Secoiridoids from Olea europaea L.

Subjects: Biology

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Iridoids, which have beneficial health properties, include a wide group of cyclopentane [c] pyran monoterpenoids present in plants and insects. The cleavage of the cyclopentane ring leads to secoiridoids. Mainly, secoiridoids have shown a variety of pharmacological effects including anti-diabetic, antioxidant, anti-inflammatory, immunosuppressive, neuroprotective, anti-cancer, and anti-obesity, which increase the interest of studying these types of bioactive compounds in depth. Secoiridoids are thoroughly distributed in several families of plants such as Oleaceae, Valerianaceae, Gentianaceae and Pedialaceae, among others. Specifically, Olea europaea L. (Oleaceae) is rich in oleuropein (OL), dimethyl-OL, and ligstroside secoiridoids, and their hydrolysis derivatives are mostly OL-aglycone, oleocanthal (OLE), oleacein (OLA), elenolate, oleoside-11-methyl ester, elenoic acid, hydroxytyrosol (HTy), and tyrosol (Ty). These compounds have proved their efficacy in the management of diabetes, cardiovascular and neurodegenerative disorders, cancer, and viral and microbial infections. Particularly, the antioxidant, anti-inflammatory, and immunomodulatory properties of secoiridoids from the olive tree (Olea europaea L. (Oleaceae)) have been suggested as a potential application in a large number of inflammatory and reactive oxygen species (ROS)-mediated diseases.

Keywords: immunomodulation ; inflammation ; olive tree ; oxidative stress ; secoirioids

1. Introduction

Iridoids, which have beneficial health properties, include a wide group of cyclopentane [*c*] pyran monoterpenoids present in plants and insects. The name iridoid derived from *Iridomyrmex*, a genus of fornices from which iridomirmecin and iridodial compounds were isolated. These products have been considered as defensive compounds. In fact, the biosynthesis of these derivatives of monoterpenes takes place in the different organisms by similar pathways; defense is its main role, and in the case of insects, they are used as sex pheromones [1].

Iridoids were first isolated in the latter part of the 19th century, but Halpern and Schmid proposed the basic skeleton of the iridoids in their investigation of the structure of plumieride in 1958 [2]. Particularly, they are secondary metabolites of terrestrial and marine flora and fauna, being found in a large number of plants families, usually as glycosides. For this reason, some of them are chemotaxonomically useful as markers of genus in various plant families. Besides, they exhibit a wide range of bioactivities including anti-inflammatory, antibacterial, anti-carcinogenic, and antiviral activities [3]. In fact, they are used as bitter tonics, sedatives, antipyretics, cough drugs, remedies for skin disorders, and as hypotensive agents. In addition, they are useful as an antidote in mushroom intoxications by *Amanita* type.

The cleavage of the cyclopentane ring of iridoids leads to secoiridoids. Mainly, secoiridoids have shown a large variety of pharmacological properties including anti-diabetic, anti-inflammatory, immunosuppressive, neuroprotective, anti-cancer, and anti-obesity. This fact encouraged us to study the bioactivities of these phytochemicals in depth and update the latest preclinical and clinical data on its bioactivity and potential therapeutic uses.

1.1. Structure and Classification

Several classifications have been developed over the years, given the variety and complexity of iridoids and secoiridoids [4][5].

From 1980 to date, bibliographic data has used the classification proposed by El-Naggar and Beal [2], who categorize these compounds according to the number of carbons included in their structure:

- Group 1: C_8 iridoids (di-nor-iridoids)
- Group 2: C_9 iridoids (nor-iridoids)
- Group 3: C_{10} iridoids, which occur mainly as glycosides

- Group 4: Aglycones and some iridoids included in the other three groups lacking a sugar residue in their structure
- Group 5: Iridoids derivatives. This group comprises compounds derived from the opening of the pyran ring
- Group 6: Included bis-iridoids as a result of condensation of two monomers, (a) directly as in iridolinalin A, or (b) through a sugar residue as in globuloside A.

At the same time, there are other classifications of secoiridoids according to the presence of these compounds in certain families, including the Oleaceae family. In fact, a total of 232 secoiridoids (aglycones, glycosides, derivatives, and dimers) have been isolated from nine genus of the family Oleaceae. These genera include Fontanesia, Fraxinus, Jasminum, Ligustrum, Olea, Osmanthus, Phillyrea, Picconia, and Syringa, and these secoiridoids were classified into other five groups [6]:

- Simple secoiridoids: Generally, for the simple secoiridoids, positions C_7 and C_{11} have either a free carboxylic acid group or a methyl ethyl ester derivative of the acid. The configurations of the positions C_1 and C_5 are *S*.
- Conjugated secoiridoids: This group of compounds is the most numerous secoiridoids isolated from the Oleaceae family. The name of the class derives from the type of compound that is linked or conjugated to the secoiridoid nucleus. Based on this, this class is further categorized into seven subgroups: aromatic-conjugated, sugar-conjugated, terpene-conjugated, cyclopentane-conjugated, coumarin-conjugated, lignans-conjugated, and other secoiridoids. Normally, the conjugations occur in C_7 due to this position, which is is usually oxidized to a carboxylic acid and esterified with diverse groups.
- 10-Oxyderivative of oleoside secoiridoids: This group contains the oleoside nucleus with distinct structural differences. The C_8 and C_9 positions exist as double bonds, with a hydroxy group at the C_8 position or an ester formed by an oxygen atom with different groups. A total of 40 10-Oxyderivative of oleoside secoiridoids have been isolated from the Oleaceae family.
- *Z*-Secoiridoids: This class of secoiridoids is characterized by the presence of double-bond geometry at the C_8 in *Z*-configuration; however, only five compounds have been isolated from the Oleaceae family.
- Secologanosides and oxidized secologanoside secoiridoids: Compounds of this class are based on the secologanoside nucleus. They are differentiated by the positions on the C–C double bond between C_8 and C_{10} and C_{10} oxidation level.

1.2. Main Naturally Occurring Iridoids and Secoiridoids Present in Olea europaea L

Iridoids and secoriridoids are thoroughly distributed in the plants of class Magnoliopside, concretely belonging to the following families: *Scropulariaceae, Verbenaceae, Lamiaceae, Apocynaceae, Loganiaceae, Bignoniaceae, Plantaginaceae, Rubiaceae, Pedaliaceae, Cornaceae, Acantheceae, Loasaceae, Lentibulariaceae, Gentianaceae, Oleaceae, Nyctanthaceae, Caprifoliaceae, Dispsacaceae,* and *Valerianaceae*.

For instance, *Valeriana officinalis* L. (Valerianaceae), *Harpagophytum procumbens* L. (Pedaliaceae), *Genciana lutea* L. (Gentianaceae), *Fraxinus excelsior* L. (Oleaceae) and *Olea europaea* L. (Oleaceae) are the most representative medicinal plants commonly used in medicine, due to their iridod/secoiridoid content [3]. Particularly, *Olea europaea* L. (Oleaceae) is a small evergreen tree with firm branches and a grayish bark. The leaves are lanceolate, opposite, short-petioled, mucronate, green above and hoary on the underside. On the other hand, the flowers are small, short, erect racemes, axillary, very much shorter than the leaves, and the fruit is a small smooth, purple, or green drup, with a nauseous, bitter flesh, enclosing a sharp-pointed stone [7].

