37**)	AP	First isolation from the part	Kil et al. (2016)
(±)-4,2′,4′-Trihydroxy-3′-[(3-hydroxy-2,2-dimethyl-6-methylenecyclohexyl)methyl]chalcone (**38**)	AP	First isolation from the part	Kil et al. (2016)
2″-Hydroxy angelichalcone (**39**)	AP	First isolation from the part	Kil et al. (2016)
Artocarmitin A (**40**)	AP	First isolation from the part	Kil et al. (2016)
Dihydrochalcones			
Deoxydihydroxanthoan	EXD	First isolation from the part	Akihisa et al. (2006)
Gelol H (**41**)	ST	whitening activity: melanin formation in melanoma cells	Arung et al. (2012)
Erioschalcone A (**42**)	AP	First isolation from the part	Luo et al. (2012)
Flavones			
Cynaroside (**43**) (=luteolin-7-*O*-β-D-glucopyranoside)	AP	Anti-hyperlipidemic acitivity	Park et al. (1995)
	AP	Anti-cholesterogenic activity: HMG-CoA reductase	Park et al. (1997b)
	AP	Anti-mutagenic activity (AFB1)	Park et al. (1997a)
	AP	Anti-oxidative activity: epoxide hydrolase in liver	Park et al. (2002)
	AP	Anti-oxidative activity: DPPH radical scavenging	Kim et al. (2005)
	AP	Anti-depressant activity: DBH	Kim et al. (2013)
	ST	Anti-diabetic activity: PTP1B	Li et al. (2015)
Luteolin-7-*O*-β-D-rutinoside (**44**)	AP	First isolation from the part	Park et al. (1995)
	AP	Anti-mutagenic activity (AFB1)	Park et al. (1997a)
	AP	Anti-oxidative activity: DPPH radical scavenging	Kim et al. (2005)

Table 3 continued

Compound class/name	Part[a]	Biological activity	Reference(s)
Luteolin (**45**)	LF	First isolation from the part	Sugamoto et al. (2008)
Flavonol glycosides			
Kaempferol-3-*O*-α-D-arabinopyranoside (**46**)	AP	Anti-oxidative activity: DPPH radical scavenging	Kim et al. (2005)
Isoquercitrin (=quercetin-3-*O*-β-D-glucopyranoside) (**47**)	AP	Anti-oxidative activity: DPPH radical scavenging	Kim et al. (2005)
Hyperoside (=quercetin-3-*O*-β-D-galactopyranoside) (**48**)	AP	First isolation from the part	Park et al. (1996)
	AP	Anti-cholesterogenic activity: HMG-CoA reductase	Park et al. (1997b)
	AP	Anti-mutagenic activity (AFB1)	Park et al. (1997a)
	AP	Anti-oxidative activity: DPPH radical scavenging	Kim et al. (2005)
Quercitrin (**49**) (=quercetin-3-*O*-β-D-rhamnopyranoside)	LF	First isolation from the part	Sugamoto et al. (2008)
Quercetin-3-*O*-α-D-arabinopyranoside (**50**)	AP	Anti-oxidative activity: DPPH radical scavenging	Kim et al. (2005)
Flavanones			
Munduleaflavanone A (**51**)	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2003)
	AP	Anti-diabetic activity: α-glucosidase	Luo et al. (2012)
Munduleaflavanone B (**52**)	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2006)
		Anti-tumor-initiator activity: NOR 1	
	EXD	anti-inflammatory activity: TPA-induced mouse ear edema	Akihisa et al. (2007)
Isobavachin (**53**)	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2006)
Prostratol F (**54**)	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2003)
Sophoraflavanone A (**55**) (=8-geranylnaringenin)	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2006)
		Anti-tumor-initiator activity: NOR 1	
	EXD	Anti-inflammatory activity: TPA-induced mouse ear edema	Akihisa et al. (2007)
4′-*O*-Geranylnaringenin (**56**)	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2003)
Coumarins			
Umbelliferone (**57**)	RT	First isolation from the part	Baba et al. (1990b)
Scopoletin (**58**)	RT	First isolation from the part	Baba et al. (1990b)
Demethylsuberosin (**59**)	AP	Anti-diabetic activity: α-glucosidase	Luo et al. (2012)
Osthenol (**60**)	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2006)
		Anti-tumor-initiator activity: NOR 1	
	EXD	Anti-inflammatory activity (details in the patent)	Akihisa et al. (2007)
7-*O*-β-D-Glucopyranosyloxy-8-prenyl coumarin (**61**)	RT	NGF production enhancive effect on in mouse fibroblasts (details in the patent)	Ohnogi et al. (2002)
Psoralen (**62**)	RT	First isolation from the part	Hata and Kozawa (1961)
	AP	First isolation from the part	Luo et al. (2012)
Ergapten (**63**)	RT	First isolation from the part	Hata and Kozawa (1961)
	FR	First isolation from the part	Baba et al. (1990a)
	AP	First isolation from the part	Luo et al. (2012)
	ST	Anti-diabetic activity: PTP1B	Li et al. (2015)
Xanthotoxin (**64**)	RT	First isolation from the part	Hata and Kozawa (1961)
	FR	First isolation from the part	Baba et al. (1990a)
	EXD	First isolation from the part	Akihisa et al. (2006)
	AP	First isolation from the part	Luo et al. (2012)
Isopimpinellin (**65**)	RT	First isolation from the part	Baba et al. (1990b)
	FR	First isolation from the part	Nakata et al. (1997)
	EXD	First isolation from the part	Akihisa et al. (2006)

