doi.org/10.1002/cbdv.202201071 Review CHEMISTRY & BIODIVERSITY

www.cb.wiley.com

A Review on *Torilis japonica*: Ethnomedicinal, Phytochemical, and Biological Features

Yahya Rahimpour[+],[a] Mina Doorandishan[+],[b] Anahita Boveiri Dehsheikh,[c] Mohammad Mahmoodi Sourestani,[c] and Javad Mottaghipisheh*[d, e]

The present study was aimed at comprehensive overviewing a phytochemically and biologically important species namely *Torilis japonica* (Apiaceae family). Treatment of dysentery, fever, haemorrhoids, spasm, uterine tumors, lymphadenitis, rheumatism, impotence, infertility, women's diseases, and chronic diarrhea are reported as the main folk medicinal applications of the *T. japonica* fruits. So far, the plant is phytochemically characterized for its diverse terpene derivatives, predominantly sesquiterpenes. The plant's fruit is a rich source of torlin, a guaiane-type sesquiterpene, possessing various potent bioactivities. To date, anticancer, anti-inflammatory, antimicrobial, antioxidant, skin photoaging activities of the plant extracts and its constituents have been evaluated. Further investigation of the plant, specifically bioassay-guided isolation and identification of its major bioactive constituents can lead to discover potential phytopharmaceutical candidates.

1. Introduction

The genus *Torilis* Gaertn. belonging to the Apiaceae (Umbelliferae) family. The plants in this large family comprising over 434 genera and 3,780 species, are mostly considered as hollow stems aromatic plants, whilst many of them are consumed as vegetables or condiments.[1]

The *Torilis* genus consisting 13 species, are majorly distributed in the Mediterranean area along with growing in Southern and Central Asia. The plants of the genus are well-known in the folk medicine to treat infections and cancer.[2]

Among all the species, *Torilis japonica* (Houtt.) DC. (http://www.theplantlist.org/tpl1.1/record/kew-2438341), as a biennial plant is the most reputed and investigated plant. The fruits have traditionally been consumed to cure impotence, inflammation, testitis, anthroneuralgia, and skin disease.[3]

Terpenes (hemiterpenoids, monoterpenoid, sesquiterpenoids), flavonoids, fatty acids, and steroids have previously been isolated and identified from *T. japonica* as the predominant non-volatile phytoconstituents, whereas sesquiterpenes (hydrocarbon and oxygenated) derivatives including β-eudesmene, eudesm-7(11)-en-4-ol, β-elemene, and caryophyllene oxide were characterized as its major volatile compounds.

Nonetheless, torilin, a guaiane-type sesquiterpene, is characterized as the major bioactive plant constituent, the plant extracts have further been investigated to be potent natural antimicrobial, antioxidant, anti-cancer, and anti-inflammatory agents.

Due to the plant folk medicinal applications, the present study was aimed at overviewing its phytochemicals, traditional uses, and biological properties. The keyword *'Torilis japonica'* was utilized to search related English language articles through databases 'Web of Science', 'PubMed', and 'Sci-Finder' (Last access date: 01.11.2022).

2. Ethnobotanical uses of *Torilis japonica*

Ethnobotanical studies of *T. japonica* have documented various pharmacological effects such as anti-allergenic, antifungal, antibacterial, anti-inflammatory, anti-proliferative[3] and sedative activities (Table 1).[4–7] The fruit part possesses medicinal properties and is used to treat various diseases and disorders such as lymphadenitis, rheumatism, infertility, chronic diarrhea, carbuncle,[8–11] dysentery, fever, hemorrhoids, spasm, and uterine tumors.[12] In Japan, the fruit is used to cure skin diseases, testitis, arthroneuralgia, impotence, and renal disorders,[13–15] besides its consumption for healing amnesia, pruritis, acidosis, women's diseases, and scabies in Korea and China.[16] Due to anti-inflammatory properties of the fruit, it has also been considered for the treatment of skin diseases and urogenital.[17] Although various bioactivity experiments have been conducted

[a] *Y. Rahimpour[+]*
Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

[b] *M. Doorandishan[+]*
Department of Chemistry, Faculty of Sciences, Golestan University, Gorgan, Iran

[c] *A. B. Dehsheikh, M. M. Sourestani*
Department of Horticultural Science, Faculty of Agriculture, Shahid Chamran University of Ahvaz, Ahvaz, Iran

[d] *J. Mottaghipisheh*
Center for Molecular Biosciences (CMBI), Institute of Pharmacy/Pharmacognosy, University of Innsbruck, Innrain 80–82, 6020 Innsbruck, Austria

[e] *J. Mottaghipisheh*
Department of Aquatic Sciences and Assessment, Swedish University of Agricultural Sciences (SLU), SE-750 07, Uppsala, Sweden,
E-mail: imanmottaghipisheh@yahoo.com

[+] *Equal contribution as first authorship.*

Table 1. Ethnomedicinal uses of *Torilis japonica*.

Ethnomedicinal uses	Plant part	Ref.
treatment of inflammation, skin disease, and impotence	Fr	[15]
as pesticide, astrictive, and a medicine for dermatopathy	Fr	[18]
treatment of skin disease, testitis, impotence, and inflammation	–	[13]
treatment of dysentery, fever, haemorrhoids, spasm, and uterine tumors	–	[12]
as anti-fungal, anti-allergenic, antibacterial, and sedative agent	Fr	[7]
treatment of lymphadenitis, rheumatism, impotence, infertility, women's diseases, chronic diarrhea, carbuncle	Fr	[9, 10, 19, 20]
As anti-inflammatory to treat skin diseases and urogenital disorders	Fr	[17]
treatment of skin disease, testitis, arthroneuralgia, impotence and renal disorder in Japan	Fr	[14]
to treat amnesia, pruritis, acidosis, women's diseases and scabies in Korea and China	fresh or driedH or Fr	[16]
As a crude drug "He shi" in Chinese medicine ("Kanpo")	Fr	[4]
as an anti-allergenic, antifungal, antibacterial, and sedative agent; a principal Chinese medicament prescribed	Fr	[5, 6]
promoting healthy libido and fertility levels as a substitute medicament of the She-Chuang-Zi (Cnidium monnieri fructi, snowparsley)	Fr	[21]
anti-proliferative activities on the U87MG human glioblastoma cell lines	Fr	[3]
Antibiofilm properties against *Staphylococcus aureus*	Fr	[22]

F: flower; Fr: fruit; H: Herb; L: leaf.

on the plant, ethnobotanical reports can direct further phytochemical and biological evaluations.

3. Phytochemicals

3.1. Non-volatile secondary metabolites

Various phytochemicals have previously been isolated from *Torilis japonica* mainly including terpenes (hemiterpenoids, monoterpenoid, sesquiterpenoids), flavonoids, fatty acids, and steroids (Table 2). Most of the studies have been performed on the *T. japonica* fruit part, except in Güzel et al. 2011 study, in which flavonoids were isolated from the aerial parts and these compounds have been reported as chemotaxonomic markers of the *Torilis* genus. Although, due to the similarity of TLC pattern in fruit compared to the aerial part, the fruit part has also been introduced as a suitable candidate for chemotaxonomic purposes,[2] whereas phytochemical investigations of aerial parts including stem, flower, and fruit may be the promising topics to be considered.

Notably, *T. japonica* is rich in sesquiterpenes with a wide range of structural diversity: 10 guaiane, three eudesmane, two cadinane, two germacrene, one humulene, one elemane, and a cadinene type. All the sesquiterpenes have been isolated from the fruit part (Figure 1); consequently, the *T. japonica* fruit can be pondered as a rich source in sesquiterpenes. The guaiane-type sesquiterpenes have the most structural abundance among the isolated sesquiterpenes. Torilin (**1**) (syn. 8,11-dihydroxy-4-guaien-8-angeloyl-11-acetyl-3-one), a guaiane-type sesquiterpene, has been isolated and identified as the major phytochemical of *T. japonica*, showing wide biological activities such as antimicrobial,[23] anti-neosporal,[24] anti-protozoal,[25] analgesic, and anti-inflammatory effects.[26,27] The wide range properties of torilin are principally correlated to its structure and functional groups.

Torilin has been separated for the first time from the hydro-methanolic (70%) extract of the *T. japonica* fruit in 1994. This compound was isolated from hexane (Hex) fraction *via* column chromatography on Silica gel with Hex: ethyl acetate (AcOEt) (gradient) as the eluent. In another study, it was purified by recrystallization from MeOH (methanol) as colorless stout needles.[28] In an investigation performed by Lee et al. (2008) torilin and three new guaiane-type sesquiterpenes including 11-acetoxy-8-isobutyryl-4-guaien-3-one (**2**), 11-acetoxy-8-methacrylyl-4-guaien-3-one (**3**), and 11-acetoxy-8-propionyl-4-guaien-3-one (**4**) were isolated from the $CHCl_3$ (chloroform): MeOH (50:50 v/v) extract.[29] Hydro-alcoholic and alcoholic soluble-extracts of *T. japonica*, particularly the fruit methanolic extract has been introduced as rich source of torilin, the chemomarker of *T. japonica*.

Besides torilin, other guaiane-type sesquiterpenes including torilolone (**5**), (1β)-1-hydroxytorilin (**6**), (1α)-1-hydroxytorilin (**7**), 11-(acetyloxy)-1,8-dihydroxyguai-4-en-3-one (**8**) and (1α,6β)-1,6-dihydroxytorilin (**9**) were also isolated from the methanolic extract.[17] Thirteen sesquiterpene derivatives have further been isolated from the fruit methanolic extract of *T. japonica*: eight guaiane-, one eudesmane-, one cadinane-, two cardinane- and an elemane-type derivative namely as torilin (**1**), epoxytorilinol (**10**), elematorilone (**11**), cardinatoriloside (**12**), (1β)-1-hydroxy-torilin (**6**), 11-acetoxy-8-propionyl-4-guaien-3-one (**13**), 11-O-acetyl-torilolone 8-O-β-D-glucopyranoside (**14**), torilolone (**5**), 1β-hydroxytorilolone (**15**), 2α, 7-dihydroxykessane (**16**), oxy-torilolide (**17**), 1β-hydroxy-4(15),5E,10(14)-germacratriene (**18**), and 4α,5,6,7,8,8α-hexahydro-4,8α-dimethyl-6-(1-methylethenyl)-2(1H)-naphthalenone (**19**).[30]

In another study, the fruit methanolic extract was partitioned with Et_2O (diethyl ether), AcOEt, and aqueous residue. The ether fraction was then chromatographed in a Hex: AcOEt gradient as eluent system, the sesquiterpenoids 4(15)-eudesmene-1β,6α-diol (**20**); 4(15)-eudesmene-1β,5-diol (**21**); 4α,15-epoxyeudesmene-1β,6α-diol (**22**), 3(12),7(13),9(E)-humulatriene-2,6-diol (**23**) were subsequently isolated and identified; in

Table 2. Secondary metabolites isolated from *T. japonica*.

