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Review

The Oleaceae family: A source of secoiridoids with multiple biological activities

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ABSTRACT

In the quest to search and discover bioactive compounds from nature, terpenoids have emerged as one of the most interesting and researched classes of compounds. Secoiridoid, a type of the terpenoid, has also been extensively studied, especially their chemical structures and pharmacological effects. Oleaceae is a family of woody dicotyledonous plants with broad economic and medicinal values. This family contains a large number of flavonoids, monoterpenoids, iridoids, secoiridoids and phenylethyl alcohols, of which the secoiridoids have various biological activities. The purpose of this review is to summarize the phytochemical and pharmacological of the secoiridoids (glycosides, aglycones, derivatives and dimers) in the Oleaceae family from 1987 to 2018. This review will also serve as a reference for further studies.

1. Introduction

Oleaceae is a family of dicotyledonous flowering plants which is widely distributed in the temperate and tropical regions. This family includes 25 genera with approximately 688 species [1]. The species of *Syringa oblata* var. *diatata*, *Jasminum nudiflorum* Lindl., *Osmanthus fragrans* (Thunb.) Lour., *J. sambac* (L.) Ait. and *Forsythia suspensa* are famous ornamental plants. *O. fragrans* (Thunb.) Lour. and *J. sambac* (L.) Ait. also serve as sources of aromatic oil or food. *Fraxinus mandshurica* Rupr. is an excellent wood, which can be made into furniture. The samara of *F. suspensa* and the fruits of *Ligustrum purpurascens* Y. C. Yang are available for medicinal purposes [2].

Phytochemical investigations have revealed that the main chemical constituents from this family are flavonoids, monoterpenoids, iridoids, secoiridoids and phenylethanoid glycosides. Seoiridoids are a group of compounds in the cyclopentane monoterpene derivatives formed by the cleavage of the cyclomethene oxime compounds at C-7 and C-8. Secoiridoids have shown a variety of pharmacological effects including anti-diabetic, anti-inflammatory, immunosuppressive, neuroprotective, anti-cancer and anti-obesity.

Several reviews on naturally occurring iridoids and secoiridoids have been published with the most recent one compiling secoiridoids, their physical constants, spectral data and their bioactivity between 1980 and 2010 [3–10]. However, this review aims to provide a systematic classification of the secoiridoids from the Oleaceae family and compile their pharmacological effects in order to provide reference for futher studies.

2. Traditional uses

Oleaceae family has significant economic, horticultural and medicinal importance. For example, many species in the genus *Syringa* are grown for beautification purposes and their flowers are extracted for essence [2]. In the Liubań district of Belarus, the buds of *S. vulgaris* L. are processed as medicinal wine for the treatment of joint pain and dried flowers are used as recreational tea [11]. The seeds of the *F. excelsior* L. are used to treat diabetes because of their hypoglycemic effect [12]. In the Peninsula Sorrentina (Southern Italy), the bark of *F. ornus* L. is used for treating diarrhea and lowering cholesterol [13]. The leaves of *Olea europaea* L. are used in Greece for lowering blood pressure [14]. The olive oil from *O. europaea* has shown anti-cancer and anti-oxidation effects [15]. In the Peninsula Sorrentina (Southern Italy), essential oil extracted from *O. europaea* L. is used to treat rheumatism and promote blood circulation [13]. In the northern and central Oman (Arabia),

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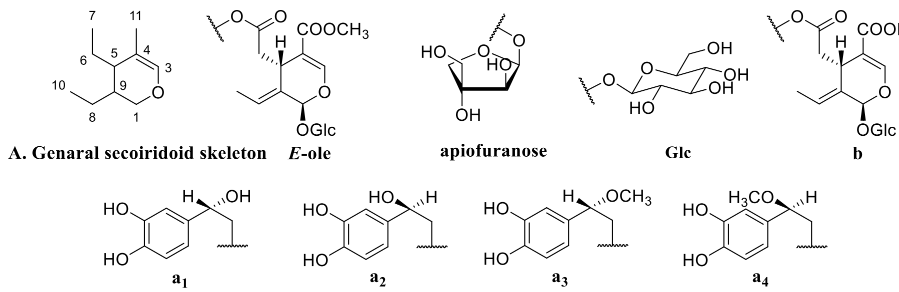

Fig. 1. Substituents and general structure of secoiridoid skeleton showing the numbering system.

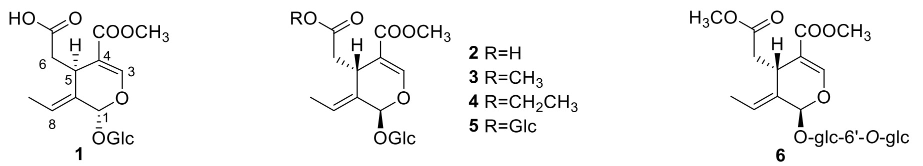

Fig. 2. Structures of simple secoiridoids isolated from plants of Oleaceae family.

essential oil extracted from the fruit of *O. europaea* L. is used as a laxative [16]. The leaves of *L. purpurascens* Y. C. Yang have been used as "Kuding Tea", a kind of health drink [17]. The dry and mature fruit of *L. lucidum* Ait. has the effects of nourishing liver and kidney, and improving the appearance of liver and kidney (a therapeutic method to treat kidney-liver Yin deficiency pattern/syndrome). It is often used to treat liver and kidney Yin deficiency (a chronic deficient state where the liver and the kidney are unable to function normally), dizziness, tinnitus, weak waist and knees, premature greying of the hair, promote clear vision, internal heat and thirst (accumulation of heat within tissues resulting in loss of body fluids and thirst sensation), 'bone steaming hot flashes' (tidal fever in which heat is felt to emanate from the bones). The dry branches of *Fraxinus rhynchophylla* Hance have the functions of clearing away heat and dampness (a therapeutic method for relieving accumulation of dampness-heat), expelling phlegm and clearing the eye. They are often used to treat damp heat and diarrhea, conjunctivitis and phlegm [18].

3. Classification

Secoiridoids are a class of compounds in the cyclopentane monoterpene derivatives, which are formed by cleavage of the cyclomethene oxime compounds at C-7 and C-8 (monoterpenoids based on the 7,8-secocyclopenta[c]-pyranoid skeleton). Their basic structural nucleus

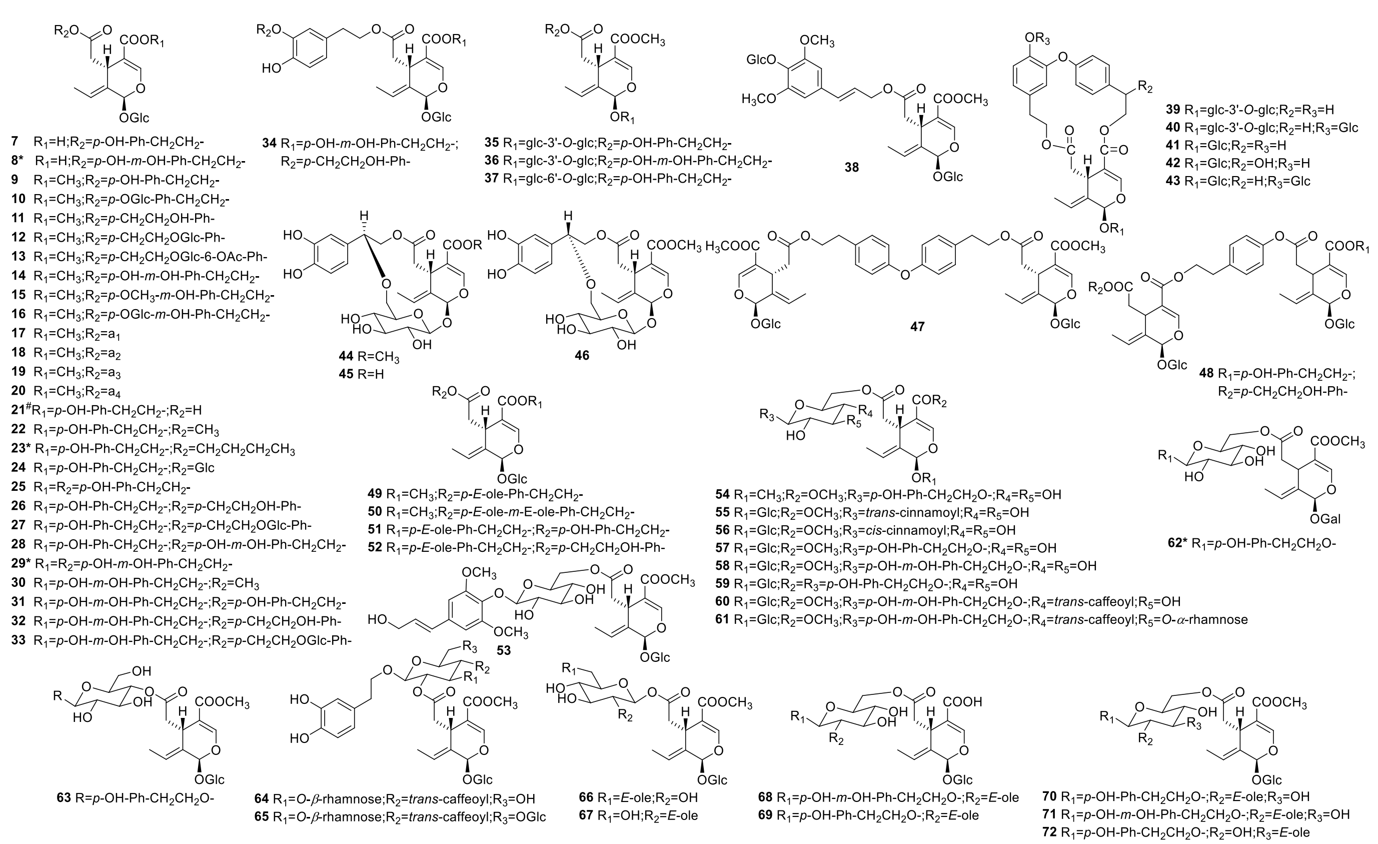

Fig. 3. Structures of conjugated secoiridoids isolated from plants of Oleaceae family

