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Review

Natural Sources, Pharmacological Properties, and Health Benefits of Daucosterol: Versatility of Actions

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Abstract: Daucosterol is a saponin present in various natural sources, including medicinal plant families. This secondary metabolite is produced at different contents depending on species, extraction techniques, and plant parts used. Currently, daucosterol has been tested and explored for its various biological activities. The results reveal potential pharmacological properties such as antioxidant, antidiabetic, hypolipidemic, anti-inflammatory, immunomodulatory, neuroprotective, and anticancer. Indeed, daucosterol possesses important anticancer effects in many signaling pathways, such as an increase in pro-apoptotic proteins Bax and Bcl2, a decrease in the Bcl-2/Bax ratio, upregulation of the phosphatase and tensin homolog (PTEN) gene, inhibition of the PI3K/Akt pathway, and distortion of cell-cycle progression and tumor cell evolution. Its neuroprotective effect is via decreased caspase-3 activation in neurons and during simulated reperfusion (OGD/R), increased IGF1 protein expression (decreasing the downregulation of p-AKT3 and p-GSK-3b4), and activation of the AKT5 signaling pathway. At the same time, daucosterol inhibits key glucose metabolism enzymes to keep blood sugar levels within normal ranges. Therefore, this review describes the principal research on the pharmacological activities of daucosterol and the mechanisms of action underlying some of these effects. Moreover, further investigation of pharmacodynamics, pharmacokinetics, and toxicology are suggested.

Keywords: daucosterol; anticancer; pharmacodynamic; signaling pathways; therapeutic effects

1. Introduction

Daucosterol [(3β)-stigmast-5-en-3-yl β-D-glucopyranoside], a natural β-sitosterol glucoside, is a saponin phytosterol belonging to different families and genera found in several countries such as China, Vietnam, Mexico, Algeria, Tunisia, Italy, Iran, Cameroon, Saudi Arabia, Nigeria, Korea, and India [1–4].

Daucosterol is the major component of several plant extracts, namely Chinese *Fallopia cillinerve* root extract [1], *Dendrobium huoshanense* and *Dendrobium officinale* stem extract [5], and *Hyssopus cuspidatus* Boriss aerial part extract [6]. In addition, this natural agent was found to be the main component of aerial part extracts of *Centaurea resupinata* subsp. *dufourii* [7] and *Ononis mitissima* L. [8] from Algeria. It was also detected at high concentrations in leaf and stem extracts of *Prangos ferulacea* from Iran [9], aerial part extracts of *Cassia italic* collected from Saudi Arabia [3], and leaf extracts of *Ficus deltoidea* from Indonesia [10] and *Dioscorea batatas* collected from Korea [11]. Furthermore, daucosterol is the principal component of aerial part extracts of *Astragalus tanae* found in Italy [12] and *Landolphia owariensis* collected from Nigeria [13], as well as whole plant and root extracts of *Rheum turkestanicum* from Iran [14,15]. Other investigations have reported high contents of daucosterol in plant extracts, namely *Archidendron clypearia* harvested in Vietnam [16] and *Parasenecio pseudotaimingasa* leaf extract [17] and *Grewia optiva* Drummond ex Burret stem bark extract in Pakistan [18].

Concerning the purification and isolation of daucosterol from plants, several methods have been used as spectroscopic techniques, including NMR and FT-IR, on the stems and leaves of *Prangos ferulacea* [9] and the aerial parts of *Cassia italica* [3] and *Ononis mitissima* L. [8]. NMR (^{1}H NMR, ^{13}C NMR, COSY, HSQC, and HMBC) and mass spectroscopy (ESI–MS) have been used to elucidate daucosterol in *Centaurea resupinata* subsp. *Dufourii* [7]. This molecule has been elucidated from *Dioscorea opposite* with silica gel column chromatography (SGCC) using CHCl3-MeOH [19], from *Phyllenthus emblica* L. with thin layer chromatography (TLC) [20], from *Portulaca oleracea* L. [21] and *Eriobotrya fragrans* Champ [22] with ^{1}H and ^{13}C aided by HMQC, and from *Arctotis arctotoides* [23] using NMR (COSY, NOESY, HMQC, and HMBC) and mass spectra.

Several studies have highlighted the pharmacological properties of daucosterol, including chemopreventive [24–26], neuroprotective [27–30], antioxidant [7–9], anti-inflammatory [31], antidiabetic [32], inhibition and interactions of alpha-amylase by daucosterol from the peel of Chinese water chestnut [33], and immunomodulatory [34]. Immunoregulatory activity by daucosterol, a β-sitosterol glycoside, induces a protective Th1 immune response against disseminated Candidiasis in mice [35]. Regarding its chemopreventive potential, daucosterol was found to possess important anticancer activity on various tumor cell lines and could be considered as one of the novel pharmacological treatment strategies for cancer: for breast adenocarcinoma through different cellular and molecular mechanisms, such as an increase in pro-apoptotic protein Bax and Bcl2, a decrease in the Bcl-2/Bax ratio, upregulation of the PTEN gene, inhibition of the PI3K/Akt pathway, loss of mitochondrial membrane potential and cytochrome c (Cyt c) [36,37], repression of cell migration and invasion, and induction of cell death by cell-cycle arrest and apoptosis [38,39]; for lung cancer by increasing reactive oxygen species (ROS) level and promoting intrinsic apoptotic cell death on A549 cells mediated by increased expression of caspase-3, caspase-9, Bax, PARP inactivation, Cyt c release, and diminished bcl-2 protein expression; and for hepatocellular carcinoma by inhibiting the proliferation, migration, and invasion of hepatocellular carcinoma cells via Wnt/β-Catenin signaling [40]. Daucosterol has also been shown to exert a neuroprotective action by decreasing caspase-3 activation in neurons treated with oxygen–glucose deprivation and simulated reperfusion (OGD/R), as well as increasing the expression level of IGF1

protein, reducing the downregulation of p-AKT3 and p-GSK-3b4, thus activating the AKT5 signal pathway [28]. Further, daucosterol showed a neuroprotective property against H_2O_2-induced oxidative stress mediated through downregulation of MAPK pathways, minimizing ROS, and upregulation of antioxidant gene expression (HO-1, CAT, and SOD_2) [41]. It could play a key role as an antioxidant by fighting against free radicals [3,8,9], which lead to a potential reduction of the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical. This molecule can also act as an antidiabetic agent; it could be considered a great candidate to prevent hyperglycemia due to its antidiabetic activity through the inhibition of α-glucosidase [42] and α-amylase enzymes [33]. In addition, this molecule has been shown to act as a promising anti-inflammatory drug that notably decreases nitric oxide (NO) content in different inflammatory tests [43,44]. Furthermore, other studies have demonstrated that daucosterol possesses immunomodulatory potential [34]. It was able to regulate the population and activation of immune cells, including Treg cells, macrophages, B1 cells, and NK cells in colitis mediated by suppressing the release of inflammatory cytokines such as IL-6, TNF-α, IFN-γ, and IL-1β [31]. Further, this natural compound has shown potent lipolysis activity and could be used by physicians in the management of certain types of disease, thus conferring medicinal principles [35]. It was found to exhibit hypolipidemic actions with a sharp decrease in serum total cholesterol, triglyceride, and low-density lipoprotein cholesterol (LDL-C) levels [45] Nevertheless, daucosterol did not show antibacterial activity [23].

This review has attempted to compile a complete and current understanding of the origin, phytochemical, biological, and pharmacological process analysis of the daucosterol molecule, providing an overview to explain its mechanism of action (in vitro and in vivo) and its future applications in drug discovery, particularly for neuroprotective and chemopreventive effects.

2. Sources of Daucosterol

Daucosterol (Figure 1), a natural sterol, is a glucoside of β-sitosterol, mainly synthesized by plants (Table 1). Daucosterol is the major component of Chinese *Fallopia cillinerve* root extract [1], *Dendrobium huoshanense* stem extract, and *Dendrobium officinale* [5]. The richness of the compound depends on geographical factors and the plant part used. *Hechtia glomerata* Zucc from Mexico is characterized by its richness in daucosterol [2]. Additionally, daucosterol is the major compound in *Crataegus gracilior* flowers [46,47], *Litsea cubeba* extract [4], and Chinese plants *Eleocharis dulcis* [33] and *Ipomoea batatas* [25]. Other works have mentioned the richness of Cameroonian plants such as *Crateva adansonii* (stem bark and leaves) in this compound [24,48].