Compounds	Type	Plant part	Extraction solvent	Chromatographic techniques	Ref.
Torilin (syn. 8,11-dihydroxy-4 guaien-8-angeloyl-11-acetyl-3-one)	Guaiane-type sesquiterpene	dried Fr	$CHCl_3$: MeOH (50:50 v/v)	CC [*n*-Hex-AcOEt (1-50%)]	[29]
			MeOH (70%)	CC [AcOEt-MeOH (nd)]	[28]
			MeOH	CC [*n*-Hex; *n*-Hex-AcOEt (100:1, 50:1, 25:1, 10:1, 5:1, 3:1, 2:1, 1:1, 1:0)]	[44]
				CC [$CHCl_3$-MeOH (30:1)]; CC [$CHCl_3$-MeOH (35:1)]; CC [n-Hex-AcOEt (3:1)]; CC [n-Hex-AcOEt (1:1)]	[19]
				CC [CH_2Cl_2, CH_2Cl_2-MeOH (19: 1, 9:1, 1: 1, MeOH)]; RP-MPLC [(n-Hex-AcOEt (10:1, 5:1, MeOH)]	[45]
				CC [90% MeOH fraction using a CH_2Cl_2–MeOH step gradient system as eluent]	[46]
				CC [n-Hex/ACE (95:5, 90:10, 85:15, 80:20, 70:30, 60:40, 40:60, 20:80, and 0:100)]; HPLC [MeOH/H_2O (40:60, 75:25)]	[17]
				CC [MeOH-H_2O (3:7)] HPLC [CH_3CN-H_2O (3:17)]	[33]
				CC [n-Hex-AcOEt (3:1)]	[47]
			MeOH (100%)	CC [n-Hex-ACE (95:5, 90: 10, 85: 15, 80: 20, 70: 30, 60: 40, 40: 60, 20:80, 0: 100)]	[48]
				CC [PET-AcOEt (7:1, 1:7)]	[31]
			EtOH	CC [$CHCl_3$-MeOH (1:1)]	
				CC [$CHCl_3$-MeOH (15:1–8:1)]	
				CC [n-Hex-AcOEt (3:1, v/v)]	[49]
			EtOH (75%)	CC [n-Hex-AcOEt (3:1, v/v)]	[23]
Deangeloyloxytorilin (syn. 1β,7α, 10α,H-11-acetoxyguaia-4-en-3-one	Guaiane type sesquiterpene	dried Fr	MeOH	CC [n-Hex-$CHCl_3$ (1:1)]; CC [n-Hex-ACN (30:1)]; HPLC	[32]
1-β-Hydroxytorilin 1-β-Hydroxytorilin	Guaiane-type sesquiterpene	dried Fr	MeOH	CC [$CHCl_3$-MeOH (30:1)]; CC [$CHCl_3$-MeOH (35:1)]; CC [n-Hex-AcOEt (3:1)]; CC [n-Hex-AcOEt (1:1)]	[19]
11-acetoxy-8-isobutyryl-4-guaien-3-one, 11-acetoxy-8-methacrylyl-4-guaien-3-one, 11-acetoxy-8-propionyl-4-guaien-3-one	Guaiane-type sesquiterpenoid	dried Fr	$CHCl_3$: MeOH (50:50 v/v)	CC [n-Hex-AcOEt (1-50%)]	[29]
*Torilolone *(1α)-1-Hydroxytorilin, *(1β)-1-Hydroxytorilin, (1α,6β)-1,6-dihydroxytorilin, 11-(acetyloxy)-1,8-dihydroxyguai-4-en-3-one	Guaiane-type sesquiterpenoid	dried Fr	MeOH	CC [CH_2Cl_2/ACE (99:1, 97:3, 95:5, 93:7, 90:10, 80 20, 50:50, and 0:100)]; HPLC [MeOH/H_2O (40:60, 75:25)] CC [CH_2Cl_2/ACE (95:5, 0:100)]; HPLC [MeOH/H_2O (40:60, 75:25)]	[17]
Voleneol	Eudesmane-type sesquiterpenoid	dried Fr	EtOH	CC [PET-AcOEt (7:1, 1:7)] CC [$CHCl_3$-MeOH (1:1)] CC [$CHCl_3$-MeOH (15:1–8:1)]	[14, 31]
4(15)-Eudesmene-1β,6α-diol; 4(15)-Eudesmene-1β,5-diol; 4α,15-Epoxyeudesmene-1β,6α-diol	Eudesmane-type sesquiterpenoid	Fr	MeOH	CC [n-Hex-AcOEt (9:1, 7:3, 1:1), AcOEt, MeOH] HPLC [nd]	[14]
Torilolone; 2α,7,8β-Trihydroxykessan; 2α,7-Dihydroxykessane	Guaiane-type sesquiterpenoid				
3(12),7(13),9(E)-Humulatriene-2,6-diol	Humulane-type sesquiterpenoid				
Epoxytorilinol	Guaiane-type sesquiterpene	dried Fr	MeOH	RP-MPLC [MeOH-H_2O (80:20, 0:100)]	[30]
Elematorilone	Eudesmane-sesquiterpene type			semi-preparative HPLC [MeCN-H_2O (45:55)]	
Cardinatoriloside	Cadinane-type sesquiterpene			RP-MPLC [MeOH-H_2O (80:20, 0:100)]	
1β-hydroxy-4(15),5E,10(14)-germacratriene 4α,5,6,7,8,8ahexahydro-4,8α-dimethyl-6-(1-methylethenyl)-2(1H)-naphthalenone	Cardinane-type sesquiterpenes		Hex	Sephadex LH-20 [Hex-CH_2Cl_2–MeOH (10:10:1))	
5,17-β-dihydroxy-de-A-estra-5,7,9,14-tetraene	Steroids	dried Fr	EtOH (80%)	HPLC [MeCN-H_2O [3:1 v/v]]	[24]
(Z,Z)-9,12-octadecadienoic acid	Fatty acid			GC/MS	
Furanodiene	Germacrene-type sesquiterpenoid				
Torilolide	Germacrene-type sesquiterpene	dried Fr	EtOH	CC [C_6H_6-AcOEt (2:1), n-Hex-AcOEt (7:3), n-Hex-AcOEt-MeCN (7:2:1)]; HPLC [nd]	[50]
Oxytorilolide	Elemane-type sesquiterpene			CC [C_6H_6-AcOEt (2:1), C_6H_6: AcOEt-MeCN (10:2:1), n-Hex: AcOEt (7:3), n-Hex-AcOEt-MeCN (7:2:1)]; HPLC [nd]	
(3R)-2-hydroxy-methylbutane-1,2,3,4-tetrol (2S,3R)-2-methylbutane-1,2,3,4-tetrol (2E)-2-methyl-2-butene-1,4-diol 1-O-β-D-glucopyranoside	Hemiterpenoid	fresh Fr	MeOH	Sephadex LH-20 (MeOH), silica gel [$CHCl_3$-MeOH-H_2O (7:3:0.5)] and Lobar RP-8 column (20% MeOH)	[33]
(1S,2S,4R)-2-hydroxy-1,8-cineol β-D-apiofuranosyl-1-β-D-glucopyranoside	Monoterpenoid glucoside				
Quercetin (0.003%), Luteolin (0.004%), Kaempferol (0.003%)	Flavonoids	nd	-	HPLC	[18]
Apigenin, Chrysoeriol, Luteolin, Apigenin 7-O-glucoside, Apigenin 7-O-apiosylglucoside (apiin), Apigenin 7-O-rutinoside, Luteolin 7-O-glucoside, Luteolin 7-O-rutinoside, Chrysoeriol 7-O-neohesperidoside	Flavonoids	dried AP	MeOH	HPLC [FA (0.1% in H_2O)-MeCN [40:60%)] LC/MS/MS [FA (0.05% in H_2O)-MeCN (80:20%)]	[2]

ACE: acetone; ACN: acetonitrile; AcOH: acetic acid; AP: aerial part; C_6H_6: benzene; CC: column chromatography; CH_2Cl_2: dichloromethane; $CHCl_3$: chloroform; AcOEt: ethyl acetate; EtOH: ethanol; F: flower; FA: formic acid; Fr: fruit; GC/MS: gas chromatography–mass spectrometry; HEX: hexane; HPLC: high performance liquid chromatography; L: leaf; LC/MS/MS: liquid chromatography with tandem mass spectrometry; MeCN: acetonitrile; MeOH: methanol; nd: not determined; PET: petroleum ether; R: root; RP- MPLC: reversed-phase medium-pressure liquid chromatography; S: stem; TLC: thin-layer chromatography; TOL: toluene.

addition, from the aqueous fraction, torilolone (**5**); 2α,7,8β-trihydroxykessan (**24**), and 2α,7-dihydroxykessane (**25**) were isolated.[14] The sesquiterpenes of torilolide (**26**) and oxytorilolide (**27**) have been purified from the benzene extract via HPLC;[4] asides from isolation ad characterization of other sesquiterpenoids comprising voleneol (**28**),[31] furanodiene (**29**),[24] and deangeloyloxy torilin (**30**).[32]

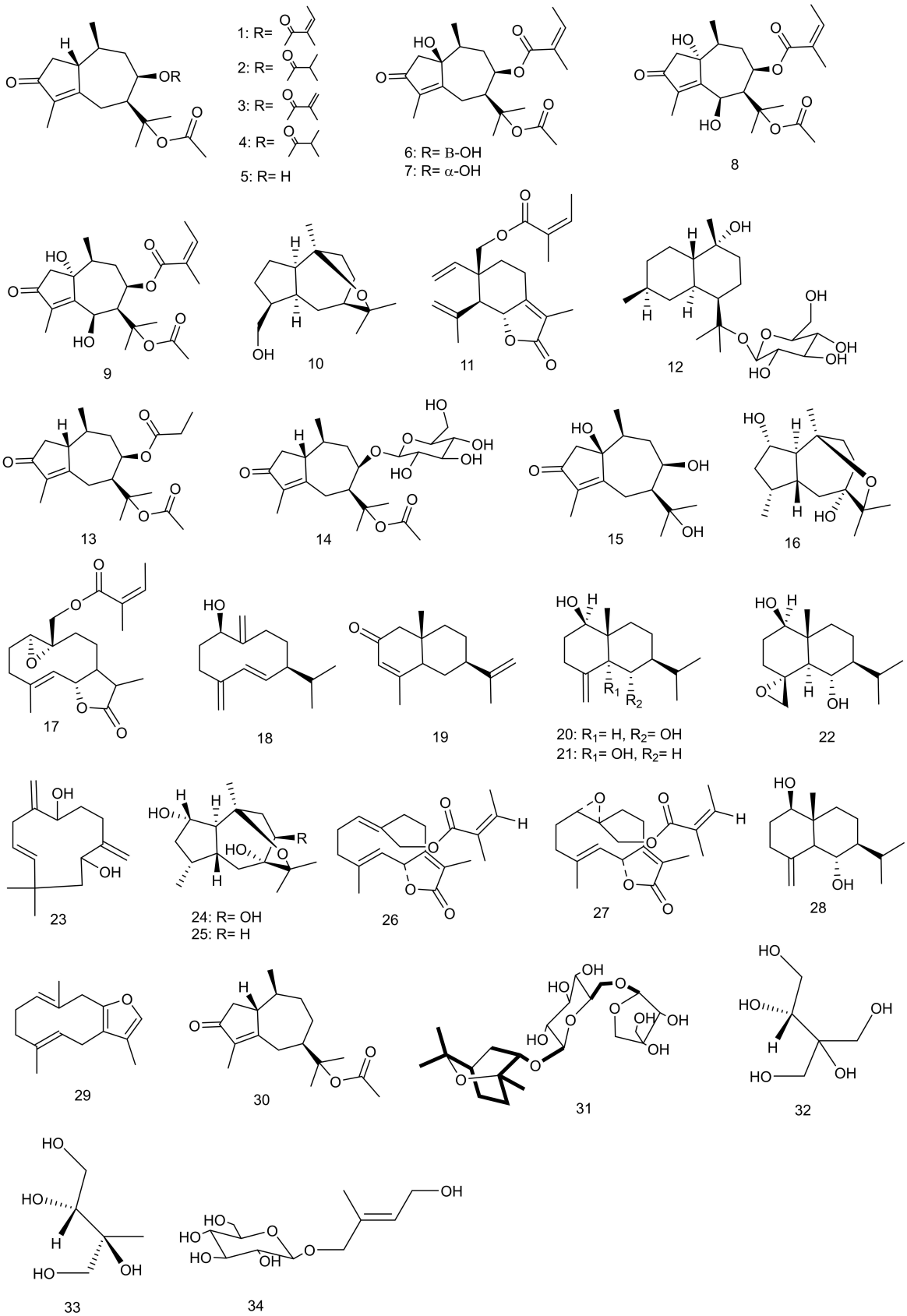

Figure 1. Chemical structure of isolated terpenoids from *T. japonica*.