Table 3 continued

Compound class/name	Part[a]	Biological activity	Reference(s)
Imperatorin (**66**)	FR	First isolation from the part	Baba et al. (1990a)
	RT	First isolation from the part	Nakata et al. (1997)
	AP	First isolation from the part	Luo et al. (2012)
Isogosferol (**67**)	FR	First isolation from the part	Baba et al. (1990a)
Isoimperatorin (**68**)	FR	First isolation from the part	Baba et al. (1990a)
	RT	First isolation from the part	Nakata et al. (1997)
Saxaline (**69**)	FR	First isolation from the part	Nakata et al. (1997)
Marmesin (**70**)	RT	First isolation from the part	Baba et al. (1990b)
(−)-Oxypeucedanin (**71**)	FR	First isolation from the part	Baba et al. (1990a)
	RT	First isolation from the part	Nakata et al. (1997)
(+)-Oxypeucedanin hydrate (**72**)	FR,	First isolation from the part	Nakata et al. (1997)
	RT	First isolation from the part	
(−)-Oxypeucedanin hydrate (**73**)	FR	First isolation from the part	Baba et al. (1990a)
(−)-*Tert-O*-methoxy peucedanin hydrate (**74**)	FR	First isolation from the part	Baba et al. (1990a)
(−)-*Sec-O*-acetoxy peucedanin hydrate(**75**)	FR	First isolation from the part	Baba et al. (1990a)
Pseudoisopsoralen (**76**)	AP	First isolation from the part	Luo et al. (2012)
Angelicin (**77**)	RT	First isolation from the part	Hata and Kozawa (1961)
Columbianadin (**78**)	RT	First isolation from the part	Kozawa et al. (1978)
	FR	First isolation from the part	Baba et al. 1990a)
(3′*R*)-Hydroxy columbianadin (**79**) (=(8*S*,9*R*)-8-angeloyl oxy-8,9-dihydrooroselol)	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2003)
	RT	First isolation from the part	Sugamoto et al. (2009)
(8*S*,9*R*)-9-Angeloyloxy-8,9-dihydrooroselol (**80**)	RT	First isolation from the part	Kozawa et al. (1978)
	RT	Anti-tumor-promoter activity: TPA-stimulated ^{32}Pi-incorporation	Okuyama et al. (1991)
Archangelicin (**81**)	RT	First isolation from the part	Kozawa et al. (1978)
	FR	First isolation from the part	Baba et al. (1990a)
	RT	Anti-tumor-promoter activity: TPA-stimulated ^{32}Pi-incorporation	Okuyama et al. (1991)
Lomatin (**82**)	FR	First isolation from the part	Baba et al. (1990a)
Selinidin (**83**)	RT	First isolation from the part	Baba et al. (1990b)
	FR	First isolation from the part	Baba et al. (1990a)
	EXD	Anti-tumor-initiator activity: NOR 1	Akihisa et al. (2003)
	EXD	Anti-allergic activity: lgE-mediated mast cell activation (β-hexosaninidase, LTC4, TNF-α, FcεRI β-chain PLCγ1, p38 MAPK, IκB-α)	Kishiro et al. (2008)
	AP	First isolation from the part	Luo et al. (2012)
	ST	Anti-diabetic activity: PTP1B	Li et al. (2015)
Selidinin (**84**)	EXD	Anti-inflammatory activity (details in the patent)	Akihisa et al. (2007)
O-Isobutyroyllomatin (**85**)	ST	Anti-diabetic activity: PTP1B	Li et al. (2015)
Khellactone (**86**)	AP	First isolation from the part	Luo et al. (2012)
	ST	Anti-diabetic activity: PTP1B	Li et al. (2015)
3′-Senecioyl khellactone (**87**)	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2003)
		Anti-tumor-initiator activity: NOR 1	
	AP	Anti-diabetic activity: α-glucosidase	Luo et al. (2012)

Table 3 continued

Compound class/name	Part[a]	Biological activity	Reference(s)
Peguangxienin (**88**)	EXD	Anti-inflammatory activity: TPA-induced mouse ear edema	Akihisa et al. (2007)
(3′*R*,4′*R*)-3′-Angeloyl khellactone (**89**) (miswritten as isolaserpitin)	RT	First isolation from the part	Baba et al. (1990b)
	FR	First isolation from the part	Baba et al. (1990a)
	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2003)
		Anti-tumor-initiator activity: NOR 1	
	EXD	Anti-inflammatory activity (details in the patent)	Akihisa et al. (2007)
4′-Senecioyl khellactone (**90**)	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2003)
		Anti-tumor-initiator activity: NOR 1	
Isolemanidin (**91**) (miswritten as laserpitin)	RT	First isolation from the part	Baba et al. (1990b)
	FR	First isolation from the part	Baba et al. (1990a)
	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2003)
		Anti-tumor-initiator activity: NOR 1	
	ST	Anti-hyperlipidemic activity: serum HDL↑, hepatic TG↓ (hepatic TG lipase, differentiation factor 1)	Ogawa et al. (2005b)
	EXD	Anti-inflammatory activity: TPA-induced mouse ear edema	Akihisa et al. (2007)
Pteryxin (**92**)	EXD	Anti-tumor-promoter activity: EBV-EA by TPA	Akihisa et al. (2003)
		Anti-tumor-initiator activity: NOR 1	
	EXD	Anti-inflammatory activity (details in the patent)	Akihisa et al. (2007)
(+)-*Cis*-(3′*R*,4′*R*)-methylkhellactone (**93**)	AP	First isolation from the part	Kil et al. (2016)
(−)-*Trans*-(3′*R*,4′*S*)-methylkhellactone (**94**),	AP	First isolation from the part	Kil et al. (2016)
Dihydrocoumarin			
3,4-Dihydroxanthotoxin (**95**)	AP	First isolation from the part	Kil et al. (2016)
Phenolics			
5-*n*-Pentadecylresorcinol (**96**)	EXD	First isolation from the part	Akihisa et al. (2003)
(*Z*)-*p*-Coumaryl alcohol (**97**)	AP	First isolation from the part	Kil et al. (2016)
Acetylenes			
Falcarindiol (**98**)	EXD	First isolation from the part	Akihisa et al. (2003)
	AP	Anti-diabetic activity: α-glucosidase	Luo et al. (2012)
	ST	Anti-diabetic activity: PTP1B	Li et al. (2015)
Acetylenes			
(11*S*,16*R*,*Z*)-11,16-Dihydroxyoctadeca-9,17-dien-12,14-diynyl acetate (**99**)	EXD	First isolation from the part	Akihisa et al. (2006)
(10*S*,15*R*,*Z*)-10,15-Dihydroxyheptadeca-8,16-dien-11,13-diynyl acetate (**100**)	AP	Anti-diabetic activity: α-glucosidase	Luo et al. (2012)
(11*S*,16*R*,*Z*)-Octadeca-9,17-dien-12,14-diyne-1,11,16-triol (**101**)	AP	First isolation from the part	Luo et al. (2012)
Angelicol B (**102**)	AP	First isolation from the part	Luo et al. (2012)
Sesquiterpene			
Ashitabaol A (**103**)	SD	Anti-oxidative: free radical scavenging	Aoki and Ohta (2010)
Diterpene			
Steviol-13-*O*-β-D-glucopyranoside 19-β-D-glucopyranosyl ester (**104**)	LF	First isolation from the part	Zhou et al. (2012)
Triterpenes			
Daucosterol (**105**)	LF	First isolation from the part	Zhou et al. (2012)
Stigmasterol (**106**)	LF	First isolation from the part	Zhou et al. (2012)
Triterpenes			
Pregnenolone (**107**)	AP	Anti-oxidative activity: DPPH radical scavenging	Luo et al. (2012)
Nucleoside			