Olea europaea L. preparations have been traditional used in folk medicine in the European Mediterranean area, Arabia peninsula, India and other tropical and subtropical regions, as a diuretic, emollient, hypotensive, and for urinary and bladder infections [8]. Most of the plant parts of *Olea europaea* L. are used in the traditional system of medicine around the world. Oil is taken with lemon juice to treat gall stones [9]. Leaves are taken orally for stomach and intestinal diseases and used as mouth cleanser [10], and the decoction of dried leaves is taken orally for diabetes [11]. An extract of the fresh leaves is taken orally to treat hypertension and to induce diuresis [12], whereas an infusion of the fresh leaves is taken orally as an alternative treatment for inflammatory diseases [13]. Similarly, essential oil extracted from the fruit is also used to treat rheumatism, promote blood circulation [14], and as a laxative [15].

The main biophenol secoiridoids found in the olive tree include: oleuropein (OL), dimethyl-OL, ligstroside, and their hydrolysis derivatives such as OL-aglycone, oleocanthal (OLE), oleacein (OLA), elenolate, oleoside-11-methyl ester, elenoic acid, hydroxytyrosol (HTy), and tyrosol (Ty) (Figure 1).

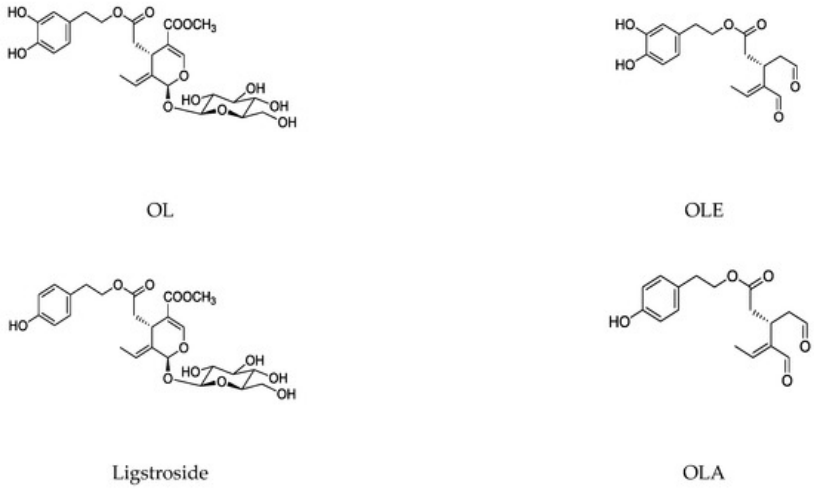


Figure 1. Chemical structures of secoiridoids most abundant in olive trees. OL: oleuropein, OLA: oleacein, OLE: oleocanthal.

1.3. Biosynthesis and Biotransformation of Secoiridoids in Olive Tree

The amount and distribution of secoiridoids present in olive tissues depend on various environmental factors such as the ripening cycle, geographical origin, and cultivation practices, among others. Besides, the content of phenolic glycosides as patterns and the activity of endogenous enzymes can play a role in the quantitative composition of secoiridoids in the olive tree [16].

The fact that secoiridoids are mostly present in early stages is due to the enzymatic and chemistry reactions that take place in the maturation time. In this sense, three different states in fruit maturation have been described: growth phase, green maturation phase, and black maturation phase, which is characterized by the presence of anthocyans.

OL is mainly abundant in early stages, although its levels decrease during the maturation process. In fact, OL decreases quickly in black crops and is not present in some varieties of Oleaceae.

The main precursor of OL and ligstroside is oleoside 11-methyl ester (elenolic acid glucoside). Firstly, geraniol synthase (GES) catalyzes the transformation of genaryl diphosphate to geraniol, which is converted to 10-hydroxygeraniol by the geraniol 10-hydroxylase enzyme. The iridioids in Oleaceae must be formed from this point with 10-hydroxygeraniol as the starting compound via iridial and iridotrial up to deoxyloganic acid, which is the precursor of loganin and loganic acid, as well as secologanin and secologanic acid [17]. From this point, up to five routes have been proposed to explain the origin of all iridoids found in this family. However, it is known that most of the secoiridoids present in *Olea europaea L.* are derived from deoxyloganic acid as a common intermediate [17][18]. Following this line, nicotinamide adenine dinucleotide deshydrogenase (NADH) acts on 10-hydroxygeraniol to form deoxyloganic acid aglucone. The transfer of glucosyl groups to deoxyloganic acid aglucone (precursor of monoterpene indolic alcaloids and OL) is catalyzed by glucosyltransferase (GT). Deoxyloganic acid experiments a 7-α-hydroxylation of the cyclopentane ring and forms 7-epiloganic acid, which quickly goes to 7-ketologanic acid through hydroxyl group oxidation. Loganic acid methyltransferase catalyzes 7-ketologanin syntheses. In this point, secologanin synthase (SLS) oxides a ketonic group to form 11-methyl oleoside, which is immediately glucosylated by GT. Finally, 7-β-1-D-glucopyranosyl-11-methyl oleoside is esterified with Ty to produce ligstroside, and then OL is formed [17][19] (Figure 2).

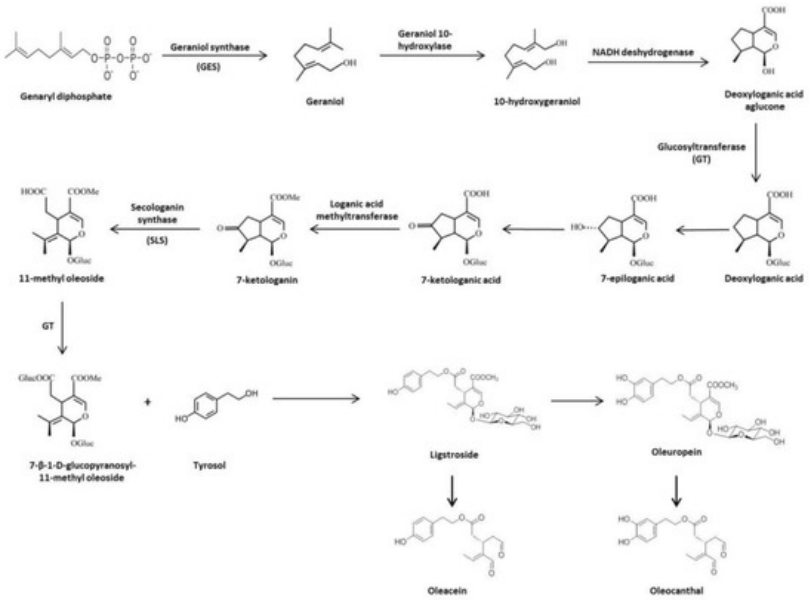


Figure 2. Biosynthesis and biotransformation of secoiridoids in *Olea europaea* L.

