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Targeting PPAR Signaling for Neurovascular Protection: Advances in Natural Product-Based Therapeutics

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Table 1. Natural compounds targeting PPAR signaling pathways in experimental models of neurovascular injury

Drug Class	Representative Compound	Botanical source	type of model	Extract Type / Solvent	working concentration	Signaling Pathway / Target	Mechanism	Level of Evidence	Ref.
Alkaloids	Berberine	An isoquinoline alkaloid isolated from the rhizomes of *Coptis chinensis* Franch. (Ranunculaceae).	In vivo: Naturally aged Wistar rats.	Purified monomer	In vivo: 100 mg/kg/day (p.o., 6 mo; starting at 18 mo).	AMPK/SIRT1/PGC-1α, GLUT4, ATP synthase, ROS-related markers (4-HNE, 8-OHdG)	Improves aging-induced cognitive deficits (shuttle box test)	In vivo	[1]
			In vitro: LPS-stimulated BV2 microglia; $A\beta_{25-35}$-induced primary cortical neurons.		In vitro: 0.1–10 μM (12 h pretreat + LPS 24 h, BV2); 1–10 μM ($A\beta_{25-35}$, 3 d, cortical neurons).	PPAR-γ, NF-κB p65, MAPK p38, M1/M2 microglial markers (iNOS, TNF-α, IL-1β; CD206, Arg1, IL-10)	Inhibits LPS-induced M1 microglial polarization and exerts anti-inflammatory effects	In vitro	[2]
Flavonoids	Luteolin	A flavone isolated from the aerial parts of *Lonicera japonica* Thunb. (Caprifoliaceae).	In vivo: Middle cerebral artery occlusion and reperfusion (MCAO/R) model in rats.	Purified monomer	In vivo: 25–50 mg/kg/day (p.o., 7 d post-reperfusion).	PPAR-γ; NF-κB; LC3B	Ameliorates neuroinflammation and regulates autophagy via PPARγ activation	In vivo	[3]
			In vivo: 3×Tg-AD mouse model; In vitro: Primary hippocampal neurons.		In vivo: 20 or 40 mg/kg (i.p., 8 w). In vitro: 2.5 or 5 μM (24 h; after 9 d culture).	PPAR-γ; BACE1; IDE; PGC-1α/NRF1/NRF2/TFAM; Drp1/Fis1/Mfn2; UCP2	Improves memory and cognitive function, and inhibits Aβ pathology via PPARγ activation	In vitro & In vivo	[4]

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Flavonoids	Baicalein	A flavone isolated from *Scutellaria baicalensis* Georgi (Lamiaceae).	In vivo: Postnatal myelinogenesis and cuprizone (CPZ)-induced demyelination models in C57BL/6 mice (including PPARγ$^{+/-}$); In vitro: Primary OPCs from neonatal C57BL/6 mice.	Purified monomer	In vivo: 100 mg/kg/day (s.c., P3–14; i.p., CPZ 0–6+3 w). In vitro: 1, 5, 10 μg/mL for 5 days	PPAR-γ, MBP (myelin basic protein), Olig2, APC, GFAP, IBA1	Enhances CNS myelinogenesis and promotes remyelination via PPARγ pathway	In vitro & In vivo	[5]
			In vivo: MCAO rat model (60 min occlusion, 2–24 h reperfusion).		In vivo: 150–300 mg/kg (i.p., 30 min before MCAO).	12/15-Lipoxygenase, PPAR-γ, NF-κB	Inhibits I/R-induced PPARγ upregulation and reduces inflammatory responses	In vivo	[6]
Flavonoids	Baicalin	A flavone glycoside isolated from the roots of *Scutellaria baicalensis* Georgi (Lamiaceae).	In vivo: Postnatal and CPZ-induced demyelination models (C57BL/6; PPARγ$^{+/-}$); In vitro: Primary OPCs (neonatal C57BL/6).	Purified monomer	In vivo: 100 mg/kg/day (s.c., P3–14); 100 mg/kg/day (i.p., CPZ 0–6+3 w); In vitro: 1, 5, 10 μg/mL for 5 days.	PPAR-γ, MBP, Olig2, APC, GFAP, NF-κB, IL-1β, TNF-α, IL-6, IL-10	Enhances postnatal CNS myelinogenesis and promotes OPC differentiation via PPARγ	In vitro & In vivo	[5]
Flavonoids	Cyanidin-3-O-glucoside	An anthocyanin glycoside isolated from various fruits, particularly *Vaccinium myrtillus* L. (Ericaceae).	In vivo: APP/PS1 transgenic AD mouse model; In vitro: Aβ42-induced HMC3 human microglial cells.	Purified monomer	In vivo: 30 mg/kg/day (p.o., 38 w); In vitro: 50 μM (Aβ42 1 μM, 24 h).	PPAR-γ, TREM2, CD86, CD80, CD206, CD163, IL-1β, TNF-α, IL-6, IL-4, IL-10	Shifts microglia from M1 to M2 phenotype and alleviates neuroinflammation	In vitro & In vivo	[7]