Furthermore, other terpenoid derivatives have been reported from the *T. japonica* fruit including monoterpenoid of apiosyl-glucoside; (1S,2S,4R)-2-hydroxy-1,8-cineol-β-D-apiofuranosyl-1-β-D-glucopyranoside (**31**), besides three hemiterpenoids of (3R)-2-hydroxy-methylbutane-1,2,3,4-tetrol (**32**), (2S,3R)-2-methyl-2-butane-1,2,3,4-tetrol (**33**), and (2E)-2-methyl-2-butene-1,4-diol 1-O-β-D-glucopyranoside (**34**) (Figure 1).[33] Due to few but rare and interesting sesquiterpenes identified from *T. japonica*, particularly torilin derivatives, the fruit alcoholic extracts can be subjected for further phytochemical studies, leading to identification of new compounds possessing remarkable biological effects.

3.1.1. Flavonoid derivatives

Chemical structures of the flavonoids isolated from the *T. japonica* aerial parts are demonstrated in Figure 2. Nine flavones apigenin (**35**), apigenin 7-O-glucoside (**36**), apigenin 7-O-rutinoside (**37**), apigenin 7-O-apiosylgucoside (apiin) (**38**), luteolin (**39**), luteolin 7-O-glucoside (**40**), luteolin 7-O-rutinoside (**41**), chrysoeriol (**42**), chrysoeriol 7-O-neohesperidoside (**43**),[2] along with two flavonols quercetin (**44**) and kaempferol (**45**)[18] have previously been isolated and identified from this species, whilst apigenin 7-O-rutinoside (**37**) and apiin (**38**) are introduced as the *Torilis* genus marker compounds.[34] Flavonoids, an important class of phytochemicals, possess diverse beneficial bioactivities, specifically well-known significant antioxidant and anti-tumor activities. Due to identification of few flavonoids from the plant, further investigations particularly bio-assay guided approach can lead to identify possibly new flavonoids with significant bioactivities[35–37]

3.2. Volatile compounds

The major volatile compounds (>3%) of *T. japonica* are summarized in Table 3 and their chemical structures are shown in Figure 3. Through several phytochemical studies, the essential oil (EO) composition of the aerial parts was hydro-distillated

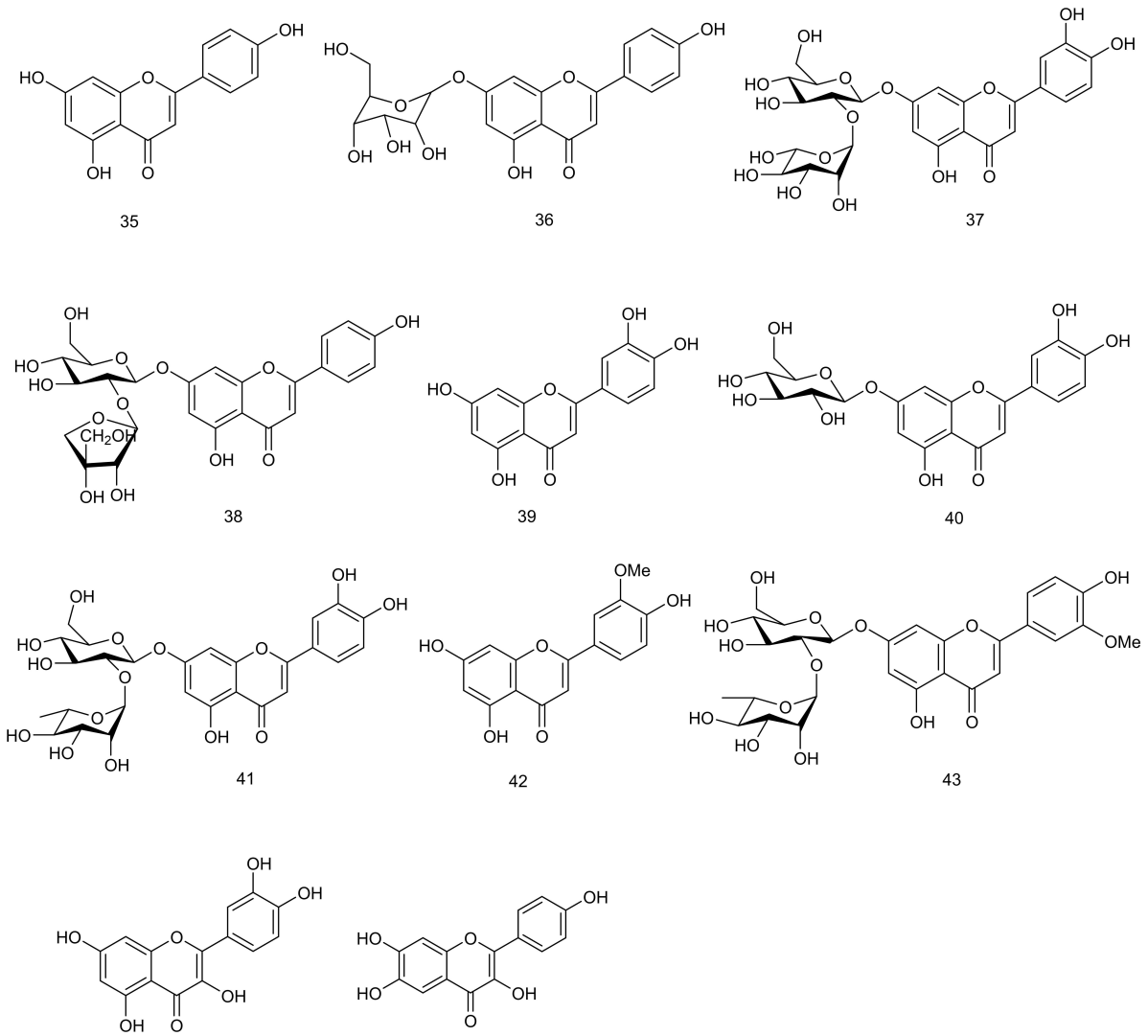

Figure 2. Chemical structure of the flavonoids isolated from *T. japonica*.

Table 3. Major volatile compounds identified from *T. japonica*.

Origin	Analysed plant part	Extraction type	Yield (%)	Major compounds (%)	Ref.
China	dried AP	HD	0.928% (w/w)	β-Eudesmene (22.87), Eudesm-7(11)-en-4-ol (12.95), α-Selinene (12.94), Eudesm-7(11)-en-4-ol (10.42), β-Elemene (8.22), Caryophyllene oxide (3.87), β-Cubebene (3.85), Caryophyllene (3.59)	[13]
Japan	fresh AP and Fr	ND	0.08-0.26% (w/w)	Germacrene D (57.9–71.8%), α-Humulene (2.4–13.2%), Bicyclogermacrene (1.9–5.4%), β-Caryophyllene (1.5–4.6%), δ-Cadinene (1–1.9%)	[38]
India	fresh AP	HD	0.02% (v/w)	Germacrene D (25.86%), α-Humulene (14.64%), β-Caryophyllene (11.33%), Nootkatone (10.80%), Caryophyllene oxide (5.07%), (E, E)-α-Farnesene (4.09)	[39]
Poland	dried Fr	HD	0.25% (w/w)	1,6-Germacradien-5-ol (38.46), β-elemene (18.12), β-Caryophyllene (11.02), Germacrene D (9.33), α-Germacrene (8.29)	[21]

AP: aerial part; Fr: fruit; HD: hydrodistillation; ND: not determined.

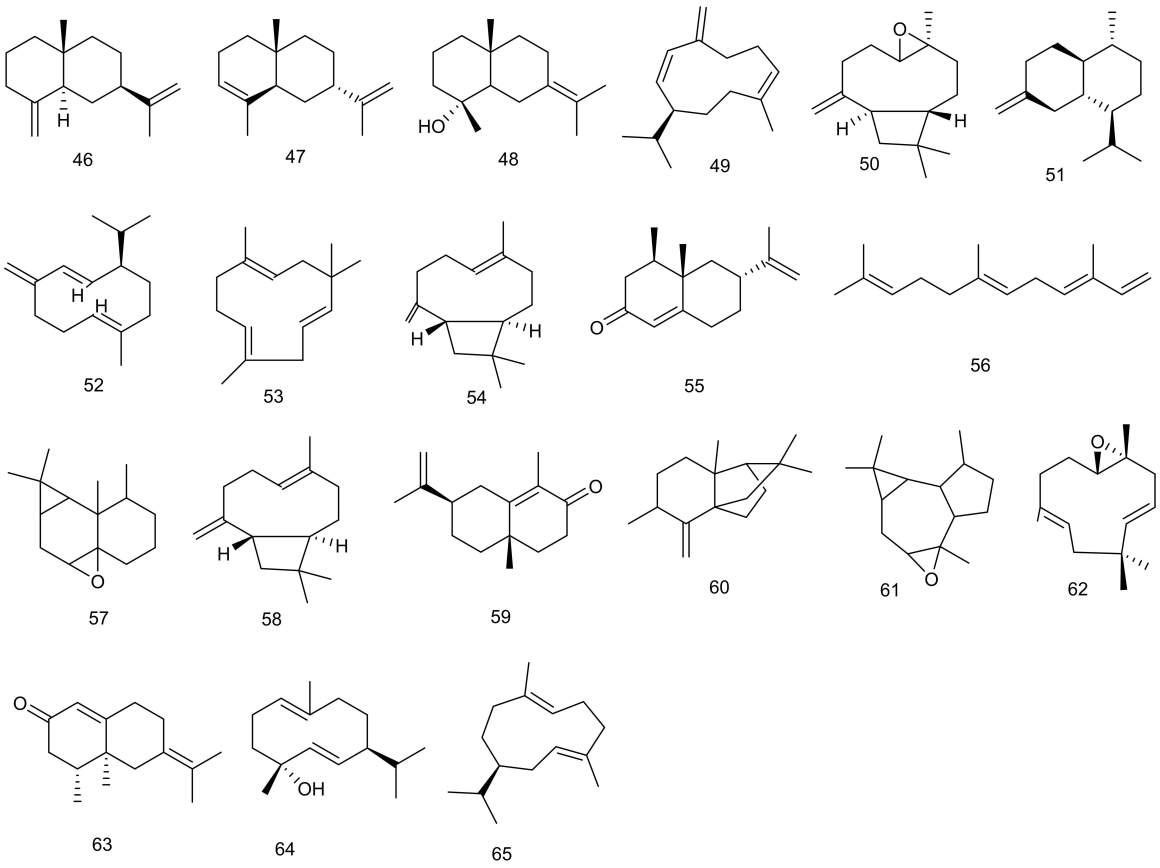

Figure 3. Chemical structures of the major secondary metabolites from *T. japonica* essential oi.