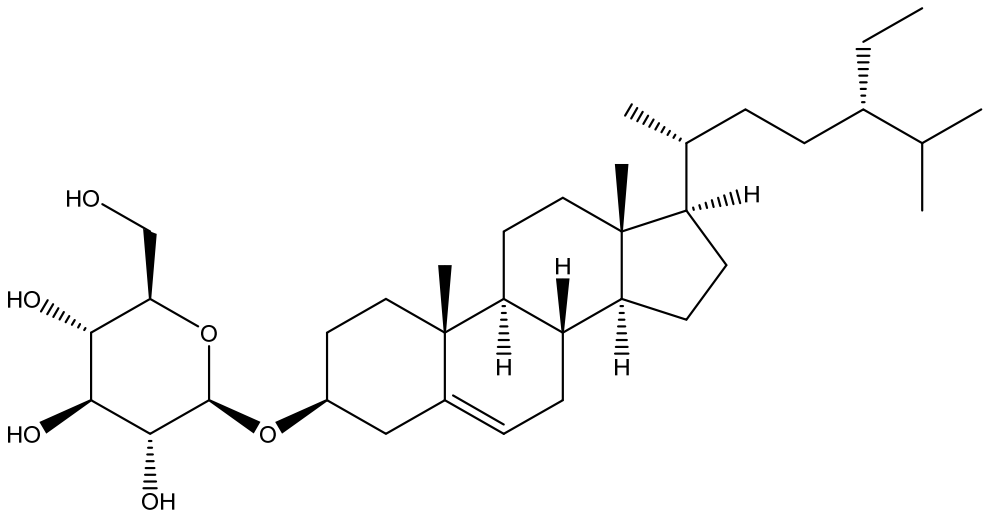

Figure 1. Chemical structure of Daucosterol.

Hyssopus cuspidatus Boriss aerial part extract showed that daucosterol is the major compound of this plant collected in China [6], as well as of *Dioscorea batatas* collected in Korea [11] and *Ficus deltoidea* leaf extract harvested from Indonesia [10]. Daucosterol is the major compound of the extract of *Astragalus tanae* aerial parts collected in Italy [12], of the fruit extract of *Acanthopanax sessiliflorus* (Rupr. and Maxim.), collected in China [49], of the aerial part extracts of *Centaurea resupinata* subsp. *Dufourii* [7] and *Ononis mitissima* L. [8] collected in Algeria. It has also been detected in the extracts of *Prangos ferulacea* leaves and stems collected in Iran [9] and the extract of *Cassia italic* aerial parts collected in Saudi Arabia [3].

Daucosterol is an isolate of different plants of the caprifoliaceae family harvested in China: Dipsacus chinensis, Dipsacus asperoides, Dipsacus japonicas, Dipsacus kangdigensis, and Dipsacus daliensis [50]. Analysis of Rheum turkestanicum whole plant and root extract showed that daucosterol is the major compound of this plant collected in Iran [14,15], of Heracleum persicum [15] and Landolphia owariensis collected from Nigeria [13], and of Streptocaulon griffithii [51] and Streptocaulon griffithii whole plant extract [51].

Richness in daucosterol has also been recorded in other plant extracts, namely *Archidendron clypearia* collected in Vietnam [16], *Shibataea chinensis* Nakai leaves from China [52], and *Morus alba* leaves from Korea [35]. Likewise, other extracts have been characterized by the dominance of this compound, such as the roots of *Geranium collinum* [53] and the leaves of *Lasianthus hartii* [54], *Salvia syriaca*, *Sedum caeruleum*, *Adenophora triphylla*, *Pulicaria inuloides*, *Salvia miltiorrhiza*, *Salvia officinalis*, and *Rosa canina* L. [27,28,55–58].

Indeed, daucosterol is the major compound of many plant extracts, such as extracts of the whole plant *Clematis heracleifolia* collected in Korea [59], aerial parts of *Dorema glabrum* Fisch. and C.A. Mey. collected in Iran [60], *Artemisia apiacea* [34,61], seeds of *Juglans regia* [28], peels and pulps of *Pyrus* spp. [62], *salvia sahendica*, *Punica granatum*, *Helicteres isora* L., *Ceiba pentandra* L., *Eria spicata*, *Lysimachia clethroides*, and *Randia dumetorum* [63–68].

Daucosterol has been isolated from *Litchi chinensis* seed extract [69], *Parasenecio pseudotaimingasa* leaf extract [17], *Grewia optiva* Drummond ex Burret stem bark extract collected in Pakistan [18], *Urtica angustifolia* leaf, root, and stem extracts [70], and *Salvia limbata* aerial part extracts from Iran, Turkey, and Afghanistan [71]. Further, it has been found in stem extracts of *Lindera glauca* [72], *Sphallerocarpus gracilis*, *Hypericum ascyron* L., *Paeonia lactiflora, Paeonia suffruticosa*, *Alangium kurzi*, *Boerhaavia diffusa*, and *Cassia mimosoides* var. [72–78].

Furthermore, daucosterol is among the major compounds of *Phyllenthus emblica* L. [20], *Mitragyna speciose* [79], *Astragalus membranaceus* [80], stem bark and twig extracts of *Bennettiodendron leprosipes* [81], *Flacourtia ramontchi* [81], *Alchornea cordifolia* (Schumach. and Thonn.) Müll. Arg. [82], *Flueggea virosa* [83], *Eriobotrya fragrans* [22], *Portulaca oleracea* L. [21], *Pteridium aquilinum* [84], and *Brassica campestris* ssp *rapa* [85].

This has also been observed with extracts of Penthorum chinense, Arctotis arctotoides, Selinum cryptotaenium, Embelia ribes, Punica granatum, Dioscorea opposita, Junellia aspera, Sitophilus oryzae, Astragalus mongholicus Bunge, Hemiphragma heterophyllum, Dendrobium moniliforme, Punica granatum, *Nepeta cataria* L. var. citriodora [19,23,86–95], Euphorbia altotibetic [96], Rhodiola sachalinensis roots [97], Gnetum montanum [98], and Ajania fruticulosa aerial parts.

Table 1. Sources of Daucosterol.

Plant Family	Country	Parts Used	References
Fallopia cillinerve Polygonaceae	China	Roots	[1]
Litsea cubeba Lauraceae	Vietnam	Not reported	[4]
Hechtia glomerata Zucc Bromeliaceae	Mexico	Leaves	[2]
Eleocharis dulcis Cyperaceae	China	Not reported	[33]
Ipomoea batatas Convolvulaceae	China	Not reported	[25]
Dendrobium huoshanense Orchidaceae	China	Stems	[5]
Dendrobium officinale Orchidaceae			
Crataegus gracilior Rosaceae	Mexico	Flowers	[46]
Hyssopus cuspidatus Boriss. Lamiaceae	China	Aerial parts	[6]
Ficus deltoidea Moraceae	Indonesia	Leaves	[10]
Dioscorea batatas Dioscoreaceae	Korea	Not reported	[11]
Crateva adansonii Capparaceae	Cameroon	Stem bark	[24]
		Leaves	[48]
Astragalus tanae Fabaceae	Italy	Aerial parts	[12]
Acanthopanax sessiliflorus (Rupr. and Maxim.) Seem. Araliaceae	China	Fruits	[49]
Centaurea resupinata subsp. *dufourii* Asteraceae	Algeria	Aerial parts	[7]
Ononis mitissima L. Fabaceae	Algeria	Aerial parts	[8]
Prangos ferulacea Apiaceae	Iran	Leaves and stems	[9]
Cassia italica Fabaceae	Saudi Arabia	Aerial parts	[3]
Dipsacus chinensis Caprifoliaceae	China	Roots	[50]
Dipsacus asperoides Caprifoliaceae			
Dipsacus japonicas Caprifoliaceae			
Dipsacus kangdigensis Caprifoliaceae			
Dipsacus daliensis Caprifoliaceae			

Rheum turkestanicum Polygonaceae	Iran	Whole plant Roots	[14,15]
Heracleum persicum Apiaceae	Iran	Whole plant	[15]
Landolphia owariensis Apocynaceae	Nigeria	Leaves	[13]
Streptocaulon griffithii Asclepiadaceae	China	Not reported	[51]
Streptocaulon griffithii Asclepiadaceae	China	Whole plant	[51]
Archidendron clypearia Fabaceae	Vietnam	Whole plant	[16]
Shibataea chinensis Nakai Gramineae	China	Leaves	[52]
Morus alba Moraceae	Korea	Leaves	[35]
Geranium collinum Geraniaceae	China	Roots	[53]
Lasianthus hartii Rubiaceae	China	Leaves	[54]
Salvia syriaca Lamiaceae	Iran	Roots	[55]
Sedum caeruleum Crassulaceae	Algeria	Aerial parts	[56]
Adenophora triphylla Campanulaceae	Korea	Not reported	[27]
Pulicaria inuloides Asteraceae	Yemen	Aerial parts	[57]
Salvia miltiorrhiza Lamiaceae	China	Roots	[28]
Salvia officinalis Lamiaceae	China	Roots	[28]
Rosa canina L. Rosaceae	Iran	Fruits	[58]
Dorema glabrum Fisch. and C.A. Mey. Apiaceae	Iran	Aerial parts	[60]
Clematis heracleifolia Ranunculaceae	Korea	Whole plant	[59]
Artemisia apiacea Asteraceae	Korea	Not reported	[61,99]
Pyrus spp. Rosaceae	China	Peels and pulps	[62]
Salvia sahendica Lamiaceae	Iran	Aerial parts	[36]
Punica granatum Lythraceae	Tunisia	Flowers	[64]
Helicteres isora L. Sterculiaceae	India	Fruits	[65]
Ceiba pentandra L.		Seeds	