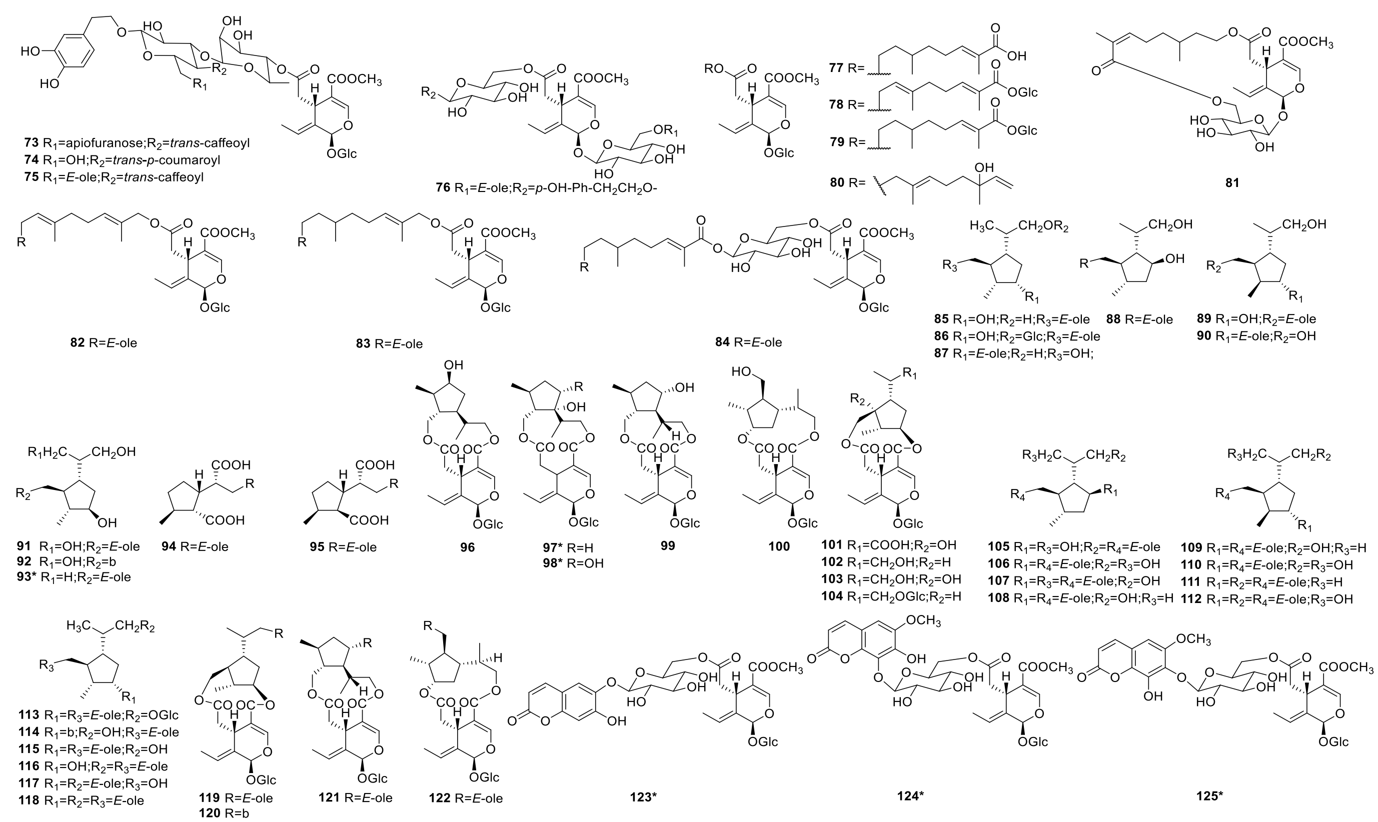

Fig. 3. (*continued*)

and substituents are shown in Fig. 1. A total of 232 secoiridoids (glycosides, aglycones, derivatives and dimers) isolated from 9 genus of the family Oleaceae. These genera include *Fontanesia*, *Fraxinus*, *Jasminum*, *Ligustrum*, *Olea*, *Osmanthus*, *Phillyrea*, *Picconia* and *Syringa*. These secoiridoids were classified into 5 groups namely, simple secoiridoids, conjugated secoiridoids, 10-oxyderivative of oleoside secoiridoids, *Z*-secoiridoids, secologanosides [3,5] and oxidized secologanoside secoiridoids based on the number of carbons contained in their seco-iridane skeleton and their degree of oxidation. The structures of the compounds are summarized in Figs. 2–6. Compound names, species, molecular formula, source and references are summarized in Tables 1–5.

4. Chemical constituents

4.1. Simple secoiridoids

Generally, for the simple secoiridoids (1–6) (Table 1, Fig. 2), positions C-7 and C-11 have either a free carboxylic acid group or a methyl ethyl ester derivative of the acid. In addition, the configurations of positions C-1 and C-5 are *S*. However, the configurations of the positions C-1 and C-5 of jaspolyside (**1**) are *R* [19].

4.2. Conjugated secoiridoids

This group of compounds constitute the majority of secoiridoids isolated from the Oleaceae family. The name of the class stems from the type of compound that is linked or conjugated to the secoiridoid nucleus. Based on this, the class is further into seven groups (Table 2, Fig. 3) including aromatic-conjugated (**7–52**), sugar-conjugated (**53–76**), terpene-conjugated (**77–84**), cyclopentane-conjugated (**85–122**), coumarin-conjugated (**123–125**), lignans-conjugated (**126–129**) and others (**130–143**) secoiridoids. Most of the conjugations occur at C-7. The C-7 position is usually oxidized to a carboxylic acid and esterified with different groups. The double bond between the C-8 and C-9 positions and the hydrogen at the C-8 position is replaced by a methyl group. Also, most of the aromatic-conjugated secoiridoids are also oxidized to carboxylic acids at the C-11 which may either be free or esterified with either 1,2-dihydroxyphenylethanol or *p*-hydroxyphenylethanol.

4.3. 10-Oxyderivative of oleoside secoiridoids

This class possesses the oleoside nucleus with distinct structural differences. The C-8 and C-9 positions exist as double bonds and the hydrogen at the C-8 position is replaced by a hydroxy group or an ester is formed by an oxygen atom with different groups. These groups typically include an acetyl and phenolic moieties. A total of 40 10-oxyderivative of oleoside secoiridoids (**144–183**) (Table 3, Fig. 4) have been isolated from Oleaceae family, including 34 monomeric (**144–177**) and 6 dimeric (**178–183**) secoiridoid glucosides.

4.4. Z-Secoiridoids

Only five compounds isolated from the Oleaceae family have a double bond geometry at the C-8 in *Z*-configuration (**184–188**) (Table 4, Fig. 5).

4.5. Secologanosides and oxidized secologanoside secoiridoids

Majority of compounds in this class are based on the secologanoside nucleus (**190**). The unique structural features of this class are: the

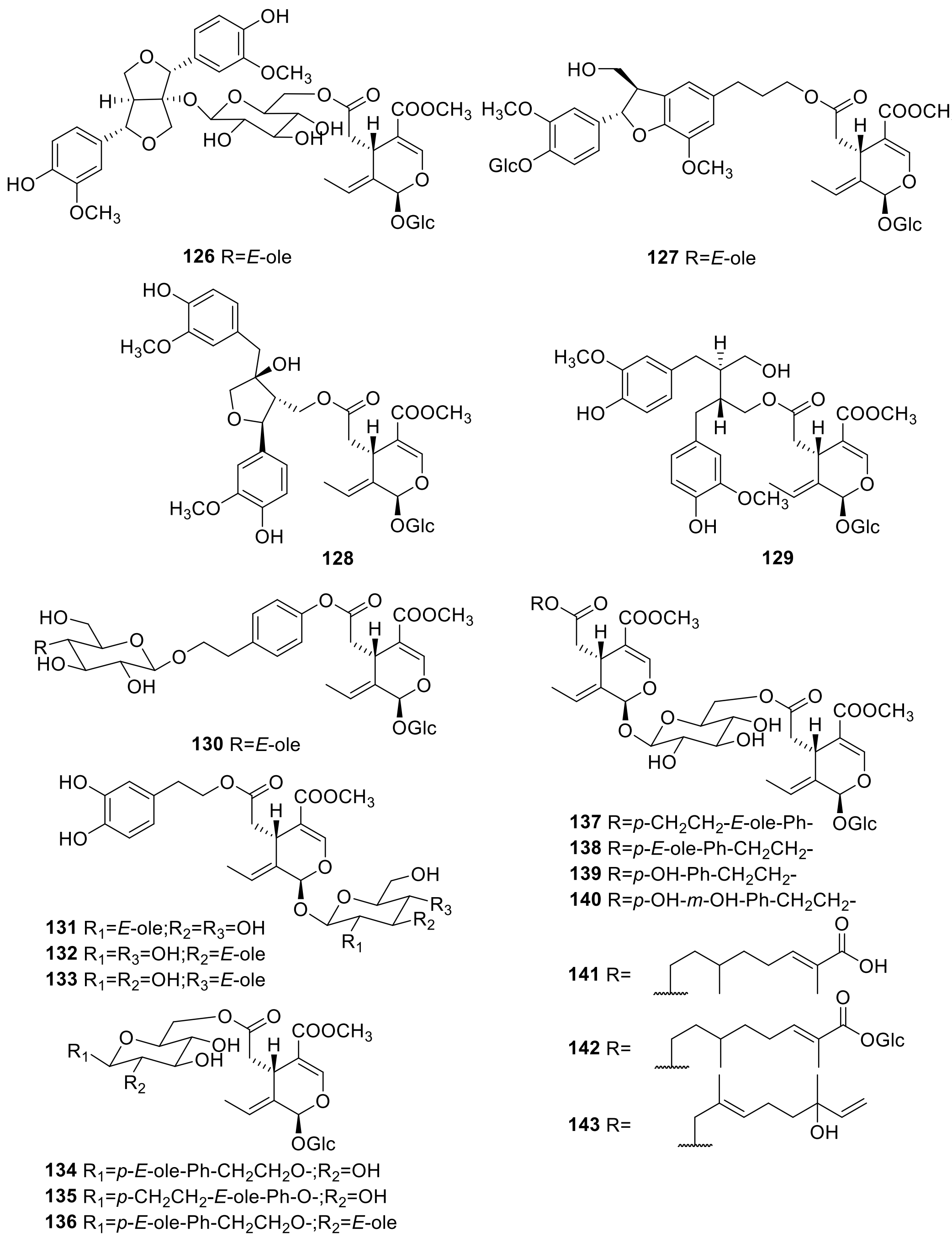

Fig. 3. (*continued*)

position of the carbon-carbon double bond is between C-8 and C-10 in most compounds and the level oxidation of C-10.

Forty-four secologanosides and oxidized secologanoside glycosides (Table 5, Fig. 6) have been isolated from the Oleaceae family, including secologanosides (**189–208**) and non-glycosidic secologanosides (**209–219**). From **220** to **232**, the C-10 position is either an aldehyde or a carboxylic acid.

5. Pharmacological effects

5.1. Anti-diabetic effects

Protein tyrosine phosphatase 1B (PTP1B) is a member of the non-transmembrane phosphotyrosine phosphatase family. It is a negative regulator of the leptin and insulin signaling pathways. Recently, PTP1B has been proposed to be a novel target of anti-cancer and anti-diabetic