and analyzed using gas chromatography coupled with flame ionization (GC-FID) or mass spectrometry detectors (GC/MS). The major secondary metabolites distributed in China were reported as sesquiterpenes β-eudesmene (**46**), α-selinene (**47**), eudesm-7(11)-en-4-ol (**48**), β-elemene (**49**) caryophyllene oxide (**50**), and β-cubebene (**51**), with the highest yield 0.928% (w/w),[13] whereas germacrene D (**52**), α-humulene (**53**), β-caryophyllene (**54**), nootkatone (**55**), caryophyllene oxide (**50**), and (E, E)-α-farnesene (**56**) were identified from the plant grown in India and Japan.[38,39] Other minor compounds have also been identified as aristolene epoxide (**57**), α-caryophyllene (**58**), (+)-α-cyperone (**59**), tricyclo[5.2.2.0(1,6)]undecan-3-ol, 2-methylene-6,8,8-trimethyl- (**60**), isoaromadendrene epoxide (**61**), humulene epoxide II (**62**), and α-vetivone (**63**).[13,39] Many researchers showed the ecological impacts on quantity and quality of the phytochemicals. Indeed, plants try to adapt themselves against various abiotic and biotic stressors *via* regulating production of the most beneficial secondary metabolites in specific growth conditions.[40–42] The major volatile compounds of the plant's fruit grown in Poland were reported as sesquiterpenes hydrocarbons (48.8%) and alcohols (38.4%), predominantly including 1,6-germacradien-5-ol (**64**), β-elemene (**49**), β-caryophyllene (**54**), germacrene D (**52**), α-germacrene (**65**), and α-humulene (**53**).[21] Overall germacrene D is introduced as the predominant plant's volatile component. Although its biological role in plants is still un-recognized, proposing its precursor function for

biosynthesis of other sesquiterpenes (e.g., cadinenes), it has been suggested to possess anti-herbivore effects particularly insecticidal activity against mosquitoes.[43]

4. Biological activity of *Torilis japonica* and its components

4.1. Anti-Viral Properties

Acute hepatitis initiated by hepatitis A virus (HAV), an RNA virus of the family Picornaviridae, is a global health issue.[51] In a study conducted by Seo et al. (2017), the antiviral activity of *T. japonica* and 15 herbal extracts were examined by plaque assay on FRhK-4 cells at doses of 10 and 50 μg/mL for each extract.[52] Ten herbal extracts showed significant anti-HAV activity without exhibiting cytotoxicity and the *T. japonica* extracts reduced HAV titer by 1.90 ± 0.33 logs.

4.2. Antimicrobial and anti-protozoal activities

In food sterilizing, inactivating endospores bacteria like *Bacillus subtilis* is crucial to maximize quality and safety. Therefore, applying medicinal herbs as food preservatives are promising strategy. Cho et al. (2007) assessed the anti-microbial activity of 37 medicinal plants used in traditional medicine in China and Korea against *B. subtilis* spores.[23,53] They found that ethanolic extracts of 13 herbs including *T. japonica* at concentration 1% (w/v) have high sporicidal activity and reduced spore count by 99%. The ethanolic extract diminished the spore concentration by 3 log cycles and the vegetative cell concentration to lesser than the detection level. Torilin also decreased vegetative cells and spores counts by 5 to 6 and 1 order of magnitude, respectively. In another study, the *T. japonica* ethanolic extract and UV irradiation at a wavelength of 254 nm was used to study their synergistic effects on the inactivation of *B. subtilis* spores.[54] The UV irradiation alone reduced the level of spores count by 3.6- and 4.7-log cycles at time exposure of 3 and 10 min at an irradiation distance of 15 cm, and it was 3.0-log cycles for 1 h of treatment with the ethanolic extract at concentration 1% (w/v). In the presence of 1% ethanolic extract, the energy required for inactivating the spores by UV irradiation was reduced to 50%, the level of spores count reached 4.2–5.0-log at time exposure of 3 min.

In a study, anti-microbial activity of the *T. japonica* extract against *Escherichia coli* was investigated in Piglets.[55] The results demonstrated that the additive *T. japonica* extract had effects on the suppression of *E. coli*-induced lesions, and suggested that the additive could be applied as the alternative material for anti-microbial feed additives. In two separate studies, the EO attained from the plant aerial part and its antimicrobial effects were evaluated against different microorganisms.[13,39] The EO showed moderate anti-microbial activity against bacteria including *S. aureus*, *E. coli*, *L. monocytogenes*, *Sh. dysenteriae*, *S. typhimurium*, *V. parahemolyticus*, *K. pneumonia*, *S. enterica*, *E. coli*, *P. vulgaris*, *P. aeruginosa*, while the *B. subtilis* was the most sensitive bacteria against the EO with ZI: 8 ± 0.14 mm, MIC: 0.16 μL/mL. The EO also presented moderate activity against *C. albicans* (ZI: 9.67 ± 0.29 mm, MIC: 175 μL/mL) and *P. guilliermondii* (ZI: 7.67 ± 0.05 mm, MIC: 175 μL/mL).[39] This moderate effects might be related to the sesquiterpenes enriched in the EO, since antimicrobial effects of these compounds have formerly been documented.[56]

Some bacteria strains such as *S. aureus* can produce a biofilm in the presence of immune cells or antibiotics to combat the situation. A biofilm contains extracellular DNA, polysaccharides, and proteins that protect bacteria from the external environment.[57] Therefore, preventing biofilm formation around bacteria with plant extract is a good strategy for controlling infections. Kim et al. (2022) experimented inhibitory activity of the *T. japonica* ethanolic extract towards biofilm production in methicillin-resistant *S. aureus* (MRSA) KCCM 40511, MRSA KCCM 40510, and methicillin-sensitive *S. aureus* (MSSA) KCTC 1927.[22] The result presented that the *T. japonica* extract inhibited biofilm formation in all strains and suppressed virulence factor-related gene expression in MRSA and MSSA strains, suggesting that the extract could be helpful for the treatments of infections produced by antibiotic-resistant *S. aureus*.

Neospora is an obligate intracellular parasite that was first isolated from dogs in 1984 and it is a common cause of abortion in wildlife.[58,59] Youn et al. (2003) analyzed the *in vitro* anti-protozoal activity of the ethanolic extract of *T. Japonica against T. gondii*, and *N. caninum* tachyzoites in concentrations ranging from 625 to 19.5 ng/mL.[60] The ethanolic extract suppressed *N. caninum* proliferation by 97.8, 97.9, 85.3, and 46.4%, and *T. gondii* proliferation by 99.3, 95.5, 73.0, and 54.0% in the range 156 to 19.5 ng/mL. In order to finding out the responsible fractions for the anti-protozoal activity, all fractions were separated with HPLC and their activity was assessed *in vitro* against *N. caninum*, *and T. gondii*.[25] One fraction of the ethanolic extract inhibited *N. caninum* proliferation by 98.3, 95.5, 79.7, 30.6%, and *T. gondii* proliferation by 99.2, 94.4, 88.6, and 27.0% ranging 2.850 to 0.356 ng/mL. In another study, active components of the *T. japonica* extracts were isolated using HPLC, and the anti-neosporal activity of each fraction was investigated against *N. caninum*.[24] All HPLC fractions showed a better levels of the anti-neosporal effect compared to the control group. The abovementioned effects can be caused by torilin and its derivatives, due to its predominance in plant ethanolic extract. The anti-coccidial activity of aqueous extract of 15 herbs, including *T. japonica*, were evaluated against *Eimeria tenella* in chicks by Youn and Noh (2001). The *T. japonica* extract showed anti-protozoal efficacies, initial weight gains, and enhanced survival rates compared to the infected control group.[61]

4.3. Antioxidant activity

Natural antioxidant agents through acting as free radical scavengers deteriorate the level of oxidative damage and might combat several degenerative disorders such as cancers, and

cardiovascular disease, and are substitute constituents to artificial additives including butylated hydroxytoluene (BHT) in food industry.[61] Oh et al. (2014) evaluated the antioxidant activity of the *T. japonica* aqueous extract and found that it could scavenge DPPH radical in a dose-dependent manner up to 63.8%. Oh et al. (2014) assessed the antioxidant activity of the methanolic extract assessed by ABTS assay reporting less than 50% of the effect.[62]

Flavonoids isolated from *T. japonica* demonstrated antioxidant and antidiabetic activities.[63–65] Quercetin (**44**) was reported as the most potent flavonoid against two diabetes enzymes α- glucosidase and α-amylase.[66,67] Since the plant extracts are described to be rich in several flavonoids specially flavones and flavonols, considering significant antiradical effects of these compounds, different plant products including plant extracts can be options for development of food supplements.

4.4. Anticancer properties

Cancer is one of the main reasons for death, especially in developed countries. Recently, studies on the natural products for treating cancers gained more attention and *T. japonica* presented therapeutic effects against several types of cancer comprising lung, breast, and colorectal cancers.

The anti-melanogenesis activity was carried out on 13 sesquiterpenes (**1**, **5**, **6**, **10–19**) using MTT assay (Table 4). Among the sesquiterpenes tested, torilin exhibited the most inhibitory effect on melanin production while compounds **6**, **13**, **17–19** showed the lowest inhibitory effect. The presence of angeloyl moiety in the guaiane skeleton was reported essential for inhibitory activity, also the presence of functional groups such as hydroxy on carbon 2 reduces the inhibitory effect.[30,48] Moreover, torilin was introduced as anti-tumor agent. In Kim et al. studies, torilin indicated anti-angiogenic properties of vascular endothelialcells,[46] anti-abnormal metastasis in A549 lung cancer cells[68] and reversing multidrug-resistance in cancer cells.[45] Apigenin (**35**) and apigenin 7-O-glucoside (**36**) isolated from this plant showed antifungal and cytotoxic activity.[69]

In another study, cytotoxicity of torilin (**1**) and five guaiane sesquiterpenoids namely torilolone (**5**), (1β)-1-hydroxytorilin (**6**), (1α)-1-hydroxytorilin (**7**), 11-(acetyloxy)-1,8-dihydroxyguai-4-en-3-one (**8**), and (1α,6β)-1,6-dihydroxytorilin (**9**) were evaluated against MCF-7 (breast cancer) and LLC (Lewis lung carcinoma) cell lines using MTT assay. Compounds of **1**, **6** and **7** revealed cytotoxic activity against the LLC cells while none of the compounds were significantly toxic against the MCF-7 cells.[17]

One of the critical factors in abnormal metastasis of lung cancer cells is the over-activity of the epidermal growth factor receptor (EGFR). Kim et al. (2017) experimented the inhibitory effect of the *T. japonica* extract of EGFR in A549 lung cancer cells, and the mechanism of expression suppression of abnormal metastasis-related factors *via* translocation to the cancer cell nucleus. The result presented that treatment of the *T. japonica* extract could inhibit the EGFR signalling pathway, co-binding with Stat3 and dimer formation, and suppress the expression of cancer cell abnormal metastasis and metastasis-related factor in comparison with the EGF-stimulated group.[68]

Angiogenesis and invasion of tumor cells contain several mechanisms including embryonic development, tissue regeneration, invasion of extracellular matrix, and invasion of the blood vessel wall leading to degradation of extracellular matrix and basement membrane.[70] Kim et al. investigated the anti-angiogenic and anti-invasive activity of torilin via *in-vitro*, and *in-vivo* assay systems.[46,71] The result showed that torilin reduced basic fibroblast growth factor–induced vessel formation and neovascularization of chick embryos in the chorioallantoic membrane assay in the mouse Matrigel plug assay. It diminished tube formation and the proliferation of human umbilical vein endothelial cells and down-regulated the expression of insulin-like growth factor-II and hypoxia-inducible vascular endothelial growth factor.[46]

Torilin inhibited HT1080 cell invasion in a time-dependent order in an *in-vitro* Transwell invasion model and reduced the expression and activity of matrix metalloproteinase-9. It also blocks the intravasation of HT1080 cells inoculated on the chorioallantoic membrane of chick embryos.[71] These results suggested that torilin has potent anti-angiogenic and anti-invasive activity and might be used in cancer chemotherapy. One of the main problems related to cancer chemotherapy is multidrug resistance (MDR) which is responsible for more than 90% of deaths in cancer patients receiving chemotherapeutics medicine. Several mechanisms are behind the MDR, such as increasing efflux of drugs due to the overexpression of P-glycoprotein (Pgp) in plasma membranes of resistant cells, augmented DNA repair capacity, raised metabolism of xenobiotics, and genetic factors.[72] Therefore, inhibition of these mechanisms enhances the therapeutic efficacy of drugs administered in tumor treatment. In a study, multidrug resistance reversing effects of the *T. japonica* methanolic extract was investigated through multidrug resistance KB–V1 and drug-sensitive KB-3-1.[73] The result shows that the extract significantly potentiated vinblastine cytotoxicity in KB–V1, while its cytotoxicity to both multidrug resistance KB–V1 and drug-sensitive KB-3-1 were in the same order of magnitude. In another study, MDR caused by vinblastine, colchicine, adriamycin, and taxol was abrogated by torilin on multidrug resistant MCF7IADR and KB–V1cells.[45]

Nakano et al. (1998) looked for antiproliferative compounds among the Umbelliferae plant and checked their activities through MTT assay against the tumor cell lines B16F10, HeLa, and MK-1. The MeOH extract of the *T. japonica* fruit exhibited B/B0 values of less than 50% at 250 times dilution, and it showed remarkable antiproliferative activity against tumor cells.[74] Jung and Ghil (2010) evaluated the antiproliferative activity of methanolic extract of *T. japonica* towards the U87MG human glioblastoma cell lines, discovering their molecular mechanisms underlying activity.[3] The MeOH extract suppressed cell proliferation in a dose- and time-dependent manner, induced apoptotic cell death and S-phase cell cycle arrest. It also inhibited cell proliferation and the expression of cell cycle regulatory proteins such as E2F1, cyclin A, and cyclin-dependent protein kinase 2.