Bombacaceae			
Eria spicata Orchidaceae	China	Whole plant	[68]
Lysimachia clethroides Primulaceae	China	Aerial parts	[66]
Randia dumetorum Rubiaceae	Not reported	Bark	[67]
Litchi chinensis Sapindaceae	China	Seeds	[69]
Parasenecio pseudotaimingasa Asteraceae	Korea	Leaves	[17]
Grewia optiva Drummond ex Burret Tiliaceae	Pakistan	Stem bark	[18]
Urtica angustifolia Urticaceae	China	Leaves, roots, and stems	[74]
Salvia limbata Lamiaceae	Iran, Turkey, and Afghanistan	Aerial parts	[71]
Lindera glauca Lauraceae	Korea	Stems	[72]
Sphallerocarpus gracilis Apiaceae	China	Roots	[73]
Hypericum ascyron L. Hypericaceae	China	Whole plant	[74]
Paeonia lactiflora Paeoniaceae	Korea	Roots	[75]
Paeonia suffruticosa Paeoniaceae		Root bark	
Alangium kurzi Alangiaceae	Indonesia	Stem bark	[76]
Boerhaavia diffusa Nyctaginaceae	Nigeria	Leaves	[77]
Cassia mimosoides var. *nomame* Makino Fabaceae	Korea	Seeds	[78]
Phyllenthus emblica L. Phyllanthaceae	China	Fruits	[20]
Mitragyna speciosa Rubiaceae	America	Leaves	[79]
Astragalus membranaceus Fabaceae	Korea	Roots	[80]
Bennettiodendron leprosipes Flacourtiaceae	China	Stem bark and twigs	[81]
Flacourtia ramontchi Flacourtiaceae		Bark and twigs	
Alchornea cordifolia (Schumach. and Thonn.) Müll. Arg. Euphorbiaceae	Belgium	Leaves and root bark	[82]
Flueggea virosa Euphorbiaceae	China	Twigs and leaves	[83]
Eriobotrya fragrans Champ	China	Fruits and leaves	[22]

Rosaceae			
Portulaca oleracea L. Portulacaceae	Egypt	Not reported	[21]
Pteridium aquilinum Pteridaceae	China	Not reported	[84]
Brassica campestris ssp *rapa* Brassicaceae	Korea	Roots	[85]
Penthorum chinense Penthoraceae	China	Whole plant	[86]
Arctotis arctotoides Asteraceae	Not reported	Not reported	[23]
Selinum cryptotaenium Umbelliferae	China	Roots	[87]
Embelia ribes Myrsinaceae	China	Roots	[88]
Punica granatum Lythraceae	China	Flowers	[89]
Dioscorea opposita Dioscoreaceae	China	Aerial parts	[19]
Junellia aspera Verbenaceae	Spain	Aerial parts	[90]
Sitophilus oryzae Curculionidae		Not reported	
Astragalus mongholicus Bunge Fabaceae	China	Roots	[91]
Hemiphragma heterophyllum Scrophulariaceae	China	Whole plant	[92]
Dendrobium moniliforme Orchidaceae	China	Stems	[95]
Punica granatum Lythraceae	China	Seeds	[93]
Nepeta cataria L. var. citriodora Lamiaceae	Poland	Seeds	[94]
Euphorbia altotibetic Euphorbiaceae	China	Whole plant	[96]
Rhodiola sachalinensis Crassulaceae	Korea	Roots	[97]
Gnetum montanum Gnetaceae	China	Not reported	[98]
Ajania fruticulosa Asteraceae	China	Aerial parts	[100]
Rhodiola fastigiata Crassulaceae	China	Rhizomes	[101]
Jatropha curcas Euphorbiaceae	China	Roots	[102]
Gentiana algida Gentianaceae	China	Whole plant	[103]
Gentiana siphonantha Gentianaceae	China	Rhizomes and roots	[104]
Gentiana scabra Bunge	China	Roots	[105]

Gentianaceae			
Rabdosia coetsa Lamiaceae	China	Leaves	[106]
Artemisia sieversiana Asteraceae	China	Aerial parts	[105]
Inula racemosa Asteraceae		Roots	
Amanoa oblongifolia Euphorbiaceae	Peru	Stem bark	[107]
Rhodiola rosea L. Crassulaceae	Russia	Rhizomes	[108]
Acanthopanax sessiliflorum Araliaceae	Not reported	Roots	[109]
		Leaves	

3. Extraction and Characterization

Many research groups have isolated and purified daucosterol from various medicinal plants [3,7,49], as showed in Table 2.

Table 2. Extraction and characterization of Daucosterol.

Plant Family	Parts Used	Extraction Method	Extraction Parameters	Purification Method	Yields	References
Prangos ferulacea Apiaceae	Leaves and stems	Maceration	750 g extracted by 3 L of *n*-hexane, dichloromethan, ethyl acetate, and methanol	NMR and FT-IR	-	[9]
Cassia italica Fabaceae	Aerial parts	Not reported	Not reported	NMR and HMBC	-	[3]
Ononis mitissima L. Fabaceae	Aerial parts	Not reported	Not reported	1D and 2D NMR, mass spectrometry	-	[8]
Centaurea resupinata subsp. *dufourii* Asteraceae	Aerial parts	Not reported	Not reported	NMR techniques (^{1}H NMR, ^{13}C NMR, COSY, HSQC, HMBC) and mass spectroscopy (ESI-MS)	-	[7]
Acanthopanax sessiliflorus (Rupr. and Maxim.) Seem. Araliaceae	Fruits	Not reported	Not reported	Electro-spray ionization/mass spectrometry (ESI/MS), 1H- and ^{13}C-NMR	-	[49]
Hyssopus cuspidatus Boriss. Lamiaceae	Aerial parts	Not reported	17 kg were extracted in triplicate with EtOH (75%) at room temperature (50 L each time). The crude EtOH extract was concentrated under reduced pressure,	Silica gel column chromatography (SGCC) and further purified with MeOH	15 mg	[6]

			followed by suspension in water and successive extraction with petroleum ether, ethyl acetate, and n-butanol			
Rheum turkestanicum Polygonaceae	Roots	Maceration	3.8 kg extracted with 8 L of *n*-hexane (24 h × 2)	^{1}H-, ^{13}C-, 2D NMR, EI-MS, and single-crystal X-ray diffraction	-	[14]
Morus alba Moraceae	Leaves	Ultrasound	1933.76 g extracted in triplicate and successively with *n*-hexane, EtOAc, and MeOH in sonicator at room temperature (1h)	NMR, using ^{1}H, ^{13}C, DEPT, COSY, HSQC, and HMBC NMR	-	[35]
Pulicaria inuloides Asteraceae	Aerial parts	Not reported	-	^{1}H-NMR, ^{13}C-NMR, and HMQC	-	[57]
Salvia syriaca Lamiaceae	Roots	Maceration	2.2 kg of powdered material were extracted with acetone (3 × 10 L) by maceration at room temperature	Preparative thin layer chromatography (TLC) ($CHCl_3$–MeOH (85:15))	45 mg	[55]
Adenophora triphylla Campanulaceae	Not reported	Not reported	Not reported	^{1}H-NMR, ^{13}C-NMR, and EI mass spectra	-	[27]
Sedum caeruleum Crassulaceae	Aerial parts	Not reported	1500 g of powder was extracted with 80% MeOH. After evaporating the methanol under vacuum, the residue was dissolved in water and extracted with petroleum ether, chloroform, ethyl acetate, and butanol	UV, 1D , 2D NMR, and MS	7.2 mg	[56]
Rosa canina L. Rosaceae	Fruits	Maceration	1.6 kg of powder was extracted with 4 L of *n*-hexane, ethyl acetate, acetone, and methanol	^{1}H- and ^{13}C-NMR	-	[58]
Dorema glabrum Fisch. and C.A. Mey. Apiaceae	Aerial parts	Maceration	0.8 kg was macerated with methanol (4 L × 5) at room temperature	UV and ^{1}H, ^{13}C-NMR	-	[60]
Salvia sahendica Lamiaceae	Aerial parts	maceration	3 kg extracted with Me_2CO (7 × 5 L)	^{1}H and ^{13}C NMR	-	[36]
Pyrus spp. Rosaceae	Peels and pulps	Not reported	10 g extracted with methanol: water (6:4), acid (solvent A) and 1% (*v*/*v*) formic acid in acetonitrile (solvent B)	-	-	[62]