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Flavonoids	Didymin	A flavanone glycoside isolated from the peels of *Citrus aurantium* L. (Rutaceae).	In vivo: Rat cerebral IR model; In vitro: PC12 cells OGD/R model.	Purified monomer	In vivo: 0.5–1.0 mg/kg/day (i.p., 7 d pre-MCAO); In vitro: 10–40 μM (24 h pretreat before OGD/R).	PPAR-γ; RXRA; NF-κB (related to IL-1β, IL-6, TNF-α, MCP-1)	Reduces brain injury and inhibits apoptosis via PPAR pathway activation	In vitro & In vivo	[8]
Flavonoids	Estradiol & Genistein	Estradiol is a steroid hormone isolated from mammalian tissues, especially the ovaries; genistein is a isoflavone isolated from soybeans, particularly *Glycine max* (L.) Merr. (Fabaceae).	In vitro: Primary rat cortical astrocytes (Aβ1-42-induced injury model).	Purified monomer	In vitro: 0.5 μM (pretreated for 48 h) + 5 μM Aβ1-42 (incubated for 24 h)	PPAR-γ, NF-κB, IL-1β, TNF-α, iNOS, COX-2	Inhibits Aβ-induced upregulation of proinflammatory cytokines	In vitro	[9]
Flavonoids	Galangin	A flavonol isolated from the rhizomes of *Alpinia officinarum* Hance (Zingiberaceae).	In vivo: LPS-induced neuroinflammation model (male ICR mice, 7 weeks old) In vitro: BV2 microglial cells (LPS-stimulated).	Purified monomer	In vivo: 50 mg/kg/day (i.p., 4 d; pre-LPS 5 mg/kg); In vitro: 10–50 μM (1 h pretreat) + LPS (100 ng/mL, 16 h).	PPAR-γ, NF-κB, Nrf2, CREB, iNOS, COX-2, TNF-α, IL-6, IL-10, HO-1, p47phox, gp91phox, p38 MAPK, JNK, PI3K/Akt	Inhibits NF-κB, reduces iNOS, and upregulates Nrf2 expression	In vitro & In vivo	[10]

