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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.

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**Citation:** El Omari, N.; Jaouadi, I.; Lahyaoui, M.; Benali, T.; Taha, D.; Bakrim, S.; El Menyiy, N.; El Kamari, F.; Zengin, G.; Bangar, S.P.; et al. Natural Sources, Pharmacological Properties, and Health Benefits of Daucosterol: Versatility of Actions. *Appl. Sci.* **2022**, *12*, 5779. https://doi.org/10.3390/app12125779

Academic Editor: Ana M. L. Seca

Received: 30 April 2022
Accepted: 2 June 2022
Published: 7 June 2022

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**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].

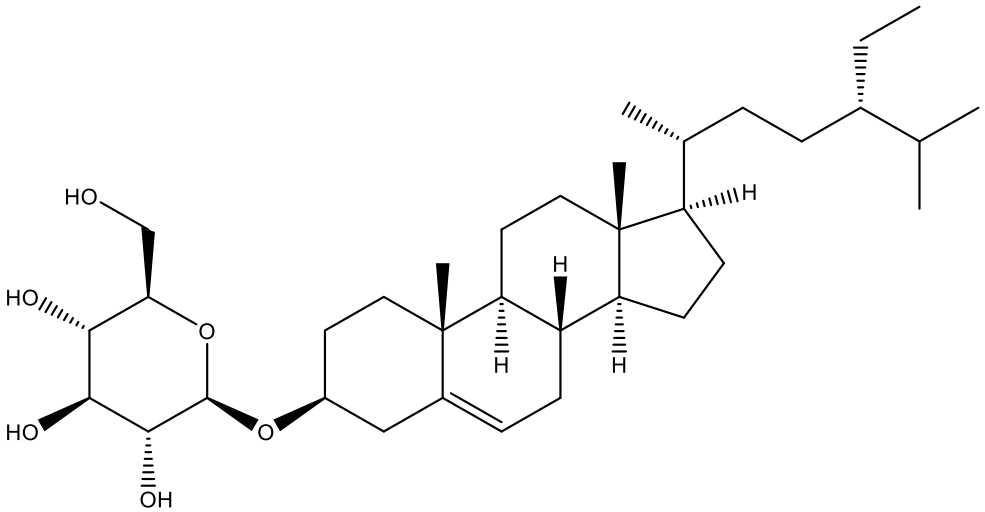


**Figure 1.** Chemical structure of Daucosterol.

*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] |

**Table 1.** *Cont.*

| Plant Family | Country | Parts Used | References |
|---|---|---|---|
| *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<br>Roots | [14,15] |
| *Heracleum persicum* Apiaceae | Iran | Whole plant | [15] |

**Table 1.** *Cont.*

| Plant Family | Country | Parts Used | References |
|---|---|---|---|
| *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. Bombacaceae | | Seeds | |

**Table 1.** *Cont.*

| Plant Family | Country | Parts Used | References |
|---|---|---|---|
| *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] |

**Table 1.** *Cont.*

| Plant Family | Country | Parts Used | References |
|---|---|---|---|
| *Eriobotrya fragrans* Champ Rosaceae | China | Fruits and leaves | [22] |
| *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] |

**Table 1.** *Cont.*

| Plant Family | Country | Parts Used | References |
|---|---|---|---|
| *Gentiana algida* Gentianaceae | China | Whole plant | [103] |
| *Gentiana siphonantha* Gentianaceae | China | Rhizomes and roots | [104] |
| *Gentiana scabra* Bunge Gentianaceae | China | Roots | [105] |
| *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, followed by suspension in water and successive extraction with petroleum ether, ethyl acetate, and n-butanol | Silica gel column chromatography (SGCC) and further purified with MeOH | 15 mg | [6] |

**Table 2.** *Cont.*

| Plant Family | Parts Used | Extraction Method | Extraction Parameters | Purification Method | Yields | References |
|---|---|---|---|---|---|---|
| *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 (1 h) | 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] |

**Table 2.** *Cont.*

| Plant Family | Parts Used | Extraction Method | Extraction Parameters | Purification Method | Yields | References |
|---|---|---|---|---|---|---|
| *Hypericum ascyron* L. Hypericaceae | Whole plant | Not reported | 450 g was refluxed three times with petroleum ether, EtOAC, and MeOH for 2 h | $^{13}$C-NMR | 20.9 mg | [74] |
| *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. The ethanol crude extract (115 g) was suspended in water and partitioned successively with petroleum ether, EtOAc, and *n*-butanol | Silica gel column chromatography using $CHCl_3$-MeOH mixtures (95:5 f 3:1) | 300 mg | [19] |
| *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] |

**Table 3.** *Cont.*

| Methods Used | Key Results | References |
|---|---|---|
| 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.