Table 3 continued

Compound class/name	Part[a]	Biological activity	Reference(s)
Adenosine (**108**)	AP	First isolation from the part	Park et al. (1996)
Saccharide			
Sucrose (**109**)	AP	First isolation from the part	Park et al. (1996)
	AP	Anti-mutagenic activity (AFB1)	Park et al. (1997a)
Acids			
Angelic acid (**110**)	RT	First isolation from the part	Hata and Kozawa (1961)
Behenic acid (**111**)	RT	First isolation from the part	Hata and Kozawa (1961)
Others			
1-Cerotol (**112**)	LF	First isolation from the part	Zhou et al. (2012)
(*E*)-2,6-Dimethylocta-5,7-diene-2,3-diol (**113**)	AP	First isolation from the part	Luo et al. (2012)
Angelicol A (**114**)	AP	Anti-oxidative activity: DPPH radical scavenging	Luo et al. (2012)

[a] Plant part code: *WP* whole plant, *RT* root, *AP* aerial part (including stem and leaf), *ST* stem, *LF* leaf, *EXD* exudate, *FR* fruit, *SD* seed; other source code: *Syn* synthetic, *Com* commercial

and 4-nitroquinoline-1-oxide in a salmonella assay system (Park et al. 1997a).

Anti-diabetic activity

The ethanol extract exhibited insulin-like activities through a pathway independent of peroxisome proliferator-activated receptor-γ (PPAR-γ) activation (Enoki et al. 2007). Long-term ingestion of a powder of *A. keiskei* improved blood glucose control and moderately and safely reduced blood glucose (Ohnogi et al. 2007). A patent is filed on the beneficial effects of *A. keiskei* on diabetes (Lee et al. 2013).

Anti-bacterial activity

An exudate of *A. keiskei* showed anti-bacterial activity against *Helicobacter pylori*, suggesting *A. keiskei* as a preventive agent for gastritis (Fukuo et al. 2005). A patent on this exudate is filed for controlling mouth odor by an anti-bacterial activity against *Fusobacterium nucleatum* (Saeki et al. 2013).

Hepato-protective activity

A clinical trial for habitual alcohol drinkers with abnormal liver function tests also showed that intake of the extracts significantly reduced γ-glutamyl transferase (GGT) levels (Noh et al. 2015). A patent is filed on the beneficial activity of an ethanol extract of the roots to improve liver functions and relieve fatigue (Kim et al. 2006).

Other biological activities

In addition to these activities, an ethanol extract also showed an anti-hypertensive activity by inhibiting angiotensin 1-converting enzyme (ACE) in spontaneously hypertensive rats, similar to nicotianamine (Shimizu et al. 1999). Green juice of *A. keiskei* was proven to protect lymphocytic DNA damage of smokers, which was reported to potentially reduce the risk of lung cancer in a clinical trial (Kang et al. 2004). In another clinical study, consuming a drink powder of the leaves three times a day for 2 weeks alleviated mild constipation and improved defecation (Kusaba et al. 2008). Deficit of learning and memory caused by Alzheimer's disease and aging may be alleviated by *A. keiskei* since it has been shown that the plant is capable of restoring scopolamine-reduced phosphorylation of cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) and expression of brain-derived neurotrophic factor (BDNF) in the mouse hippocampus (Oh et al. 2013). Topical uses of the extracts were shown to whiten skin with tyrosinase inhibitory effect (Higa 1985; Lee et al. 2012b) and promote hair growth (Sakaguchi et al. 1996) in patent applications.

Biological activities of isolates from *A. keiskei*

Isolates from *A. keiskei* have showed diverse biological activities. Especially two major chalcones, xanthoangelol (**1**) and 4-hydroxyderricin (**3**), have been extensively