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Flavonoids	Ginkgetin	A biflavonoid isolated from the leaves of *Ginkgo biloba* L. (Ginkgoaceae).	In vivo: MCAO rat model; In vitro: Primary rat microglia (oxygen-glucose deprivation (OGD) model); neuron-microglia co-culture system.	Purified monomer	In vivo: 50 mg/kg (i.p., 0/24/48 h post-MCAO); In vitro: 0.1 mg/mL ginkgetin + OGD (24 h).	PPAR-γ, iNOS, Arg1, CD16, CD206, IL-1β, TNF-α, IL-4, IL-10	Promotes microglial M2 polarization and inhibits inflammation and oxidative stress	In vitro & In vivo	[11]
Flavonoids	Icariin	A prenylated flavonol glycoside isolated from the aerial parts of *Epimedium brevicornum* Maxim. (Berberidaceae).	In vivo: Middle cerebral artery occlusion (MCAO) rat model (cerebral ischemia-reperfusion injury)	Purified monomer	In vivo: 10–30 mg/kg (p.o., b.i.d., 3 d pretreat; MCAO 2 h + 24 h reperfusion).	NF-κB, PPAR-α, PPAR-γ, IκB-α	Improves neurological scores and alleviates inflammation via PPARα/γ upregulation	In vivo	[12]
Flavonoids	Icariside II	A prenylated flavonol glycoside isolated from the aerial parts of *Epimedium brevicornum* Maxim. (Berberidaceae).	In vivo: MCAO rat model (2 h occlusion, 24 h reperfusion).	Purified monomer	In vivo: 10–30 mg/kg (p.o., b.i.d., 3 d pretreat).	PPAR-α, PPAR-γ, NF-κB, IκBα, IL-1β, TGF-β_1	Improves neurological deficits and reduces cerebral infarct volume via PPARγ	In vivo	[13]
Flavonoids	Luteolin-7-O-glucoside	A flavone glycoside isolated from the aerial parts of *Lonicera japonica* Thunb. (Caprifoliaceae).	In vitro: 6-OHDA-treated SH-SY5Y cells and LPS-treated RAW264.7 macrophages.	Purified monomer	In vitro: 0.1–1 μM (30 min pre-6-OHDA; 1 h pre-LPS). RAW264.7: 0.1–1 μM (1 h pre-LPS, 1 μg/mL).	JNK-3, Caspase-3, AChE, TNF-α, IL-10, Mitochondrial Membrane Potential (ΔΨm)	Protects SH-SY5Y cells against 6-OHDA-induced apoptosis and exerts antioxidant effects	In vitro	[14]

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Flavonoids	Luteolosi de	A flavone glycoside isolated from the aerial parts of *Lonicera japonica* Thunb. (Caprifolia ceae).	In vivo: MCAO rat model (cerebral ischemia-reperfusion injury).	Purifi ed mono mer	In vivo: 20–80 mg/kg (i.p., 0 & 12 h post-MCAO).	PPAR-γ, Nrf2, NF-κB, IκBα, p-IκBα, p-p65, IL-1β, TNF-α, iNOS, COX-2	Alleviates neurological deficits and reduces cerebral edema via PPARγ activation	In vivo	[15]
Flavonoids	Morin	A flavonol isolated from the wood of *Maclura pomifera* (Raf.) C.K. Schneid. (Moraceae).	In vivo: APPswe/PS1 ΔE9 transgenic AD mouse model (6-month-old female mice).	Purifi ed mono mer	In vivo: 20 mg/kg (i.p., q.d., 12 w).	ADAM10, BACE1, PS1, IDE, NEP, CDK5, GFAP, Iba1, PSD-95, SYP	Improves spatial learning and memory deficits in AD models	In vivo	[16]
Flavonoids	Naringin	A flavanone glycoside isolated from the peels of *Citrus grandis* (L.) Osbeck (Rutaceae) .	In vivo: Quinolinic acid (QA)-induced neurotoxicity model in male Wistar rats (single intrastriatal injection of QA 300 nmol/4 μL saline)	Purifi ed mono mer	In vivo: 20–80 mg/kg (p.o., 28 d).	PPAR-γ, Bax/Bcl-2, Caspase-3, NF-κB, TNF-α, IL-1β, IL-6, Mitochondrial Complex (I-IV), SOD, GSH, MDA, NO	Attenuates locomotor dysfunction and reduces oxidative stress via PPARγ upregulation	In vivo	[17]
Flavonoids	Naringen in	A flavanone isolated from citrus fruits, particularl y *Citrus aurantium* L. (Rutaceae) .	In vivo: MCAO rat model (1 h occlusion, 23 h reperfusion).	Purifi ed mono mer	In vivo: 50 mg/kg (p.o., q.d., 21 d pretreat).	NF-κB, iNOS, COX-2, TNF-α, IL-1β, SOD, GSH	Reduces cerebral infarct volume and neurological deficits, and exerts anti-inflammatory effects	In vivo	[18]
Flavonoids	Quercetin	A flavonol isolated from various fruits and vegetables, including *Allium cepa* L. (Amaryllid aceae).	In vivo: Aluminum chloride ($AlCl_3$)-induced AD model (male Wistar rats, 8 weeks old).	Purifi ed mono mer	In vivo: 25–50 mg/kg/d ay (p.o., 28 d; post-$AlCl_3$ 50 mg/kg, 28 d).	ADAM10, ADAM17, APP, BACE1, APH1, PSEN1, AChE, DA, GFAP, Aβ plaques	Improves behavioral deficits via stimulation of the non-amyloidogeni c pathway	In vivo	[19]