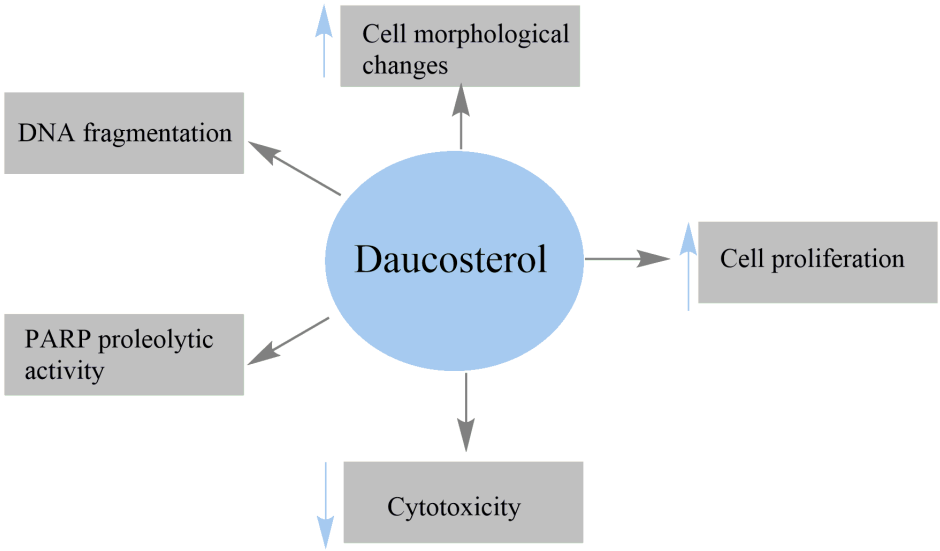


**Figure 2.** Anticancer mechanisms of Daucosterol. The arrow indicates increasing or decreasing.

**Table 4.** Anticancer effects of Daucosterol.

| Cell Lines | Key Results | References |
| --- | --- | --- |
| Human breast adenocarcinoma MCF-7 | Suppressed the proliferation of MCF-7 cells<br>Induced the cytotoxicity of MCF-7 cells<br>Modulated Bax, Bcl2, and PARP<br>Reduced the mitochondrial membrane potential<br>Increased the levels of cytochrome c (Cyt c) released<br>Upregulated the PTEN gene and inhibited the PI3K/Akt pathway<br>Decreased the intracellular GSH content | [36] |
| Human breast cancer MCF-7 | $IC_{50}$ = 16.95 μM<br>Inhibited colony formation of MCF-7 cells<br>Induced autophagy<br>Induced the conversion and aggregation of LC3-II<br>Increased the expression of Beclin-1 | [110] |
| Gastric cancer MGC803 | $IC_{50}$ = 19.96 μM<br>Induced autophagy<br>Induced the conversion and aggregation of LC3-II<br>Increased the expression of Beclin-1 | |
| Gastric cancer BGC823 | $IC_{50}$ = 3.13 μM<br>Inhibited colony formation of BGC823 cells<br>Increased ROS production<br>Induced autophagy<br>Induced the conversion and aggregation of LC3-II<br>Increased the expression of Beclin-1 | |
| Gastric cancer AGS | $IC_{50}$ = 24.19 μM<br>Induced autophagy<br>Induced the conversion and aggregation of LC3-II<br>Increased the expression of Beclin-1 | |
| Human colon cancer HCT-116 | $IC_{50}$ = 26.6 μM at 24 h<br>$IC_{50}$ = 47.3 μM at 48 h<br>Decreased the percentage of migrated cells by 14.4% at 100 μM<br>Increased the percentage of apoptotic cells by 74.2% at 100 μM<br>Induced cell-cycle arrest at sub-$G_1$ phase | [38] |
| Human lung cancer A549 | Inhibited the proliferation of A549 cells<br>$IC_{50}$ = 17.46 μg/mL at 48 h<br>Perturbed cell cycle<br>Induced apoptotic cell death | [112] |
| Human HCC HepG2;<br>Human HCC SMMC-7721 | Reduced the proliferation of HepG2 and SMMC-7721 cells<br>Decreased cell migration and invasion abilities of both cells<br>Reduced the levels of β-catenin and *p*-β-catenin<br>Suppressed the expression of Wnt/ β-catenin signaling proteins | [40] |
| Breast cancer MCF-7;<br>MCF-7 xenografts in nude mice | $IC_{50}$ = 53.27 μg/mL<br>Inhibited cell viability in ER-positive MCF-7 cells<br>Induced apoptosis in MCF-7 cells<br>Diminished the expression of Bcl-xl, Bcl-2, and XIAP<br>Increased Bax, Bad, and activated caspase<br>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<br>Blocked metastasis progression<br>Decreased the number of visible metastasis foci<br>Inhibited metastasis size distribution in lung tissue | |
| Nontumorigenic breast epithelial MCF-10A | No cytotoxicity | |