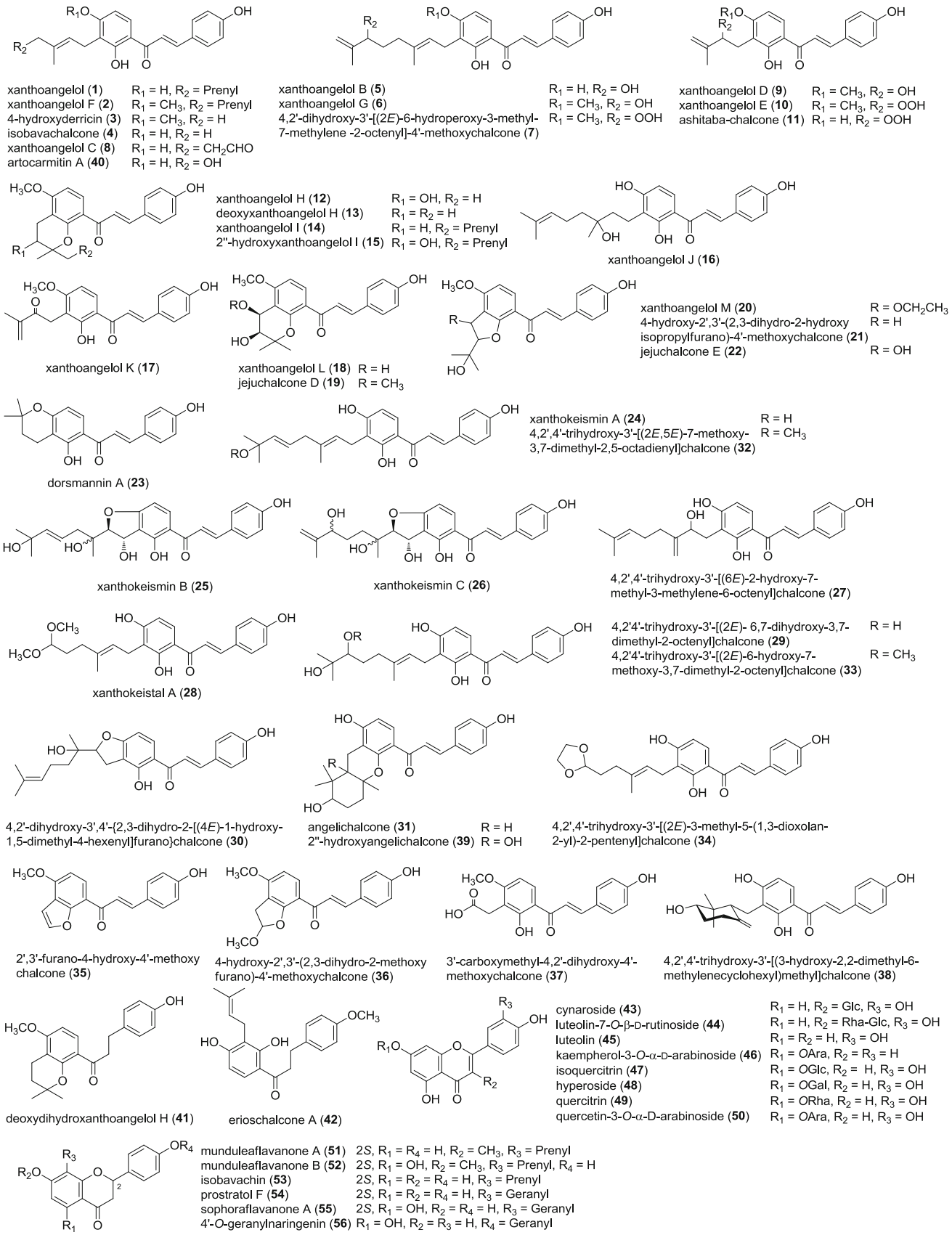

Fig. 1 Chemical structures of compounds isolated from *A. keiskei*

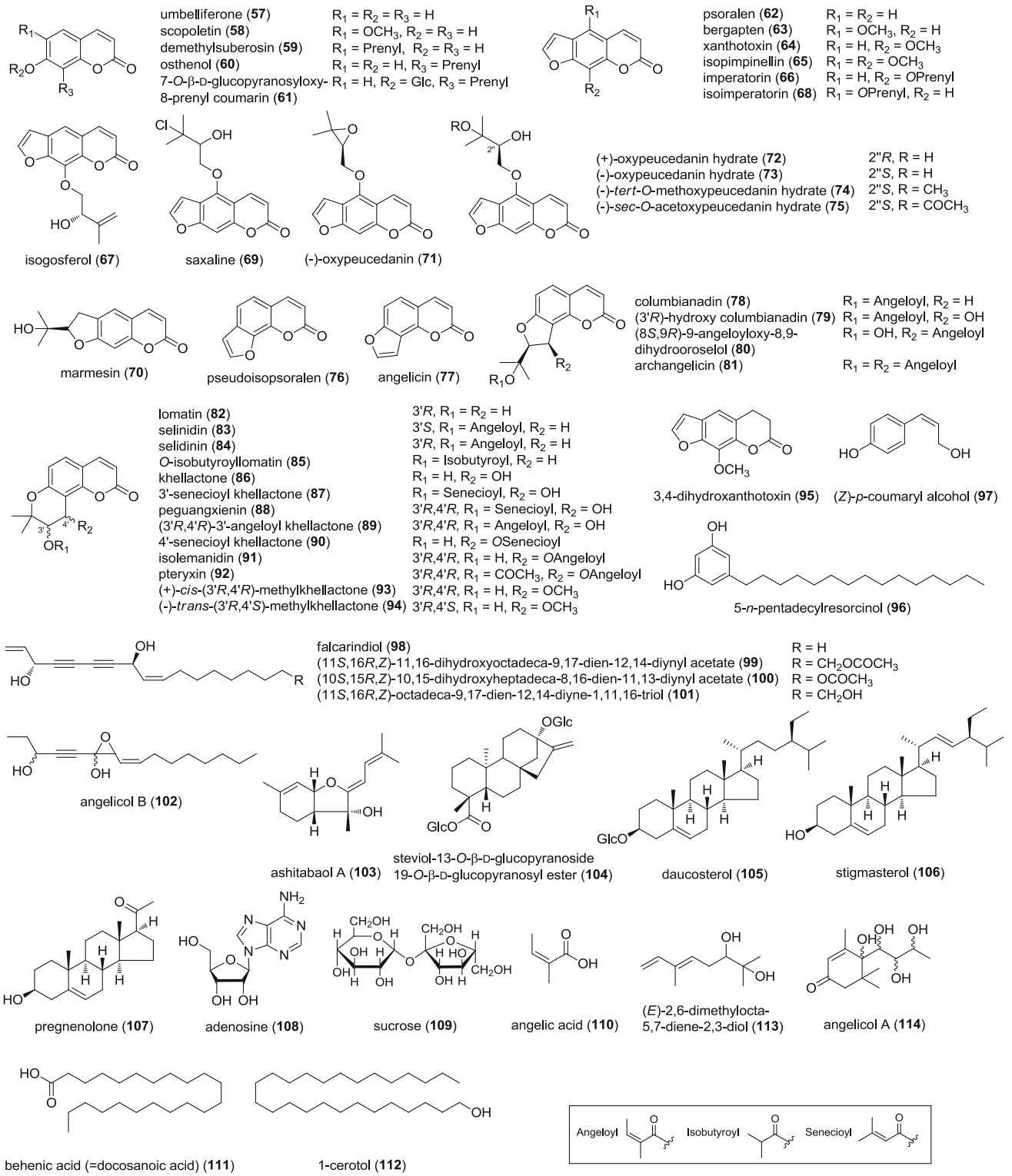

Fig. 1 continued

studied and reported to have anti-tumor, anti-inflammatory, anti-depressant, anti-obesity, anti-thrombotic, anti-diabetic, anti-hyperlipidemic, anti-hypertensive, and anti-ulcer effects. The various effects of isolates will be discussed in the subsequent sections and summarized in Tables 1, 2 and 3. In our recent research, several compounds from *A. keiskei* were evaluated for their effects on heat shock protein (HSP) expression. HSPs are known to have

protective effects on damaged cells, and HSP-inducible agents may act as prospective agents to protect normal cells from chemotherapy induced adverse effects. (±)-4,2′,4′-Trihydroxy-3′-[(6*E*)-2-hydroxy-7-methyl-3-methylene-6-octenyl] chalcone (**27**) of 2 μM increased expressions of HSF1 (4.3-fold), HSP70 (1.5-fold), and HSP27 (4.6-fold) proteins at 6 h of treatment and mRNA levels of HSP70 (5.0-fold) and HSP27 (1.5-fold) at 3 h with lower cytotoxicity than celastrol, a positive control (Kil et al. 2015a).

Anti-ulcer activity

Xanthoangelol (**1**) and 4-hydroxyderricin (**3**) inhibited H^+, K^+-ATPase of gastric microsomal vesicles which were prepared from pig fundic mucosa. Additionally, they downregulated K^+-stimulated *p*-nitrophenyl phosphatase. Xanthoangelol (**1**) reduced the formation of stress-induced gastric lesion as well as acid secretion in rats (Murakami et al. 1990). Xanthoangelol E (**10**) was also found to have the anti-ulcer activity as patented by Murakami et al. (Murakami et al. 1992).