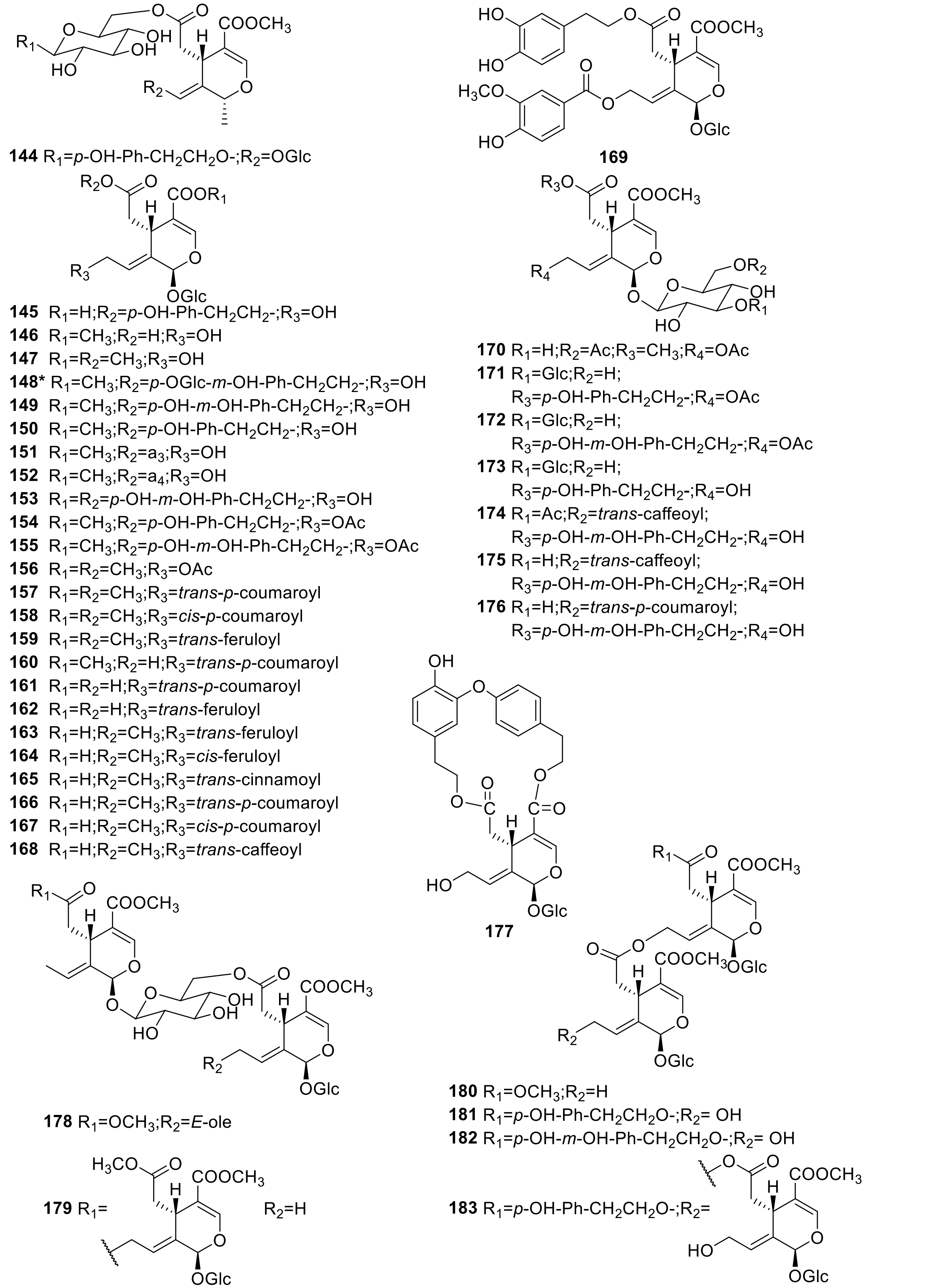

Fig. 4. Structures of 10-oxyderivative of oleoside type secoiridoids isolated from plants of Oleaceae family.

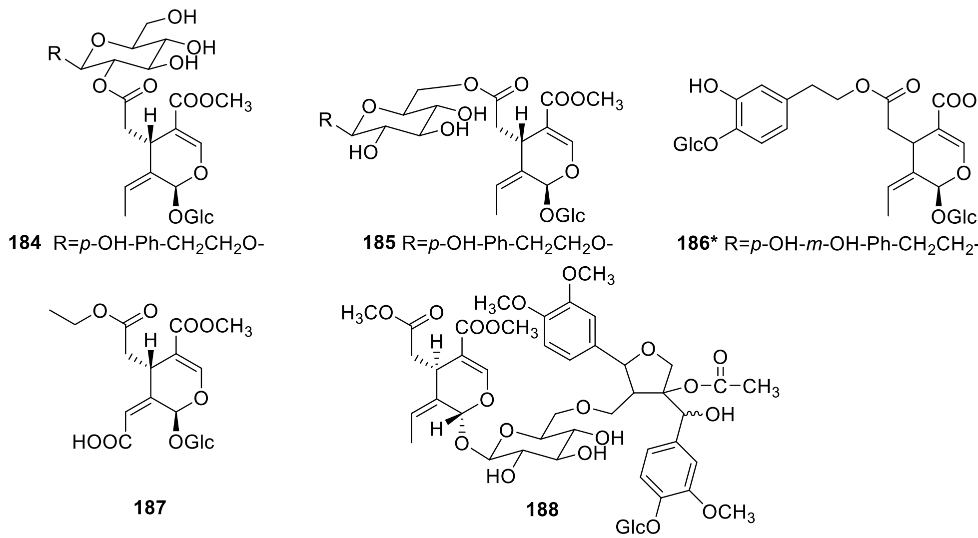

Fig. 5. Structures of *Z*-secoiridoids isolated from plants of Oleaceae family.

drugs. Currently, validation of PTP1B as a therapeutic target for obesity and diabetes prompted efforts to develop potent and selective inhibitors of PTP1B [105]. The investigations of Xiao et al. [50] has revealed that hydroxyframoside A (**28**) and fraxisecoside (**124**) exhibited moderate PTP1B inhibition activity with IC_{50} of 50 and 21 μM respectively.

5.2. Anti-inflammatory effects

PTP1B has also been identified as an important positive regulator of neuroinflammation and is a promising therapeutic target for neuroinflammatory and neurodegenerative diseases [106]. Xiao et al. [50] has reported that hydroxyframoside A (**28**) and fraxisecoside (**124**) showed moderate PTP1B inhibition activity with IC_{50} of 50 and 21 μM respectively. It is therefore necessary to further explore its potential in neuroinflammatory and neurodegenerative diseases.

The studies of Dudek et al. [29] also demonstrated that oleoechinacoside (**65**), demethylhydroxyoleonuezhenide (**68**), demethyloleonuezhenide (**69**) and syringaoleoacteoside (**75**) moderately suppressed the Lipopolysaccharide (LPS)-stimulated release of proinflammatory chemokine Interleukin −8 (IL-8) and Tumor necrosis factor α (TNF-α) from human neutrophils.

5.3. Immunosuppressive effects

Autoimmunity is an irregular immune response, in which antibodies attack the host tissues they are supposed to protect [107]. T cells play an important role in autoimmune responses because they can act as a regulator and an effector of immune function. Also, T cells have been demonstrated to be activated and dysfunctional in patients with autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus [108]. IL-2 is a potent T cell growth factor and is produced primarily by activated T cells. Therefore, regulation of T cell activation is a potential strategy for treatment of autoimmune diseases as well as transplant rejection [109].

B Cells are also known to play significant roles including secretion of autoantibodies, autoantigen presentation and ensuing reciprocal interactions with T cells, secretion of inflammatory cytokines, and the generation of ectopic germinal centers in autoimmune diseases. It has been reported to be involved in diseases like systemic lupus erythematosus, rheumatoid arthritis, and type 1 diabetes [110] and currently novel therapies aimed at the selective targeting of pathogenic B cells are being investigated. Hydroxyframoside A (**28**) and fraxisecoside (**124**) have been reported to inhibit B and T cell proliferation, without cytotoxicity in an MTT assay [50]. They are therefore worth investigating further for their immunosuppressive potentials [50].

5.4. Neuroprotective effects

Nerve growth factor (NGF) facilitates the growth, development, and survival of neurons, and has been suggested to play an important role in neurodegenerative diseases. NGF also helps the differentiation of sensory and sympathetic neurons in the central and peripheral nervous systems. Thus, NGF signaling serves neuroprotective and repair functions [111]. Higher NGF production ensures the protection of axons and myelin sheathes against inflammation via modulation of the immune system and reduction of endotoxin- or inflammation-induced toxicity in the brain. Low levels of NGF results in neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, and diabetic polyneuropathy [112,113]. Thus, regulation of NGF secretion or treatment with NGF mimetics is one method for the prevention and management of neurodegenerative disorders. The immune modulatory and strong neuroprotective efficacy of NGF has resulted in it becoming a potential target for the screening of phytochemicals for neurodegenerative diseases. Several secoiridoids have been reported to upregulate NGF without causing significant cell toxicity. The work of Park et al. [39] revealed that 50 μM each of oleuropein (**14**), hydroxyframoside A (**28**), fraxamoside (**46**) and jaspolyoside (**140**) exhibited potent stimulation of NGF release in a C6 rat glioma cell line, with stimulation levels of 201.58 ± 4.41, 205.64 ± 4.84, 207.48 ± 15.41 and 171.64 ± 1.61%, respectively. They found that these compounds had a better NGF regulation effect than 6-shogaol (positive control) which had a stimulation level of 168.58 ± 7.16%. However, (2″*R*)-2″-methoxyoleuropein (**20**), jaspolyoside (**140**) and (8*Z*)-nuezhenide A (**184**) exhibited moderate activities [39].

The human neuroblastoma SH-SY5Y cell is widely used as a model for Parkinson's disease (PD) since it possesses many characteristics of dopaminergic neurons such as dopamine transporters. It also has the machinery to synthesize dopamine the main neurotransmitter implicated in PD [114]. 6-Hydroxydopamine is a selective neurotoxin that causes the death of dopaminergic neuronal cells in vivo and in vitro

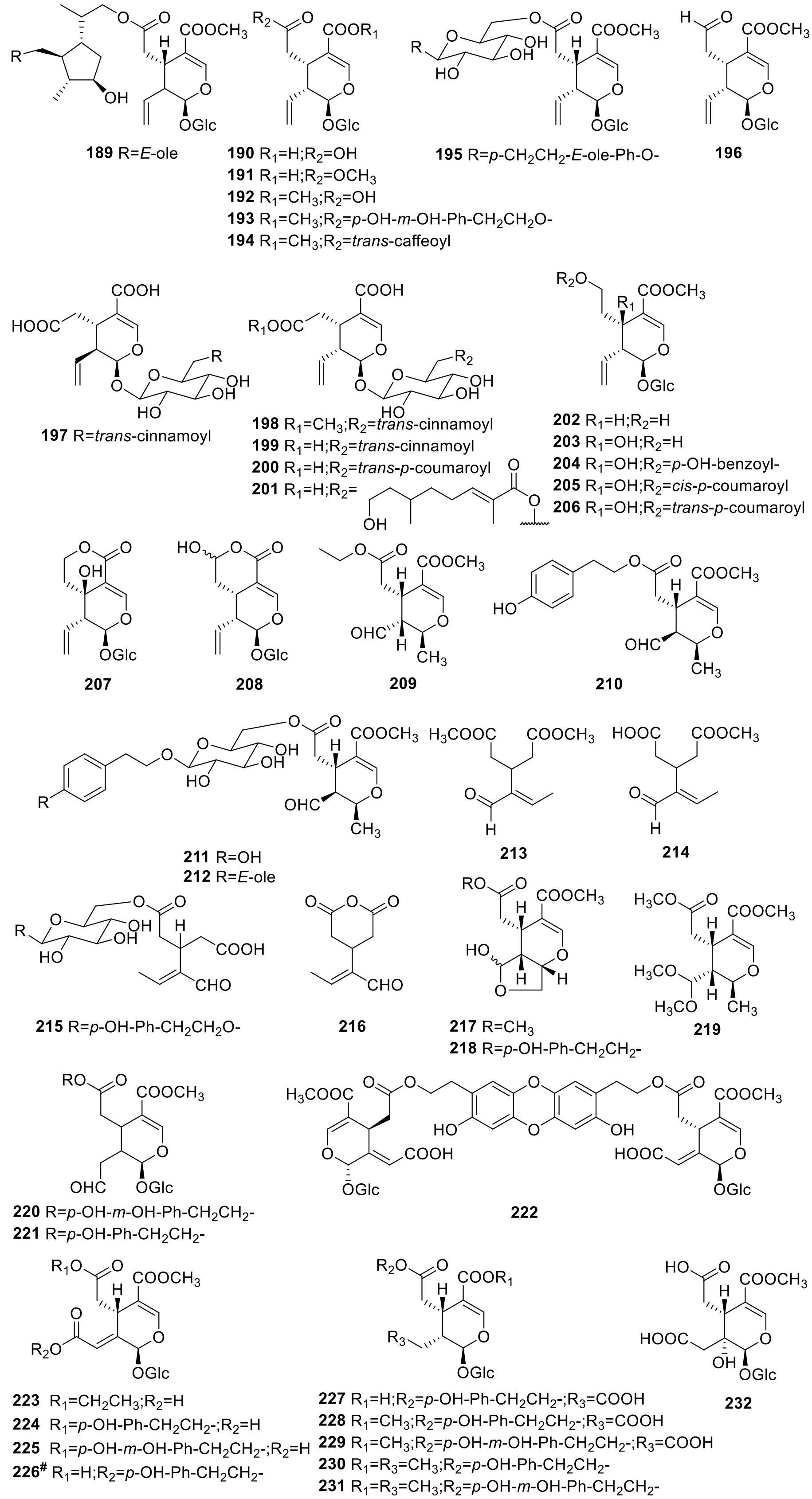

Fig. 6. Structures of secologanosides and oxidized secologanoside secoiridoids isolated from plants of Oleaceae family.