Punica granatum Lythraceae	Flowers	Not reported	5 g of powder was extracted with 80% ethanol	-	-	[64]
Helicteres isora L. Sterculiaceae	Fruits	Not reported	Powdered material was extracted by stirring with 50 mL of 50% methanol at 25 °C for 24 h and centrifuged at 7000 rpm for 10 min. The pellet was re-extracted with an additional 50 mL of 50% methanol	-	-	[65]
Ceiba pentandra L. Bombacaceae	Seeds	Not reported	Powdered material was extracted by stirring with 50 mL of 50% methanol at 25 °C for 24 h and centrifuged at 7000 rpm for 10 min. The pellet was re-extracted with an additional 50 mL of 50% methanol	-	-	[65]
Litchi chinensis Sapindaceae	Seeds	Not reported	10 kg exhaustively extracted three times with 95% ethanol (50 L) at room temperature	-	-	[69]
Randia dumetorum Rubiaceae	Bark	Not reported	-	^{13}C-NMR spectra using 2D NMR (HSQC, HMBC, and DQF-COSY)		[67]
Lysimachia clethroides Primulaceae	Aerial parts	Not reported	6.75 kg extracted three times with 75% alcohol for 7 days at room temperature. The concentrated extract (480 g), after evaporation of the solvent in a vacuum pump, was suspended in water and extracted with petroleum ether, EtOAC, and *n*-BuOH	^{1}H and ^{13}C NMR	-	[66]
Urtica angustifolia Urticaceae	Leaves, roots, and stems	Decoction	1 kg was extracted with water (90 °C, 20 BV) 3 times (15 min/time)	TLC, IR, and ESI-MS spectral	-	[70]
Sphallerocarpus gracilis Apiaceae	Roots	Not reported	-	-	-	[73]
Hypericum ascyron L. Hypericaceae	Whole plant	Not reported	450 g was refluxed three times with petroleum ether,	^{13}C-NMR	20.9 mg	[74]

			EtOAC, and MeOH for 2 h			
Grewia optiva Drummond ex Burret. Tiliaceae	Stem bark	Not reported	7 kg was extracted three times with ethanol at room temperature. The combined ethanolic extracts were partitioned between EtOAc and water. The EtOAc layer was washed with H_2O, dried (anhydrous Na_2SO_4), and evaporated under reduced pressure to give a gummy residue that was further fractionated into petroleum ether soluble and insoluble fractions	1D and 2D NMR (HMQC, HMBC, COSY, NOESY, and J-resolved) and EI and HRMS	6 mg	[18]
Boerhaavia diffusa Nyctaginaceae	Leaves	Maceration	150 g extracted with 1 L of distilled water for 24 h			[77]
Astragalus membranaceus Fabaceae	Roots	Not reported	17.8 kg was chopped into small pieces and refluxed with 70% ethanol for 3 h at 70–80 °C	-	-	[80]
Phyllenthus emblica L. Phyllanthaceae	Fruits	Not reported	1100 g extracted with 95% ethanol at room temperature for 7 days	SGCC and TLC	-	[20]
Portulaca oleracea L. Portulacaceae	Not reported	Not reported	1450 g extracted with CHCl3	^{1}H and ^{13}C aided with HMQC	-	[21]
Eriobotrya fragrans Champ Rosaceae	Fruits and leaves	Not reported	4.5 kg extracted with 95% EtOH three times for 3 days with 2 shakings per day	^{13}C-NMR	20.8 mg	[22]
Alchornea cordifolia (Schumach. and Thonn.) Müll. Arg. Euphorbiaceae	Leaves and root bark	Not reported	-	1D and 2D NMR spectra were recorded in $CDCl_3$	-	[82]
Arctotis arctotoides Asteraceae	Not reported			NMR (COSY, NOESY, HMQC, and HMBC) and mass spectra		[23]
Dioscorea opposita Dioscoreaceae	Aerial parts	Not reported	4 kg extracted with 95% ethanol under reflux.	Silica gel column chromatography using $CHCl_3$-	300 mg	[19]

			The ethanol crude extract (115 g) was suspended in water and partitioned successively with petroleum ether, EtOAc, and *n*-butanol	MeOH mixtures (95:5 f 3:1)		
Astragalus mongholicus Bunge Fabaceae	Roots	Maceration	10 kg extracted with 90% ethanol at room temperature. The alcoholic solution was concentrated under vacuum The concentrated extract was diluted with water. The water solution was successively extracted with petroleum ether, ethyl acetate, and, finally, *n*-butanol	^{13}C-NMR	-	[91]
Punica granatum Punicaceae	Seeds	Not reported	4 kg extracted with 95% ethanol under reflux. The ethanol crude extract (489 g) was suspended in water and partitioned successively with petroleum ether, EtOAc, and *n*-butanol	^{1}H and ^{13}C NMR	205 mg	[93]
Artemisia sieversiana Asteraceae	Aerial parts	Not reported	14 kg extracted twice for 37 h at room temperature with MeOH	Combination of spectral methods (IR, EIMS, H and 2CNMR, DEPT, COSY, NOESY, and HETCOR)	64 mg	[105]

Spectroscopic techniques such as NMR, FT-IR, and elemental analysis have been used to elucidate the structure of daucosterol isolated and purified from the leaves and stems of *Prangos ferulacea* [9], as well as the aerial parts of *Cassia italica* [3] and *Ononis mitissima* L. [8]. NMR techniques (^{1}H NMR, ^{13}C NMR, COSY, HSQC, and HMBC) and mass spectroscopy (ESI-MS) have also been used to elucidate this molecule from *Centaurea resupinata* subsp. *Dufourii* [7], while spectroscopic techniques such as ESI/MS, ^{1}H- and ^{13}C-NMR have been used for its purification from the fruit of *Acanthopanax sessiliflorus* (Rupr. and Maxim.) Seem. [49]; SGCC with further purification with MeOH was the characterization method for *Hyssopus cuspidatus* Boriss. aerial parts [6]. Similarly, daucosterol was elucidated from many plants such as *Rheum turkestanicum* [14], *Morus alba* using NMR by ^{1}H, ^{13}C, DEPT, COSY, HSQC, and HMBC NMR [35], and from *Pulicaria inuloides* [57], *Salvia syriaca* [55], *Adenophora triphylla* using ^{1}H-NMR, ^{13}C-NMR; and electron-impact (EI) mass spectra [27] for *Sedum caeruleum* [56], *Rosa canina* L. [58], *Dorema glabrum* Fisch. and C.A. Mey. [60], *Salvia sahendica* [36], *Pyrus* spp., *Punica granatum*,

Helicteres isora L., and *Ceiba pentandra* L. [62,64,65]. The complete interpretation of ^{1}H and ^{13}C NMR spectra using 2D NMR (HSQC, HMBC, and DQF-COSY) allowed the identification of daucosterol in extracts of *Litchi chinensis* [69], *Randia dumetorum* [67], and *Lysimachia clethroides* [66]. TLC, IR, and ESI-MS spectra have been used for identification in *Sphallerocarpus gracilis* [73] and *Hypericum ascyron* L. [74].

It was obtained from *Grewia optiva* Drummond ex Burret [18], *Boerhaavia diffusa* [77], and *Astragalus membranaceus* [80] using 1D and 2D NMR (HMQC, HMBC, COSY, NOESY, and J-resolved) with EI and HRMS; from *Phyllenthus emblica* L. [20] using SGCC and thin-layer chromatography (TLC); and from *Portulaca oleracea* L. [21] and *Eriobotrya fragrans* Champ [22] using ^{1}H and ^{13}C aided with HMQC. Besides, daucosterol was found in *Alchornea cordifolia* (Schumach. and Thonn.) Müll. Arg. [82] and *Arctotis arctotoides* [23] using NMR (COSY, NOESY, HMQC and HMBC). Daucosterol was eluted from *Dioscorea opposite* with SGCC using CHCl3-MeOH [19], with ^{13}C-NMR from *Astragalus mongholicus* Bunge and *Punica granatum* [91,93], and with a combination of spectral methods (IR, EIMS, H and 2CNMR, DEPT, COSY, NOESY, and HETCOR) from *Artemisia sieversiana* [105].

4. Evaluation of Biological Properties

4.1. Antioxidant Activity

Daucosterol is an antioxidant molecule with an essential role in the fight against free radicals (Table 3). Abdollahnezhad et al. [9] demonstrated that this constituent has potent antioxidant properties, with significant activity using the DPPH (2, 2-diphenyl-1-picrylhydrazyl) free radical assay. Indeed, it showed a potential reduction of DPPH radicals, with 50% of inhibition (IC_{50} = 490 ± 2.9 μg/mL) and a percentage inhibition of 19.7% at 100 mg/mL [3] and a potential reduction with IC_{50} = 27.3 ± 0.015 μg/mL in another, similar study [8]. Other methods such as H_2O_2, FTC, FRAP, and PPM showed DPPH radical inhibition equal to 31.18 ± 0.5%, 37.12 ± 0.44%, 122.23 ± 0.014 μg EAA/mg ex, and 16.44 ± 0.0012 μg EAA/mg ex, respectively [8]. Several studies have confirmed this potential for DPPH radical inhibition with varying results: IC_{50} = 36.263 ± 0.005 μg/mL [7], IC_{50} = 155.0 ± 0.5 μM [14], IC_{50} = 224.1 ± 8.2 μg/mL [60], IC_{50} = 6.0 ± 0.1 mg/L [64], EC_{50} > 250 μg/mL [69], IC_{50} = 11.42 ± 0.07 μg/mL [66], IC_{50} = 108.14 ± 9.54 μg GAE/ mL [73], and IC_{50} = 38.86 μg/mL [20]. However, Shomirzoeva and collaborators demonstrated that daucosterol does not affect the DPPH radical [6]. On the other hand, it inhibited the activity of the ABTS radical with a potential inhibition at 50% equal to 4.8 ± 0.04 mg/mL and a percentage inhibition of 27% at the concentration of 0.04 mg/mL [110], plus EC_{50} = 143.4 μg/mL [69], IC_{50} = 9.02±0.11 μg/mL [66], IC_{50} = 1.66 ± 0.15 μmol TE/g of DW [73], and IC_{50} = 0.71 ± 0.01 μg/mL [20].