Anti-bacterial activity

Xanthoangelol (**1**) and 4-hydroxyderricin (**3**) showed antibacterial activities against gram-positive bacteria, *Bacillus subtilis* PCI-219, *B. subtilis* ATCC-6633, *B. cereus* FDA-5, *Staphylococcus aureus* 209-P, *S. aureus* IFO-3060, *S. aureus* IFO-3762, and *Micrococcus luteus* IFO-12708, but not gram-negative bacteria. Although the antibacterial activities were lower than gentamicin for the aforementioned bacteria, the anti-bacterial activity of xanthoangelol (**1**) against *M. luteus* IFO-12708 was as strong as that of gentamicin (MIC 0.76 μg/mL) (Inamori et al. 1991). Mechanism of anti-bacterial activity of 4-hydroxyderricin (**3**) against *S. aureus* was elucidated by utilizing a chemical cleavable linker due to its heat sensitivity, reporting that the isolate inhibits amino acylation of tRNAs catalyzed by *S. aureus* seryl-tRNA synthetase which is an essential enzymatic pathway for bacterial viability (Battenberg et al. 2013). The two chalcones exhibited antibacterial activities against plant-pathogenic bacteria, *Agrobacteriu tumefaciens* IFO-3058, *Pseudomonas syringae pv. phaseolicola* IFO-12656, *P. syringae pv. tabaci* IFO-3508, and *P. stutzeri* IFO-12510 (Inamori et al. 1991). Sumanoto et al. reported anti-bacterial activities of xanthoangelol (**1**), xanthoangelol F (**2**), 4-hydroxyderricin (**3**), and isobavachalcone (**4**), against gram-positive bacteria, *Escherichia coli* NBRC 3301, *P. mirabilis* NBRC 13300, *P. fluorescens* NBRC 3757, *B. subtilis* NBRC 3757, *S. epidermidis* NBRC 12993, and *M. luteus* NBRC 3333 (Sugamoto et al. 2011).

Chemopreventive activity

Bioactive compounds with anti-tumor-promoter, anti-tumor-initiator, and anti-mutagenic activities may be considered as chemopreventive therapeutic agents.

Two angular furanocoumarin, (8*S*,9*R*)-8-angeloxy-8,9-dihydrooroseol (**79,** (3′*R*)-hydroxycolumbianadin) and archangelicin (**81**), and three chalcones, xanthoangelol (**1**), 4-hydroxyderricin (**3**), and ashitaba-chalcone (**11**) inhibited 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-stimulated ^{32}Pi-incorporation of phospholipids of cultured cells. Xanthoangelol (**1**) and 4-hydroxyderricin (**3**) showed anti-tumor-promoting activities in mouse skin carcinogenesis induced by 7,12-dimethylbenz[α]anthracene (DMBA) plus TPA via the modulation of Ca^+-calmodulin system (Okuyama et al. 1991). Isobavachalcone (**4**) exhibited inhibitory effects on skin tumor promotion in in vivo two-stage mouse skin carcinogenesis test (Akihisa et al. 2006). Inhibitory effects on the induction of Epstein-Barr virus early antigen (EBV-EA) by TPA in Raji cells were found for xanthoangelol (**1**), xanthoangelol F (**2**), 4-hydroxyderricin (**3**), isobavachalcone (**4**), xanthoangelol H (**12**), xanthoangelol I (**14**), xanthoangelol J (**16**), munduleaflavanone A (**51**), munduleaflavanone B (**52**), isobavachin (**53**), prostratol F (**54**), 8-geranylnaringenin (**55**, 8-geranulnaringenin), 4′-*O*-geranylnaringenin (**56**), osthenol (**60**), (3′*R*)-hydroxycolumbianidin (**79**, (8*S*,9*R*)-8-angeloxy-8,9-dihydrooroseol), 3′-senecioyl khellactone (**87**), (3′*R*,4′*R*)-3′-angeloyl khellactone (**89**, miswritten as "isolaserapitin" in the article), 4′-senecioyl khellactone (**90**), isolemanidin (**91**, miswritten as "laserapitin" in the article), and pteryxin (**92**) (Akihisa et al. 2003, 2006). Xanthoangelol F (**2**), isobavachalcone (**4**), xanthoangelol I (**14**), xanthoangelol J (**16**), munduleaflavanone B (**52**), 8-geranylnaringenin (**55**, sophoraflavanone A), osthenol (**60**), selinidin (**83**), 3′-senecioyl khellactone (**87**), (3′*R*,4′*R*)-3′-angeloyl khellactone (**89**, miswritten as "isolaserapitin" in the article), 4′-senecioyl khellactone (**90**), isolemanidin (**91**, miswritten as "laserapitin" in the article), and pteryxin (**92**) inhibited activation of (±)-(*E*)-methyl-2-[(*E*)-hydroxy-imino]-5-nitro-6-methoxy-3-hexemide (NOR 1), a NO donor (Akihisa et al. 2003, 2006). Cynaroside (**43**, luteolin-7-*O*-β-D-glucopyranoside), luteolin-7-*O*-β-D-rutinoside (**44**), hyperoside (**48**, quercetin-3-*O*-β-D-galactopyranoside), and sucrose (**109**) showed anti-mutagenic activities against aflatoxin B1 (AFB1) (Park et al. 1997a).

Anti-tumor activity

In a previous study, xanthoangelol (**1**) and 4-hydroxyderricin (**3**) were identified as active compounds to inhibit tumor growth in Lewis lung carcinoma (LLC)-bearing mice and to prolong survival time and to suppress