Table 1
Simple secoiridoids isolated from plants of Oleaceae family.

NO.	Compound	Molecular formula	CAS number	Source	Plant species	References
1	Jaspolyside	$C_{17}H_{24}O_{11}$	180063-39-2	Leaves	*J. polyanthum* Franch.	[19]
2	Oleoside 11-methyl ester	$C_{17}H_{24}O_{11}$	60539-23-3	Leaves	*F. americana* L.	[20]
				Seeds	*F. excelsior* L.	[12]
				Leaves	*J. nudiflorum* Lindl.	[21]
				Leaves	*J. polyanthum* Franch.	[19]
				Leaves		[22]
				Leaves	*J. sambac* (L.) Ait.	[23]
				Barks	*J. tortuosum* Willd.	[24]
				Fruits	*L. lucidum* Ait.	[25]
				Twigs	*L. obtusifolium*	[26]
				Leaves	*P. azorica*	[27]
				Flowers and leaves	*S. pubescens* Turcz	[28]
				Flowers	*S. vulgaris* L.	[29]
3	7,11-Oleoside dimethyl ester (Oleoside dimethyl ester)	$C_{18}H_{26}O_{11}$	30164-95-5	Leaves	*F. americana* L.	[20]
				Seeds	*F. excelsior* L.	[12]
				Leaves		[30]
				Leaves	*F. pallisiae*	[31]
				Seeds	*F. rhynchophylla* Hance	[32]
				Leaves	*J. polyanthum* Franch.	[19]
				Leaves		[22]
				Barks	*J. tortuosum* Willd.	[24]
				Fruits	*L. japonicum* Thunb.	[33]
				Fruits	*L. lucidum* Ait.	[34]
				Fruits		[35]
				Twigs	*L. obtusifolium*	[26]
				Barks	*O. asiaticus* Nakai	[36]
				Leaves	*O. europaea*	[37]
				Leaves	*S. afghanica* C. K. Schneid.	[38]
				Twigs	*S. oblata* var. *dilatata*	[39]
4	Oleoside-7-ethyl 11-methyl ester	$C_{19}H_{28}O_{11}$	1215179-36-4	Fruits	*L. lucidum* Ait.	[25]
5	Methylglucooleoside (7-*β*-D-glucopyranosyl 11-methyl oleoside)	$C_{23}H_{34}O_{16}$	115623-36-4	Leaves	*F. excelsior*	[30]
				Leaves	*J. polyanthum* Franch.	[19]
				Leaves		[22]
				Berries	*L. japonicum* Thunb.	[40]
6	Excelside A	$C_{24}H_{36}O_{16}$	1149762-75-3	Seeds	*F. excelsior* L.	[12]

[115]. Several secoiridoids including (8*E*)-nuezhenide (**57**), oleonuezhenide (**70**), (8*Z*)-nuezhenide A (**184**), (8*Z*)-nuezhenide (**185**) have demonstrated significant protection of SH-SY5Y cells from 6-hydroxydopamine induced neurotoxicity with percentage relative protection ranging from 23.6 ± 4.9 to 26.7 ± 3.1 and 40.3 ± 4.0 to 49.2 ± 4.3 at 1.0 μM and 10.0 μM respectively [71].

5.5. Anti-cancer effects

Oleuropein (**14**) has been reported to modulate several oncogenic signaling pathways. Both *in vivo* and *in vitro* studies have demonstrated its anti-cancer potentials.

Hypoxia-inducible factor 1α (HIF1α) transcriptionally represses miR-519d in the nucleus. MiR-519d is involved in negative regulation of damage-regulated protein 1 in cancer cells. However, treatment of cancer cells with oleuropein (**14**) inhibits HIF1α-mediated transcriptional repression of miR-519d and consequently miR-519d quantitatively inhibits p53 and DNA PDRG1 [116]. p53 and DNA damage-regulated gene 1 (PDRG1), an oncogene frequently overexpressed in different cancers, can be regulated by miRNA. MiR-519d has been reported to post-transcriptionally modulate 3′- untranslated regions (UTR) of PDRG1 mRNA in nasopharyngeal carcinoma cells. Mutated 3'-UTR of PDRG1 transfected into miR-519d expressing cells revealed that mutant PDRG1 was not inhibited by miR-519d as evidenced by higher luciferase activity of mutated PDRG1 3'-UTR reporter. HIF1α is involved in transcriptional downregulation of miR-519d by binding to hypoxia response elements (HRE) present in promoter region of miR-519d. Oleuropein (**14**) inhibits the binding of HIF1α to miR-519d promoter and consequently the expression if this microRNA is enhanced. It has been described that microRNA-519d inhibits the expression of PDRG1 [116].

TPC-1 and BCPAP cells are validated models of human papillary thyroid cancer (PTC), in that they host the RET/PTC1 rearrangement and BRAF V600E mutation respectively [117,118] the most common genetic alterations detected in human PTC [119]. Their tumorigenic action is related to activation of intracellular signaling pathways controlling cell growth and survival. The work of Bulotta et al. [120] revealed that 10–100 μM of oleuropein (14) demonstrated a concentration dependent inhibition of TPC-1 and BCPAP cells proliferation acting on growth-promoting signal pathways. It also showed a dose-dependent reduction in endogenously generated reactive oxygen species (ROS) level in BCPAP and TPC-1 [120].

Also, an increased level of phosphorylated c-Jun NH_2-terminal kinase (JNK) has been reported to positively regulate apoptosis in HeLa cells. Oleuropein (**14**) treatment increased apoptosis in HeLa cells through a mitochondrial apoptotic cascade derived from JNK activation [121]. Oleuropein (**14**) is also reported to increase the levels of B cell lymphoma 2-associated X protein (BAX) and cytochrome *c* in HeLa cells. Phosphorylated JNK was found to be necessary to induce apoptosis in HeLa cells. Oleuropein (**14**) treatment induced an upregulation of p-JNK in HeLa cells. Accordingly, inhibition of JNK abrogated oleuropein-mediated apoptotic cell death in HeLa cells [121]. Expression levels of BAX and p53 (positive regulator of apoptosis) were increased in oleuropein-treated MCF-7 cells. Furthermore, Bcl2 (anti-

Table 2
Conjugated secoiridoids isolated from plants of Oleaceae family.

NO.	Compound	Molecular formula	CAS number	Source	Plant species	References
7	Demethylligstroside	$C_{24}H_{30}O_{12}$	326491-76-3	Leaves	*F. americana* L.	[20]
8*	Demethyloleuropein	$C_{24}H_{30}O_{13}$	52077-55-1	Fruits	*O. europaea* L.	[41]
				Flowers	*S. vulgaris* L.	[29]
9	Ligstroside (Ligustroside)	$C_{25}H_{32}O_{12}$	35897-92-8	Leaves	*F. americana* L.	[20]
				Leaves	*F. angustifolia* Vahl	[42]
				Seeds	*F. excelsior* L.	[12]
				Leaves	*F. excelsior*	[30]
				Leaves	*F. excelsior* L.	[43]
				Leaves	*F. formosana* Hay.	[44]
				Leaves	*F. insularis* Hemsl.	[45]
				Barks	*F. ornus*	[46]
				Leaves	*F. oxycarba* Willd.	[47]
				Leaves	*F. pallisiae*	[31]
				Seeds	*F. rhynchophylla* Hance	[32]
				Barks		[48]
				Leaves		[49]
				Barks	*F. rhynchophylla*	[50]
				Leaves	*F. uhdei* (Wenzig) Lingelsh.	[51]
				Leaves	*J. polyanthum* Franch.	[19]
				Leaves		[22]
				Flowers		[52]
				Berries	*L. japonicum* Thunb.	[40]
				Fruits		[33]
				Fruits	*L. lucidum* Ait.	[35]
				Twigs	*L. obtusifolium*	[26]
				Leaves and twigs	*L. vulgare* L.	[53]
				Barks	*O. asiaticus* Nakai	[36]
				Leaves	*O. europaea*	[54]
				Leaves	*P. azorica*	[27]
				Leaves	*P. latifolia* L.	[55]
				Leaves	*S. afghanica* C. K. Schneid.	[38]
				Twigs	*S. oblata* var. *dilatata*	[39]
				Flowers and leaves	*S. pubescens* Turcz	[28]
				Barks	*S. reticulata*	[56]
				Flowers	*S. vulgaris* L.	[29]
10	Angustifolioside B	$C_{31}H_{42}O_{17}$	152343-46-9	Leaves	*F. angustifolia* Vahl	[42]
				Leaves	*J. polyanthum* Franch.	[19]
				Leaves		[22]
				Flowers		[57]
11	Formoside (Excelsioside)	$C_{25}H_{32}O_{12}$	148139-95-1	Leaves	*F. excelsior*	[30]
				Leaves	*F. excelsior* L.	[43]
				Leaves	*F. formosana* Hay.	[58]
				Leaves	*S. afghanica* C. K. Schneid.	[38]
12	1‴′-*O*-*β*-*D*-Glucosylformoside (Nicotiflorine)	$C_{31}H_{42}O_{17}$	148245-77-6	Seeds	*F. excelsior* L.	[12]
				Leaves	*F. formosana* Hay.	[58]
				Fruits	*L. lucidum* Ait.	[34]
				Fruits		[25]
				Leaves	*S. afghanica* C. K. Schneid.	[38]
13	6‴′-Acetylnicotiflorine	$C_{33}H_{44}O_{18}$	1215179-35-3	Fruits	*L. lucidum* Ait.	[25]
14	Oleuropein	$C_{25}H_{32}O_{13}$	32619-42-4	Leaves	*F. americana* L.	[20]
				Leaves	*F. angustifolia* Vahl	[42]
				Leaves	*F. excelsior*	[30]
				Leaves	*F. excelsior* L.	[43]
				Barks	*F. ornus*	[46]
				Leaves	*F. oxycarba* Willd.	[47]
				Leaves	*F. pallisiae*	[31]
				Barks	*F. rhynchophylla* Hance	[48]
				Leaves		[49]
				Leaves	*J. polyanthum* Franch.	[19]
				Leaves		[22]
				Flowers		[52]
				Fruits	*L. lucidum* Ait.	[35]
				Fruits		[59]
				Twigs	*L. obtusifolium*	[26]
				Barks	*O. asiaticus* Nakai	[36]
				Leaves	*O. europaea*	[37]
				Leaves		[54]
				Leaves	*P. azorica*	[27]
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				Leaves	*S. afghanica* C. K. Schneid.	[38]
				Twigs	*S. oblata* var. *dilatata*	[39]
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				Flowers	*S. vulgaris* L.	[29]

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Table 2 (*continued*)