Table 3. Antioxidant effects of Daucosterol.

Methods Used	Key Results	References
DPPH	IC_{50} = 490 ± 2.9 μg/Ml	[9]
DPPH	RSA% = 19.7% at 100 mg/mL	[3]
DPPH	IC_{50} = 27.3 ± 0.015 μg/mL	[8]
H_2O_2	I% = 31.18 ± 0.5%	
FTC	I% = 37.12 ± 0.44%	
FRAP	EC_{50} = 122.23 ± 0.014 μg EAA/mg ex	
PPM	EC_{50} = 16.44 ± 0.0012 μg EAA/mg ex	
DPPH	IC_{50} = 36.263 ± 0.005 μg/mL	[7]
DPPH	No effect	[6]
DPPH	IC_{50} = 155.0 ± 0.5 μM	[14]
DPPH	IC_{50} = 224.1 ± 8.2 μg/mL	[60]
DPPH	IC_{50} = 6.0 ± 0.1 mg/L	[64]
ABTS	IC_{50} = 4.8 ± 0.04 mg/mL	[111]
ABTS	I% = 27% at 0.04 mg/mL	
FRAP	EC_{50} = 1.09 ± 0.12 mg/mL	
DPPH	EC_{50} > 250 μg/mL	[69]
ABTS	EC_{50} = 143.4 μg/mL	
DPPH	IC_{50} = 11.42 ± 0.07 μg/mL	[66]
ABTS	IC_{50} = 9.02 ± 0.11 μg/mL	
DPPH	IC_{50} = 108.14 ± 9.54 μg GAE/mL	[73]
FRAP	IC_{50} = 4.91 ± 0.39 μmol Fe(II)/g of DW	
ABTS	IC_{50} = 1.66 ± 0.15 μmol TE/g of DW	
DPPH	IC_{50} = 38.86 μg/mL	[20]
ABTS	IC_{50} = 0.71 ± 0.01 μg/mL	

4.2. Anticancer Activity

Several works have shown that daucosterol possesses important anticancer activity on various tumor cell lines and could be considered one of the novel pharmacological treatment strategies for cancer (Table 4). Esmaeili et al. [36] isolated this molecule from *Salvia sahendica* to assess its apoptotic and anti-proliferative activity against human breast adenocarcinoma MCF-7 cells using MTT assay, lactate dehydrogenase (LDH) leakage assay, and flow cytometry. They found that daucosterol inhibits cell proliferation and induces cytotoxicity in MCF-7 cells, including PARP proteolytic activity, DNA fragmentation, and cell morphological changes. Indeed, at 80 μM, maximum inhibition of cell growth and survival was approximately 60%. Anti-cancer drug mechanisms move from the subcellular to the molecular level by increasing the levels of the pro-apoptotic proteins (Bax and Bcl2) and decreasing the Bcl-2/Bax ratio, upregulating the PTEN gene to inhibit the PI3K/Akt pathway, inducing the loss of mitochondrial membrane potential, and by Cyt c release in breast cancer cells [110,112,113]. On the other hand, Zhao et al. [110] assessed the anticancer effect of daucosterol against human breast cancer cell line MCF-7 and gastric cancer cell lines MGC803, BGC823, and AGS. The results demonstrated that this compound exerts an important antiproliferative activity against the studied cell lines, with IC_{50} values of 16.95, 19.96, 3.13, and 24.19 μM, respectively. This effect was induced by autophagy in a ROS-dependent manner. Wang et al. [38] recorded an IC_{50} value of 26.6 μM on human colon cancer cell line HCT-116. Daucosterol can repress cell migration and cell invasion in these cells and cause cell death by cell-cycle arrest and apoptosis. Indeed, it significantly inhibited the proliferation of human lung cancer cell line A549, with an IC_{50} value of 17.46 μg/mL targeting multiple checkpoints, including cell-cycle arrest at the G_2/M phase and induction of cell apoptosis [112]. Using MCF-7,

MDA-MB-231, and 4T1 breast cancer cells, Han et al. [37] revealed that daucosterol exhibits antitumor activities, with an IC_{50} = 53.27 μg/mL on MCF-7 and IC_{50} > 1000 on MDA-MB-231 and 4T1. This molecule also inhibited tumor growth in vivo using MCF-7 xenografts in nude mice by decreasing the expression of Bcl-xl, Bcl-2, and XIAP, increasing Bax, Bad, inducing the activation of caspase-dependent apoptosis in tumor tissues, and inactivation of the upstream PI3K/Akt/NF-κB pathway. Moreover, Gao et al. [114] reported that daucosterol inhibits cell proliferation, induces cell-cycle arrest, and promotes autophagy-dependent apoptosis in human prostate cancer cell lines (PC3 and LNCap) via activation of JNK signaling. Indeed, this phytosterol strongly inhibited the growth of human lung cancer cell line A549, with an IC_{50} value of 20.9 μM, by increasing ROS levels and promoting intrinsic apoptotic cell death of A549 cells. This effect was mediated by increased expression of caspase-3, caspase-9, and Bax, PARP inactivation, Cyt c release, and diminished expression of bcl-2 protein (Figure 2) [26]. Recently, Han et al. [25] evaluated the antiproliferative effect of daucosterol extracted from sweet potatoes on three breast cancer cell lines (MCF-7, MDA-MB-231, and 4T1) and nontumorigenic breast epithelial cell line MCF-10A using MTT assay. The results showed that this compound inhibited the proliferation of breast cancer MCF-7 cells by inactivating the phosphoinositide 3-kinase/protein kinase B pathway, but had only weak effects on the proliferation of MDA-MB-231, 4T1, and MCF-10A cells. Nguedia and coworkers [24] investigated antitumor effects in vivo using the environmental carcinogen 7,12-dimethylbenz[*a*]anthracene (DMBA). The results demonstrated that daucosterol reduced, at all doses, tumor volume as well as proteins and cancer antigen 1. It also exhibited an antioxidant effect by decreasing malondialdehyde (MDA) levels and increasing catalase activity. In another study, it inhibited LNCaP, DU145, and PC3 prostate carcinoma cell growth and proliferation via downregulated cell cycle proteins (cdk1, cdk2, pcdk1, cyclin A and B), downregulated anti-apoptotic proteins (Akt, pAKT, and Bcl-2), and upregulated the pro-apoptotic protein Bax [114–116]. On the other hand, the in vivo anticancer effect of daucosterol on primary tumor growth and pulmonary metastasis was studied using a BALB/c mouse model of a breast tumor. After 35 days of treatment, daucosterol suppressed primary tumor growth, reduced the number of lung metastases, and delayed the trend of increasing numbers of captured CTCs in the blood circulation [117]. Using a murine H22 hepatoma allograft model in ICR mice, Zhao et al. [110] showed that daucosterol treatment inhibits tumor growth in vivo by inducing intracellular ROS generation and subsequent autophagic cell death.

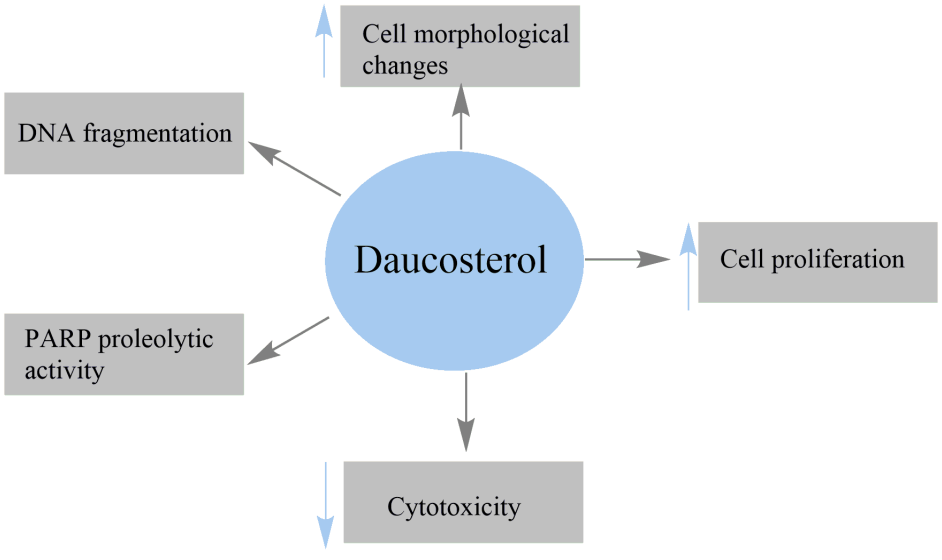

Figure 2. Anticancer mechanisms of Daucosterol. The arrow indicates increasing or decreasing.