metastasis to the lung after surgical removal of primary tumors from an active ethyl acetate fraction of a 50% ethanol extract (Kimura and Baba 2003; Kimura et al. 2004). The anti-tumor activities of xanthoangelol (**1**) might be derived from its inhibitory effects on DNA synthesis in LLC cells and on tumor-induced neovascularization by reducing formation of capillary-like tubes by vascular endothelial cells and adhesion of vascular endothelial growth factor (VEGF) to human umbilical vein endothelial cells (HUVECs) (Kimura and Baba 2003). 4-Hydroxyderricin (**3**) also inhibited the DNA synthesis in LLC cells and the formation of capillary-like tubes, but did not reduce adhesion of vascular endothelial growth factor (VEGF) to HUVECs. Instead, it suppressed reduction of lymphocytes, $CD4^+$, $CD8^+$, and natural killer (NK)-T cells in spleen of tumor-removed mice (Kimura et al. 2004). Xanthoangelol (**1**) induced apoptotic cell death by activation of caspase-3 in neuroblastoma (IMR-32) and leukemia (Jurkat) cells through a mechanism, independent of Bax/Bcl-2 signal transduction (Tabata et al. 2005). Their ongoing study revealed details of the mechanism of action of xanthoangelol (**1**) inducing apoptosis by triggering oxidative stress through generating reactive oxygen species and downregulating antioxidant DJ-1 protein in IMR-32 cells (Motani et al. 2008). Xanthoangelol (**1**) showed cytotoxic effects on several neuroblastoma cell lines including drug-resistant LA–N-1 and NB-39 cells as well as drug-sensitive IMR-32 and SK-N-SH cells (Nishimura et al. 2007; Motani et al. 2008). Xanthoangelol F (**2**), 4-hydroxyderricin (**3**), isobavachalcone (**4**), xanthoangelol H (**12**), and xanthoangelol I (**14**) were cytotoxic to the NB-39 and IMR-32 cells. Isobavachalcone (**4**) was found to induce apoptotic cell death in the neuroblastoma cells via the mitochondrial pathway including reduction of procaspase-3 and procaspase-9 and induction of Bax level with no cytotoxicity against normal cells (Nishimura et al. 2007). Xanthoangelol (**1**) and 4-hydroxyderricin (**3**) inhibited growth of human stomach cancer (KATO III) cells through induction of apoptosis by fragmenting DNA (Takaoka et al. 2008). 4-Hydroxyderricin (**3**) exhibited cytotoxic activities in human leukemia (HL60), melanoma (CRL1579), lung cancer (A549), and stomach cancer (AZ521) cells. The cytotoxicity to HL60 cells was caused by induction of apoptosis through inhibiting DNA topoisomerase and reducing procasparases-3, -8, and -9 (Akihisa et al. 2011).

Anti-diabetic activity

In a genetically diabetic KK-A^y mouse model, xanthoangelol (**1**) and 4-hydroxyderricin (**3**) showed insulin-like activities to enhance glucose uptake and induce preadipocyte differentiation into adipocytes without activating PPAR-γ. 4-Hydroxyderricin (**3**) also prevented the progression of diabetes in these mice (Enoki et al. 2007). On the basis of the preventive effect, a clinical trial was performed with *A. keiskei* powder containing 4-hydroxyderricin (**3**), resulting in reduction of blood glucose and improvement of blood glucose control through increasing adiponectin in subjects with borderline or mild hyperglycemia after 12 weeks of consumption of *A. keiskei* (Ohnogi et al. 2007). Xanthoangelol (**1**), 4-hydroxyderricin (**3**), isobavachalcone (**4**), munduleaflavanone A (**51**), demethylsuberosin (**59**), 3′-senecioyl khellactone (**87**), falcarindiol (**98**), and (10*S*,15*R*,*Z*)-10,15-dihydroxyheptadeca-8,16-dien-11,13-diynyl acetate (**100**) appeared to inhibit α-glucosidase, which involved in glucose metabolism (Luo et al. 2012). Xanthoangelol (**1**) and 4-hydroxyderricin (**3**) stimulated skeletal muscle-associated glucose uptake by inducing glucose transporter 4 (GLUT-4) translocation, resulting in normal blood glucose level (Kawabata et al. 2011). Recently, protein tyrosine phosphatase 1B (PTP1B) has been suggested as a therapeutic target for treatment of type 2 diabetes based on its downregulating effect on insulin signaling. Li et al. evaluated isolates from the stems of *A. keiskei* for their PTP1B inhibitory effects using oleanolic acid as a positive control. Xanthoangelol (**1**), xanthoangelol F (**2**), 4-hydroxyderricin (**3**), xanthoangelol D (**9**), xanthoangelol E (**10**), xanthoangelol K (**17**), xanthoangelol M (**20**) and bergapten (**63**, 5-methoxypsoralen; miswritten as "methoxsalen" in the article) showed strong PTP1B inhibitory effect (IC_{50} 0.82–4.42 μg/mL), together with moderately active four compounds (selinidin, **83**; *O*-isobutyroyllomatin, **85**; khellactone, **86**; falcarindiol, **98**, IC_{50} 4.42–11.55 μg/mL) and a weakly active one (cynaroside, **43**, IC_{50} 17.49 μg/mL). Furthermore, in a kinetic study, xanthoangelol (**1**) with IC_{50} values of 0.82 μg/mL exhibited typical characteristics of the competitive PTP1B inhibitor and in molecular docking simulations, it was suggested that the ring B of the chalcone skeleton may anchor in a pocket of PTP1B (Li et al. 2015).

Nerve cell protective activity

Onogi et al. filed a patent application presenting angelichalcone (**31**) with its nerve cell protective effect (Onogi et al. 2004). In addition, 7-*O*-β-D-glucopyranosyloxy-8-prenyl coumarin (**61**) was reported for its enhancing effect on nerve growth factor (NGF) production in mouse fibroblast L-M cells in a patent (Ohnogi et al. 2002).

Anti-hyperlipidemic activity

Cynaroside (**43**, luteolin-7-*O*-β-D-glucopyranoside) showed hypolipidemic activity when administrated by intraperitoneal injection in rats (Park et al. 1995).

Cynaroside (**43**) and hyperoside (**48**, quercetin-3-*O*-β-D-galactopyranoside) exhibited anti-cholesterogenic activity by inhibiting HMG-CoA reductase (Park et al. 1997b). When SHRSP was fed diets containing 4-hydroxyderricin for 7 weeks, serum very low-density lipoprotein (VLDL) and hepatic triglycerides (TG) levels were significantly reduced, without any effect on serum HDL levels. It was considered that microsomal TG transfer-protein may be responsible for the decrease in serum VLDL levels and differentiation factor 1 and fatty acid synthase may induce the decrease in hepatic TG content (Ogawa et al. 2005b). In case of isolemanidin (**91**, miswritten as "laserapitin" in the article), the serum HDL levels, especially apoE-HDL, increased and the hepatic TG content decreased, which might be relevant with a decrease in hepatic TG lipase and differentiation factor 1, respectively (Ogawa et al. 2005a).