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Flavonoids	Tectorigenin	An isoflavone isolated from the rhizomes of *Belamcanda chinensis* (L.) DC. (Iridaceae).	In vitro: Mouse hippocampal neuron HT22 cells (oxygen-glucose deprivation/reperfusion (OGD/R)-induced injury model).	Purified monomer	In vitro: 1–20 μM (1 h pretreat; OGD 2 h + 24 h reperfusion).	PI3K/Akt, PPAR-γ, NF-κB, IL-1β, TNF-α, iNOS, COX-2, ROS	Promotes survival of OGD/R-injured HT22 cells and reduces oxidative stress	In vitro	[20]
Flavonoids	Wogonin	A flavone isolated from *Scutellaria baicalensis* Georgi (Lamiaceae).	In vivo: Intracerebral hemorrhage (ICH) model in C57BL/6 mice; In vitro: OxyHb- or RBC-exposed BV2 microglial cells.	Purified monomer	In vivo: 20 mg/kg (i.p., 30 min post-ICH); In vitro: 20 μM (24 h pretreat; OxyHb 100 μM, 6 h).	PPAR-γ, Axl, MerTK, CD36, LAMP2, NF-κB, iNOS	Promotes hematoma clearance and inhibits inflammation via PPARγ pathway	In vitro & In vivo	[21]
Glycosides	Echinacoside	A phenylethanoid glycoside isolated from the whole plants of *Cistanche deserticola* Ma (Orobanchaceae).	In vivo: APPswe/PS1 ΔE9 transgenic AD mouse model	Purified monomer	In vivo: 50 mg/kg/day (i.p., 3 mo).	PI3K/Akt/Nrf2/PPAR-γ, BACE1, APP, SOD1, SOD2, GP91, 8-OHdG, TXNIP/Trx-1/NLRP3, IL-1β, TNF-α	Improves cognitive impairment in AD models (Morris water maze)	In vivo	[22]
			In vivo: MPTP-induced Parkinson's disease model in C57BL/6 mice; In vitro: MPP^+-treated SH-SY5Y cells and N9 microglia.		In vivo: 10–40 mg/kg (p.o., 14 d; 7 d pre-MPTP + 7 d post-MPTP). In vitro: 1–100 μM ECH (12 h pretreat) + MPP^+ (500 μM, 4 h).	TH (tyrosine hydroxylase), NLRP3/Caspase-1/IL-1β, Iba1, ROS	Ameliorates PD-like motor deficits (open field test)	In vitro & In vivo	[23]