NO.	Compound	Molecular formula	CAS number	Source	Plant species	References
15	Oleuropein-4″-methyl ether	$C_{26}H_{34}O_{13}$	1016636-78-4	Leaves	*F. rhynchophylla* Hance	[49]
16	Angustifolioside A	$C_{31}H_{42}O_{18}$	152343-45-8	Leaves	*F. angustifolia* Vahl	[42]
	(6″-*O*-*β*-D-Glucopyranosyloleuropein)			Flowers	*J. polyanthum* Franch.	[57]
17	(2″*S*)-2″-Hydroxyoleuropein	$C_{25}H_{32}O_{14}$	326491-78-5	Leaves	*F. americana* L.	[20]
18	(2″*R*)-2″-Hydroxyoleuropein	$C_{25}H_{32}O_{14}$	326491-77-4	Leaves	*F. americana* L.	[20]
19	(2″*S*)-2″-Methoxyoleuropein	$C_{26}H_{34}O_{14}$	256498-10-9	Leaves	*F. americana* L.	[20]
20	(2″*R*)-2″-Methoxyoleuropein	$C_{26}H_{34}O_{14}$	256498-11-0	Leaves	*F. americana* L.	[20]
				Twigs	*L. obtusifolium*	[26]
				Twigs	*S. oblata* var. *dilatata*	[39]
21#	Isoligustrosidic acid	$C_{24}H_{30}O_{12}$	1407544-14-2	Leaves	*F. formosana* Hay.	[58]
				Leaves	*F. malacophylla* Hemsl.	[60]
22	Isoligustroside	$C_{25}H_{32}O_{12}$	108789-18-0	Leaves	*F. formosana* Hay.	[44]
				Leaves	*F. malacophylla* Hemsl.	[60]
				Leaves	*S. afghanica* C. K. Schneid.	[38]
23*	Butylisoligustrosidate	$C_{28}H_{38}O_{12}$	155014-04-3	Leaves	*F. malacophylla* Hemsl.	[60]
24	Safghanoside C	$C_{30}H_{40}O_{17}$	482648-17-9	Leaves	*S. afghanica* C. K. Schneid.	[38]
25	Framoside	$C_{32}H_{38}O_{13}$	148225-35-8	Leaves	*F. formosana* Hay.	[58]
				Barks	*F. ornus*	[46]
26	Fraxiformoside	$C_{32}H_{38}O_{13}$	142998-21-8	Leaves	*F. formosana* Hay.	[44]
				Leaves	*F. malacophylla* Hemsl.	[60]
				Leaves	*S. afghanica* C. K. Schneid.	[38]
27	1‴-*O*-*β*-D-Glucosylfraxiformoside	$C_{38}H_{48}O_{18}$	148245-78-7	Leaves	*F. formosana* Hay.	[58]
				Leaves	*F. malacophylla* Hemsl.	[60]
				Leaves	*S. afghanica* C. K. Schneid.	[38]
28	Hydroxyframoside A	$C_{32}H_{38}O_{14}$	219781-74-5	Barks	*F. ornus*	[46]
				Barks	*F. rhynchophylla*	[50]
				Twigs	*S. oblata* var. *dilatata*	[39]
29*	Jasmultiside	$C_{32}H_{38}O_{15}$	108789-16-8	Barks	*F. rhynchophylla*	[50]
30	Isooleuropein	$C_{25}H_{32}O_{13}$	108789-17-9	Leaves	*S. afghanica* C. K. Schneid.	[38]
				Leaves	*S. vulgaris* Linn.	[61]
31	Hydroxyframoside B	$C_{32}H_{38}O_{14}$	219781-75-6	Barks	*F. ornus*	[46]
32	Safghanoside D	$C_{32}H_{38}O_{14}$	482648-19-1	Leaves	*S. afghanica* C. K. Schneid.	[38]
33	Safghanoside E	$C_{38}H_{48}O_{19}$	482648-20-4	Leaves	*S. afghanica* C. K. Schneid.	[38]
34	Insuloside	$C_{40}H_{46}O_{16}$	219786-99-9	Leaves	*F. insularis* Hemsl.	[45]
35	3'-*O*-*β*-D-Glucopyranosyl ligustroside	$C_{31}H_{42}O_{17}$	1115023-44-3	Leaves	*O. ilicifolius*	[62]
36	3'-*O*-*β*-D-Glucopyranosyl oleuropein	$C_{31}H_{42}O_{18}$	1115023-46-5	Leaves	*O. ilicifolius*	[62]
37	Excelside B	$C_{31}H_{42}O_{17}$	1,149762-83-3	Seeds	*F. excelsior* L.	[12]
				Fruits	*L. lucidum* Ait.	[59]
38	Dilatioside B	$C_{34}H_{46}O_{19}$		Twigs	*S. oblata* var. *dilatata*	[39]
39	Insularoside-3'-*O*-*β*-D-glucoside	$C_{38}H_{46}O_{18}$	204522-47-4	Leaves	*F. insularis* Hemsl.	[45]
40	Insularoside-3',6‴-di-*O*-*β*-D-glucoside	$C_{44}H_{56}O_{23}$	204522-49-6	Leaves	*F. insularis* Hemsl.	[45]
41	Insularoside	$C_{32}H_{36}O_{13}$	150044-49-8	Leaves	*F. insularis* Hemsl.	[63]
	(Uhdoside A)			Barks	*F. ornus*	[64]
	(Ornoside)			Leaves	*F. uhdei* L.	[65]
				Leaves	*F. uhdei* (Wenzig) Lingelsh.	[66]
42	Hydroxyornoside	$C_{32}H_{36}O_{14}$	172045-85-1	Barks	*F. ornus*	[46]
43	fraxuhdoside	$C_{38}H_{46}O_{18}$	151654-81-8	Leaves	*F. uhdei* L.	[65]
44	2″-Epifraxamoside	$C_{25}H_{30}O_{13}$	946569-82-0	Aerial parts	*J. grandiflorum* Linn.	[67]
				Fruits	*L. lucidum* Ait.	[59]
45	Demethyl-2″-epifraxamoside	$C_{24}H_{28}O_{13}$	946568-33-8	Aerial parts	*J. grandiflorum* Linn.	[67]
46	Fraxamoside	$C_{25}H_{30}O_{13}$	326594-34-7	Leaves	*F. americana* L.	[20]
				Fruits	*L. lucidum* Ait.	[59]
				Twigs	*S. oblata* var. *dilatata*	[39]
47	Oleferrugine B	$C_{50}H_{62}O_{23}$	1788897-03-9	Leaves	*O. ferruginea* Royle	[68]
48	Fraximalacoside	$C_{56}H_{66}O_{24}$	155179-17-2	Leaves	*F. malacophylla* Hemsl.	[60]
49	GI5	$C_{42}H_{54}O_{22}$	60037-40-3	Seeds	*F. excelsior* L.	[12]
				Leaves		[43]
				Seeds	*F. rhynchophylla* Hance	[32]
				Flowers	*J. polyanthum* Franch.	[52]
50	Jaspolyoleoside A	$C_{59}H_{76}O_{33}$	211306-60-4	Flowers	*J. polyanthum* Franch.	[69]
51	Safghanoside G	$C_{49}H_{60}O_{23}$	482648-22-6	Leaves	*S. afghanica* C. K. Schneid.	[38]
52	Safghanoside H	$C_{49}H_{60}O_{23}$	482648-23-7	Leaves	*S. afghanica* C. K. Schneid.	[38]
53	Reticuloside	$C_{34}H_{46}O_{19}$	1349682-20-7	Barks	*S. reticulata*	[56]
54	Ligulucidumoside A	$C_{26}H_{34}O_{12}$	1619925-46-0	Fruits	*L. lucidum* Ait.	[70]
55	Safghanoside A	$C_{32}H_{40}O_{17}$	482648-11-3	Leaves	*S. afghanica* C. K. Schneid.	[38]
56	Safghanoside B	$C_{32}H_{40}O_{17}$	482648-12-4	Leaves	*S. afghanica* C. K. Schneid.	[38]
57	(8*E*)-Nuezhenide	$C_{31}H_{42}O_{17}$	39011-92-2	Leaves	*F. americana* L.	[20]
				Seeds	*F. excelsior* L.	[12]
				seeds	*F. rhynchophylla* Hance	[32]
				Leaves	*L. japonicum* Thunb.	[71]
				Berries		[40]
				Fruits		[33]
				Fruits	*L. lucidi fructus*	[72]
				Fruits	*L. lucidum* Ait.	[35]
				Fruits		[34]

(*continued on next page*)

Table 2 (*continued*)