Table 4. Biological activities of the *Torilis japonica* extracts and its pure compounds.

Activity	Assayed extract /compound	Measure of activity	Assay	Outcomes	Cell lines/Strain/Model	Ref.
Hepatitis A virus	MeOH Ex.	(10, 50, 100) μg/mL	MTT and plaque assay	MeOH Ex. showed significant activity against HAV and reduced HAV titer 1.90 ± 0.33 logs.	FRhK-4 cells/ *in-vitro*	[51]
Coronavirus	MeOH Ex.	50 μg/mL	Plaque assay, Northern and Western blot analyses	The extract decreased intracellular viral RNA levels with a comparable reduction in viral proteins and MHV–A59 production by inducing cyclooxygenase-2 expression via p38 or ERK.	MHV–A59, MHV-JHM, PEDV, VSV/ *in-vitro*	[52]
Antibacterial	75% EtOH Ex./ Torilin	1% (w/v)	Antimicrobial assay	The EtOH Ex. diminished the spore concentration by 3 log cycles and the vegetative cell concentration to lesser than the detection level. Inactivation of EtOH Ex. at a dosage of 0.1 and 0.5-1.0% were 100- and 1000-fold (reduction of 99 and 99.9%), respectively. Torilin decreased vegetative cells and spores counts by 5 to 6 and 1 order of magnitude, respectively.	ATCC 6633 spores and vegetative cells of *B. subtilis*/ *in-vitro*	[23, 53]
	EtOH Ex.	1% (w/v) and UV_{254} irradiation	Sporicidal activity	Better reduction of *Bacillus* spores at different growth stages was achieved (4.2–5.0-log) with the combined treatment of UV_{254} and EtOH Ex. than UV irradiation (3.6- and 4.7-log cycles) and EtOH Ex. (3.0-log cycles) alone. The energy required from UV irradiation was 50% lower in the presence of 1% EtOH Ex.	ATCC 6633 *B. subtilis* cells/ *in-vitro*	[54]
	TJ Ex.	ND	Clinical signs, weight increase rate, Fecal scores, Gross findings	*TJ* Ex. additive have the effects on suppression of *E. coli*-induced lesions	*E. coli*/ *in-vivo in Piglet*	[55]
	EO of aerial part	5 μL of the pure EO	Agar disk diffusion method and Broth microdilution bioassay	The EO was effective against *S. typhimurium* (*ZI:* 16.5 ± 0.07 mm, MIC > 7.5 μL/mL), *B. subtilis* (*ZI:8* ± 0.14 mm, MIC: 0.16 μL/mL), and *L. monocytogenes* (*ZI:* 7.5 ± 0.07 mm, MIC > 7.5 μL/mL).	*S. aureus*, *B. subtilis*, *E. coli*, *L. monocytogenes*, *Sh. dysenteriae*, *S. typhimurium* and *V. parahemolyticus*	[13]
	EO of aerial part	5 to 1000 μL/mL	Agar well diffusion method	The EO displayed moderate activity against *E. coli*(*ZI:* 11.67 ± 0.15 mm, MIC:150 μL/mL), *S. aureus* (ZI: 9.67 ± 0.12 mm, MIC:175 μL/mL), P. *aeruginosa* (ZI:10.33 ± 0.14 mm, MIC: 150 μL/mL), *P. vulgaris* (ZI: 9.67 ± 0.04 mm, MIC: 150 μL/mL), *K. pneumonia* (ZI: 8.33 ± 0.30 mm, MIC:150 μL/mL), and *S. enteric* (ZI: 8.67 ± 0.06 mm, MIC: 175 μL/mL).	*K. pneumoniae*, *S. aureus*, *S. enterica*, *E. coli*, *P. aeruginosa*, and *P. vulgaris*	[39]
	95% EtOH Ex.	0 to 100 μg/mL	Hemolysis assay, and Biofilm assay	TJE can inhibit biofilm formation and virulence factor-related gene expression in MRSA and MSSA strains.	methicillin-sensitive *S. aureus* (MSSA) KCTC 1927, methicillin-resistant *S. aureus* (MRSA) KCCM 40510, and MRSA KCCM 40511	[22]
Anti-fungal	EO of aerial part	5 to 1000 μL/mL	Agar well diffusion method	The EO presented moderate activity against *C. albicans* (ZI: 9.67 ± 0.29 mm, MIC: 175 μL/mL) and *P. guilliermondii* (ZI: 7.67 ± 0.05 mm, MIC:175 μL/mL)	*P. guilliermondii*, and *C. albicans*	[39]
Anti-protozoal	EtOH Ex.	625 to 19.5 ng/mL	*in-vitro* cultures	EtOH Ex. inhibited *N. caninum* proliferation by 97.8, 97.9, 85.3, and 46.4% and *T. gondii* proliferation by 99.3, 95.5, 73.0, and 54.0% in the range from 156 to 19.5 ng/mL.	*T. gondii* and *N. caninum*/ *in-vitro*	[60]
	EtOH Ex.	2.850 to 0.356 ng/mL	*in-vitro* cultures	One fraction of EtOH Ex. inhibited *N. caninum* proliferation by 98.3, 95.5, 79.7, and 30.6% *T. gondii* proliferation by 99.2, 94.4, 88.6 and 27.0%.	*T. gondii* and *N. caninum*/ *in-vitro*	[25]
	80% EtOH Ex./ furanodiene and two others compounds	2.85 ng dry weigh/well along with serial dilutions	*in-vitro* cultures	all HPLC fractions showed a better level of anti-neosporal activity compared to the control group.	*N. caninum* / *in-vitro*	[24]
	Water Ex.	6–30 g/ 1000 mL	Survival rates, Lesion scores, body weight gains, Bloody diarrhea, and Oocysts excretions	Survival rates with water Ex. in the treated groups were higher (90%) than in the infected control group (70%), and excreted oocysts were 93,000/g of feces with Ex. vs. control group (227,000/g of feces). No significant difference in body weight gains was observed between the Ex. and control groups.	*Eimeria tenella*/chicken/ *in-vivo*	[61]
Antioxidant	Water Ex.	(5, 100) μg/mL	DPPH assay	Water Ex. scavenged DPPH radical in a dose-dependent order up to 63.8%.	*In-vitro*	[62]
	MeOH Ex.	(10, 50) μg/mL	ABTS assay	The antioxidant activity of MeOH Ex. was less than 50%, and it was significantly higher at 50 mg/mL than 10 mg/mL		
Cancer chemotherapy	TJ Ex.	ND	Invasion assay, CAM assay, and 3D cell culture method	TJ Ex. regulate the EGFR signaling pathway and suppress its activity via the targeting of EGFR	A549 lung cancer cells/ *ex-vitro*	[68]
	MeOH Ex./ torilin and several compounds	ND	MTT assay	Compounds torilin, (1b)-1-hydroxytorilin, and 1a)-1-hydroxytorilin displayed cytotoxic effects against the LLC cells with IC_{50} values of 31.3, 32.5, and 34.0 μg/mL, respectively	MCF-7 and LLC cells	[17]
	MeOH Ex./ torilin, 1β-hydroxytorilin, 1α-hydroxytorilin	ND	Sulforhodamin B bioassay	The isolated compounds displayed moderate cytotoxicity against the selected human cancer cells	A549, SK-OV-3, SK-MEL-2, and HCT15 tumor cells.	[19]
	95% EtOH Ex.	(20, 40 60, 80) μg/mL	Caspase-3 activity assay, MTT assay, Western blot analysis	The EtOH Ex. regulate the AMPK/p38 signalling pathway and induce apoptosis in cells led to knock down p53 using siRNA. It also regulated apoptosis related-proteins and induced apoptosis in an HCT 116 xenograft model in an *in-vitro* study.	HCT116 colorectal cancer cells/ *in-vitro*, *in-vivo*	[6]
	MeOH Ex./ polyacetylenic compounds	50 μL	ELISA and MTT assay	MeOH Ex. exhibited B/B0 values of less than 50% at 250 times dilution and high antiproliferative activity against tumor cells.	MK-1, HeLa, B16F10/ *in-vitro*	[74]
	MeOH Ex.	0–100 μg/mL	MTT assay and Western blot analysis	MeOH Ex. induced apoptotic cell death and S-phase cell cycle arrest. It also inhibited cell proliferation and the expression of cell cycle regulatory proteins, such as E2F1, cyclin A, and cyclin-dependent protein kinase 2.	U87MG human glioblastoma cell lines/ *in-vitro*	[3]
	MeOH Ex.	ND	*in vitro* drug sensitivity	MeOH Ex. significantly potentiated vinblastine cytotoxicity in KB–V1 cells.	KB–V1 and KB-3-1 cell	[73]