Secoiridoids are distributed throughout the tissues of the olive tree, but their nature and concentration change among different parts of the plant. Thus, biosynthetic or mechanicals transformation during production are decisive to quantify alterations of the bioactive small molecules [18]. Particularly, OL is the major secoiridoid constituent of unripe drupes (peel, pulp, and seed). The amount of OL decreases along fruit maturation, as commented above, whereas its aglycon form increases its levels. OL-aglycone is formed by the cleavage of the glycosidic bond mediated by β-glucosidase activity. Ligstroside has been described as a common phenolic component in different olive tissues (leaf, fruit pulp, and stone) and olive oil, but it has been rarely found in olive seeds [20].

In the course of maturation, OL and ligstroside are considered pattern components. Both of them are present in the olive fruit, but they are almost non-existent in olive oil (85–95% reduction) [21][22]. β-glucosidase acts by decreasing OL and ligstroside levels, aglycon forms from OL, and ligstroside can be detected as isomers due to the keto-enolic tautomeric equilibrium of the elenolic acid moiety [23][24].

Other dialdehydics structurally related to these secoiridoid precursors are OLA and OLE. Different authors have reported that both OLA and OLE levels increase during ripening due to OL and ligstroside degradation, respectively [25]. Thus, they concluded that OL and ligstroside are natural precursors of OLA and OLE as breakdown products resulting from enzymatic activity during the extraction and maturation processes [26][27][28][29].

OL and ligstroside have been detected in olive leaves. In turn, OLA and OLE levels are augmented in mature fruits, such as OL and ligstroside aglycons. Moreover, OLA and OL-aglycone are more plentiful in olive oil [16].

2. Protective Role of the Olive Tree Secoiridois in Diseases with an Important Pathogenic Contribution of Oxidative and Peroxidative Damage

2.1. Olive Tree Secoiridoids and Cancer

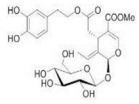
Cancer is a complex chronic degenerative disease characterized by a multistep process in which normal cells turn into malignant cells, acquiring several properties such as abnormal proliferation and reduced apoptosis.

The main factors that cause the majority of cancer cases are tobacco and dietary habits. In fact, there is an estimation that around 30% of all cancers may be avoidable by changing food intake [30][31]. Therefore, the identification and characterization of foods and their components, which could prevent the incidence and development of cancer, is an important objective for modern nutritional research [30][32]. In this sense, it is important to take into account that populations who are living near to the Mediterranean area have a lower incidence of cancer compared to other regions. This fact is probably due to the consumption of the diet known as the Mediterranean diet [33]. Besides, it is well-known that the pathophysiology of common diseases states such as cancer, cardiovascular disease, arthritis, and neurodegenerative diseases, among others, are associated with chronic inflammation [34].

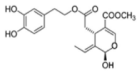
There are a large numbers of studies that support the chemopreventive role of natural compounds derived from EVOO and the olive tree such as OL, OLE, OLA, or ligstroside against different cancers and inflammation process. Particularly,

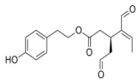
the role of secoiridoids derived from *Olea europaea* L. has been investigated in different types of cancerous processes (Table 1 and Table 2).

Table 1. Most recent in vitro studies that corroborate the important role of secoiridoids from the olive tree in the control and progression of different types of cancer.

Phenolic Compound	Cell Line	Concentration	Effects	Reference
 OL	NL-Fib: normal human skin fibroblasts; LN-18: poorly differentiated glioblastoma; TF-1a: erythroleukemia; 786O: renal cell adenocarcinoma; T-47D: infiltrating ductal carcinoma of breast-pleural effusion; MCF-7: human breast cancer; RPMI-7951: malignant melanoma skin-lymphoide metastasis; LoVo: colorectal adenocarcinoma-supraclavicular region metastasis	0.005%, 0.01% and 0.025% of OL in fibroblast tissue culture medium	OL inhibited cell growth, motility and invasiveness	[35]
	HT29 and SW260 human colon adenocarcinoma cell line	[0–100 μM]	OL might induce anti-proliferative and pro-apoptotic effects	[36]
	HT29	200, 400, and 800 μM	OL limited the growth and induced apoptosis via the p53 pathway	[37]
	MDA-MB-231 human breast cancer cell line	200 μg/mL	OL produced the up-regulating of TIMPs gene expression and the down-regulation MMPs overexpression gene	[38]
	MDA-MB-231; MCF-10A and MCF-7 human breast cancer cell lines	[0–300 μM]	OL exhibited specific cytoxicity against breast cancer cells, which is probably mediated through the induction of apoptosis via mitochondrial pathway	[39]
	SKBR3 breast cancer cell line	100 μM	OL worked as G-protein-coupled receptor (GPER) inverse agonists in estrogen receptor (ER)-negative and GPER-positive SKBR3	[40]
	MCF-7	100 and 200 μM	OL induced apoptosis in breast tumor cells via p53-dependent pathway	[41]
	MDA-MB-231 and MCF-7	[0–100 μM]	OL inhibited the viability of breast cancer cells and induced apoptosis via modulating NF-κB activation cascade	[42]
	MCF-7	[0–1200 μg/mL]	OL suppressed cells migration through suppression of epithelial-mesenchymal transition and could reduce DOX-induced side effects by reducing its effective dose	[43]
	MCF-7	[0–100 μM]	OL decreased the expression of both HDAC2 and HDAC3, induced apoptosis, and retarded cell migration and cell invasion in a dose-dependent manner	[44]
	MCF-7	200, 400, 600, and 1000 μM	OL inhibited the proliferation and invasion of cells by inducing apoptosis	[45]
	MDA-MB-231	[0–100 μM]	OL reduced cell viability in a dose-dependent manner; suppressed HGF or 3-MA, and induced cell migration and invasion	[46]
	MCF-7	[0–250 μM]	OL inhibited protein tyrosine phosphatase 1B (PTB1B)	[47]
	HepG2 and Huh7 human HCC cell lines	[0–100 μM]	OL induced apoptosis in HCC cells via the suppression of PI3K/Akt	[48]