NO.	Compound	Molecular formula	CAS number	Source	Plant species	References
				Fruits		[25]
				Twigs	*S. oblata* var. *dilatata*	[39]
				Flowers	*S. vulgaris* L.	[29]
58	Neonuezhenide	$C_{31}H_{42}O_{18}$	96382-91-1	Fruits	*L. lucidum* Ait.	[35]
				Fruits		[25]
				Twigs	*L. obtusifolium*	[26]
				Flowers	*S. vulgaris* L.	[29]
59	Safghanoside F	$C_{38}H_{48}O_{18}$	482648-21-5	Leaves	*S. afghanica* C. K. Schneid.	[38]
60	Desrhamnosyloleoacteoside	$C_{40}H_{48}O_{21}$	219782-62-4	Leaves	*F. insularis* Hemsl.	[45]
61	Isooleoacteoside	$C_{46}H_{58}O_{25}$	454216-06-9	Leaves	*J. nudiflorum* Lindl.	[21]
				Flowers	*S. vulgaris* L.	[29]
62*	Specnuezhenide	$C_{31}H_{42}O_{17}$	39011-92-2	Fruits	*L. lucidi fructus*	[72]
63	Isonuezhenide	$C_{31}H_{42}O_{17}$	112693-22-8	Fruits	*L. japonicum* Thunb.	[73]
				Fruits	*L. lucidum* Ait.	[35]
				Fruits		[25]
64	Oleoacetoside	$C_{46}H_{58}O_{25}$		Leaves	*J. polyanthum* Franch.	[19]
				Leaves		[22]
				Flowers	*S. vulgaris* L.	[29]
65	Oleoechinacoside	$C_{52}H_{68}O_{30}$	122960-94-5	Flowers	*S. vulgaris* L.	[29]
66	Ilicifolioside A	$C_{40}H_{56}O_{26}$	1007558-31-7	Leaves	*O. ilicifolius*	[74]
67	Ilicifolioside B	$C_{40}H_{56}O_{26}$	1005197-22-7	Leaves	*O. ilicifolius*	[74]
68	Demethylhydroxyoleonuezhenide	$C_{47}H_{62}O_{28}$		Flowers	*S. vulgaris* L.	[29]
69	Demethyloleonuezhenide	$C_{47}H_{62}O_{27}$		Flowers	*S. vulgaris* L.	[29]
70	Oleonuezhenide	$C_{48}H_{64}O_{27}$	112693-21-7	Leaves	*L. japonicum* Thunb.	[71]
				Fruits		[73]
				Fruits	*L. lucidum* Ait.	[34]
				Twigs	*S. oblata* var. *dilatata*	[39]
				Flowers	*S. vulgaris* L.	[29]
71	Hydroxyoleonuezhenide	$C_{48}H_{64}O_{28}$		Flowers	*S. vulgaris* L.	[29]
72	Liguside B	$C_{48}H_{64}O_{27}$	1307904-08-0	Fruits	*L. lucidum* Ait.	[34]
73	Oleoforsythoside B	$C_{51}H_{66}O_{29}$		Flowers	*S. vulgaris* L.	[29]
74	Oleolipedoside A	$C_{46}H_{58}O_{24}$		Flowers	*S. vulgaris* L.	[29]
75	Syringaoleoacteoside	$C_{63}H_{80}O_{35}$		Flowers	*S. vulgaris* L.	[29]
76	Iso-oleonuzhenide	$C_{48}H_{64}O_{27}$	2112851-04-2	Fruits	*L. japonicum* Thunb.	[33]
77	Jaspofoliamoside C	$C_{27}H_{40}O_{13}$	219926-50-8	Flowers	*J. polyanthum* Franch.	[75]
78	Jaspofoliamoside B	$C_{33}H_{48}O_{18}$	190073-46-2	Flowers	*J. polyanthum* Franch.	[76]
79	Jaspofoliamoside A	$C_{33}H_{50}O_{18}$	190073-43-9	Flowers	*J. polyanthum* Franch.	[76]
80	Jaspolinaloside	$C_{27}H_{40}O_{12}$	190073-50-8	Flowers	*J. polyanthum* Franch.	[76]
81	Jaspofoliamoside D	$C_{27}H_{38}O_{12}$	219926-51-9	Flowers	*J. polyanthum* Franch.	[75]
82	Jaspogeranoside A	$C_{44}H_{62}O_{22}$	219926-13-3	Flowers	*J. polyanthum* Franch.	[75]
83	Jaspogeranoside B	$C_{44}H_{64}O_{22}$	219926-55-3	Flowers	*J. polyanthum* Franch.	[75]
84	Jaspofoliamoside G	$C_{50}H_{72}O_{28}$	219926-54-2	Flowers	*J. polyanthum* Franch.	[75]
85	Jasnudifloside F	$C_{27}H_{42}O_{13}$	454205-02-8	Leaves	*J. nudiflorum* Lindl.	[21]
86	Jasnudifloside K	$C_{33}H_{52}O_{18}$	454208-80-1	Leaves	*J. nudiflorum* Lindl.	[21]
87	Jasnudifloside G	$C_{27}H_{42}O_{13}$	454205-06-2	Leaves	*J. nudiflorum* Lindl.	[21]
88	Nudifloside D	$C_{27}H_{42}O_{13}$	454212-54-5	Leaves	*J. nudiflorum* Lindl.	[21]
89	Jasuroside E	$C_{27}H_{42}O_{13}$	201594-24-3	Leaves	*J. urophyllum*	[77]
90	Jasuroside F	$C_{27}H_{42}O_{13}$	201594-25-4	Leaves	*J. urophyllum*	[77]
91	9″-Hydroxyjasmesoside	$C_{27}H_{42}O_{14}$	121979-17-7	Leaves	*J. mesnyi* Hance	[78]
92	9″-hydroxyjasmesosidic acid	$C_{26}H_{40}O_{14}$	121994-03-4	leaves	*J. mesnyi* Hance	[78]
93*	Jasmesoside	$C_{27}H_{42}O_{13}$	97777-70-3	Leaves	*J. mesnyi* Hance	[79]
94	Frameroside	$C_{27}H_{38}O_{15}$	326594-35-8	Leaves	*F. americana* L.	[20]
95	2″-*epi*-frameroside	$C_{27}H_{38}O_{15}$	477332-54-0	Leaves	*S. afghanica* C. K. Schneid.	[38]
96	Jasnudifloside J	$C_{26}H_{38}O_{12}$	454206-10-1	Leaves	*J. nudiflorum* Lindl.	[21]
97*	Isojasminin	$C_{26}H_{38}O_{12}$	135378-08-4	Leaves	*J. mesnyi* Hance	[79]
98*	4″-Hydroxyisojasminin	$C_{26}H_{38}O_{13}$	135378-09-5	Leaves	*J. mesnyi* Hance	[79]
99	Nudifloside C	$C_{26}H_{38}O_{12}$	297740-99-9	Stems	*J. nudiflorum* Lindl.	[80]
				Leaves		[21]
100	Jasnudifloside I	$C_{26}H_{38}O_{12}$	454205-12-0	Leaves	*J. nudiflorum* Lindl.	[21]
101	Jasmisnyiroside	$C_{26}H_{36}O_{14}$	123967-69-1	Leaves	*J. mesnyi* Hance	[81]
102	Jasminin	$C_{26}H_{38}O_{12}$	30164-93-3	Leaves	*J. mesnyi* Hance	[79]
				Leaves		[81]
103	2″-Hydroxyjasminin	$C_{26}H_{38}O_{13}$	121979-15-5	Leaves	*J. mesnyi* Hance	[79]
104	Jasminin 10”-*O*-*β*-D-glucoside	$C_{32}H_{48}O_{17}$	121979-16-6	Leaves	*J. mesnyi* Hance	[79]
				Leaves		[78]
105	Craigoside C	$C_{44}H_{64}O_{24}$	879562-22-8	Root bark	*J. abyssinicum*	[82]
106	Craigoside B	$C_{44}H_{64}O_{24}$	878760-60-2	Root bark	*J. abyssinicum*	[82]
107	Craigoside A	$C_{61}H_{86}O_{34}$	879561-99-6	Root bark	*J. abyssinicum*	[82]
108	Nudifloside A	$C_{44}H_{64}O_{23}$	297740-97-7	Stems	*J. nudiflorum* Lindl.	[80]
109	Jasuroside A	$C_{44}H_{64}O_{23}$	190896-93-6	Leaves	*J. urophyllum*	[77]
				Whole plant	*J. urophyllum* Hemsley	[83]
110	Jasuroside C	$C_{44}H_{64}O_{24}$	190896-95-8	Leaves	*J. urophyllum*	[77]
				Whole plant	*J. urophyllum* Hemsley	[83]
111	Jasuroside B	$C_{61}H_{86}O_{33}$	190896-94-7	Leaves	*J. urophyllum*	[77]
				Whole plant	*J. urophyllum* Hemsley	[83]

(*continued on next page*)

Table 2 (*continued*)

NO.	Compound	Molecular formula	CAS number	Source	Plant species	References
112	Jasuroside D	$C_{61}H_{86}O_{34}$	190896-96-9	Whole plant	*J. urophyllum* Hemsley	[83]
113	Jasnudifloside L	$C_{50}H_{74}O_{28}$	454211-10-0	Leaves	*J. nudiflorum* Lindl.	[21]
114	Jasnudifloside H	$C_{43}H_{62}O_{23}$	454205-11-9	Leaves	*J. nudiflorum* Lindl.	[21]
115	Jasnudifloside A	$C_{44}H_{64}O_{23}$	244230-20-4	Leaves	*J. nudiflorum* Lindl.	[21]
				Leaves and stems		[84]
116	Jasnudifloside E	$C_{44}H_{64}O_{23}$	297740-96-6	Stems	*J. nudiflorum* Lindl.	[80]
				Leaves		[21]
117	Jasnudifloside D	$C_{44}H_{64}O_{23}$	297740-95-5	Stems	*J. nudiflorum* Lindl.	[80]
				Leaves		[21]
118	Jasnudifloside B	$C_{61}H_{86}O_{33}$	244230-40-8	Leaves and stems	*J. nudiflorum* Lindl.	[84]
				Leaves		[21]
119	Jasmoside	$C_{43}H_{60}O_{22}$	97763-17-2	Leaves	*J. mesnyi* Hance	[81]
120	Jasmosidic acid	$C_{42}H_{58}O_{22}$	135378-10-8	Leaves	*J. mesnyi* Hance	[79]
121	Nudifloside B	$C_{43}H_{60}O_{22}$	297740-98-8	Stems	*J. nudiflorum* Lindl.	[80]
				Leaves		[21]
122	Jasnudifloside C	$C_{43}H_{60}O_{22}$	244230-42-0	Leaves and stems	*J. nudiflorum* Lindl.	[84]
				Leaves		[21]
123*	Escuside	$C_{32}H_{38}O_{19}$	478182-19-3	Barks	*F. ornus* L.	[85]
124*	Fraxisecoside	$C_{33}H_{40}O_{20}$	2232211-90-2	Barks	*F. rhynchophylla*	[50]
				Stem bark	*F. xanthoxyloides* (G. Don) Wall.	[86]
125*	Isofraxisecoside	$C_{33}H_{40}O_{20}$	2232221-07-5	Stem bark	*F. xanthoxyloides* (G. Don) Wall.	[86]
126	Sambacolignoside	$C_{43}H_{54}O_{22}$	114449-12-6	Leaves	*J. sambac* (L.) Ait.	[23]
127	JASUROLIGNOSIDE	$C_{43}H_{56}O_{21}$	212065-15-1	Whole plants	*J. urophyllum*	[87]
128	Obtusifoliside A	$C_{37}H_{46}O_{17}$		Twigs	*L. obtusifolium*	[26]
129	Dilatioside A	$C_{37}H_{48}O_{16}$		Twigs	*S. oblata* var. *dilatata*	[39]
130	Liguside A	$C_{48}H_{64}O_{27}$	1307904-07-9	Fruits	*L. lucidum* Ait.	[34]
131	Isojaspolyoside A	$C_{42}H_{54}O_{23}$	188689-91-0	Flowers	*J. polyanthum* Franch.	[57]
132	Isojaspolyoside B	$C_{42}H_{54}O_{23}$	188689-94-3	Flowers	*J. polyanthum* Franch.	[57]
133	Isojaspolyoside C	$C_{42}H_{54}O_{23}$	188690-06-4	Flowers	*J. polyanthum* Franch.	[57]
134	GI3	$C_{48}H_{64}O_{27}$	60037-39-0	Seeds	*F. excelsior* L.	[12]
				Seeds	*F. rhynchophylla* Hance	[32]
				Fruits	*L. japonicum* Thunb.	[33]
				Fruits	*L. lucidum* Ait.	[34]
				Fruits		[25]
135	Polyanoside	$C_{48}H_{64}O_{27}$	188689-90-9	Flowers	*J. polyanthum* Franch.	[57]
136	Oleopolynuzhenide A	$C_{65}H_{86}O_{37}$	1,407544-82-4	Fruits	*L. lucidum* Ait.	[88]
137	Jaspolyoleoside B	$C_{59}H_{76}O_{32}$	211306-67-1	Flowers	*J. polyanthum* Franch.	[69]
138	Jaspolyoleoside C	$C_{59}H_{76}O_{32}$	211306-68-2	Flowers	*J. polyanthum* Franch.	[69]
139	Jaspolyanoside	$C_{42}H_{54}O_{22}$	188689-86-3	Flowers	*J. polyanthum* Franch.	[57]
				Twigs	*S. oblata* var. *dilatata*	[39]
140	Jaspolyoside	$C_{42}H_{54}O_{23}$	175448-04-1	Flowers	*J. polyanthum* Franch.	[52]
				Twigs	*S. oblata* var. *dilatata*	[39]
				Barks	*S. reticulata*	[56]
141	Jaspofoliamoside E	$C_{44}H_{62}O_{23}$	219926-52-0	Flowers	*J. polyanthum* Franch.	[75]
142	Jaspofoliamoside F	$C_{50}H_{72}O_{28}$	219926-53-1	Flowers	*J. polyanthum* Franch.	[75]
143	Jaspolinaloside B	$C_{44}H_{62}O_{22}$	219926-56-4	Flowers	*J. polyanthum* Franch.	[75]

A compound having no configuration at the C-5 position in *E*-ole, and is indicated by a * after its serial number

#: Compounds 21# and 226# have the same name but different structures

apoptotic protein) was found to be reduced in oleuropein-treated cancer cells [122]. Oleuropein (**14**) also increased BAX and simultaneously suppressed Bcl2 in oleuropein-treated ER-negative breast cancer cells (SKBR3) [123].