Table 4. continued

Activity	Assayed extract /compound	Measure of activity	Assay	Outcomes	Cell lines/Strain/Model	Ref.
	MeOH Ex./ Torilin	2–20 μg/mL	*in vitro* drug sensitivity	Torilin potentiated the cytotoxicity of vinblastine, colchicine, adriamycin, and taxol against multi-drug resistant MCF7IADR and KB–V1 cells.	KB–V1 and MCF7IADR cells/ *in-vitro*	[45]
	Torilin	ND	CAM assay, *in-vivo* mouse Matrigel plug assay, (Q-CAM) assay, Tube formation assay, MTT assay	Torilin reduced basic fibroblast growth factor–induced vessel formation and neovascularization of chick embryos in the chorioallantoic membrane assay in the mouse Matrigel plug assay. It diminished tube formation, and the proliferation of human umbilical vein endothelial cells and down-regulated the expression of insulin-like growth factor-II and hypoxia-inducible vascular endothelial growth factor.	chick embryos, HUVECs cell, HepG2 human hepatoblastoma cells/*in-vivo* and *in-vitro*	[46]
	Torilin	25 μM	MTT assay, Western blot analysis	Torilin blocks invasion of HT1080 cells *in-vivo* and *in-vitro*. It also reduces the adhesiveness of HT1080 to HUVEC cells and the activity and expression of MMP-9.	HT 1080 and HUVECs cell/ *in-vitro and in-vivo*	[71]
Hyperpigmentation disorders	MeOH Ex./ AcOEt and aq. Fr./ Torilin	Ex. (50 μg/mL) and 10 nM α-MSH for 72 h	Western blot analysis	The extracts downregulate α-MSH-induced protein levels of tyrosinase in B16 cells. Torilin suppress (IC_{50} = 25 μM) melanin production.	B16 melanoma cells/*in-vitro*	[48]
	Torilin and several compounds		Tyrosinase inhibitory assays and MTT assay	Some isolated compounds inhibit a-MSH-activated melanin production in B16 melanoma cells with IC_{50} values from 72.9 to 191.0 μM.	B16 melanoma cells/*in-vitro*	[30]
Skin photoaging	TJ Ex.	(25, 50) μg/mL	MTT assay, Western blot analysis	TJ Ex. efficiently decreased UVB-induced MMP-3 and MMP-1 protein and mRNA levels. It also blocked the UVB-induced activation of MAPK (p38 and JNK) and transcription factors (NF-κB and AP-1).	human dermal fibroblasts (HDFs)/ *in-vitro*	[81]
	Red ginseng Ex. mixed with TJ and Corni fructus	0.5 and 1% Red ginseng Ex.	Real-time PCR analysis and HPLC	dietary supplementation enhanced the epidermal level of ceramides together with the elevated expression of SPT protein.	Albino mice /*in-vivo*	[92]
Anti-inflammatory	EtOH Ex.	Tf-EE (0-75 mg/mL) and LPS (1 mg/mL).	The Griess assay and Prostaglandin (PGE2) ELISA assay	Tf-EE significantly suppressed the inflammatory response of macrophages, like PGE2 production and lipopolysaccharide (LPS)-induced nitric oxide (NO) with IC_{50} values of 62.47 and 35.66 mg/mL, respectively. Anti-inflammatory activity of Tf-EE triggered by inhibition of the Src/ NF-jB pathway	RAW264.7 cells/ *in-vitro*	[83]
	Hex, AcOEt, and BuOH Ex.	(10, 50) μg/mL	Nitrite assay, Western blot analysis	The expression of iNOS protein is inhibited in LPS-activated macrophages by the AcOEt fraction.	RAW264.7 cells/ *in-vitro*	[84]
	MeOH Ex./ (DW, BuOH, AcOEt, Hex, Chl) Fr.	60 – 1000 mg/kg P.O.	Carrageenan-induced paw edema	MeOH Ex. and Hex Fr. had anti-edematous in the rat at (500 – 1000 mg/kg p.o.) and (237 mg/kg p.o.), respectively. Hex Fr. presented inhibitory activity at 77 mg/kg p.o. on vascular permeability in mice, at 120 mg/kg p.o. on adjuvant arthritis in rats, and 8 mg/pouch on leucocyte emigration in rats.	Rat and mice/*in-vivo*	[85]
	Hex Ex./ Torilin	30, 90 and 270 mg/kg P.O. and 3 and 9 mg/rat SC.	Acetic acid-induced and phenylqiunone induced writing syndrome, Tail pressure method, and Randall-Selitto method	Torilin showed strong anti-carrageenan activity at P.O. of 90 and 270 mg/kg and increased the pain threshold in rats.	Mice and rat/ *in-vivo*	[27]
	Torilin	6.25–25 μM	Immunoprecipitation and In Vitro TAK1 Kinase assays, Electrophoretic mobility shift assay, Transient transfection Luciferase assay, Enzyme-linked immunosorbent assay.	Torilin inhibited cytokines and inflammatory mediators by inhibition of AP-1, TAK1-mediated MAPK, and NF-κB activation	RAW 264.7 cells/*in-vitro*	[26]
Contact dermatitis	aq. Ex.	(10, 50) μg/mL	Histamine assay	aq. Ex. of TJ stopped infiltration of inflammatory cells and attenuated release of histamine from DNCB induced CD models. It also repressed the expression of Th2-type cytokines and chemokine.	DNCB-induced contact dermatitis in BALB/c mice/ *in-vivo*	[7]
Anti-wrinkle	DW, BuOH, AcOEt, Hex Fr./ Torilin	1-5 ppm	MTT assay	Cell viability for all fractions was 84–102%. Active forms of MMP-1 were decreased, and collagen synthesis was increased in all fractions, especially in the torilin-treated group.	human dermal fibroblast/ *in-vitro*	[90]
Anti-arrhythmic	Torilin	0-10 μM	Gigaohm-seal patch clamp method	Torilin inhibits the kinetics of the hKvl.5 channel in voltage and - time manners, with an IC_{50} = 2.51 + 0.34 μM.	Ltk cells/*in-vitro*	[47]
Anti-obesity	70% EtOH Ex.	100 μg/mL	Oil Red O assay, Western blot analysis	70% EtOH Ex. meaningfully inhibited intracellular triglyceride level and adipocyte differentiation via decreasing protein expression of C/EBPα, PPARγ, and ACC phosphorylation.	3T3-L1 pre-adipocytes cells/*in-vitro*	[91]
Benign prostate hyperplasia	MeOH Ex./ Torilin, (–)-*guaiol*, *guaiazulene and azulene*	(25, 50, 100) μg/mL	Reaction mixture	Torilin presented a strong inhibition (IC_{50} = 31.7 ± 4.23 μM) against 5α-reductase than α-linolenic acid (IC_{50} = 160.3 ± 24.62 μM) lower than finasteride (IC_{50} = 0.38 ± 0.06 μM).	Male Sprague-Dawley rat/*in-vitro*	[44]

ND: not determined, MeOH: methanol, EtOH: ethanol, Hex: hexane, DW: distillate water, Chl: chloroform, BuOH: butanol, AcOEt: ethyl acetate, aq: aqueous, Ex.: extract, Fr.: fraction, TJ: *Torilis japonica*, EO: essential oil, MHV: mouse hepatitis virus, JHM: john howard mueller, PEDV: porcine epidemic diarrhoea virus, VSV: vesicular stomatitis virus, *B. subtilis: Bacillus subtilis*, *S. aureus*: *Staphylococcus aureus*, *E. coli*: *Escherichia coli*, *L. monocytogenes*: *Listeria monocytogenes*, *Sh. Dysenteriae*: *Shigella dysenteriae*, *S. typhimurium*: *Salmonella typhimurium*, *V. parahemolyticus*: *Vibrio parahemolyticus*, *K. pneumoniae: Klebsiella pneumoniae*, *S. enterica: Salmonella enterica*, MSSA: methicillin-sensitive S. aureus, MRSA: methicillin-resistant S. aureus, *P. aeruginosa: Pseudomonas aeruginosa*, *P. vulgaris: Proteus vulgare*, *P. guilliermondii: Pichia guilliermondii*, *C. albicans: Candida albicans*, *T. gondii: Toxoplasma gondii*, *N. caninum: Neospora caninum*, ZI: zone of inhibition, MIC: minimum inhibitory concentration, CAM assay: chorioallantoic membrane assay, Q-CAM assay: quantitative chorioallantoic membrane assay, LPS: lipopolysaccharide, LLC: lewis lung carcinoma cells, MCF-7: human breast cancer cells, SPT: serine palmitoyl transferase, P.O.: oral administration, SC.: subcutaneous, Tf-EE: *Torilidis fructus* ethanol extract, iNOS: inducible nitric oxide synthase, HPLC: high performance liquid chromatograph.

In a study, six isolated compounds from the *T. japonica* fruits were experimented against LLC cells, and human breast cancer cells (MCF-7). Non of compounds exhibited meaningful cytotoxicity against the MCF-7 cells, while 1α-hydroxytorilin, 1β-

hydroxytorilin, and torilin showed effect against the LLC cells with IC_{50} values of 34.0, 32.5, and 31.3 μg/mL, respectively.[17] In another study, these abovementioned compounds displayed moderate cytotoxicity against the selected human cancer cells.[19] Indeed sesquiterpenes enrichment may be responsible for the potencies. Many studies reported anticancer effects of sesquiterpenes,[75,76] however more focused studies are recommended to identify plant's anti-tumor constituents.

4.5. Hyperpigmentation disorders

Melanin is a dark pigment of hair and skin created by melanogenesis in melanocytes.[77] Several factors including tyrosinase, a-melanocyte stimulating hormone (a-MSH), cyclic adenosine monophosphate (cAMP)-elevating agents, ultraviolet (UV), and phytochemicals are involved in the biosynthesis of melanin.[78,79] Abnormal accumulation of melanin causes critical cosmetic problems such as melasma and freckles;[80] therefore, discovering new melanogenesis inhibitors are vital in the cosmetic industry. Yun et al. (2009) stated that torilin might suppress melanin production in a dose-dependent manner in α-melanocyte stimulating hormone (α-MSH)-activated B16 melanoma cells with an IC_{50} value 25 μM, while arbutin, as positive control, inhibited α-MSH-induced melanin production with an IC_{50} value of 170 μM.[48]

To better understand the mechanism underlying treating hyperpigmentation disorders, similar study was accomplished on torilin and other *T. japonica* constituents.[30] In which torilin demonstrated the highest melanin production inhibition with an IC_{50} value 64.6 μM, while the other two guaiane-type, two cardinane-type, and one elemane-type sesquiterpenes exhibited moderate inhibitory activity ($IC_{50} > 300$ μg/mL). The study proposed that the inhibitory effect is related to the functional group on compounds not the sesquiterpene skeleton, and constituents inhibited melanin production through downregulating tyrosinase levels, not by inhibiting tyrosinase activity.

4.6. Skin photoaging

UV radiation is the main factor for a variety of different effects on the skin and causes photoaging in long-term exposure.[78] Noh et al. (2019) experimented the molecular mechanism and effect of the *T. japonica* extract on matrix metalloproteinase (MMP)-1 and MMP-3 expressions in UVB-irradiated primary human dermal fibroblasts (HDFs).[81] They confirmed that the plant extract meaningfully blocked the UVB-induced activation of MAPK (JNK and p38) and transcription factors (AP-1 and NF-κB) leading to the reduction of UVB-induced MMP-3 and MMP-1 protein and mRNA levels.

4.7. Anti-Inflammatory Activity

Although inflammatory responses protect the body from infection initiated by viruses, fungi, and bacteria, severe diseases such as diabetes, and cancer will not be terminated if the infectious condition continues;[82] consequently, it is crucial to suppress prolonged inflammation with anti-inflammatory agents. Park et al. assessed the anti-inflammatory activity of the fruit ethanolic extract of *T. japonica* on the macrophage-mediated inflammatory response.[83] The plant product significantly inhibited the inflammatory response of macrophages, including PGE2 production and lipopolysaccharide (LPS)-induced nitric oxide with IC_{50} values of 62.47 and 35.66 mg/mL, respectively. It further declined the expression of cyclooxygenase (COX) - 2 and inducible NO synthase (iNOS) by 80%.

Lee et al. (2005) evaluated the inhibitory activity of NO production in 82 kinds of herbal extracts by measuring the NO production in LPS-activated RAW 264.7 cells to identify new iNOS inhibitors.[84] The *T. japonica* methanolic extract showed 93% and 28% inhibitory activity against the LPS-activated NO production in macrophages in concentrations of 50, and 10 μg/mL, respectively. It seems that the high activity is caused by glycosylated sesquiterpenes such as torilin derivatives enriched in the methanolic extract, however through bio-assay guided strategy the bioactive constituents can be discovered.