**Table 4.** *Cont.*

| Cell Lines | Key Results | References |
| --- | --- | --- |
| Human prostate cancer (PC3 and LNCap) | Inhibited cell proliferation<br>Induced cell-cycle arrest<br>Promoted apoptosis and autophagy<br>Increased phosphorylation of c-Jun N-terminal kinase (JNK) | [113] |
| Human lung cancer A549 | $IC_{50}$ = 20.9 Mm<br>Inhibited the growth of A549 cells<br>Increased reactive oxygen species (ROS) level<br>Promoted intrinsic apoptotic cell death<br>Increased the expression of caspase-3, caspase-9, Bax, PARP inactivation, and Cyt c release<br>Diminished the expression of Bcl-2 protein<br>Inhibited the thioredoxin (TrxR) redox system | [26] |
| Breast cancer MCF-7;<br>MCF-7 xenografts in nude mice | Induced cytotoxicity<br>Decreased the proliferation rates<br>Increased the number of apoptotic cells<br>Activated the expressions of caspase 3 and PARP1<br>Reduced the tumor volume<br>Decreased the levels of CEA, CA125, and CA153<br>Increased the expression of cleaved caspase 3<br>Decreased the BCL-2 and VEGF<br>Downregulated the expression of PI3K/Akt<br>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<br>Decreased the levels of protein and malondialdehyde (MDA)<br>Reduced cancer antigen (CA) 15-3 level<br>Decreased MDA levels<br>Increased catalase activity<br>Reduced proliferation of mammary duct cells | [24] |
| Prostate carcinoma LNCaP | Inhibited cell growth and proliferation | [48] |
| Prostate carcinoma DU145 | Inhibited cell growth and proliferation<br>Increased the number of late apoptotic cells<br>Increased the number of cells in S phase<br>Decreased the number of $G_0/G_1$ cells<br>Downregulated the cell-cycle proteins (cdk1, pcdk1, cyclin A and B) | |
| Prostate carcinoma PC3 | Inhibited cell growth and proliferation<br>Increased the number of late apoptotic cells<br>Downregulated the cell-cycle proteins (cdk1, pcdk1, cyclin A and B)<br>Downregulated cdk2<br>Downregulated Akt, pAKT, and Bcl-2 proteins<br>Upregulated the pro-apoptotic protein Bax | |
| Breast tumor BALB/c mouse model | Suppressed primary tumor growth<br>Reduced lung metastases<br>Increased the number of captured CTCs in the blood circulation | [117] |
| Murine H22 hepatoma allograft model in ICR mice | Inhibited murine hepatoma H22 cell growth<br>Induced intracellular ROS generation<br>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 neuro-

protective 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.

**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<br>Suppressed caspase-3 activity<br>Upregulated the expression of IGF1 protein<br>Activated the AKT signal pathway<br>Diminished the downregulation of the Mcl-1 and Bcl-2<br>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<br>Reduced intracellular ROS levels by 37.7%<br>Reduced $H_2O_2$-induced apoptotic cell death<br>Reduced $H_2O_2$-mediated fragmented DNA<br>Increased CAT and SOD2 mRNA levels<br>Attenuated $H_2O_2$-induced phosphorylation of p38 and JNK | [41] |
| Cerebral ischemia/reperfusion (I/R) rat model | Decreased apoptotic cell death<br>Suppressed iNOS expression in ischemic zone<br>Upregulated the PI3K/Akt/mTOR signaling pathway | [30] |