Phenolic Compound	Cell Line	Concentration	Effects	Reference
	HepG2	100, 200 and 300 μM	OL could control the influencing of pro-nerve growth factor (NGF) and NGF balance via affecting MMP-7 activity without affecting the gene expression of NGF in HCC.	[49]
	LNCaP human prostate cancer androgen-responsive and DU145 androgen non-responsive cell lines	100 and 500 μM	OL reduced cell viability and induced thiol group modification	[50]
	TCP-1 and BCPAP thyroid tumor cell line	10, 50, and 100 μM	OL was able to inhibit in vitro thyroid cancer cell proliferation acting on the growth-promoting signal pathway	[51]
	HeLa human cervical carcinoma cell line	150 and 200 μM	OL-induced apoptosis was activated by the JNK/SPAK signal pathway	[52]
	SH-SY5Y human neuroblastoma cell line	350 μM	OL caused cell cycle arrest by down-regulating CyclinD1, CyclinD2, CyclingD3, CDK4, and CDK6 and up-regulating p53 and CDKN2A, CDKN2B, CDKN1A gene expressions. OL also induced apoptosis	[53]
	U251 and A172 human glioma cancer cell lines	0, 200, and 400 μM	OL inhibited cell viability and reduced the expression levels of MMP-2 and MMP-9. In addition, a specific PI3K inhibitor enhanced the pro-apoptotic and anti-invasive effects induced by OL	[54]
	HNE1 and HONE1 human nasopharyngeal carcinoma (NPC) cell lines	0 and 200 μM	OL treatments reduced the activity of the HIF-1α-miR-519d-PDRG1 pathway, which is essential to the radio-sensitizing effect of OL	[55]
	A549 human non-small cell lung cancer (NSCLC)	[0–200 μM]	OL caused a decrease in mithocondrial membrane potential, increase in Bax/Bcl2 ratio, release of mithocondrial cytochrome C, and activation of caspase 9 and caspase 3	[56]
	H1299 lung cancer cell line	[0–200 μM]	OL-induced apoptosis via the mitochondrial apoptotic cascade was activated by the p38 MAPK signaling pathway in H1299 cells	[57]
	A549 and BEAS-2B human noncancerous cell line	50 and 150 μM	OL induced apoptosis in A549 cells	[58]
	MIA PaCa-2, BxPC-3, and CFPAC-1 pancreatic cancer and HPDE non-tumorigenic pancreas cell lines	200 μM	OL arrested cell cycle, increased the Bax/Bcl-2 ratio, increased the activation of caspase 3/7, and induced apoptosis in MIA-PaCa-2	[59]
	A375 human melanoma cell line	[250–500 μM]	OL was able to stimulate apoptosis (500 μM), while at a dose of 250 μM it affected cell proliferation and induced the down-regulation of the pAkt/pS6 pathway	[60]
	OE-19 human esophagical cancer (EC) cell line	200 μM	OL inhibited the growth of EC cells as well as inhibiting HIF-1α and up-regulating BTG anti-proliferation F factor 3 (BTG3) expressions	[61]

Phenolic Compound	Cell Line	Concentration	Effects	Reference
	143B human osteosarcoma (OS) cell line	100 µM	OL showed alone and in combination with 2-methoxyestradiol a potent anti-cancer potential in highly metastatic OS cell	[62]
	AGS Human gastric adenocarcinoma cell line	[0–1000 µg/mL]	Magnetic nano-OL could trigger apoptosis in the AGS cell line	[63]
 OL-aglycone	SH-SY5Y and RIN-5F insulinoma cell lines	100 µM	OL-aglycone triggered autophagy in cultured cells through the $Ca2^{+}$-CAMKKβ–AMPK axis.	[64]

Phenolic Compound	Cell Line	Concentration	Effects	Reference
	HT29 and HCT-116 human colon adenocarcinoma cell line	1, 2, 5, and 10 µg/mL	OLE produced an inhibition of AP1 activity and cyclooxygenase 2 (COX2) expression in HT29 cells	[65]
	MDA-MB-231, MCF-7, and PC3 prostate cancer cell lines	[0–20 µM]	OLE inhibited the proliferation, migration, and invasion of the epithelial human breast and prostate cancer cell lines and demonstrated anti-angiogenic activity	[66]
	BT-474, MDA-MB-231, and MCF-7	[0–60 µM]	OLE reduced the c-Met kinase activity, cell growth, migration, and invasion of breast cancer cells and induced G1 cell cycle arrest and apoptosis, as well as, inhibited c-Met-dependent signaling	[67]
	MDA-MB-231	[0–10 µM]	OLE showed strong anti-proliferative and down-regulated the expression of phosphorylated mTOR	[68]
	BT-474	[0–100 µg/mL]	OLE reduced breast cancer progression and locoregional recurrence models	[69]
	MDA-MB-231	5 mg/mL	OLE was able to control breast cancer progression	[70]
 OLE	BT-474 and MDA-MB-231	[0–200 µM]	OLE with the dual HER2/EGFR inhibitor, LP, induced synergistic tumor growth inhibition	[71]
	MCF-10A, MDA-MB-231, and MCF-7	1, 10, and 20 µM	OLE could be responsible for the selective activation of TRCP6-dependent Ca^{2+} influx and TRCP6 down-regulation at low µM concentrations	[72]
	Huh-7, HepG2, and HCCLM3 HCC cancer cell lines	[0–80 µM]	OLE inhibited proliferation and cell cycle progression and also inhibited HCC cell migration and invasion	[73]
	Huh-7, HepG2, and HCCLM3	5 and 10 µM	OLE reduced cell proliferation and increased cell death	[74]
	U937 hystocytic lymphoma cancer cell line	30 µM	OLE significantly inhibited the expression of Hsp90, a chaperone with a key role in cancer and neurodegeneration	[75]
	A375: A2058; HUVEC and HaCat cancer cell lines	[0–60 µM]	OLE suppressed STAT3 phosphorylation, decreased STAT3 nuclear localization, and inhibited STAT3 transcriptional activity	[76]
	Inmortalized human keratinocytes stimulated with epidermal growth factor	[0–100 µM]	OLE promoted the inhibition of ERK and Akt phosphorylation and the suppression of B-raf expression	[77]

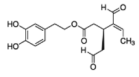
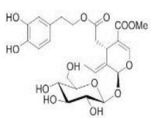
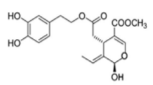
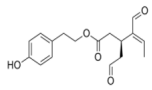
Phenolic Compound	Cell Line	Concentration	Effects	Reference
	Inmortalized human keratinocytes stimulated with epidermal growth factor	[0–100 μM]	OLA promoted the inhibition of Erk and Akt phosphorylation and the suppression of B-raf expression	[77]
 OLA	HL60 human promyelocytic leukemia cell line	[0–10 μM]	OLA reduced the DNA damage at concentrations as low as 1 μM when co-incubated in the medium with H_2O_2	[78]
	NCI-H929; RPMI-8226; U266; MM1S and IIN3 human MM cancer cell lines	2.5, 5 and 10 μM	OLA elicited significant antitumor activity by promoting cell cycle arrest and apoptosis either with a simple agent or in combination with Carfilzomib	[79]

Table 2. Most recent in vivo studies that corroborate the important role of secoiridoids from the olive tree in the control and progression of different types of cancer.