In the research of Yan et al. [124], oleuropein (**14**) demonstrated a dose-dependent induction of apoptosis in HepG2 human hepatoma cells. Oleuropein (**14**) is reportedly involved in induction of pro-survival signals in cancerous cells that overexpressed AKT/PKB. AKT/PKB inhibition was essential to maximize oleuropein-mediated apoptosis [124]. The investigations of Kimura et al. [125] also found that oleuropein (**14**) administered at a dose of 25 mg/kg body weight significantly reduced tumor volumes in mice which had been chronically exposed to ultraviolet B radiations for 17 weeks and consequently developed significant skin cancer. Additionally, the studies of Xu et al. [116] have indicated that, oleuropein (**14**) enhanced the radiosensitivity of Nasopharyngeal carcinoma (NPC) cells both *in vitro* and *in vivo*. In a colony formation assay in NPC cell lines, HNE-1 and HONE-1, 200 μM oleuropein (**14**) treatment significantly reduced the survival fractions in both cell lines, suggesting oleuropein (**14**) increased the sensitivity of these cells towards radiation. Furthermore, oleuropein (**14**) at a dose of 1% was shown to reduce the tumor volumes after radiation in a mouse xenograft model of NPC. Xu and his team also found that oleuropein (**14**) treatment reduced the activity of HIF1α-miR-519d-PDRG1 pathway, which was essential to the radiosensitizing effects of oleuropein (**14**) [116]. Sherif and his team also found that oleuropein (**14**) potentiates anti-tumor activity of cisplatin against HepG2. Their studies indicated that, the combination of 50 μM cisplatin and 200 μM oleuropein (**14**) showed the most potent effect on the molecular level when compared with oleuropein (**14**) or cisplatin alone. The combined drug showed significant elevation of NO content and pro-NGF protein level with a marked reduction of NGF protein level in addition to the upregulation of caspase-3 along with downregulation of Matrix metalloproteinase-7 (MMP-7) gene expressions [126].

Furthermore, oleuropein (**14**), (2″*R*)-2″-methoxyoleuropein (**20**)

Table 3
10-oxyderivative of oleoside secoiridoids isolated from plants of Oleaceae family.

NO.	Compound	Molecular formula	CAS number	Source	Plant species	References
144	Nuezhenelenoliciside	$C_{31}H_{42}O_{17}$		Fruits	*L. lucidum* Ait.	[89]
145	Uhdenoside	$C_{24}H_{30}O_{13}$	168074-97-3	Leaves	*F. uhdei* (Wenzig) Lingelsh.	[51]
146	10-Hydroxyoleoside-11-methyl ester	$C_{17}H_{24}O_{12}$	131836-11-8	Stems and leaves	*J. lanceolarium* Roxb.	[90]
				Aerial part	*J. multiflorum* (Burm. f.) Andr.	[91]
				Barks	*O. asiaticus* Nakai	[36]
147	10-Hydroxyoleoside dimethyl ester	$C_{18}H_{26}O_{12}$	91679-27-5	Seeds	*F. rhynchophylla* Hance	[32]
				Stems and leaves	*J. lanceolarium*	[92]
				Stems and leaves		[93]
				Stems and leaves	*J. lanceolarium* Roxb.	[90]
				Leaves	*J. odoratissimum* L.	[94]
				Leaves	*J. polyanthum* Franch.	[19]
				Leaves		[22]
				Leaves	*J.* urophyllum	[77]
				Fruits	*L. japonicum* Thunb.	[33]
				Leaves and twigs	*L. vulgare* L.	[53]
				Barks	*O. asiaticus* Nakai	[36]
				Flowers and leaves	*S. pubescens* Turcz	[28]
148*	Multiroside	$C_{31}H_{42}O_{19}$	131870-64-9	Aerial part	*J. multiflorum* (Burm. f.) Andr.	[91]
149	10-Hydroxyoleuropein	$C_{25}H_{32}O_{14}$	84638-44-8	Leaves	*F. oxycarba* Willd.	[47]
				Leaves	*F. uhdei* (Wenzig) Lingelsh.	[51]
				Aerial part	*J. multiflorum* (Burm. f.) Andr.	[91]
				Twigs	*L. obtusifolium*	[26]
				Leaves and twigs	*L. vulgare* L.	[53]
				Barks	*O. asiaticus* Nakai	[36]
				Flowers and leaves	*S. pubescens* Turcz	[28]
150	10-Hydroxyligustroside	$C_{25}H_{32}O_{13}$	35897-94-0	Leaves	*F. excelsior*	[30]
				Leaves	*F. oxycarba* Willd.	[47]
				Leaves	*F. pallisiae*	[31]
				Leaves	*F. uhdei* L.	[65]
				Stems and leaves	*J. amplexicaule* Buch.-Ham.	[95]
				Aerial part	*J. multiflorum* (Burm. f.) Andr.	[91]
				Berries	*L. japonicum* Thunb.	[40]
				Fruits		[33]
				Leaves and twigs	*L. vulgare* L.	[53]
				Barks	*O. asiaticus* Nakai	[36]
				Leaves	*P. azorica*	[27]
151	(2”*S*)-10-Hydroxy-2″-methoxyoleuropein	$C_{26}H_{34}O_{15}$	1,204829-37-7	Leaves and twigs	*L. vulgare* L.	[53]
152	(2”*R*)-10-Hydroxy-2″-methoxyoleuropein	$C_{26}H_{34}O_{15}$	1204829-36-6	Leaves and twigs	*L. vulgare* L.	[53]
153	Multifloroside	$C_{32}H_{38}O_{16}$	131836-10-7	Aerial part	*J. multiflorum* (Burm. f.) Andr.	[91]
154	10-Acetoxyligustroside	$C_{27}H_{34}O_{14}$	57799-95-8	Barks	*O. asiaticus* Nakai	[36]
				Leaves	*O. fragrans* Lour.	[96]
155	10-Acetoxyoleuropein	$C_{27}H_{34}O_{15}$	57799-96-9	Barks	*O. asiaticus* Nakai	[36]
				Leaves	*O. fragrans* Lour.	[96]
156	10-Acetoxyoleoside dimethyl ester	$C_{20}H_{28}O_{13}$	198781-87-2	Leaves	*J. odoratissimum* L.	[94]
157	*trans*-10-(*p*-coumaroyloxy) oleoside dimethyl ester	$C_{27}H_{32}O_{14}$	198781-85-0	Aerial parts	*J. odoratissimum* L.	[97]
158	*cis*-10-(*p*-coumaroyloxy) oleoside dimethyl ester	$C_{27}H_{32}O_{14}$	198781-86-1	Aerial parts	*J. odoratissimum* L.	[97]
159	Jaslanceoside F	$C_{28}H_{34}O_{15}$	1347761-11-8	Stems and leaves	*J. lanceolarium* Roxb.	[90]
160	Isojaslanceoside B	$C_{26}H_{30}O_{14}$		Fruits	*L. lucidum* Ait.	[89]
161	Jaslanceoside H	$C_{25}H_{28}O_{14}$	188300-82-5	Stems and leaves	*J. lanceolarium* Roxb.	[90]
162	Jaslanceoside G	$C_{26}H_{30}O_{15}$		Stems and leaves	*J. lanceolarium* Roxb.	[90]
163	Jaslanceoside A	$C_{27}H_{32}O_{15}$	188300-81-4	Stems and leaves	*J. lanceolarium*	[93]
				Stems and leaves		[92]
				Stems and leaves	*J. lanceolarium* Roxb.	[90]
164	Jaslanceoside C	$C_{27}H_{32}O_{15}$	188795-98-4	Stems and leaves	*J. lanceolarium* Roxb.	[90]
				Stems and leaves	*J. lanceolarium*	[93]
165	Jasminoside	$C_{26}H_{30}O_{13}$	82451-18-1	Stems and leaves	*J. amplexicaule* Buch.-Ham.	[95]
				Stems and leaves	*J. lanceolarium*	[92]
				Stems and leaves		[93]
				Stems and leaves	*J. lanceolarium* Roxb.	[90]
				Leaves	*J. urophyllum*	[77]
166	Jaslanceoside B	$C_{26}H_{30}O_{14}$	188300-82-5	Stems and leaves	*J. lanceolarium*	[93]
				Stems and leaves		[92]
				Stems and leaves	*J. lanceolarium* Roxb.	[90]
167	Jaslanceoside D	$C_{26}H_{30}O_{14}$	188795-99-5	Stems and leaves	*J. lanceolarium* Roxb.	[90]
				Stems and leaves	*J. lanceolarium*	[93]
168	Jaslanceoside E	$C_{26}H_{30}O_{15}$	188796-00-1	Stems and leaves	*J. lanceolarium* Roxb.	[90]
				Stems and leaves	*J. lanceolarium*	[93]
169	Obtusifoliside B	$C_{33}H_{38}O_{17}$		Twigs	*L. obtusifolium*	[26]
170	6'-*O*-Acetyl-10-acetoxyoleoside	$C_{22}H_{30}O_{14}$	198781-87-2	Aerial parts	*J. odoratissimum* L.	[97]
171	3'-*O*-*β*-D-Glucopyranosyl 10-acetoxyligustroside	$C_{33}H_{44}O_{19}$	1115023-45-4	Leaves	*O. ilicifolius*	[62]
172	3'-*O*-*β*-D-Glucopyranosyl 10-acetoxyoleuropein	$C_{33}H_{44}O_{20}$	1,115023-47-6	Leaves	*O. ilicifolius*	[62]
173	3'-*O*-*β*-D-Glucopyranosyl 10-hydroxyligustroside	$C_{31}H_{42}O_{18}$	97695-01-7	Leaves	*O. ilicifolius*	[62]
174	Fraxicarboside C	$C_{36}H_{40}O_{18}$	209851-36-5	Leaves	*F. oxycarba* Willd.	[47]
175	Fraxicarboside B	$C_{34}H_{38}O_{17}$	209851-35-4	Leaves	*F. oxycarba* Willd.	[47]

(*continued on next page*)

Table 3 (*continued*)

NO.	Compound	Molecular formula	CAS number	Source	Plant species	References
176	Fraxicarboside A	$C_{39}H_{46}O_{21}$	209851-23-0	Leaves	*F. oxycarba* Willd.	[47]
177	Uhdoside B	$C_{32}H_{36}O_{14}$	152434-57-6	Leaves	*F. uhdei* (Wenzig) Lingelsh.	[66]
178	Oleopolyanthoside B	$C_{52}H_{70}O_{32}$	211306-58-0	Flowers	*J. polyanthum* Franch.	[69]
179	Oleopolyanthoside A	$C_{52}H_{70}O_{32}$	211306-57-9	Flowers	*J. polyanthum* Franch.	[69]
180	Jaspolyanthoside	$C_{35}H_{48}O_{22}$	175448-05-2	Flowers	*J. polyanthum* Franch.	[52]
181	Jasamplexoside A	$C_{42}H_{54}O_{24}$	147764-93-0	Stems and leaves	*J. amplexicaule* Buch.-Ham.	[95]
182	Jasamplexoside C	$C_{42}H_{54}O_{25}$	147742-02-7	Stems and leaves	*J. amplexicaule* Buch.-Ham.	[95]
183	Jasamplexoside B	$C_{59}H_{76}O_{35}$	147742-01-6	Stems and leaves	*J. amplexicaule* Buch.-Ham.	[95]

A compound having no configuration at the C-5 position in *E*-ole, and is indicated by a * after its serial number

Table 4
Z- secoiridoids isolated from plants of Oleaceae family.