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Phenolics	Curculigoside	A phenolic glycoside isolated from the rhizomes of *Curculigo orchioides* Gaertn. (Hypoxidaceae).	In vivo: BCCAO + CUMS–induced poststroke depression (PSD) model in rats; In vitro: OGD/R + CORT-treated primary hippocampal NSCs.	Purified monomer	In vivo: 10–50 mg/kg (p.o., 4 w); In vitro: 25–100 μM Curculigoside.	PGC-1α, TFAM, ETC Complexes (I-V), ATP, Nestin, DCX, BrdU	Alleviates depressive-like behaviors (sucrose preference test)	In vitro & In vivo	[24]
Phenolics	Gastrodin	A phenolic glycoside isolated from the rhizomes of *Gastrodia elata* Blume (Orchidaceae).	In vivo: AD model in 10-month-old APP/PS1 double-transgenic mice; In vitro: Aβ1-42-stimulated primary mouse brain microglia.	Purified monomer	In vivo: 10–20 mg/kg/day GAS (p.o.); In vitro: 10–20 μM GAS (6 h pretreat) + $A\beta_{1-42}$ (25 μM).	PPAR-γ/NF-κB, p-PPAR-γ, p-NF-κB p50/p65, IBA-1, IL-6, IL-1β, TNF-α	Ameliorates AD-related cognitive impairment and inhibits Aβ aggregation	In vitro & In vivo	[25]
Phenolics	Protocatechuic acid	A phenolic acid isolated from various plant sources, including *Hibiscus sabdariffa* L. (Malvaceae).	In vivo: MCAO model in Sprague–Dawley rats; In vitro: OGD-treated differentiated SH-SY5Y cells.	Purified monomer	In vivo: 40 mg/kg (i.v., 1 h pre-reperfusion); In vitro: 10–100 μM (6 h pre-OGD; optimal 80 μM).	PKCε/Nrf2/HO-1, ROS, 4-HNE, 8-OHdG	Reduces cerebral infarct volume and improves neurological function	In vitro & In vivo	[26]

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Phenolics	Resveratrol	A stilbene polyphenol isolated from the roots of *Polygonum cuspidatum* Siebold & Zucc. (Polygonaceae).	In vivo: APP/PS1 AD mice and naturally aging Wistar rats; In vitro: Aβ-treated SH-SY5Y cells, primary cortical neurons, and PC12 cells.	Purified monomer	In vivo: 10–20 mg/kg/day (p.o., AD model); 100 mg/kg/day (p.o., 6 mo, aging rats); In vitro: 1–10 μM ($A\beta_{42}$ 5 μM, 12–24 h, SH-SY5Y); 0.25 μM (24 h pretreat, H_2O_2 cells).	AMPK/SIRT1/PGC-1α, PI3K/Akt, AMPAR, ERβ, NF-κB	Ameliorates AD-related cognitive impairment and reduces tau phosphorylation	In vitro & In vivo	[27]
Phenylpropanoids	Fraxin	A coumarin glycoside isolated from the bark of *Fraxinus rhynchophylla* Hance (Oleaceae).	In vivo: MCAO-induced cerebral I/R model in Sprague–Dawley rats; In vitro: OGD/R-treated BV2 microglia and HT22 neurons.	Purified monomer	In vivo: 5–20 mg/kg (i.p., 30 min pre-MCAO); In vitro: 5–20 μg/mL Fraxin (6 h pre-OGD; OGD/R 24 h).	PPAR-γ/NF-κB, Nrf2/HO-1, Keap1, iNOS, Arg1, SOD, GSH-PX, MDA, IL-1β, TNF-α, IL-6	Alleviates neurological deficits (mNSS, Morris water maze) via PPARγ	In vitro & In vivo	[28]
Phenylpropanoids	Phillyrin	A lignan glycoside isolated from the fruits of *Forsythia suspensa* (Thunb.) Vahl (Oleaceae).	In vivo: Traumatic brain injury (TBI) model in C57BL/10ScNJ mice (controlled cortical impact, CCI); In vitro: Primary microglia (LPS-induced activation model).	Purified monomer	In vivo: 2.5–10 mg/kg (i.p., q.d., 7 d post-surgery); In vitro: 10–50 μg/mL Phillyrin (1 h pretreat) + LPS (1 μg/mL, 24 h).	PPAR-γ, STAT6, NF-κB, Iba1, iNOS, Arg1, IL-1β, TNF-α, IL-6, IL-10	Improves neurological function (mNSS, rotarod test) via anti-inflammatory effects	In vitro & In vivo	[29]