Phenolic Compound	Animal Model	Doses	Effects	Reference
	Swiss albino with soft tissue sarcomas	1% OLE in drinking water	OL inhibited cell growth, motility, and invasiveness	[35]
	Male hairless mice (5 weeks old) were UVB irratied (36–180 mJ/cm^2)	10 and 25 mg/Kg/day	OL increased the skin thickness and reductions in skin elasticity, skin carcinogenesis, and tumor growth	[80]
	DSS-induced CRC in C57BL/6 mice	50 and 100 mg/Kg	OL prevented the development of colonic neoplasia in by ameliorating colon inflammatory processes and limiting the activation of the main transcription factors involved	[81]
	Male Sprague–Dawley rats that received an injection of cisplatin (7 mg/Kg)	50, 100, and 200 mg/Kg/day	OL enhanced antioxidant activity and prevented oxidative stress, which it turn reduced 8-hydroxy-2'deoxy-guanosine (8-OH-dG) levels in lymphocytes of cisplatin-treated animals	[82]
 OL	HNE1 and HONE1 injected into 6–8-week-old BalB/c mice	[0–200 μM]	OL was a radiation-sensitizing agent of NPC cells in an in vivo model	[55]
	Four-week-old C57BL/6N mice with HFD with or without OL and which were injected with B16F10 melanoma cells	0.02% and 0.04% enriched-diets	OL suppressed HFD-induced solid tumor growth and reduced HFD-induced expression of angiogenesis, lymphangiogenesis, and hypoxia markers	[83]
	Male Sprague–Dawley rats that received an injection of cisplatin (7 mg/Kg)	50, 100, and 200 mg/Kg/day	OL significantly decreased the formations of DNA damage and the level of malondialdehyde (MDA), and it increased the levels of total antioxidant status in pancreas tissue samples	[84]
	BalB/c OlaHsd-foxn1 injected with MDA-MB-231	50 mg/Kg	The combined treatment with OL and DOX downregulated the antiapoptosis and proliferation protein, nuclear transcription factor-kappa B (NF-κB), and its main oncogenic target Cyclin D1. It also inhibited the expression of Bcl-2	[85]
	Severe combined immunodeficiency mice (6 weeks-old) that received a subcutaneous injection of OE-19 cancer cells	200 μM	OL inhibited the growth of xenograft EC tumor as well as inhibited HIF-1α and upregulated B-cell translocation gene 3 (BTG3) expressions	[61]
 OL-aglycone	Transgenic hemizygous CRND8 mice harboring a double-mutant gene of APP695 and wild-type control lettermates with 4 and 10 months of age	100 μM	In OL-fed animals, there was a reduction of phospho-mTOR immunoreactivity and phosphorylated mTOR substrate p70 S6K levels	[64]

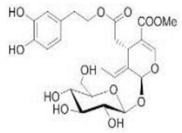
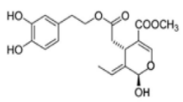
Phenolic Compound	Animal Model	Doses	Effects	Reference
 OLE	Swiss albino mice (6 weeks old)	10 mg/Kg/day	OLE reduced breast cancer progression and locoregional recurrence models	[69]
	Female athymic nude mice (Foxn1^{nu}/Foxn1^{+}) (4-5 weeks-old) inyected with BT-474 and MDa-MB-231	10 mg/Kg/day	OLE inhibited locoregional recurrence in luminal HER^{2+}/ER^{+} BT-474 tumors	[86]
	Orthotopic tumor model of HCC in BalB/c mice	0, 5 and 10 mg/Kg/day	OLE suppressed tumor growth and impeded HCC metastasis in an in vivo lung metastasis model. OLE inhibited STAT3 activation and increased the activity of protein tyrosine hosphatase	[73]

2.2. Olive Tree Secoiridoids and Cardiovascular Diseases

The Global Burden of Disease indicates that cardiovascular diseases are still the main cause of global death, representing about 31% of total deaths in the world in 2015 [87]. These pathologies affect heart and vessels, as coronary heart disease, cerebrovascular disease, peripheral arterial disease, and pulmonary embolism, among others [88]. There is evidence that suggests a possible link between inflammation, endothelial dysfunction, and cardiovascular diseases are increased by oxidative stress. Oxidative stress plays a critical role in the development and progression of atherosclerosis and their complications including characteristics affections such as the regulation of vascular tone, vascular smooth muscle growth, monocyte adhesion, platelet function, and fibrinolytic activity, among others [89]. In terms of risk factors, the three world leading factors for cardiovascular diseases are (i) high systolic blood pressure (SBP), (ii) smoking, and (iii) high body mass index (BMI). Proper nutrition habits and healthy lifestyle play a major preventive role [87].

It has been widely reported that secoiridoids play a beneficial role against cardiovascular diseases based on their antioxidant and anti-inflammatory activities. Interesting studies performed with animal and cell models suggest that secoiridoids intake may be beneficial for the prevention and adjuvant treatment of such diseases (Table 3 and Table 4). Catalán et al. confirmed changes at proteomic level in cardiovascular tissues (aorta and heart tissues), down-regulating proteins related to the proliferation and migration of endothelial cells and occlusion of blood vessels in the aorta, and proteins related to heart failure in heart tissue in Wistar rats fed a secoiridoids-enriched diet [90].

Table 3. Beneficial effects of secoiridoids from the olive tree in the control and progression of different types of cardiovascular diseases: in vitro studies.

Phenolic Compound	Cell Line	Concentration	Effects	Reference
 OL	Healthy human LDL	10 mM	OL inhibited LDL levels, lipid peroxides, malondial dehydelysine, 4-hydroxynonenal lysine adducts expression	[91]
	LPS-stimulates mouse macrophages		OL reduced superoxide anion generation, neutrophils respiratory burst, and hypochlorous acid	[92]
	Endothelial progenitors cells (CD31+ and VEGFR-2^{+})	[1–10 µM]	OL reduced senescent cells and reactive oxygen species (ROS) formation; restoration of migration, adhesion, tube formation, and the up-regulation of Nrf-2 and HO-1 expressions.	[93]
 OL-aglycone	Human umbilical vascular endotelial cells	5 and 25 mM	OL-aglycone reduced cell surface expressions and mRNA levels of ICAM-1 and VCAM-1	[94]
	Mouse atrial myocites HL-1	60 mM	OL-aglycone inhibited tranthyretin toxicity	[95]

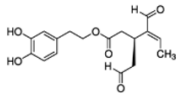
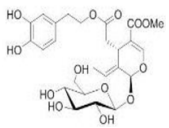
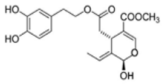
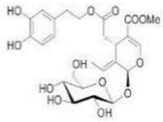
Phenolic Compound	Cell Line	Concentration	Effects	Reference
 OLA	Human neutrophils and monocytes	[1–10 μM]	OLA proved to be stronger in the reduction of formyl-met-leu-phenylalanine and phorbol-myristate-acetate-induced oxidative bursts in neutrophils and myeloperoxidase release	[96]
	Human neutrophils	50 and 100 mM	OLA reduced elastase release, IL-8, MMP-9, and NEP activity	[97]
	Human macrophages	10–20 mM	OLA increased IL-10, HO-1, and CD163 expression	[98]

Table 4. Beneficial effects of secoiridoids from the olive tree in the control and progression of different types of cardiovascular diseases: in vivo and clinical studies.