Table 4. Anticancer effects of Daucosterol.

Cell Lines	Key Results	References
Human breast adenocarcinoma MCF-7	Suppressed the proliferation of MCF-7 cells Induced the cytotoxicity of MCF-7 cells Modulated Bax, Bcl2, and PARP Reduced the mitochondrial membrane potential Increased the levels of cytochrome c (Cyt c) released Upregulated the PTEN gene and inhibited the PI3K/Akt pathway Decreased the intracellular GSH content	[36]
Human breast cancer MCF-7	IC_{50} = 16.95 μM Inhibited colony formation of MCF-7 cells Induced autophagy Induced the conversion and aggregation of LC3-II Increased the expression of Beclin-1	[110]
Gastric cancer MGC803	IC_{50} = 19.96 μM Induced autophagy Induced the conversion and aggregation of LC3-II Increased the expression of Beclin-1	
Gastric cancer BGC823	IC_{50} = 3.13 μM Inhibited colony formation of BGC823 cells Increased ROS production Induced autophagy Induced the conversion and aggregation of LC3-II Increased the expression of Beclin-1	
Gastric cancer AGS	IC_{50} = 24.19 μM Induced autophagy Induced the conversion and aggregation of LC3-II Increased the expression of Beclin-1	
Human colon cancer HCT-116	IC_{50} = 26.6 μM at 24 h IC_{50} = 47.3 μM at 48 h Decreased the percentage of migrated cells by 14.4% at 100 μM Increased the percentage of apoptotic cells by 74.2% at 100 μM Induced cell-cycle arrest at sub-G_1 phase	[38]
Human lung cancer A549	Inhibited the proliferation of A549 cells IC_{50} = 17.46 μg/mL at 48 h Perturbed cell cycle Induced apoptotic cell death	[112]
Human HCC HepG2; Human HCC SMMC-7721	Reduced the proliferation of HepG2 and SMMC-7721 cells Decreased cell migration and invasion abilities of both cells Reduced the levels of β-catenin and *p*-β-catenin Suppressed the expression of Wnt/ β-catenin signaling proteins	[40]
Breast cancer MCF-7; MCF-7 xenografts in nude mice	IC_{50} = 53.27 μg/mL Inhibited cell viability in ER-positive MCF-7 cells Induced apoptosis in MCF-7 cells Diminished the expression of Bcl-xl, Bcl-2, and XIAP Increased Bax, Bad, and activated caspase Inactivated the upstream PI3K/Akt/NF-κB pathway	[37]
Breast cancer MDA-MB-231	IC_{50} > 1000 μg/mL	
Breast cancer 4T1	IC_{50} > 1000 μg/mL Blocked metastasis progression	

	Decreased the number of visible metastasis foci Inhibited metastasis size distribution in lung tissue	
Nontumorigenic breast epithelial MCF-10A	No cytotoxicity	
Human prostate cancer (PC3 and LNCap)	Inhibited cell proliferation Induced cell-cycle arrest Promoted apoptosis and autophagy Increased phosphorylation of c-Jun N-terminal kinase (JNK)	[113]
Human lung cancer A549	IC_{50} = 20.9 Mm Inhibited the growth of A549 cells Increased reactive oxygen species (ROS) level Promoted intrinsic apoptotic cell death Increased the expression of caspase-3, caspase-9, Bax, PARP inactivation, and Cyt c release Diminished the expression of Bcl-2 protein Inhibited the thioredoxin (TrxR) redox system	[26]
Breast cancer MCF-7; MCF-7 xenografts in nude mice	Induced cytotoxicity Decreased the proliferation rates Increased the number of apoptotic cells Activated the expressions of caspase 3 and PARP1 Reduced the tumor volume Decreased the levels of CEA, CA125, and CA153 Increased the expression of cleaved caspase 3 Decreased the BCL-2 and VEGF Downregulated the expression of PI3K/Akt Repressed insulin-induced PI3K/Akt activation	[25]
MDA-MB-231	Exhibited a weak effect on cell proliferation	
4T1 nontumorigenic	Exhibited a weak effect on cell proliferation	
Breast epithelial MCF-10A	Exhibited a weak effect on cell proliferation	
7,12-dimethylbenz(a)anthracene-induced mammary tumors in Wistar rats	Reduced tumor volume Decreased the levels of protein and malondialdehyde (MDA) Reduced cancer antigen (CA) 15-3 level Decreased MDA levels Increased catalase activity Reduced proliferation of mammary duct cells	[24]
Prostate carcinoma LNCaP	Inhibited cell growth and proliferation	[48]
Prostate carcinoma DU145	Inhibited cell growth and proliferation Increased the number of late apoptotic cells Increased the number of cells in S phase Decreased the number of G_0/G_1 cells Downregulated the cell-cycle proteins (cdk1, pcdk1, cyclin A and B)	
Prostate carcinoma PC3	Inhibited cell growth and proliferation Increased the number of late apoptotic cells Downregulated the cell-cycle proteins (cdk1, pcdk1, cyclin A and B) Downregulated cdk2 Downregulated Akt, pAKT, and Bcl-2 proteins Upregulated the pro-apoptotic protein Bax	
Breast tumor BALB/c mouse model	Suppressed primary tumor growth Reduced lung metastases	[117]

	Increased the number of captured CTCs in the blood circulation	
Murine H22 hepatoma allograft model in ICR mice	Inhibited murine hepatoma H22 cell growth Induced intracellular ROS generation Induced autophagy	[110]

4.3. Neuroprotective Activity

Some studies have shown that daucosterol exhibits neuroprotective effects [29,30,40,41] (Table 5). Indeed, Jiang and collaborators [40] showed that this molecule exhibits a neuroprotective action that reduces neuronal loss and cell apoptosis by diminishing caspase-3 activation in oxygen–glucose deprivation and simulated reperfusion (OGD/R)-treated neurons. It also increased the expression level of IGF1 protein and diminished the downregulation of p-AKT3 and p-GSK-3b4, thus activating the AKT5 signal pathway. Moreover, daucosterol decreased the downregulation of the anti-apoptotic proteins Mcl-1 and Bcl-2 and diminished the expression level of the pro-apoptotic protein Bax. In another study, Chung et al. [41] investigated the neuroprotective effects of daucosterol on H_2O_2-induced cell death of human brain neuroblastoma SK-N-SH cells using MTT and lactate dehydrogenase (LDH) assays, annexin-V/PI double-staining, and flow cytometry. Therefore, daucosterol exhibited neuroprotective activity against H_2O_2-induced oxidative stress through downregulation of MAPK pathways, minimizing ROS, and upregulation of antioxidant genes (HO-1, CAT, and SOD2) (Figure 3). Moreover, oral administration of daucosterol ameliorated amyloid beta-induced learning and memory impairment in rats by inhibiting beta-amyloid-induced hippocampal ROS production, and prevented beta-amyloid-induced hippocampal neuronal damage and restored hippocampal synaptophysin expression level [29]. Recently, Zhang et al. [30] investigated the neuroprotective effects of daucosterol in a cerebral ischemia/reperfusion (I/R) rat model. Accordingly, daucosterol attenuated brain damage and neuronal cell apoptosis caused by I/R injury by upregulating the PI3K/Akt/mTOR signaling pathway and suppressing iNOS expression in the ischemic zone.

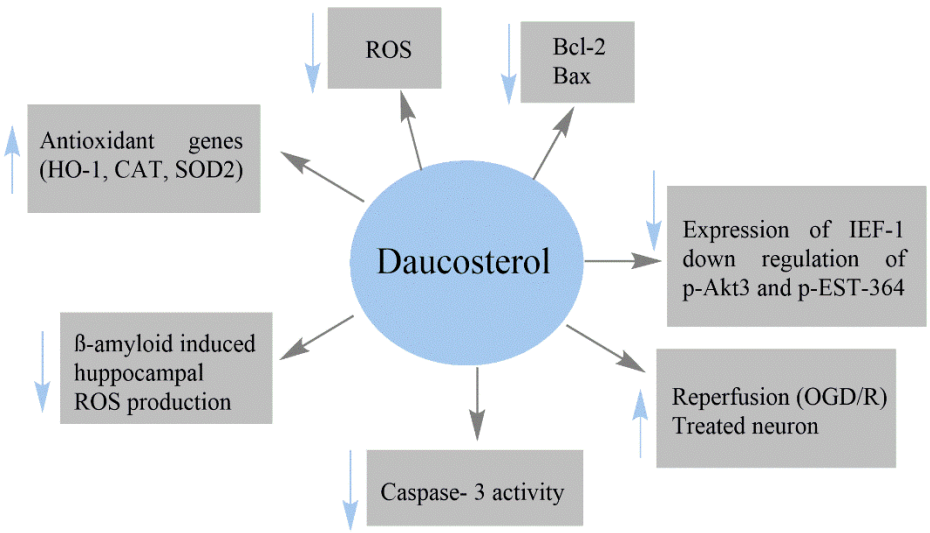

Figure 3. Neuroprotective effects of Daucosterol. The arrow indicates increasing or decreasing.