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Saponins	Asperosaponin VI	A triterpenoid saponin isolated from the roots of *Dipsacus asper* Wall. ex C.B. Clarke (Caprifoliaceae).	In vivo: Chronic mild stress (CMS)-induced depression mouse model; In vitro: Primary microglia (LPS-induced activation model); neuron-microglia co-culture system.	Purified monomer	In vivo: 40 mg/kg (i.p., 3 w post-CMS); In vitro: 40 μM Asperosaponin VI + LPS (50 ng/mL, 24 h).	PPAR-γ, NF-κB, Iba1, iNOS, Arg1, CX3CL1/CX3CR1, CD200/CD200R, PSD95, CamKIIα/β, GluA2	Ameliorates depressive-like behaviors (sucrose preference test) and exerts antioxidant effects	In vitro & In vivo	[30]
Saponins	Astragaloside IV	A triterpenoid saponin isolated from the roots of *Astragalus membranaceus* (Fisch.) Bunge (Fabaceae).	In vivo: MCAO/R-induced cerebral ischemia–reperfusion model in rats.	Purified monomer	In vivo: 20 mg/kg/day AS-IV (i.p., 14 d pre-MCAO/R).	PPAR-γ, BDNF/TrkB/PI3K/Akt/mTOR, SYN, PSD95, MAP-2	Reduces infarct volume and ameliorates neurological deficits via anti-inflammatory effects	In vivo	[31]
			In vivo: MCAO/R-induced cerebral ischemia–reperfusion model in rats.		In vivo: 40 mg/kg/day AS-IV (i.p., 14 d post-MCAO/R).	PPAR-γ, M1 markers (CD86, iNOS, TNF-α, IL-1β, IL-6), M2 markers (CD206, Arg-1, YM1/2, IL-10, TGF-β), BDNF, IGF-1, VEGF	Promotes M2 polarization of microglia/macrophages and exerts neuroprotective effects	In vivo	[32]
Terpenoids	Catalpol	An iridoid glycoside isolated from the roots of *Rehmannia glutinosa* (Gaertn.) DC. (Orobanchaceae).	In vivo: HFD/STZ-induced T2DM model in C57BL/6 mice.	Purified monomer	In vivo: 100–200 mg/kg/day Catalpol (p.o., 4 w).	AMPK/SIRT1/PGC-1α/PPAR-γ, IRS-1/PI3K/Akt, GLUT4, citrate synthase (CS)	Improves insulin sensitivity and enhances glucose uptake in skeletal muscle	In vivo	[33]
Saponins	Esculentoside A	A triterpenoid saponin isolated from the roots of *Phytolacca esculenta* Van Houtte (Phytolaccaceae).	In vitro: LPS-induced BV2 microglia activation model.	Purified monomer	In vitro: 10–40 μM EsA + LPS (0.5 μg/mL, 18–24 h).	PPAR-γ, NF-κB	Inhibits LPS-induced BV2 microglial activation and exerts anti-inflammatory effects	In vitro	[34]