In Vivo Studies				
Phenolic compound	**Animal Model**	**Doses**	**Effects**	**Reference**
	Ischemia–reperfusion in insolated rat hearts	20 μg/g	OL reduced the creatine kinase, glutathione release, membrane lipid peroxidation	[99]
	Ischemic-treated hypercholesterolemic rabbits	10 or 20 mg/Kg/day	OL reduced the infarct size, total cholesterol, triglyceride concentration, and lipid peroxidation	[100]
	Doxorubicin-induced acute cardiotoxicity rats	100 or 200 mg/Kg	OL modulated the CPK, lactate deshydrogenase, aspartate and alanine aminotransferase, and lipid peroxidation	[101]
	Doxorubicin-induced acute cardiotoxicity in rats	100 or 200 mg/Kg	OL reduced the acetate and succinate levels. Restore metabolic changes	[102]
	Doxorubicin-induced chronic cardiomyopathy in rats	1000 or 2000 mg/Kg	OL controlled cardiac histopathology, nitro-oxidative stress, IL-6, myocardial metabolomics	[103]
 OL	Rabbit model of atherosclerosis	100 mg/Kg	OL decreased lipids, cholesterol, LDL levels, TNF-α, NF-kB, ICAM-1, and VCAM-1 expressions	[104]
	Obesity-induced cardiac metabolic changes	0.023 mg/Kg/day	OL increased oxygen consumption, fat oxidation, and myocardial β-hydroxyacyl coenzyme A dehydrogenase activity and the up-regulation of antioxidant enzyme expression	[105]
	Renovascular hypertension and diabetes 2 rats	20, 40, or 60 mg/Kg/day	OL reduced blood pressure, blood glucose, serum total cholesterol, LDL, and triglycerides levels. Raised HDL levels.	[106]
	Diabetic hypertensive rats	20, 40, or 60 mg/Kg/day	OL lowered blood pressure, MDA, creatine kinase, and the induction of HDL levels	[107]
	Diabetic hypertensive rats	20, 40, or 60 mg/Kg/day	OL decreased blood pressure, glucose, and serum MDA levels. OL increased of HDL and erythrocyte SOD	[108]
	Spontaneous hypertensive rats	10 mg/Kg	OL reduced the oxidative stress, carotid and renal hemodynamics, blood pressure, and heart rate	[109]
	Rats fed with high-cholesterol diet	3 mg/Kg	OL modulated total cholesterol, triglycerides, LDL and HDL levels, and liver antioxidant enzymes	[110]

In Vivo Studies				
Phenolic compound	**Animal Model**	**Doses**	**Effects**	**Reference**
 **OL-aglycone**	**Neonatal rats ventricular myocytes with MAO-A enzyme overexpressed**	**100 µM**	**OL-aglycone decreased oxidative stress, autophagic flux blockade and cell necrosis**	**[111]**
	Mature and progenitor endotelial cells	**10 µM**	**OL-aglycone down-regulated NF-kB, IL-8, vascular endothelial growth factor (VEGF), MMP-2, and MMP-9**	**[112]**
	Rats fed with high-cholesterol diet	**3 mg/Kg**	**OL-aglycone modulated total cholesterol, triglycerides, LDL and HDL levels, and liver antioxidant enzymes**	**[110]**
		Clinical Trials		
Phenolic Compound	**Experimental System**	**Concentration**	**Effects**	**Reference**
 **OL**	**232 hypertensive patients**	**500 mg twice daily**	**OL lowered systolic and diastolic blood pressure, triglycerides, and LDL levels**	**[113]**

One of the best-documented cardiovascular protector secoiridoids is OL. OL inhibited in a dose-dependent manner the copper sulfate-induced oxidation of LDL, reducing the formation of lipid peroxides and malondhial dehydelysine and 4-hydroxynonenol-lysine adducts [91]. These data indicated the protection of the apoprotein layer. Additionally, OL was able to scavenge superoxide anions generated by either polymorphonuclear cells or by the xanthine/xanthine oxidase system [92]. In this line, pretreatment with 20 µg/g of OL before ischemia–reperfusion in isolated rats hearts resulted in a significant reduction in creatine kinase and glutathione release, supporting experimental evidences of a direct cardioprotective effect of OL [99]. More recently, Parzonko and colleagues described that OL-treated endothelial progenitors cells (type CD31+ and VEGFR-2^{+}) showed a decrease in the percentage of senescent cells and ROS formation and restored migration, adhesion, and tube formation. This effect was related to nuclear factor E2-related factor 2 (Nrf2) and heme oxigenase-1 (HO-1) expressions [93] (Table 3).

Relating to animal models, Andreadou and co-workers have developed several in vivo experimental models with OL treatment, defining the potential effect of this secoiridoid as a cardioprotector. Ischemia-treated rabbits fed with 10 or 20 mg/Kg/day OL-supplemented diets showed a reduction in infarct size, total cholesterol, and triglyceride concentrations [100]. Similarly, OL administrated via intravenous decreased some markers of cardiovascular disease in DOX-induced acute cardiotoxic rats such as creatine phosphokinase (CPK), lactate deshydrogenase, aspartate and alanine aminotransferase, and lipid peroxidation in myocardial tissue [101]. Completing this study, these authors revealed that OL down-regulated acetate and succinate levels and restored metabolic changes to normal levels in myocardial tissue [102]. Finally, Andreadou et al. concluded that OL administration could also prevent cardiomyopathy [103] (Table 4).

Concerning studies of atherosclerosis, OL could decreased serum lipids and tumor necrosis factor alpha (TNF-α) levels, which was accompanied by a down-regulation of monocyte chemostactic protein-1 and vascular cell adhesion molecule [104]. Ebaid et al. studied the effects of OL intake in obesity-induced cardiac metabolic changes. They found that an OL diet showed an increase of oxygen consumption, fat oxidation, and myocardial β-hydroxyacyl coenzyme A dehydrogenase activity and a reduction in the levels of lipid hydroperoxide and up-regulation of antioxidant enzyme confirmed that OL improved myocardial oxidative stress in standard-fed conditions [105].

With regard to OL antihypertensive effects, there are several studies performing different animal models. In this line, diabetic and hypetensive rats receiving 20, 40, or 60 mg/Kg/day of OL presented significantly reduced blood pressure, blood glucose, serum total cholesterol, LDL, triglyceride, MDA, coronary effluent creatine kinase, and coronary resistance. The animals also had high-density lipoprotein (HDL), erythrocyte SOD, left ventricular develop pressure, rate of rise, and rate of decrease of ventricular pressure [106][107][108]. Antihypertensive activity has also been supported by Ivanov et al., who reported significant changes in carotid and renal hemodynamics, reducing cardiovascular risk and improving vascular resistance in spontaneous hypertensive rat oxidative stress [109].

Regarding lipid regulation, the administration of OL and its aglycone form significantly down-regulated the serum levels of total cholesterol, triglycerides, and LDL and up-regulated HDL and liver antioxidant enzymes in Wistar rats fed a

cholesterol-rich diet. These results demonstrated that secoiridoids administration could control the lipid peroxidation process, enhancing antioxidant enzyme activity [110].

The clinical trials of the effects of secoiridoids on cardiovascular diseases are scant. In this regard, 232 hypertension patients were involved in a clinical study subjected to a 500-mg oral dose of an OL-enriched extract administration twice daily for 8 weeks. The patients presented a significant reduction of systolic and diastolic blood pressure as well as the levels of triglycerides and LDL [113][114] (Table 4). Stock and colleagues measured cholesterol efflux capacity from free cholesterol-enriched macrophages to apolipoprotein B-depleted serum as the cholesterol acceptor in patients with coronary artery disease. OL showed a positive behavior against LDL oxidation, promoting cholesterol efflux and suggesting preventive effects against coronary artery diseases and enhanced atheroprotective actions [115].