Preventive effects against metabolic syndrome

Ohnogi et al. isolated six new chalcones, 4,2′-dihydroxy-3′-[(2*E*)-6-hydroperoxy-3-methyl-7-methylene-2-octenyl]-4′-methoxychalcone (**7**), 2″-hydroxyxanthoangelol I (**15**), 4-hydroxy-2′,3′-(2,3-dihydro-2-hydroxyisopropylfurano)-4′-methoxychalcone (**21**), 4,2′4′-trihydroxy-3′-[(2*E*)-6,7-dihydroxy-3,7-dimethyl-2-octenyl]chalcone (**29**), 4,2′-dihydroxy-3′,4′-{2,3-dihydro-2-[(4*E*)-1-hydroxy-1,5-dimethyl-4-hexenyl]furano}chalcone (**30**), and angelichalcone (**31**) together with xanthoangelol (**1**) and 4-hydroxyderricin (**3**), and evaluated their effects on adiponectin mRNA and protein levels. As a result, all isolates, except for angelichalcone (**31**), increased expression of adiponectin mRNA and production of adiponectin in 3T3-L1 adipocytes. The effects on adiponectin could be expected to prevent metabolic syndrome through improving insulin resistance and dyslipidemia (Ohnogi et al. 2012b). Xanthoangelol (**1**) and 4-hydroxyderricin (**3**) suppressed adipocytes differentiation via AMPK and mitogen-activated protein kinase (MAPK) pathways, which resulted in downregulating expression of adipocyte-specific transcription factors, CCAAT/enhancer-binding protein-β (C/EBP-β), C/EBP-α, and PPAR-γ. Inhibitory effects on adipocytes differentiation could provide preventive effects against obesity and obesity-related disorders (Zhang et al. 2013).

Anti-hypertensive activity

Xanthoangelol (**1**), xanthoangelol F (**2**), 4-hydroxyderricin (**3**), xanthoangelol B (**5**), and xanthoangelol E (**10**) inhibited phenylephrine-induced vasoconstriction. Among them, xanthoangelol (**1**), xanthoangelol F (**2**), 4-hydroxyderricin (**3**), and xanthoangelol E (**10**) showed the inhibitory effects through endothelium-dependent production of endothelium-derived relaxing factor (EDRF)/NO. On the other hand, xanthoangelol B (**5**) directly inhibited smooth muscle functions through reducing intracellular free calcium $[Ca_2^+]_i$ elevation induced by phenylephrine without affecting EDRF/NO production. 4-Hydroxyderricin (**3**) also suppressed elevation of $[Ca_2^+]_i$ induced by phenylephrine (Matsuura et al. 2001). Dietary 4-hydroxyderricin (**3**) reduced elevation of systolic blood pressure in SHRSP, which also supported its anti-hypertensive activity (Ogawa et al. 2005b).

Anti-allergic activity

Xanthoangelol B (**5**), xanthoangelol C (**8**), and xanthoangelol E (**10**) inhibited the compound 48/80-induced histamine release from rat peritoneal mast cells, whereas, xanthoangelol (**1**) and 4-hydroxyderricin (**3**) enhanced it. Compound 48/80 is one of immunological stimulators, which activates the mast cell to induce allergic responses by mediates (Nakata and Baba 2001). Selinidin (**83**) was found to suppress degranulation, leukotriene C4 (LTC4) synthesis, and tumor necrosis factor-α (TNF-α) production without affecting binding of immunoglobulin E (IgE) with high affinity IgE receptor (FcεRI) and expression of cell surface FcεRI in antigen-stimulated primary mouse bone marrow-derived mast cells (BMMCs). Selinidin (**83**) inhibited tyrosine phosphorylation of FcεRI β-chain and phospholipase C γ1 (PLCγ1) not FcεRI γ-chain in BMMCs upon FcεRI stimulation, demonstrating its inhibitory effects on FcεRI-dependent signaling pathway. Phosphorylation of p38 MAPK and inhibitory κB-α (IκB-α) were also downregulated by selinidin (**83**) (Kishiro et al. 2008).

Anti-inflammatory activity

Xanthoangelol D (**9**) inhibited activation of nuclear factor-κB (NF-κB), which was involved in attenuation of basal and TNF-α-induced endothelin-1 (ET-1), a potent vasoconstrictor peptide. Its inhibitory effect against NF-κB inflammatory signaling pathway could be useful for treating vascular and inflammatory diseases because many vascular diseases are closely related to the inflammatory processes (Sugii et al. 2005). A patent covers the anti-inflammatory activities of seven flavonoids, xanthoangelol (**1**), xanthoangelol F (**2**), 4-hydroxyderricin (**3**), isobavachalcone (**4**), deoxyxanthoangelol H (**13**), munduleaflavanone B (**52**), and sophoraflavanone A (**55**, 8-geranylnaringenin), and six coumarins, osthenol (**60**), selidinin (**84**), peguangxienin (**88**), (3′*R*,4′*R*)-3′-angeloyl khellactone (**89**), isolemandin (**91**), and pteryxin (**92**) from exudates of *A. keiskei* (Akihisa et al. 2007). Shin et al. reported that xanthoangelol (**1**), 4-hydroxyderricin (**3**), xanthoangelol B (**5**), and 4,2′,4′-trihydroxy-3′-[(6*E*)-2-hydroxy-7-methyl-3-methylene-6-octenyl]chalcone (**27**) showed inhibitory

activities of IL-6 production in TNF-α-stimulated MG-63 osteosarcoma cells and they have C-4′ hydroxyl groups in common (Shin et al. 2011). Toll-like receptors (TLRs) are essential for induction of innate immune responses against invading pathogens, however, overexpression of transcription factors and pro-inflammatory genes by activation of TLR signaling pathway might cause certain inflammatory diseases. Isobavachalcone (**4**) reduced overexpression of iNOS induced by TLR agonists (lipopeptide 2-kDa, polyriboinosinic polyribocytidylic acid, or LPS) in murine macrophages (Shin et al. 2013). Xanthoangelol (**1**) and 4-hydroxyderricin (**3**) reduced production of LPS-induced NO and TNF-α, expression of iNOS and COX-2 in RAW264 mouse macrophages. Moreover, both suppressed DNA binding activities of activator protein-1 (AP-1) and NF-κB and phosphorylation level of p65 subunit of NF-κB. However, two chalcones downregulated only AP-1 not NF-κB (Yasuda et al. 2014). Inhibitory effects on LPS-induced NO and expression of iNOS and COX-2 genes were also found for xanthoangelol B (**5**), xanthoangelol E (**10**), and xanthokeismin A (**24**) as well as 4-hydroxyderricin (**3**) and their mechanisms involved inhibition of IκB degradation and NF-κB nuclear translocation (Chang et al. 2014).