In another study, the fruit methanolic extract demonstrated significant anti-edematous activity in carrageenan-induced paw edema in rats and results compared with piroxicam as positive control. The hexane fraction showed an anti-edematous effect at 77 mg/kg p.o. and inhibitory effects on vascular permeability at 77 mg/kg p.o. in mice. It also revealed inhibitory activity on leucocyte emigration in the rat at 8 mg/pouch and the adjuvant arthritis model in rats at 120 mg/kg p.o..[85] In a study, the *in vivo* anti-inflammatory properties of torilin were investigated in rats and mice with different methods. Torilin inhibited the acetic acid-induced writhing syndrome at doses of 30 and 90 mg/kg and phenylqiunone induced writing syndrome at doses of 30, 90, and 270 mg/kg in mice. Torilin enhanced the pain threshold in the Randall-Selitto method and the tail pressure method. It also demonstrated inhibitory activity on the vascular permeability in mice and a potent anti-carrageenan effect in rats.[27] Endale et al. (2017) performed an *in vitro* study for understanding the molecular mechanism of torilin against inflammation in LPS-stimulated RAW 264.7 macrophages and investigated its effect on expression levels of inflammatory cytokines and mediators. Torilin significantly inhibited LPS-induced NO release, iNOS, NF-α, IL-1β, IL-6, COX-2, PGE_2, and GM-CSF gene and protein expressions. It attenuated AP-1 and NF-kB translocation, reporter gene transcription, and DNA binding that led to regulate inflammatory cytokine and mediator expressions.[26] Findings introduced torilin as a potential anti-inflammatory candidate for further consideration, besides optimization of its bioactivity can be accomplished through semi-synthetization. Many sesquiterpenes demonstrated remarkable anti-inflammatory effects particularly sesquiterpene lactones are the widely investigated derivatives,[86,87] while mode of action has been proposed as they uncoupled the oxidative phosphorylation of human polymorphonuclear neutrophils;[88] subsequently due to rarely investigation of guaiane-type sesquiterpene including, anti-inflammatory effect directed studies can be promising.

4.8. Miscellaneous application of *Torilis japonica*

Allergic dermatitis (AD) is a chronic inflammatory skin disorder characterized by eczematous skin lesions, drying, and frequent itching associated with infiltration of immune cells. The *T. japonica* aqueous extract was subjected to examination on DNCB-induced contact dermatitis (CD) animal models. The results suggested that topical application of the plant has a therapeutic effect on AD by attenuating the release of histamine from DNCB (2,4-dinitrocholrlbenzene)-induced CD models, prohibiting infiltration of inflammatory cells, and inhibiting the expression of Th2-type cytokines and chemokine.[89]

Skin wrinkle formations are related to matrix metalloproteinase-I(MMP-1) activity and collagen synthesis. To determine skin wrinkle-reducing agents in *T. fructus*, MMP-1 activity, collagen biosynthesis, and cell viability were evaluated in human dermal fibroblast with torilin and several fractions of *T. fructus*.[90] The results demonstrated that collagen synthesis was enhanced, active forms of MMP-1 were reduced, and cell viability was exhibited 84–102% in all groups and suggesting that torilin is the main source of anti-wrinkle agents.

In another study, torilin inhibited testosterone 5α-reductase enzyme, indeed this enzyme blocking helps to treat androgen-dependent diseases. Authors suggested that the presence of angeloyl or acetyl group in guaiane skeleton plays a key role in enzyme inhibition.[44] In addition, torilin by blocking hKv1.5 channel current was considered as antiarrhythmic drug for the arrhythmia treatment.[47]

Hypertension is a chronic medical condition of increasing the blood pressure in the arteries, a major risk factor for myocardial infarction, stroke, heart failure, and peripheral arterial disease.[47] The Kv channels are various groups of membrane proteins and play a key role in determining the length of the cardiac action potential, and have become major targets for antiarrhythmic drugs.[47] Kwak et al. (2006) indicated that torilin can inhibit the hKvl.5 current in time and voltage-dependent manners with an IC_{50} value of 2.51 + 0.34 μM at +60 mV, slowing the deactivation kinetics of the hKv1.5 current and accelerating the inactivation kinetics of the hKvl.5 channel. They suggested that torilin might be an open-channel blocker of the hKvl.5 channel, whereas complementary assays should be carried out to affirm this claim.[47]

An experiment assessed the anti-obesity activities of the *T. japonica* hydro-ethanolic (70%) extract on the differentiation of 3T3-L1 pre-adipocytes to adipocytes which was evaluated by western blot analysis and Oil Red O assay. Ethanolic extract at the concentration of 100 μg/mL significantly inhibited adipocyte differentiation and intracellular triglyceride (TG) levels compared with control. This study showed that reducing protein expression of C/EBPα, PPARγ, and ACC phosphorylation might be the mechanism of reduction in TG content.[91]

The fruit methanolic extract of *T. japonica* was investigated for 5α-reductase inhibitory effect and it displayed significant inhibition against 5α-reductase. The active constituents of the extracts (torilin: IC_{50} = 31.7 ± 4.23 μM, (–)-guaiol: IC_{50} = 81.6 ± 10.15 μM, guaizulene: IC_{50} = 100.8 ± 9.26 μM) presented inhibitory activity and compared with α-linolenic acid (IC_{50} = 160.3 ± 24.62 μM) and finasteride (IC_{50} = 0.38 ± 0.06 μM).[44]

5. Conclusions

Plants have always been the natural therapeutic options to cure various human diseases and disorders. The present study has comprehensively described folk medicinal applications, biological, and phytochemical aspects of a precious medicinal plant *Torilis japonica*. In conclusion, the plant is traditionally consumed for the treatment of haemorrhoids, uterine tumors, chronic diarrhea, lymphadenitis, rheumatism, and impotence particularly in Japanese and Chinese folk medicine.

A wide-range of bioactivities reported for the plant extracts may be correlated to torilin, a guaiane-type sesquiterpene, identified as the major constituent of the plant; noteworthy it has indicated significant suppressing effect against melanin production even stronger than arbutin, as positive control, proposing performing further investigations to develop potent natural therapeutic for the treatment of hyperpigmentation disorders.

Moreover, flavonoids can be mentioned as phytoconstituents of the plant, in addition to several sesquiterpenes characterized as volatile secondary metabolites.

In brief, considerable antioxidant and anti-tumor properties of the plant and torilin has been documented. Furthermore, ethanolic extracts of the aerial parts have been reported as natural antimicrobial agents, to be further considered for complementary assays.

Due to the potent biological effect of the plant extracts and isolated compounds assessed in preclinical experiments, further consideration to evaluate their toxicity and efficacy might lead to discover natural-based healing alternatives for the exist synthetic drugs. Bio-assay guided fractionation and isolation approach is proposed to reach the abovementioned aims; however, due to terpenic chemical profile of the plant, there will be a high chance for identifying novel compounds, possibly with new skeletons.

Moreover, semi-synthesizing of torilin, can potentially optimize its bioactivities, whereas *via* further preclinical and clinical experiments possible drug candidates may be introduced.

Author Contributions

Conceptualization, J.M. and Y.R.; methodology, J.M.; investigation, M.D., A.B.D., Y.R., and M.M.S.; writing – original draft preparation, Y.R., M.D.; writing – review and editing, J.M.; visualization, X.X.; supervision, J.M. All authors have read and agreed to the published version of the manuscript.

Conflict of Interests

The authors declare no conflict of interest.

Keywords: bioactivity · ethnomedicine · phytochemistry · torilin · *Torilis japonica*