Table 5. Neuroprotective effects of Daucosterol.

Experimental Approaches	Key Results	References
Oxygen–glucose deprivation/reperfusion-mediated injury in OGD/R model	Reduced neuronal loss and apoptotic rate Suppressed caspase-3 activity Upregulated the expression of IGF1 protein Activated the AKT signal pathway Diminished the downregulation of the Mcl-1 and Bcl-2 Decreased the expression level of protein Bax	[40]
H_2O_2-induced cell death of human brain neuroblastoma SK-N-SH cells	Inhibited cell death and LDH activity Reduced intracellular ROS levels by 37.7% Reduced H_2O_2-induced apoptotic cell death Reduced H_2O_2-mediated fragmented DNA Increased CAT and SOD2 mRNA levels Attenuated H_2O_2-induced phosphorylation of p38 and JNK	[41]
Cerebral ischemia/reperfusion (I/R) rat model	Decreased apoptotic cell death Suppressed iNOS expression in ischemic zone Upregulated the PI3K/Akt/mTOR signaling pathway	[30]

4.4. Anti-Inflammatory Activity

Using in vivo inflammation experiments (e.g., xylene-induced ear edema and carrageenan-induced paw), edema could be mediated by inflammatory factors [118], such as serotonin, histamine, prostaglandins, and bradykinin. Huang et al. [119] investigated the anti-inflammatory activity of two sterols and two triterpenes extracted from *Pyrus bretschneideri* Rehd., including daucosterol, β-sitosterol, ursolic acid, and oleanolic acid. Mice treated orally with the isolated compounds showed significant dose-dependent inhibition of edema compared to control mice [119].

Daucosterol isolated from the leaves of *Liriodendron chinensis* could be a natural anti-inflammatory agent due to its strong inhibitory effect on the activated inflammatory cells. As observed in the experiment performed by Yang et al. [43], this compound could significantly decrease the NO content of LPS-induced rat peritoneal macrophages [43].

In another study, Kim et al. [120] used LPS-treated RAW 264.7 macrophage cells to assess the anti-inflammatory action of phytochemicals, including daucosterol, isolated from fermented bark of *Acanthopanax sessiliflorus* (FAS). The anti-inflammatory responses to FAS revealed decreased NO production and inhibition of COX-2, iNOS, collagenase, and pro-inflammatory cytokines (TNF-α and IL-6) (Figure 4) [120]. Additionally, Bui et al. tested the anti-inflammatory activity of bioactive compounds, including daucosterol, extracted from *Sanchezia speciosa* Leonard's leaf ethanol extract. This research reported that daucosterol might have anti-inflammatory action against heat-induced protein denaturation, with moderate inhibition (IC_{50} = 245.59 ± 3.17 μg/mL) compared to 3-methyl-1Hbenz[f]indole-4,9-dione, which exhibited the strongest inhibition (IC_{50} = 193.70 ± 5.24 μg/mL) [121].

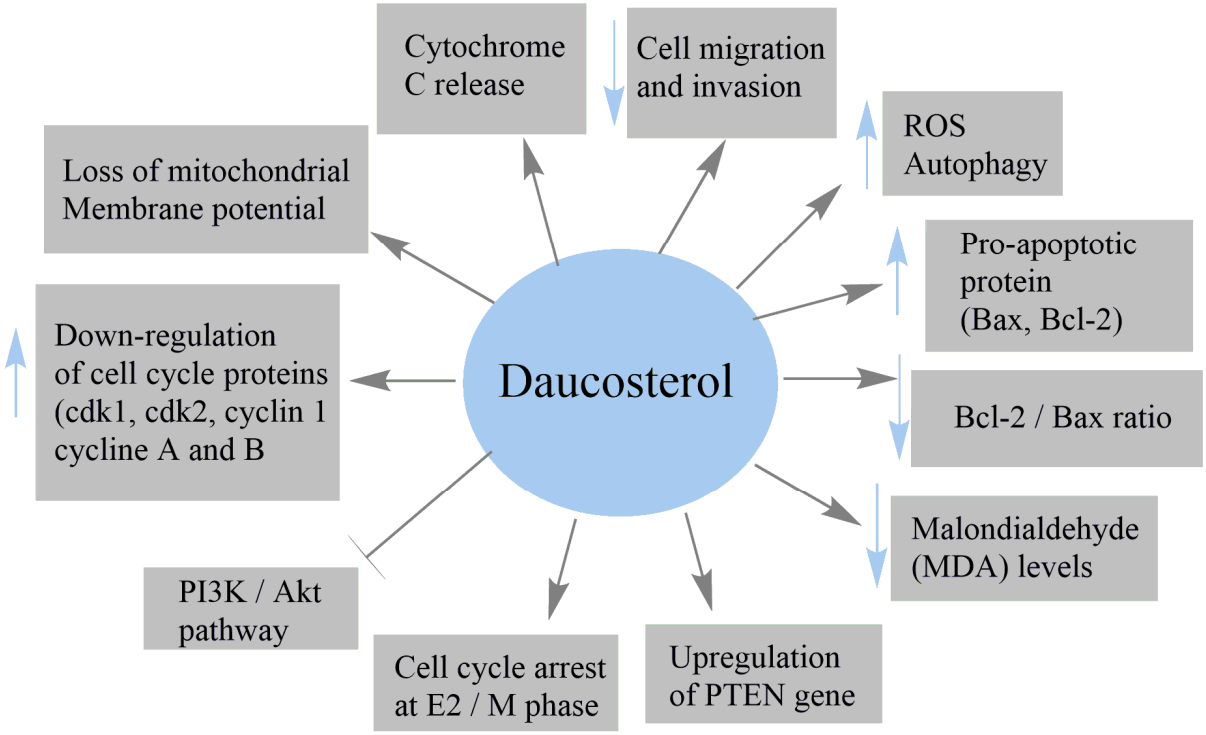

Figure 4. Anti-inflammatory mechanisms of Daucosterol. The arrow indicates increasing, decreasing or inhibiting.

The pharmacological effects of daucosterol as an anti-inflammatory agent isolated from the leaves and root bark of *Alchornea cordifolia* was also tested using a mouse ear edema model in the study carried out by Mavar-Manga and collaborators. At a dose of 90 g/cm^2, daucosterol was found to be more active (50% inhibition)—along with acetyl aleuritolic acid, N1, N2 diisopentenyl guanidine, and N1,N2,N3-triisopentenyl guanidine—than indomethacin. However, β-sitosterol and di(2-ethylhexyl) phthalate were less effective [82].

In addition, daucosterol could suppress dextran sulfate sodium (DSS)-induced colitis in mice. Colitis is an inflammatory response of the large bowel, which may be of infectious or autoimmune origin [122]. Jang et al. [31] found daucosterol decreased DSS-induced ROS production and the expression of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β [31] (Figure 4). These outcomes indicate that daucosterol may be useful as a candidate in folk medicine and for adopting new therapeutics as an alternative for treating several inflammatory diseases associated with excessive NO production.

4.5. Immunomodulatory Effects

Recently, modulation of the immune system has become a promising way to treat several human pathologies. Indeed, the reactivity of our immune system can be decreased due to several risk factors. This decrease induces a disequilibrium between immune response and disorders, including pathogenic microbial infections. In several ways, reinforcement of the immune system can establish homeostasis and remove these disorders. Moreover, it is well established that regulatory T cells (Treg) have a significant contribution to managing immune homeostasis. In particular, some previous works have indicated that Treg cells possess an essential function in inhibiting colitis-induced inflammatory responses by regulating inflammation and suppressing the release of inflammatory cytokines through modulating different genes such as NF-κB, TNF-α, interleukins (IL-1 and IL-6), and chemokines [123].

Jang et al. investigated the immunomodulatory effects of daucosterol in a mouse model of DSS-induced colitis. This research demonstrated that this molecule could

regulate the population and activation of immune cells, including Treg cells, macrophages, B1 cells, and NK cells in colitis. These cells are involved in several diseases (malignant tumors, infections, mucosal immunity, allergies, etc.). They also found that this bioactive compound suppresses ROS and colitis-induced inflammatory cytokines, such as IL-6, TNF-α, IFN-γ, and IL-1β, and is associated with downregulation of macrophage infiltration and upregulation of Treg cell number [31].