According to OL aglycone, only few studies have been carried out. Dell'agli et al. described that OL aglycone exerted a modulation in early atherogenesis, reducing cell surface expressions of intracellular and vascular cell adhesion molecules (ICAM-1 and VCAM-1) in human umbilical vascular endothelial cells [94]. Similar to OL, the aglycone form was studied in rats fed with a cholesterol-rich diet by Jemai el at. The results suggested that the hypocholesterolemic effect of OL-aglycone might be due to its abilities to lower serum total cholesterol, triglycerides, and LDL cholesterol levels, slowing the lipid peroxidation process and enhancing SOD and CAT antioxidant enzyme activities, exhibiting a cardioprotective role against lipid oxidation and cholesterol efflux [110].

More recently, Leri et al. reported that OL-aglycone was able to reduce transthyretin toxicity in mouse atrial myocytes, so it could be used as treatment for severe cardiac symptoms [95]. In addition, Miceli and coworkers explored the effects of OL-aglyone in myocytes with an overexpression of monoamine oxidase-A (MAO-A), which is an enzyme that causes oxidative stress, autophagy flux blockade, and cell necrosis as a model of cardiac stress characterized by autophagy dysfunction. They observed that OL-aglycone counteracted the cytotoxic MAO-A effects [111]. Margheri et al. also reported the effects of OL aglycone on capillary morphogenesis induced by MRC5 fibroblast "senescense associated secretory phenotype" and progenitor endothelial cells, establishing that this secoiridoid could modulate angiogenesis indirectly on senescent fibroblasts [112] (Table 4).

To date, OLE cardioprotective activity has been slightly investigated. Even so, some authors defend its cardioprotective property based on its capacity to inhibit COX-1 and COX-2 expression. It is well-known that thrombotic and cardiovascular disorders are linked to an imbalance in prostanoid homeostasis, particularly prostaglandin or thromboxane production, which are involved in vasodilatation or vasoconstriction, respectively, and platelet aggregation [116]. OLE has exerted strong inhibitory effects on COX-1 and COX-2 in several studies [117][118][119]; nevertheless, future studies are needed to confirm the property of OLE in cardiovascular disorders (Table 3).

The cardiovascular protection effects of OLA were tested in vitro in human neutrophils and monocytes. This compound was able to scavenge O_2^-, H_2O_2, and NO levels, among other parameters, which are implicated in tissue injury and chronic diseases, as atherosclerosis [96][120]. In a similar work, Czerwinska et al. studied the capacity of OLA on neutral endopeptidase (NEP) activity and other functions of human neutrophils, such as elastase, MMP-9 and interleukin (IL)-8 production, which was markedly increased in patients with myocardial infarction [96]. The authors concluded that OLA could play a role in the cardiovascular protective effects described by olive oil by inhibiting NEP activity, adhesion molecules expression, and elastase release. Likewise, Filipek and colleagues showed that OLA increased CD163 expression in human macrophages, supporting the significant role in attenuation of plaque destabilization induced by hemorrhages [98]. Later, these authors reported the beneficial effects of OLA in attenuating the destabilization of carotid plaque in 20 patients with hypertension. This work revealed the ability of OLA to modulate IL-10, HO-1, MMP-9, and high mobility group protein-1, which is a specific biomarker of cell lethality [121]. Thus, this compound could be potentially useful in the reduction of ischemic stroke risk. Concluding, the preventive and curative role of OLA, in terms of cardiovascular injury, could be attributed to its ability to regulate LDL oxidation and MPO activity, to reduce the expression of adhesion molecules, as angiotensin II production, and to confer protection to erythrocytes from oxidative hemolysis [122][123].

2.3. Olive Tree Secoiridoids and Neurodegeneration

Neurodegeneration is a process that leads to a progressive loss of structure or function of neurons, irreversible neuronal damage, death, and a common final pathway present in aging and neurodegenerative diseases. In addition, oxidative stress induced by impaired mitochondrial functions has been also reported [124]. Particularly, superoxide anion formation and the production of hydrogen peroxide are triggered by the induction of NADPH oxidase (NOX) subunit. This condition together with a high NO level, produced by the induction of inducible nitric oxide synthase (iNOS) results in the formation of peroxynitrite and nitrative stress [125]. Examples of neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and the

spinocerebellar ataxias [126]. These diseases represent a primary health problem, especially in the aging population. Powerful experimental model organisms such as the mouse, fruit fly, nematode worm, and even baker's yeast have been used for many years to explore neurodegenerative diseases and have provided key insights into these brain disorders.

Several epidemiological and observational studies support the belief that traditional alimentary regimens such as the Mediterranean diet where olive oil is the primary source of added fat is associated with improved aging and a reduced incidence of age-related diseases, including cardiovascular diseases, cancer, and cognitive decline [127]. Particularly, olive leaves and EVOO contain many functional phenolics that have been demonstrated to be able to reduce risk and offer protection against several aging and lifestyle-related diseases, including neurodegeneration, in both animal and human's models. In fact, EVOO consumption has well-documented antioxidant, anti-inflammatory, anti-proliferative, anti-carcinogenic, and antibacterial effects [128]. Among the 200 different chemical compounds detected in olive oil, quantitatively, the class of secoiridoids is the most abundant. A number of different studies investigated the effects of secoiridoids from olive trees in both in vitro and in vivo models of AD and PD (Table 5 and Table 6).

Table 5. In vitro studies that corroborate the effects of secoiridoids from the olive tree in different types of neurodegeneration processes.

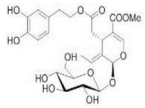
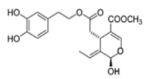
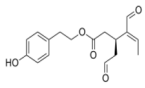
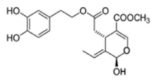
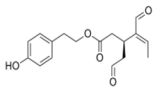
Phenolic Compound	Cell Line	Concentration	Effects	Reference
 OL	6-OHDA-induced toxicity in rat adrenal pheochromocytoma (PC12) cells	20 and 25 µg/mL	OL decreased cell damage and reduce biochemical markers of PC12 cell death	[129]
	PC12 cells exposed to the potent parkinsonian toxin 6-OHDA	10 $^{-12}$ M	OL showed neuroprotective effects in an in vitro model of PD when administered preventively as a pretreatment. OL significantly decreased neuronal death. OL could also reduce the mitochondrial production of ROS resulting from blocking SOD activity	[130]
	SH-SY5Y	[0–25 µM]	OL-aglycone prevented the growth of toxic Aβ1-42 oligomers and blocked their successive growth into mature fibrils following its interaction with the peptide N-terminus	[131]
 OL-aglycone	Exposure of SH-SY5Y cells with Aβ42	[10–1000 µM]	OL were able to attenuate cell death caused by Aβ42, copper-Aβ42, and [laevodihydroxyphenylalanine (l-DOPA)] l-DOPA-Aβ42-induced toxicity after 24 h	[132]
	NBM of adult male Wistar rats	450 µM	An apparent reduction in the amount of soluble A11-positive oligomers was detected in the NBM injected with Aβ42 aggregated with OL as compared with the NBM injected with Aβ42 alone	[133]
 OLE	Mouse brain endothelial cells (bEnd3)	25 and 50 µM	Treatment of bEnd3 cells with OLE resulted in significant increase in P-gp and LRP1 levels	[131]

Table 6. In vivo studies that corroborate the effects of secoiridoids from the olive tree in different types of neurodegeneration processes.