[1] J. Mottaghipisheh, T. Kiss, B. Tóth, D. Csupor, *Phytochem. Rev.* **2020**, *19*, 1449.
[2] Y. Güzel, E. Aktoklu, V. Roumy, R. Alkhatib, T. Hennebelle, F. Bailleul, S. Şahpaz, *Biochem. Syst. Ecol.* **2011**, *39*, 781.
[3] H.-W. Jung, S.-H. Ghil, *Mol. Med.* **2010**, *3*, 1041.
[4] H. Itokawa, K. Takeya, N. Mori, T. Sonobe, S. Mihashi, T. Hamanaka, *Chem. Pharm. Bull.* **1986**b, *34*, 3762.
[5] G. T. Kim, S. H. Lee, Y. M. Kim, *Int. J. Oncol.* **2014**, *45*, 1673.
[6] G. T. Kim, S. H. Lee, Y. M. Kim, *Int. J. Oncol.* **2016**, *49*, 1088.
[7] K.-Y. Lee, E.-H. Song, C.-H. Hong, *J. Korean Med. Ophthalmol. Otolaryngol. Dermatol.* **2016**, *29*, 61.
[8] K. S. Chung, T. Kimura, P. P.-H. But, J.-X. Guo, 'International Collation Of Traditional And Folk Medicine, Vol 3, Northeast Asia: Part 3', World scientific, 1998.
[9] H. Ji, P. Shengji, L. Chunlin, *Econ. Bot.* **2004**, *58*, S253.
[10] W. T. Lee, *Seoul: Academy publishing Co. Ltd (in Korean)* **1996**.
[11] S. A. Park, M.-S. Choi, S.-Y. Cho, J.-S. Seo, U. J. Jung, M.-J. Kim, M.-K. Sung, Y. B. Park, M.-K. Lee, *Life Sci.* **2006**, *79*, 1207.
[12] J. A. Duke, E. S. Ayensu, 'Med. Plant. China.', Reference publications, **1987**.
[13] J. Chen, X.-j. Xu, Y.-h. Fang, S. Li, Y.-l. Zhang, *J. Essent. Oil-Bear. Plants* **2013**, *16*, 499.
[14] J. Kitajima, N. Suzuki, M. Satoh, M. Watanabe, *Phytochemistry* **2002**, *59*, 811.
[15] M. Lee, K. Ryu, *Bulletin KH Pharm. Sci.* **1978**, *6*, 61.
[16] H.-Y. Hsu, 'Oriental Materia Medica: A Concise Guide, Long Oriental Healing Arts Institute', **1986**.
[17] D. C. Kim, J. A. Kim, B. S. Min, T. S. Jang, M. Na, S. H. Lee, *Helv. Chim. Acta* **2010**, *93*, 692.
[18] K. I. Park, H. Park, A. Nagappan, G. E. Hong, S. Yumnam, H. J. Lee, E. H. Kim, W. S. Lee, S. C. Shin, J. A. Kim, *Oncol. lett.* **2017**, *13*, 2521.
[19] H. W. Park, S.-U. Choi, N.-I. Baek, S.-H. Kim, J. S. Eun, J. H. Yang, D. K. Kim, *Arch. Pharmacal Res.* **2006**, *29*, 131.
[20] K.-K. Sung, T. Poggio, *IEEE Trans. Pattern Anal. Mach. Intell.* **1998**, *20*, 39.
[21] J. Widelski, K. Graikou, C. Ganos, K. Skalicka-Wozniak, I. Chinou, *Processes* **2021**, *9*, 695.
[22] G.-S. Kim, C.-R. Park, J.-E. Kim, H.-K. Kim, B.-S. Kim, *J. Microbiol. Biotechnol.* **2022**, *32*, 220.
[23] W. I. Cho, J. B. Choi, K. Lee, M. S. Chung, Y. R. Pyun, *J. Food Sci.* **2008**, *73*, M37.
[24] H.-S. Seo, K. H. Kim, D.-Y. Kim, B.-K. Park, N.-S. Shin, J.-H. Kim, H. Youn, *J. Vet. Sci.* **2013**, *14*, 241.
[25] H. Youn, J. Lakritz, G. Rottinghaus, H. Seo, D. Kim, M. Cho, A. Marsh, *Vet. Parasitol.* **2004**, *125*, 409.
[26] M. Endale, T.-H. Kim, Y.-S. Kwak, N.-M. Kim, S.-H. Kim, J. Y. Cho, B.-S. Yun, M.-H. Rhee, *Mediators Inflammation* **2017**, *2017*.
[27] S.-I. Cho, S.-S. Kang, K.-R. Kim, T.-H. Kim, E.-B. Lee, *Korean J. Pharmacogn.* **1999**, *30*, 137.
[28] S. S. Kang, E. B. Lee, T. H. Kim, K. R. Kim, J. H. Jung, *Arch. Pharmacal Res.* **1994**, *17*, 284.
[29] I.-K. Lee, J.-H. Lee, E. I. Hwang, B.-S. Yun, *Chem. Pharm. Bull.* **2008**, *56*, 1483.
[30] D. H. Song, Y. H. Jo, J. H. Ahn, S. B. Kim, C.-Y. Yun, Y. Kim, B. Y. Hwang, M. K. Lee, *J. Nat. Med.* **2018**, *72*, 155.
[31] H.-w. Fu, L. Zhang, T. Yi, Y.-l. Feng, J.-k. Tian, *Biochem. Syst. Ecol.* **2010**, *38*, 309.
[32] J.-H. Ry, Y. S. Jeong, *Arch. Pharmacal Res.* **2001**, *24*, 532.
[33] J. Kitajima, N. Suzuki, T. Ishikawa, Y. TANAKA, *Chem. Pharm. Bull.* **1998**, *46*, 1583.
[34] J. Harborne, *Phytochemistry* **1967**, *6*, 1569.
[35] J. Mottaghipisheh, M. Iriti, *Molecules* **2020**, *25*.
[36] J. Mottaghipisheh, H. Stuppner, *Int. J. Mol. Sci.* **2021**, *22*.
[37] J. Mottaghipisheh, H. Taghrir, A. Boveiri Dehsheikh, K. Zomorodian, C. Irajie, M. Mahmoodi Sourestani, A. Iraji, *Pharmaceuticals (Basel)* **2021**, *14*.
[38] S. Fujita, *J. Pharm. Soc. Jpn.* **1990**, *110*, 771.
[39] G. Kharkwala, C. Pandea, G. Tewari, A. Panwarb, V. Pandeb, *J. Indian Chem. Soc.* **2017**, *94*, 191.
[40] E. Piri, M. Mahmoodi Sourestani, E. Khaleghi, J. Mottaghipisheh, Z. P. Zomborszki, J. Hohmann, D. Csupor, *Molecules* **2019**, *24*, 1315.
[41] S. Bagherifar, M. M. Sourestani, M. Zolfaghari, J. Mottaghipisheh, Z. P. Zomborszki, D. Csupor, *Nat. Prod. Commun.* **2019**, *14*, 1934578X1985198.
[42] S. Bagherifar, M. M. Sourestani, M. Zolfaghari, J. Mottaghipisheh, Z. P. Zomborszki, D. Csupor, *Chem. Biodiversity* **2019**, *16*, e1900302.
[43] K. Noge, J. X. Becerra, *Molecules* **2009**, *14*, 5289.
[44] W. S. Park, E. D. Son, G. W. Nam, S. H. Kim, M. S. Noh, B. G. Lee, I. S. Jang, S. E. Kim, J. J. Lee, C. H. Lee, *Planta Med.* **2003**, *69*, 459.
[45] S. E. Kim, Y. H. Kim, Y. C. Kim, J. J. Lee, *Planta Med.* **1998**, *64*, 332.
[46] M. S. Kim, Y. M. Lee, E. J. Moon, S. E. Kim, J. J. Lee, K. W. Kim, *Int. J. Cancer.* **2000**, *87*, 269.
[47] Y. G. Kwak, D. K. Kim, T.-Z. Ma, S.-A. Park, H. Park, Y. H. Jung, D.-J. Yoo, J. S. Eun, *Arch. Pharmacal Res.* **2006**, *29*, 834.
[48] C.-Y. Yun, D. Kim, W.-H. Lee, Y. M. Park, S. H. Lee, M. Na, Y. Jahng, B. Y. Hwang, M. K. Lee, S.-B. Han, *Planta Med.* **2009**, *75*, 1505.
[49] S. Cho, C.-H. Won, D. H. Lee, M.-J. Lee, S. Lee, S.-H. So, S.-K. Lee, B.-S. Koo, N.-M. Kim, J. H. Chung, *J. Med. Food.* **2009**, *12*, 1252.
[50] H. Itokawa, H. Matsumoto, K. Mizuno, K. Watanabe, H. Morita, Y. Iitaka, *Chem. Pharm. Bull.* **1986**a, *34*, 4682.
[51] S. M. Lemon, J. J. Ott, P. Van Damme, D. Shouval, *J. Hepatol.* **2018**, *68*, 167.
[52] D. J. Seo, M. Lee, S. B. Jeon, H. Park, S. Jeong, B.-H. Lee, C. Choi, *Food Control* **2017**, *72*, 9.
[53] W.-I. Cho, J.-B. Choi, K.-P. Lee, S.-C. Cho, E.-J. Park, M.-S. Chung, Y.-R. Pyun, *Food Sci. Biotechnol.* **2007**, *16*, 1072.
[54] W. I. Cho, C. I. Cheigh, M. S. Chung, K. H. Park, P. S. Chang, M. S. Chung, *J. Food Saf.* **2012**, *32*, 474.
[55] S. Hong, O. Kim, *Korean J. Vet. Serv.* **2013**, *36*, 283.
[56] M. Ricardo, C. A. Montanari Luiz, J. Barbosa Antonio, J. Demuner Cleber, S. Silva Larissa, J. A. Carvalho Nelio, *Química Nova* **2011**, *34*.
[57] R. P. Novick, E. Geisinger, *Annu. Rev. Genet.* **2008**, *42*, 541.
[58] J. Gharekhani, M. Yakhchali, F. Keramat, R. Berahmat, *Avicenna. J. Clin. Microb. Infec.* **2021**, *8*, 113.
[59] S. Almería, *Int. Sch. Res. Notices* **2013**, *2013*, 1.
[60] H. Youn, J. Lakritz, D. Kim, G. Rottinghaus, A. Marsh, *Vet. Parasitol.* **2003**, *116*, 7.
[61] H. J. Youn, J. W. Noh, *Vet. Parasitol.* **2001**, *96*, 257.
[62] J. H. Oh, D. R. Kim, S. Y. Park, M. S. Chang, S. K. Park, *Korean J. Herbol.* **2014**, *29*, 111.
[63] Y.-J. Liu, J. Zhan, X.-L. Liu, Y. Wang, J. Ji, Q.-Q. He, *Clin. Nutr.* **2014**, *33*, 59.
[64] M. N. Sarian, Q. U. Ahmed, S. Z. Mat So'ad, A. M. Alhassan, S. Murugesu, V. Perumal, S. N. A. Syed Mohamad, A. Khatib, J. Latip, *BioMed Res. Int.* **2017**, *2017*.
[65] D. Semaan, J. Igoli, L. Young, E. Marrero, A. Gray, E. Rowan, *J. Ethnopharmacol.* **2017**, *203*, 39.
[66] C. Proença, M. Freitas, D. Ribeiro, E. F. Oliveira, J. L. Sousa, S. M. Tomé, M. J. Ramos, A. M. Silva, P. A. Fernandes, E. Fernandes, *J. Enzyme Inhib. Med. Chem.* **2017**, *32*, 1216.
[67] K. Tadera, Y. Minami, K. Takamatsu, T. Matsuoka, *J. Nutr. Sci. Vitaminol.* **2006**, *52*, 149.
[68] G. T. Kim, S.-Y. Kim, Y. M. Kim, *Oncol. Rep.* **2017**, *38*, 1206.
[69] M. Smiljkovic, D. Stanisavljevic, D. Stojkovic, I. Petrovic, J. M. Vicentic, J. Popovic, S. G. Grdadolnik, D. Markovic, S. Sankovic-Babice, J. Glamoclija, *EXCLI J.* **2017**, *16*, 795.
[70] V. Gkretsi, T. Stylianopoulos, *Front. Oncol.* **2018**, *8*, 145.
[71] M. S. Kim, J. H. Baek, M.-T. Park, T.-K. Sohn, S. E. Kim, J. J. Lee, K.-W. Kim, *Oncol. Rep.* **2001**, *8*, 359.
[72] K. Bukowski, M. Kciuk, R. Kontek, *Int. J. Mol. Sci.* **2020**, *21*, 3233.
[73] S.-E. Kim, B.-Y. Hwang, Y.-H. Kim, Y.-C. Kim, K.-S. Lee, J.-J. Lee, *Korean J. Pharmacogn.* **1997**, *28*, 174.
[74] Y. Nakano, H. Matsunaga, T. Saita, M. Mori, M. Katano, H. Okabe, *Biol. Pharm. Bull.* **1998**, *21*, 257.
[75] Y. Ren, J. Yu, A. D. Kinghorn, *Curr. Med. Chem.* **2016**, *23*, 2397.
[76] Y. Dong, X. Qian, J. Li, *Comput. Math. Methods Med.* **2022**, *2022*, 3744837.
[77] F. Solano, S. Briganti, M. Picardo, G. Ghanem, *Pigm. Cell Res.* **2006**, *19*, 550.
[78] Y. Rahimpour, H. Hamishehkar, *Expert Opin. Drug Delivery* **2012**, *9*, 443.
[79] L. Nieuweboer-Krobotova, *J. Eur. Acad. Dermatol. Venereol.* **2013**, *27*, 2.
[80] S. Parvez, M. Kang, H. S. Chung, H. Bae, *Phytother. Res.: An international journal devoted to pharmacological and toxicological evaluation of natural product derivatives* **2007**, *21*, 805.
[81] E. M. Noh, H. K. Song, J. M. Kim, G. S. Lee, K. B. Kwon, Y. R. Lee, *J. Physiol. & Pathol. Korean Med.* **2019**, *33*, 175.
[82] P. Dandona, A. Aljada, A. Bandyopadhyay, *Trends Immunol.* **2004**, *25*, 4.

[83] G. Park, E. Kim, Y.-J. Son, D. H. Yoon, G.-H. Sung, A. Aravinthan, Y. C. Park, J.-H. Kim, J. Y. Cho, *Pharm. Biol.* **2017**, *55*, 2074.
[84] H.-J. Lee, J.-S. Kim, C.-B. Jin, J.-H. Ryu, *Nat. Prod. Sci.* **2005**, *11*, 16.
[85] S.-M. Kim, T.-H. Kim, E.-B. Lee, *Korean J. Pharmacogn.* **1998**, *29*, 384.
[86] X. Liu, L. Bian, X. Duan, X. Zhuang, Y. Sui, L. Yang, *Chem. Biol. Drug Des.* **2021**, *98*, 1131.
[87] L. Moujir, O. Callies, P. M. C. Sousa, F. Sharopov, A. M. L. Seca, *Appl. Sci.* **2020**, *10*.
[88] I. H. Hall, C. O. Starnes, Jr., K. H. Lee, T. G. Waddell, *J. Pharm. Sci.* **1980**, *69*, 537.
[89] M. Jung, T. H. Lee, H. J. Oh, H. Kim, Y. Son, E. H. Lee, J. Kim, *J. Dermatol. Sci.* **2015**, *79*, 252.
[90] B.-S. Koo, E.-I. Hwang, S.-H. So, S.-K. Lee, G.-H. Han, N.-M. Kim, *Korean J. Pharmacogn.* **2007**, *38*, 349.
[91] G. H. Nam, J.-H. Wee, S. Y. Kim, J.-Y. Baek, Y. M. Kim, *J. Life Sci.* **2019**, *29*, 1016.
[92] Y. J. Lee, I. G. Oh, Y. Cho, *Korean J. Nutr.* **2012**, *45*, 211.

Manuscript received: November 11, 2022
Accepted manuscript online: April 19, 2023
Version of record online: May 5, 2023