To discover new immunoregulatory approaches using natural drugs isolated from medicinal plants to fight against illnesses caused by *Candida albicans*, Lee et al. evaluated the possible immunomodulatory activity of daucosterol against disseminated Candidiasis in mice by regulating the immune response. They observed that splenic CD4+ T cells (DSCD4T) in daucosterol-treated mice produce IFN-γ and IL-2 cytokines more abundantly than cytokines IL-4 and IL-10, inducing the polarization of CD4+ T cells towards a Th1-type immune response [34]. However, some studies reported that the release of Th1 cytokine would enhance host resistance to disseminated candidiasis by improving the killing capacity of different immune cells, including activated macrophages, NK cells, and cytotoxic T cells against cells infected with *C. albicans* [124] [125]. Furthermore, Yang et al. [40] proved the immunocompetent activity of daucosterol isolated from the leaves of *Liriodendron chinensis*. They demonstrated that daucosterol, among other bioactive compounds, markedly decreased the NO content of LPS-induced rat peritoneal macrophages and decreased splenic lymphocyte proliferation in mice [43]. These assessments could pave the way for new immunoregulatory strategies exerted by this biologically active compound for the treatment of numerous immunologic pathologies.

4.6. Antidiabetic Activity

Daucosterol extracted from the chloroform fraction of *Swertia longifolia* Boiss., was tested among other examined compounds in the study performed by Saeidnia and collaborators (Table 6). The results showed that daucosterol had the highest inhibitory activity against the digestive enzyme α-amylase (57.5 ± 3.1% in a 10 mg/mL) [126]. In the same context, the inhibitory activity of daucosterol purified from the peel of Chinese water chestnuts was evaluated in the study conducted by Gu et al. [33] against the same enzyme (Table 6). Using fluorescence quenching, enzyme inhibition, and molecular docking models, results showed that three saponins from Chinese water chestnut bark exhibit a potent α-amylase inhibitory effect, and that daucosterol was the major inhibitory factor of this enzyme with a mixed-mode [33].

Table 6. Antidiabetic activities of daucosterol.

Experimental Approaches	Key Results	References
α-amylase inhibitors	Inhibition = 57.5 ± 3.1% in a 10 mg/mL	[126]
α-glucosidase inhibitors	IC_{50} = 247.35 mg/L Inhibition constant = 2.34 mg/L	[42]
Normal and hyperglycemic rats	Increased fasting plasma insulin levels Enhanced oral glucose tolerance Improved glucose-induced insulin release	[127]
Molecular docking	Inhibited human α-glucosidase	[53]
α-glucosidase inhibitors	IC_{50} = 13.3 ± 1.9 μM	[58]
Glucose tolerance test	Significant hypoglycemic activity	[128]
α-glucosidase inhibitors	IC_{50} = 5.67 mg/L	[33]

To find effective strategies for the treatment of diabetes using α-glucosidase inhibitors, Sheng et al. [42] assessed the antidiabetic effect of five natural drugs isolated from the flowers of *Musa* spp. (Baxijiao), including ferulic acid, vanillic acid, β-sitosterol,

daucosterol, and 9-(4′-hydroxyphenyl)-2-methoxyphenalen-1-one, against this enzyme. Daucosterol exhibited an excellent α-glucosidase inhibitory action, with an IC_{50} value of 247.35 mg/L and an inhibition constant of 2.34 mg/L. β-sitosterol and 9-(4'-hydroxyphenyl)-2-methoxyphenalen-1-one also showed potent α-glucosidase inhibiting activity [42]. Similarly, Numonov and colleagues investigated the antidiabetic effect of ten bioactive compounds, including daucosterol isolated from the root of *Geranium collinum* [53]. Using molecular docking, they observed that daucosterol could play a key role in inhibiting human α-glucosidase, while polyphenolic agents are probably involved in inhibiting PTP-1B.

On the other hand, Ivorra and collaborators investigated the possible effects of daucosterol and its aglycone (β-sitosterol) as an antihyperglycemic and insulin releaser [128]. The action of these agents on plasma insulin and glucose levels in normal and hyperglycemic rats after oral treatment was found to increase fasting plasma insulin levels. Additionally, they noted that both compounds enhance oral glucose tolerance and improve glucose-induced insulin release. In addition, Asghari et al. [58] tested the capacity of D-glucono-1,4-lactone and daucosterol isolated from *Rosa canina* fruits to inhibit α-glucosidase using the substrate p-nitrophenyl-α-D-glucopyranoside (pNPG). The findings revealed that both agents contribute to the inhibition of α-glucosidase with a high effect; the IC_{50} values of D-glucono-1,4-lactone and daucosterol on yeast α-glucosidase were 6.5 ± 2.0 and 13.3 ± 1.9 μM, respectively [58].

From the perspective of characterizing and isolating the antidiabetic molecules present in the leaves of *Costus pictus*, Benny et al. [128] observed that β-sitosterol-3-O-β-D-glucoside extracted from *Costus pictus* leaves exhibited a significant dose-dependent hypoglycemic action in rats after enteric coating compared to the uncoated compound [128]. The inhibitory effects on α-glucosidase in vitro and the increase in postprandial glycemia in maltose-loaded mice by the saponin component of *Eleocharis dulcis* bark were investigated in a recent study by Gu et al. [33]. Using NMR spectroscopy, three saponins were detected: campesterol glucoside, daucosterol, and stigmasterol glucoside. All three saponins were found to exert potent α-glucosidase inhibition, with IC_{50} values of 10.03 mg/L (campesterol glucoside), 7.68 mg/L (stigmasterol glucoside), and 5.67 mg/L (daucosterol), which were notably greater than that of acarbose (91.50 mg/L). Further, daucosterol showed the greatest inhibitory capacity against α-glucosidase [33]. Based on these findings, daucosterol could be considered an excellent candidate to prevent hyperglycemia due to its antidiabetic activity through the inhibition of α-glucosidase and α-amylase. However, further in vivo and in vitro investigations are warranted to elucidate the mechanisms involved.

4.7. Hypolipidemic Activity

In the objective to investigate the lipolysis effect of phytosterols isolated from mulberry (*Morus alba*) leaves, Li et al. observed that daucosterol exhibits a concentration-dependent lipolysis activity with very high potency. They also hypothesized that doctors could use daucosterol to manage certain types of disease, which can confer medicinal principles [35]. Sashidhara et al. [129] screened for natural resources with hypolipidemic activity in *Bauhinia racemosa* leaves using high-fat diet (HFD)-fed hamsters. The results showed that *Bauhinia racemosa* leaf ethanolic extract exhibits a strong hypolipidemic action due to its content of sitosterol-β-D-glucoside and other phytoconstituents, which could act additively or synergistically. The authors also indicated that *Bauhinia racemosa* leaf alcoholic extract rich in daucosterol could be used as a herbal drug to treat hypercholesterolemia and hypertriglyceridemia, a comprehensive approach to hypercholesterolemia and hypertriglyceridemia dyslipidemia management [129].

In addition, red yeast rice (RYR) used in traditional Chinese medicine could be an important product to prevent hyperlipidemia and dyslipidemia due to its content of more than 101 chemical agents, including daucosterol. According to experiments, RYR has been shown to significantly reduce total cholesterol, triglyceride, and low-density lipoprotein

cholesterol (LDL-C) levels and increase high-density lipoprotein cholesterol (HDL-C) levels [130]. The underlying pathways of drug action involve increased mRNA levels of the farnesoid X receptor and peroxisome-proliferator-gamma-activated receptor, key receptors in cholesterol metabolism and bile acid homeostasis [131].

Khan and Hossain extracted two bioactive molecules, β-sitosterol glycoside and scopoletin, from *Ipomoea digitate* root ethanolic extract. The tuberous root of this plant, mainly used in traditional medicine, has been shown to exhibit hypolipidemic action, potently lowering serum total cholesterol and LDL-C [45]. In the in vivo study performed by Mironova and Kalashnikova [132] on animals suffering from hypercholesterolemia, treatment with β-sitosterol β-d-glucoside reduced β-lipoproteins by 46% and blood cholesterol by 31% while normalizing the cholesterol/phospholipid level, whereas administration of β-daucosterol did not affect the β-lipoprotein and cholesterol levels in the blood serum in control animals. In experimental hypercholesterolemia, the suspected mechanism of lipid-lowering activity of the drug is the stimulation of phospholipid synthesis [132]. Further studies investigating the hypolipidemic capacity of daucosterol are needed to clarify the different pathways implicated in this pharmacological property to prevent the various diseases associated with lipid disorders.

5. Limitations and Perspectives

Here we have reported the different natural sources and the benefits and pharmacological properties of daucosterol. According to the literature, this molecule exhibited remarkable biological activities in vitro and in vivo, and therefore may be a key candidate in drug development. Indeed, its anticancer and neuroprotective effects are promising; elucidating these different mechanisms of action may play a crucial role in the development of new drugs. However, different limitations of this study should be mentioned. The first is the lack of data related to pharmacodynamic action of daucosterol, which makes it difficult to trace and create clear molecular target pathways regarding its mechanism of action. The second limitation is related to the lack of studies assesses the toxicity and safety of daucosterol in vivo. Moreover, understanding the pharmacokinetics and pharmacodynamics of daucosterol is necessary for its incorporation as a drug to treat many diseases; on the other hand, toxicological investigations are needed to validate its safety; the results of these investigations can also inform many approaches for the development of new drugs. Moreover, the investigation of daucosterol in combination with other drugs is also limited because no work has been reported in this direction.

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