Phenolic Compound.	Animal Model	Doses	Effects	Reference
 OL-aglycone	Double transgenic TgCRND8 mice, a model of amyloid-ß deposition	8 weeks dietary supplementation of OL-aglycone (50 mg/Kg of diet)	Dietary supplementation of OL-aglycone strongly improved the cognitive performance of young/middle-aged TgCRND8 mice, with respect to age-matched littermates with unsupplemented diet	[134]
	Transgenic mice (APPswe/PS1dE9)	50 mg/Kg of OL-aglycone containing olive leaf extracts (OLE) from 7 to 23 weeks of age.	Treatment mice (OL-aglycone) were showed significantly reduced amyloid plaque deposition ($p < 0.001$) in cortex and hippocampus in comparison	[132]
	Transgenic CL2006 and CL4176 strains of *C. elegans*	50 and 100 µM	OL-aglycone-fed CL2006 worms displayed reduced Aβ plaque deposition, less abundant toxic Aβ oligomers, remarkably decreased paralysis, and increased lifespan	[135]
	Systemic amyloidosis murine model	15 µM	OL-aglycone hindered amyloid aggregation of Aβ(1-42) and its cytotoxicity and eliminated the appearance of early toxic oligomers, favoring the formation of stable harmless protofibrils, which were structurally different from the typical Aβ(1-42) fibrils	[136]
	TgCRND8 mice	50 mg/Kg of diet during 8 weeks	OL-aglycone was active against glutaminylcyclase-catalyzed pE3-Aß generation, reducing enzyme expression and interfering both with Aß42 and pE3-Aß aggregation	[133]
	TgCRND8 (Tg) mice AD	Diet supplementation with OL-aglycone at 12.5 or 0.5 mg kg-1of diet	An OL-aglycone supplementation diet and the mix of polyphenols were found to improve significantly cognitive functions ($p < 0.0001$). Aß42 and pE-3Aß plaque area and number were significantly reduced in the cortex	[137]
	5xFAD mouse model of AD	EVOO rich with OLE	EVOO-rich OLE consumption in combination with donepezil significantly reduced Aβ load and related pathological changes	[138]
 OLE	TgSwDI mice	Daily i.p. with 5 mg/Kg OLE at 4 age of months and continued for 4 weeks.	OLE significantly decreased amyloid load in the hippocampal parenchyma and microvessels, which was associated with enhanced cerebral clearance of Aβ across the BBB	[139]
	C57BL/6 wild-type male mice	10 mg/Kg of OLE twice daily from 7 to 8 weeks of age andcontinued for 2 weeks (i.p.)	OLE enhanced clearance of Aβ from the brain. A significant increase in the expression of P-gp and LRP1 was also observed in the brain microvessels	[140]

AD is characterized by the increased accumulation of intracellular neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein and of extracellular Aβ protein deposits (Aβ plaques) derived from amyloid precursor protein (APP) cleavage by γ-secretase and β-secretase. Dietary supplementation of OL (50 mg/Kg of diet) strongly improved the cognitive performance of young/middle-aged/aged TgCRND8 mice, and it also reduced ß-amyloid levels and plaque deposits. Moreover, OL-aglycone-fed mice brain displayed an astonishingly intense autophagy reaction [133][134][137]. Similar results were described in transgenic mice (APPswe/PS1dE9), where OL treatment showed significantly reduced amyloid plaque deposition in the cortex and hippocampus as compared to control mice [132]. Moreover, OL hindered the amyloid aggregation of Aβ (1-42) and its cytotoxicity and eliminated the appearance of early toxic oligomers, favoring the formation of stable harmless protofibrils, which were structurally different from the typical Aβ (1-42) fibrils [136]. Using transgenic CL2006 and CL4176 strains of *C. elegans* strains expressing Aβ42, as a simplified invertebrate model of AD, Diomede et al. evidenced that 50–100 µM OL-fed CL2006 worms displayed reduced Aβ plaque deposition, less abundant toxic Aβ oligomers, remarkably decreased paralysis, and increased lifespan with respect to untreated animals. A protective effect was also observed in CL4176 worms but only when OL was administered before the induction of the Aβ transgene expression [135] (Table 6).

In vitro studies have revealed that OL prevented the growth of toxic Aβ1-42 oligomers and blocked their successive growth into mature fibrils following its interaction with the peptide N-terminus and attenuated SH-SY5Y cell death caused by Aβ42, copper-Aβ42, and laevodihydroxyphenylalanine (l-DOPA)-Aβ42-induced toxicity after 24 h treatment, and a marked attenuated Aβ-induced astrocytes and microglia reaction was also found in the nucleus basalis magnocellularis (NBM) from adult male Wistar rats injected with Aβ42 aggregated with OL [129][132][135] (Table 5).

The potential protective effect of OLE in AD has been also investigated in TgSwDI mice. Mice treated for 4 weeks with OLE significantly decreased amyloid load in the hippocampal parenchyma and microvessels. This reduction was associated with enhanced cerebral clearance of Aβ across the blood–brain barrier (BBB), which was accompanied by an increase of P-glycoprotein (P-gp) and low density lipoprotein receptor-related protein 1 (LRP1) expressions, and activated the ApoE-dependent amyloid clearance pathway in the mice brains. The anti-inflammatory effect of OLE in the brains of these mice was also obvious where it was able to reduce astrocytes activation and IL-1β levels [139]. Similarly, 10 mg/kg of OLE administrated twice daily from 7 to 8 weeks of age and continued for 2 weeks (i.p.) enhanced the clearance of Aβ from C57BL/6 wild-type male mice brain and significantly increased the expression of P-gp and LRP1 [140]. In mouse brain endothelial cells (bEnd3), 25 and 50 μM OLE treatment resulted in a significant increase in P-gp and LRP1 levels [140]. Moreover, in a 5xFAD mouse model of AD, OLE-rich EVOO consumption, in combination with donepezil, significantly reduced Aβ load and related pathological changes, up-regulated synaptic proteins, enhanced BBB tightness, and reduced neuroinflammation associated with Aβ pathology [138] (Table 5 and Table 6).

PD is characterized by a progressive loss of dopaminergic neurons in the midbrain region known as *substantia nigra pars compacta* and by the presence of cytoplasmic protein aggregates called the Lewy body as well as Lewy neurites in remaining neurons.

Previous studies showed that OL inhibited αSN amyloidogenesis by directing αSN monomers into small αSN oligomers with lower toxicity, thereby suppressing the subsequent fibril growth phase [141]. The neuroprotective effect of OL has been explored in PC12 cells exposed to the potent parkinsonian toxin 6-hydroxydopamine (6-OHDA). OL treatment significantly decreased neuronal death and reduced the mitochondrial production of ROS resulting from blocking superoxide dismutase activity. Moreover, the quantification of autophagy and acidic vesicles in the cytoplasm alongside the expression of specific autophagy markers uncovered a regulatory role for OL against autophagy flux impairment induced by bafilomycin A1 [129][130].

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