NO.	Compound	Molecular Formula	CAS number	Source	Plant species	References
184	(8*Z*)-Nuezhenide A	$C_{31}H_{42}O_{17}$	449,733-84-0	Leaves	*L. japonicum* Thunb.	[71]
				Fruits	*L. lucidum* Ait.	[34]
				Twigs	*S. oblata* var. *dilatata*	[39]
185	(8*Z*)-Nuezhenide	$C_{31}H_{42}O_{17}$	904327-00-0	Leaves	*F. angustifolia*	[98]
				Leaves	*L. japonicum* Thunb.	[71]
186*	Angustifolioside C	$C_{38}H_{48}O_{20}$	175,889-16-4	Leaves	*F. angustifolia*	[98]
187	Ligulucidumoside C	$C_{19}H_{26}O_{13}$	1619925-53-9	Fruits	*L. lucidum* Ait.	[70]
188	Oleferrugine A	$C_{47}H_{62}O_{24}$	1648747-63-0	Leaves	*O. ferruginea*	[99]

A compound having no configuration at the C-5 position in E-ole and is indicated by a * after its serial number.

have shown antiproliferative activity against Human Melanoma Cell Line (SK-MEL-2 cells) with IC_{50} values of 10.86, 14.64 μM respectively [39].

5.6. Anti-obesity effects

The synthesis and accumulation of fatty acids are among the major causes of obesity. The work of Zhang et al. [70] has demonstrated secoiridoids possess significant triglyceride accumulation inhibitory effects. Ligulucidumosides A-C (**54**, **223**, **187**) and nuzhenal C (**213**) demonstrated a significant intracellular triglyceride inhibitory effects in HepG2 cells at concentrations of 10 μM.

5.7. Other effects

One way to reduce the cytotoxic effects of chemotherapeutic drugs is the use of antioxidants in chemotherapy since they prevent the accumulation of reactive oxygen species (ROS), such as superoxide ions and hydroxyl radicals induced by these drugs and they inhibit antioxidant enzyme activities [127].

Oleuropein (14) has been reported to possess restorative effect in stomach and lung injuries induced by Cisplatin. Studies conducted by Geyikoglu et al. [128], showed that Cisplatin at a dose of 7 mg/kg significantly increased 8-OH-dG, malondialdehyde and total oxidative stress levels and caused severe tissue damages. However, high dose of oleuropein (**14**) (200 mg/kg) induced a significant reduction in 8-OH-dG, malondialdehyde levels, an increase in total antioxidant status levels and it restored Cisplatin-induced tissue damages.

10-Hydroxyoleuropein (**149**) and multifloroside (**153**) have also been reported to exhibit coronary dilating and cardiotropic activities: effects that were observed using an isolated guinea pig preparation [91].

5.8. Structure activity relationship (SAR) of secoiridoids

From the literature available on the bioactivities of secoiridoids it could be inferred that, the presence of a carboxylic acid functionality at C-13, whether in the free acid form or the methyl ester form is critical for their activity. For example oleonuezhenide (**70**) which has a methyl ester at C-13 possess neuroprotective effects and demethyloleonuezhenide (**69**) which is a free acid derivative also possess anti-inflammatory effects. Also, it is realized that, the cardio – effects of these secoiridoids are associated with the presence of hydroxy at C-10. For instance, both 10-Hydroxyoleuropein (**149**) and multifloroside (**153**) which are 10–hydroxy secoiridoids exhibit coronary dilating and cardiotropic activities. Furthermore, the presence of 1,2-dihydroxyphenylethanol or *p*-hydroxyphenylethanol moiety esterified to the carboxylic acid at C-7 and C-11 might be crucial for activity, and also the range of bioactivity increases when both C-7 and C-11 carboxylic groups are esterified. They effect is shown by the wide range of effects of Hydroxyframoside A (**28**) which exhibits anti-diabetic, anti-inflammatory, immunesuppressive, and neuroprotective effects.

6. Conclusions

In this review, the phytochemical constituents of the secoiridoids (glycosides, aglycones, derivatives and dimers) isolated from Oleaceae family from 1987 to 2018 are systematically classified. From our extensive review of literatures on secoiridoids, it was found that most conjugations occur at C-7 and such compounds exhibit a variety of pharmacological activities, including: anti-diabetic, anti-inflammatory, immunosuppressive, neuroprotective, anti-cancer effects and anti-obesity. There are 25 genera of Oleaceae, however, the 232 secoiridoids summarized in this review have been isolated from only 9 genera with majority of them reported from *Fraxinus* and *Jasminum*. Therefore, it is necessary to carry out further chemical and pharmacological studies on other plants in the family Oleaceae, compare their chemical compositions and pharmacological activities, clarify their structure-activity relationships, and provide a theoretical basis for the rational use of alternatives. At the same time, it is necessary to carry out centralized and detailed *in vivo* studies on the secoiridoids to determine their mechanisms of action, safety and effective doses, which are necessary for future new drug development and clinical treatment.

Table 5
Secologanosides and oxidized secologanoside secoiridoids isolated from plants of Oleaceae family.

NO.	Compound	Molecular formula	CAS number	Source	Plant species	References
189	Jasuroside G	$C_{44}H_{64}O_{23}$	201594-27-6	Leaves	*J. urophyllum*	[77]
190	Secologanoside	$C_{16}H_{22}O_{11}$	59472-23-0	Aerial parts	*F. fortunei*	[100]
				Leaves	*F. phillyreoides* Labill.	[101]
				Leaves and twigs	*L. vulgare* L.	[53]
				Leaves	*O. europaea*	[37]
191	Secologanoside 7-methyl ester	$C_{17}H_{24}O_{11}$	152100-11-3	Barks	*O. asiaticus* Nakai	[36]
				Leaves	*S. reticulata* (Blume) Hara	[102]
192	Secoxyloganin	$C_{17}H_{24}O_{11}$	58822-47-2	Leaves	*P. azorica*	[27]
193	Oleuroside	$C_{25}H_{32}O_{13}$	116383-31-4	Leaves	*O. europaea*	[54]
194	Grandifloroside 11-methyl ester	$C_{26}H_{32}O_{13}$	557790-50-8	Flowers and leaves	*S. pubescens* Turcz	[28]
195	Neopolyanoside	$C_{48}H_{64}O_{27}$	190073-52-0	Flowers	*J. polyanthum* Franch.	[76]
196	Secologanin	$C_{17}H_{24}O_{10}$	19351-63-4	Aerial parts	*F. fortunei*	[100]
197	6′-*O*-*trans*-cinnamoyl-secologanoside	$C_{25}H_{28}O_{12}$		Fruits	*L. lucidum* Ait.	[89]
198	Liguluciside B	$C_{26}H_{30}O_{12}$	2231139-35-6	Fruits	*L. lucidum* Ait.	[59]
199	Liguluciside A	$C_{25}H_{28}O_{12}$	2,231139-30-1	Fruits	*L. lucidum* Ait.	[59]
200	6′-*E*-*p*-coumaroyl-secologanoside	$C_{25}H_{28}O_{13}$	905295-43-4	Leaves	*O. europaea*	[37]
201	6′-*O*-[(2*E*)-2,6-dimethyl-8-hydroxy-2-octenoyloxy]-secologanoside	$C_{26}H_{38}O_{13}$	927173-25-9	Leaves	*O. europaea*	[37]
202	Secologanol	$C_{17}H_{26}O_{10}$	72463-81-1	Aerial parts	*F. fortunei*	[100]
				Leaves	*F. phillyreoides* Labill.	[101]
203	5-Hydroxysecologanol	$C_{17}H_{26}O_{11}$	156184-43-9	Leaves	*F. phillyreoides* Labill.	[101]
204	Fontanesioside	$C_{24}H_{30}O_{13}$	156312-06-0	Aerial parts	*F. fortunei*	[100]
				Leaves	*F. phillyreoides* Labill.	[101]
205	*cis*-7(*p*-coumaroyl)-5-hydroxysecologanol	$C_{26}H_{32}O_{13}$		Aerial parts	*F. fortunei*	[100]
206	*trans*-7(*p*-coumaroyl)-5-hydroxysecologanol	$C_{26}H_{32}O_{13}$		Aerial parts	*F. fortunei*	[100]
207	Swertiamarin	$C_{16}H_{22}O_{10}$	17388-39-5	Leaves	*F. phillyreoides* Labill.	[101]
208	Secologanic acid	$C_{16}H_{22}O_{10}$	60077-46-5	Aerial parts	*F. fortunei*	[100]
				Leaves	*F. phillyreoides* Labill.	[101]
209	Liguluciridoid A	$C_{13}H_{18}O_6$	2231139-40-3	Fruits	*L. lucidum* Ait.	[59]
210	Ligstral	$C_{19}H_{22}O_7$	152369-63-6	Leaves	*F. angustifolia* Vahl	[42]
211	*p*-Hydroxyphenethyl 7-*β*-*D*-glucosideelenolic ester	$C_{25}H_{32}O_{12}$	1215179-33-1	Fruits	*L. lucidum* Ait.	[25]
212	6′-Elenolylnicotiflorine	$C_{42}H_{54}O_{22}$	1215179-34-2	Fruits	*L. lucidum* Ait.	[25]
213	Nuzhenal C	$C_{11}H_{16}O_5$	1619925-59-5	Fruits	*L. lucidum* Ait.	[70]
214	Nuzhenal A	$C_{10}H_{14}O_5$	1,407544-83-5	Fruits	*L. lucidum* Ait.	[88]
215	Nuzhenal B	$C_{23}H_{30}O_{11}$	1407544-84-6	Fruits	*L. lucidum* Ait.	[88]
216	Jasminanhydride	$C_9H_{10}O_4$	946569-83-1	Aerial parts	*J. grandiflorum* Linn.	[67]
217	Ligustrohemiacetal A	$C_{12}H_{16}O_7$	1,206554-84-8	Leaves and twigs	*L. vulgare* L.	[53]
218	Ligustrohemiacetal B	$C_{19}H_{22}O_8$	1206554-85-9	Leaves and twigs	*L. vulgare* L.	[53]
219	Liguluciridoid B	$C_{14}H_{22}O_7$	2231139-45-8	Fruits	*L. lucidum* Ait.	[59]
220	Ligustaloside A	$C_{25}H_{32}O_{14}$	85527-07-7	Berries	*L. japonicum* Thunb.	[40]
221	Ligustaloside B	$C_{25}H_{32}O_{13}$	85527-08-8	Berries	*L. japonicum* Thunb.	[40]
222	4′, 5′-(2′-Hydroxy ligustrosidic acid) dimer	$C_{50}H_{56}O_{30}$	1919872-68-6	Fruits	*L. lucidi fructus*	[72]
223	Ligulucidumoside B	$C_{19}H_{26}O_{13}$	1619925-47-1	Fruits	*L. lucidum* Ait.	[70]
224	Liguluciside C	$C_{25}H_{30}O_{14}$	96382-89-7	Fruits	*L. lucidum* Ait.	[59]
225	Oleuropeinic acid	$C_{25}H_{30}O_{15}$	96382-90-0	Fruits	*L. lucidum* Ait.	[34]
226#	Isoligustrosidic acid	$C_{25}H_{30}O_{14}$	1407544-14-2	Fruits	*L. lucidum* Ait.	[88]
227	Ligupurpuroside K	$C_{24}H_{30}O_{14}$	2,072124-82-2	Leaves	*L. purpurascens* Y. C. Yang	[103]
228	Ligujaponoside A	$C_{25}H_{32}O_{14}$	2,112851-02-0	Fruits	*L. japonicum* Thunb.	[33]
229	Ligujaponoside B	$C_{25}H_{32}O_{15}$	2112851-03-1	Fruits	*L. japonicum* Thunb.	[33]
230	Lucidumoside A	$C_{25}H_{34}O_{12}$	339158-20-2	Fruits	*L. lucidum* Ait.	[35]
231	Lucidumoside B	$C_{25}H_{34}O_{13}$	85527-19-1	Fruits	*L. lucidum* Ait.	[35]
232	Nuezhenidic acid	$C_{17}H_{24}O_{14}$	183238-67-7		*L. lucidum* Ait.	[104]
				Fruits		[59]

: Compounds 21# and 226# have the same name but different structures.

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Conflicts of interest

The authors declare no conflict of interest.

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