Anti-oxidative activity

Cynaroside (**43**, luteolin-7-*O*-β-D-glucopyranoside) inhibited bromobenzene-induced hepatic lipid peroxidation by restoring epoxide hydrolase activity in liver of rats (Park et al. 2002). Xanthoangelol B (**5**), xanthokeismin A (**24**), xanthokeismin B (**25**), and xanthokeismin C (**26**) showed strong superoxide-scavenging activities. Xanthoangelol (**1**), 4-hydroxyderricin (**3**), and isobavachalcone (**4**) induced reduced nicotinamide adenine dinucleotide (phosphate) (NAD(P)H):quinone oxidoreductase 1 (NQO1) which protects against quinone-mediated oxidative damage. In addition, xanthoangelol (**1**), isobavachalcone (**4**), cynaroside (**43**, luteolin-7-*O*-β-D-glucopyranoside), luteolin-7-*O*-β-D-rutinoside (**44**), kaempferol-3-*O*-α-D-arabinopyranoside (**46**), isoquercitrin (**47**, quercetin-3-*O*-β-D-glucopyranoside), hyperoside (**48**, quercetin-3-*O*-β-D-galactopyranoside), quercetin-3-*O*-α-D-arabinopyranoside (**50**), pregnenolone (**107**), and angelicol A (**114**) showed DPPH radical scavenging activities (Luo et al. 2012; Kim et al. 2005). Ashitabaol A (**103**), an isolate from the seeds of *A. keiskei,* was found to be more abundant in the seed coat during germination through HPLC analysis. Ashitabaol A (**103**) exhibited 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) free radical scavenging activity and was expected to protect the seed against oxidative damage induced by free radicals during germination (Aoki and Ohta 2010). Xanthine oxidase (XO) leads to formation of free radicals, and cause oxidative damage to living tissues. Xanthoangelol (**1**), xanthoangelol F (**2**), 4-hydroxyderricin (**3**), isobavachalcone (**4**), and xanthoangelol B (**5**) showed inhibitory effects on XO activity, which could be relevant with attenuation of inflammation (Kim et al. 2014).

Anti-thrombotic activity

Xanthoangelol E (**10**) was evaluated for effects on arachidonic acid metabolism in gastric antral mucosa and platelet of rabbit. Xanthoangelol E (**10**) showed no significant effect on production of PGE2, PGF2α, and their metabolites in gastric antral mucosal slices, whereas, suppressed production of thromboxane B2 (TXB2) and 12-hydroxy-5,8,10-heptadecatrienoic acid (HHT) from exogenous arachidonic acid in platelets (Fujita et al. 1992). Ohkura et al. reported that xanthoangelol (**1**), xanthoangelol B (**5**), and xanthoangelol D (**9**) isolated from the exudates of *A. keiskei* suppressed production of TNFα-induced PAI-1, an inhibitor of fibrinolysis, in human umbilical vein endothelial cells (HUVECs) (Ohkura et al. 2011). Regarding to anti-thrombotic activities, xanthoangelol (**1**) and 4-hydroxyderricin (**3**) also exhibited inhibitory effects on platelet aggregation induced by collagen, platelet-activating factor, and phorbol 12-myristate 13-acetate not thrombin (Son et al. 2014).

Anti-depressant activity

Xanthoangelol (**1**) was compared to iproniazid, an antidepressant nonselective MAO inhibitor. Xanthoangelol (**1**) inhibited monoamine oxidase (MAO) in a nonselective manner and suppressed dopamine *β*-hydroxylase (DBH). On the other hands, 4-hydroxyderricin selectively inhibited MAO-B and mildly suppressed DBH, which was higher than deprenyl, a selective MAO-B inhibitor. Because MAO inhibitors have been widely applied for treating depression, xanthoangelol (**1**) and 4-hydroxyderricin (**3**) were suggested as candidates for developing combined antidepressant drug. Additionally, cynaroside (**43**, luteolin-7-*O*-β-D-glucopyranoside) showed strong inhibitory effect against DBH (Kim et al. 2013).

Anti-viral activity

Park et al. reported that xanthoangelol F (**2**), 4-hydroxyderricin (**3**), xanthoangelol B (**5**), xanthoangelol G (**6**), xanthoangelol D (**9**), and xanthokeistal A (**28**) have inhibitory effects against hydrolysis of influenza virus neuraminidase (NA) which has been an effective target to develop drugs treating patients infected with influenza

virus. All active compounds showed reversible nonselective characteristics and xanthoangelol D (**9**) was the most potent inhibitor. Furthermore, it was suggested that the influenza virus NA inhibitory activities of the alkylated chalcones are associated with their alkyl groups (Park et al. 2011). Because enzymatic activities of a chymotrypsin-like protease ($3CL^{pro}$) and a papain-like protease (PL^{pro}) are essential for a viral life cycle of severe acute respiratory syndrome corovirus (SARS-CoV), the two viral cysteine proteases are attractive targets for development of anti-SARS-CoV drugs. Xanthoangelol (**1**), xanthoangelol F (**2**), 4-hydroxyderricin (**3**), isobavachalcone (**4**), xanthoangelol B (**5**), xanthoangelol G (**6**), xanthoangelol D (**9**), xanthoangelol E (**10**), and xanthokeistal A (**28**) showed competitive inhibitory characteristics to $3CL^{pro}$ and noncompetitive ones to PL^{pro}, except for mixed inhibition manner of isobavachalcone (**4**) against PL^{pro}. Especially, xanthoangelol E (**10**) exhibited the most potent inhibitory activity, and docking simulation of xanthoangelol E (**10**) to both protease revealed that its hydroperoxy group plays a role in enzyme binding by forming hydrogen bonding (Park et al. 2015).

Osteogenesis promotive activity

Angelichalcone (**31**) was presented as an osteogenesis promotive agent in a patent application (Ohnogi et al. 2004).

Whitening activity

Xanthoangelol (**1**), 4-hydroxyderricin (**3**), xanthoangelol H (**12**), deoxyxanthoangelol H (**13**), and deoxydihydroxanthoangelol H (**41**) exhibited inhibitory effects against melanin formation in B16 melanoma cells with low cytotoxicity (Arung et al. 2012).

Discussion

As presented in this review, the pharmacological studies on *A. keiskei* and its putative active compounds support a number of biological activities that can potentially impact human health. In spite of these reported biological activities and a number of filed patent applications on this plant, *A. keiskei* has not been developed as a pharmaceutical agent and is currently available on the market as health drinks. This review presented a summary of the studies published to date on this promising plant. Although the majority of these studies are mechanistic, but they can be used as a solid platform to design and conduct clinical studies.

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Compliance with ethical standards

Conflict of interest The co-authors have declared no conflict of interest.

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