

Table S1: Natural products with other targets.

Compound	Effective dose	Animal model	Seizure-inducing agent	Mechanism	Source
Oleuropein (secoiridoid)	10, 20, and 30 mg/kg i.p.	Male NMRI mice	PTZ	Possibly <i>via</i> opioidergic/nitrgergic pathways	[127]
Tanshinone IIA (diterpene)	59 mg/kg of larvae 0.5–1 mg/kg mouse i.v.	Zebrafish larvae Male NMRI mice	PTZ 6-Hz test	Reduction of <i>c-fos</i> expression	[128]
	30 mg/kg i.p.	Wild-type Std-ddY male mice	KA	↓ in bulk histone H4 acetylation ↓ in <i>c-fos</i> and <i>c-jun</i> mRNA expression	[129]
Curcumin (phenolic)	1500 ppm w/w	Male Wistar rats	Ferric chloride	Antioxidant activity Binding Fe ²⁺ /Fe ³⁺ ions Amelioration of membrane fluidity Inhibition of cytosolic PKC activity- ↓ PKC-mediated excitotoxicity ↑ Na ⁺ -K ⁺ ATPase activity Neuroprotective activity in cortex	[130]
Resveratrol (stilbenoid)	20, 40, and 80 mg/kg RE (40 mg/kg i.p.) + sodium valproate (150 mg/kg) RE+DZP (2 mg/kg)	Male Wistar rats	PTZ	Adenosinergic activity	[131]
Berberine (alkaloid)	25, 50, and 100 mg/kg/day i.g. (for 7 days)	Male Sprague-Dawley rats	Pilocarpine	Anticonvulsant and neuroprotective effect, block of potassium currents	[132]
	10 and 20 mg/kg i.p.	Male Swiss mice	PTZ, MES, KA	Modulation of neurotransmitter systems	[133]
Harmane (alkaloid)	2.5, 5, and 10 mg/kg i.p.	Male and female Swiss mice	MES PTZ	Interaction with imidazoline and benzodiazepine receptors	[134]
Mesaconitine (alkaloid)	0.003–1 μM	Hippocampal slices of male Wistar rats	Low Mg ²⁺ /high K ⁺ -ACSF Bicuculline	Activation of α-adrenoceptors	[135]
Piperine (alkaloid)	40 and 80 mg/kg i.p.	Male KM mice	MES PTZ	Probably TRPV1 receptor agonist	[136]

Quinine (alkaloid)	60 mg/kg i.p. 200, 400, and 1000 nmol i.c.v.	Male BALB/c mice Male Wistar rats	PTZ Penicillin	Blockade of Cx36 channels Blockade of Cx36 channels	[137] [138]
Sanjoinine A (alkaloid)	4 and 8 mg/kg p.o.	Male ICR mice Male Sprague- Dawley rats	KA	Increasing intracellular Cl ⁻ and reducing intracellular Ca ²⁺ levels	[139]
Tetrahydropalmatine (alkaloid)	10 or 15 mg/kg i.p.	Male Sprague- Dawley rats	PTX	Inhibition of amygdaloid dopamine release	[140]

Table S2: Unknown targets.

Compound	Effective dose	Animal model	Seizure-inducing agent	Mechanism	Source
β-caryophyllene (sesquiterpene)	100 mg/kg i.p.	C57BL/6 mice	PTZ	Unknown	[141]
	30 mg/kg i.p. 50 and 100 mg/kg i.p.	Male ICR mice	MES KA	CB2 receptor agonist	[142]
Valerenic acid (sesquiterpene)	37 µg/mL	Adult zebrafish	PTZ	Unknown (possibly modulation of GABA receptors)	[143]
Abietic acid (diterpene)	30 and 100 mg/kg p.o., i.p.	Swiss mice	MES	Unknown	[144]
Phytol (diterpene)	25, 50, and 75 mg/kg i.p.	Male Swiss mice	Pilocarpine	Unknown	[145]
Caudatin-3- <i>O</i> -β-D- Cym-(1→4)-β-D- Cym-(1→4)-β-D- Cym (steroid)	10 µg/mL	Zebrafish larvae	PTZ	Unknown	[146]
Caudatin-3- <i>O</i> -β-D- Ole-(1→4)-β-D-Ole- (1→4)-β-D-Cym- (1→4)-β-D-Cym (steroid)	10 µg/mL	Zebrafish larvae	PTZ	Unknown	[146]