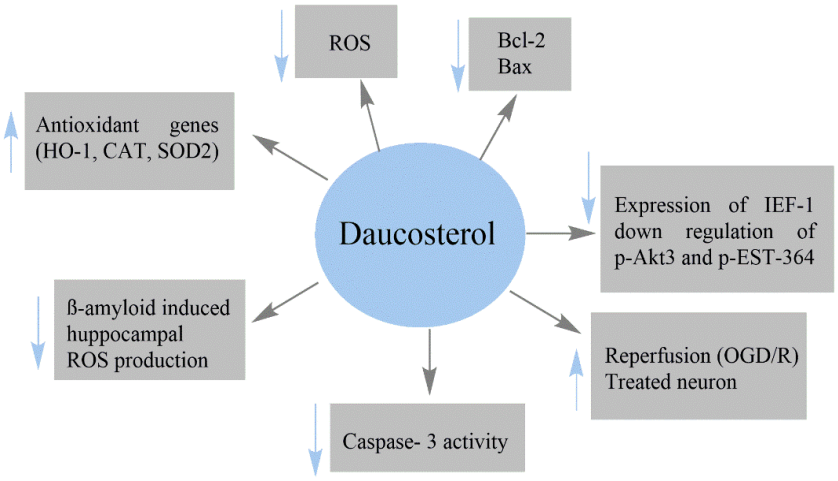


**Figure 3.** Neuroprotective effects of Daucosterol. The arrow indicates increasing or decreasing.

### *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].

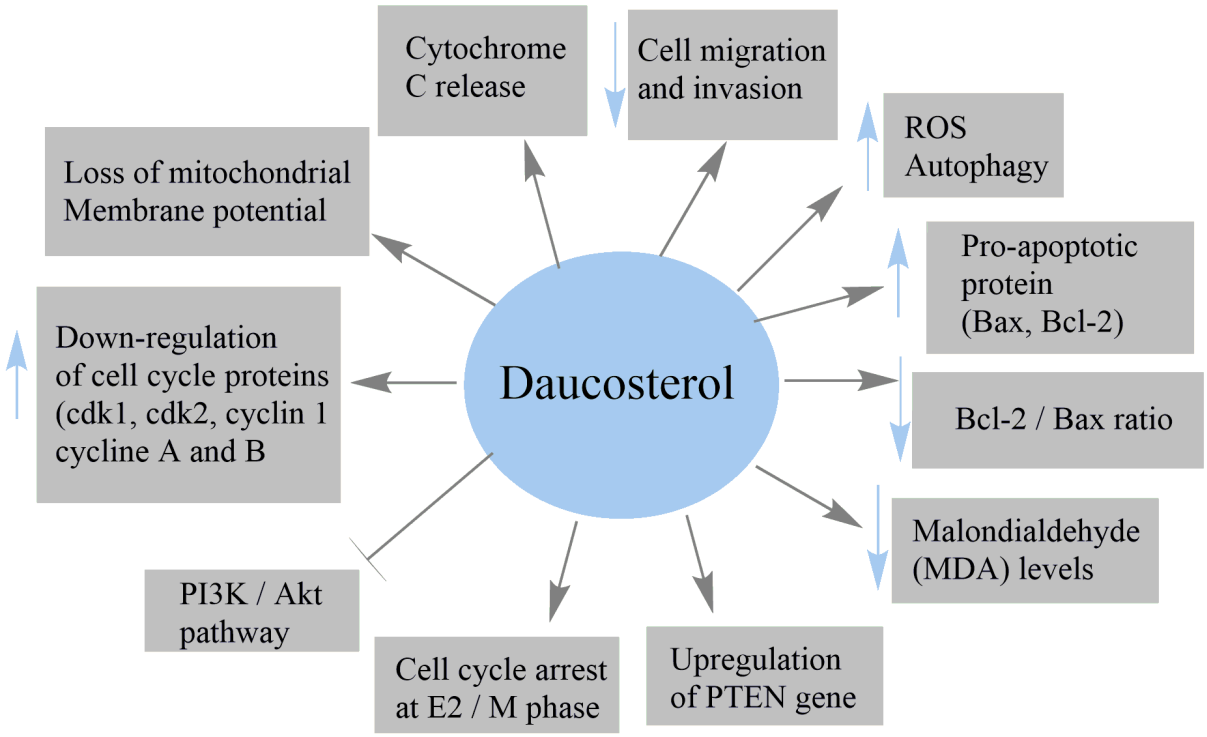


**Figure 4.** Anti-inflammatory mechanisms of Daucosterol. The arrow indicates increasing, decreasing or inhibiting.

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<br>Inhibition constant = 2.34 mg/L | [42] |
| Normal and hyperglycemic rats | Increased fasting plasma insulin levels<br>Enhanced oral glucose tolerance<br>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.

**Author Contributions:** Conceptualization, A.B. and T.B.; methodology, I.J. and N.E.M.; software, M.L.; F.E.K., validation, A.B., G.Z., S.P.B. and J.M.L.; formal analysis, A.B.; investigation, A.B. and N.E.O.; resources, S.B.; data curation, N.E.O.; writing—original draft preparation, N.E.O., I.J.; D.T.; and F.E.K., writing—review and editing, A.B., M.G. and D.M.; visualization, G.Z., S.P.B. and J.M.L.; supervision, A.B.; project administration, A.B.; funding acquisition, M.G. and D.M. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

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