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Saponins	Ginsenoside Rb1	A triterpenoid saponin isolated from the roots of *Panax ginseng* C.A. Mey. (Araliaceae).	In vivo: MCAO/R mouse model.	Purified monomer	In vivo: 20 mg/kg/day (i.p., 7 d post-MCAO/R).	PPAR-γ, NF-κB, ZO-1, Occludin, VE-cadherin, Claudin-5, TNF-α, IFN-γ	Reduces cerebral infarct volume (TTC staining) and exerts anti-inflammatory effects	In vivo	[35]
Saponins	Ginsenoside Rg1	A triterpenoid saponin isolated from the roots of *Panax ginseng* C.A. Mey. (Araliaceae).	In vivo: MCAO-induced cerebral ischemia–reperfusion model in rats.	Purified monomer	In vivo: 20–60 mg/kg GRg1 (i.v., 1 h pre-MCAO).	PPAR-γ/HO-1, Bcl-2, cleaved caspase-3, cleaved caspase-9, RAGE	Suppresses inflammation (reduces IL-1β, TNF-α, iNOS) and exerts antioxidant effects	In vivo	[36]
Saponins	Ginsenoside Rd	A triterpenoid saponin isolated from the roots of *Panax ginseng* C.A. Mey. (Araliaceae).	In vivo: BCAS-induced chronic cerebral hypoperfusion model in C57BL/6J mice. In vitro: OGD/R-treated primary hippocampal neurons.	Purified monomer	In vivo: 10–30 mg/kg/day GSRd (i.p., 21 d; start 15 d post-BCAS); In vitro: 0.1–10 μM GSRd (2 h pretreat; OGD/R 24 h).	HDAC2/Ac-H3/BDNF, PI3K/Akt/mTOR, β-tubulin III, MAP2	Ameliorates CCH-induced cognitive impairment and exerts anti-inflammatory effects	In vitro & In vivo	[37]
Saponins	Jujuboside A	A triterpenoid saponin isolated from the seeds of *Ziziphus jujuba* Mill. (Rhamnaceae).	In vivo: APP/PS1 transgenic mouse model of AD; In vitro: Aβ-treated BV2 microglia, primary microglia.	Purified monomer	In vivo: 0.5–5 mg/kg/day JuA (i.t. or p.o., 7 d); In vitro: 1–25 μM JuA (30 min pretreat) + $A\beta_{42}$ (5 μM, 12–24 h).	Axl/HSP90β/PPAR-γ, BDNF/TrkB/PI3K/Akt/mTOR	Promotes Aβ clearance and ameliorates cognitive deficits in AD	In vitro & In vivo	[38]

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Saponins	Platycodigenin	A triterpenoid sapogenin isolated from the roots of *Platycodon grandiflorus* (Jacq.) A.DC. (Campanulaceae).	In vitro: LPS-stimulated BV2 microglia, primary microglia; Aβ25-35-treated primary cortical neurons.	Purified monomer	In vitro: 0.1–10 μM PLA (12 h pre-LPS; 24 h, microglia); 1–10 μM PLA + $A\beta_{25-35}$ (10 μM, 3 d, neurons).	PPAR-γ, NF-κB p65, MAPK p38, M1 markers (Cox2, iNOS, TNF-α, IL-1β, IL-6), M2 markers (Ym1/2, CD206, Arg1, IL-10)	Inhibits LPS-induced M1 microglial polarization and exerts anti-inflammatory effects	In vitro	[39]
Terpenoids	Steviosid e	A diterpene glycoside isolated from the leaves of *Stevia rebaudiana* (Bertoni) (Asteraceae).	In vivo: High-fat diet–induced prediabetic model in C57BL/6J mice. In vitro: PA-induced insulin-resistant AML-12 hepatocytes.	Purified monomer	In vivo: 200–400 mg/L Steviosi de (drinking water, 8 w). In vitro: 0.1 mM Steviosi de + PA (0.3 mM, 18 h).	IRS1/PI3K/AKT, p-IRS1 (Ser307), p-PI3K p85α, p-AKT (Ser473), G6pc1, Gsk3b	Improves glucose tolerance and alleviates hepatic insulin resistance	In vitro & In vivo	[40]
			In vivo: MCAO/R rat model.		In vivo: 30 mg/kg/day (p.o., 2 w post-MCAO/R).	PPAR-γ, PI3K/AKT, NF-κB, IL-1β, TNF-α, Bcl-2, Bax, Cleaved Caspase-3	Reduces neurological deficits (mNSS scores) and infarct volume	In vivo	[41]

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