Cyanoauriculoside G (steroid)	100 mg/kg p.o. (ED ₅₀ = 88.1 mg/kg)	Male KM mice	MES	Unknown	[147]
Cynawilfoside A (steroid)	100 mg/kg p.o. (ED ₅₀ = 48.5 mg/kg)	Male KM mice	MES	Unknown	[147]
Cynauricoside A (steroid)	100 mg/kg p.o. (ED ₅₀ = 95.3 mg/kg)	Male KM mice	MES	Unknown	[147]
Otophyllósíde B (steroid)	10 µg/mL	Zebrafish larvae	PTZ	Unknown	[146]
	100 and 200 µM	Zebrafish larvae	PTZ	Unknown	[148]
Otophyllósíde F (steroid)	300 µM	Zebrafish larvae	PTZ	Unknown	[148]
Rostratamine 3- <i>O</i> -β- D-Ole-(1→4)-β-D- Cym-(1→4)-β-D- Cym (steroid)	100 and 200 µM	Zebrafish larvae	PTZ	Unknown	[148]
Torvoside J (steroid)	140 µM	Zebrafish larvae <i>Xenopus laevis</i> oocytes	PTZ	Unknown (weak GABA _A modulation)	[149]
Wilfoside C1N (steroid)	100 mg/kg p.o. (ED ₅₀ = 124.1 mg/kg)	Male KM mice	MES	Unknown	[147]
Wilfoside K1N (steroid)	100 mg/kg p.o. (ED ₅₀ = 72.3 mg/kg)	Male KM mice	MES	Unknown	[147]
	2.3 mg/kg i.g.	Male Swiss mice	PTZ	Unknown	[150]
Ursolic acid (triterpene)	50 and 100 mg/kg i.p.	Naïve male Swiss mice	6-Hz test MES	Unknown	[151]
	10, 30, and 100 mg/kg i.p.	Male Swiss mice	PTZ	Modulation of GABA _A receptor	[152]
Decursin (coumarin)	20 mg/kg i.p.	Male C57BL/6 mice	KA	Protective effect against glutamate-induced neurotoxicity	[153]
Acacetin (flavonoid)	10 and 20 mg/kg/day p.o. (for 2 weeks)	ICR male mice	PTZ	Unknown	[154]

				(possibly modulation of GABA, opioid, and serotonin receptors)	
Apigenin (flavonoid)	25 and 50 mg/kg i.p.	Male Sprague-Dawley rats	PTX	Unknown (possibly modulation of GABA receptors)	[155]
Goodyerin (flavonoid)	25 and 50 mg/kg i.p.	Male ICR mice	PTX	Unknown (possibly modulation of GABA receptors)	[156]
Kaempferitrin (flavonoid)	1 µg/µL i.c.v.	Male Swiss Webster mice	PTZ	Unknown (agonistic 5-HT _{1A} activity)	[157]
Linarin (flavonoid)	10 and 20 mg/kg/day p.o. (for 2 weeks)	ICR male mice	PTZ	Unknown	[154]
Naringenin-7- <i>O</i> -methyl ether (flavonoid)	25 µM	Zebrafish larvae	PTZ	Unknown	[158]
Naringenin-4',7- <i>O</i> -dimethyl ether (flavonoid)	12.5 µM 12.5 mg/kg i.p. 6.25 mg/kg i.p.	Zebrafish larvae Male C57BL/6 mice Male NMRI mice	PTZ 6-Hz test	Unknown	[158]
Erysothrone (alkaloid)	0.125–3 µg/µL i.c.v.	Male Wistar rats	Bicuculline, PTZ, NMDA, KA	Unknown	[159]
TMC-120A (alkaloid)	20 µg/µL 1.25, 2.5, and 10 mg/kg i.p.	Zebrafish larvae Male NMRI mice	PTZ 6-Hz test	Unknown	[160]
TMC-120B (alkaloid)	20 µg/µL 10 mg/kg i.p.	Zebrafish larvae Male NMRI mice	PTZ 6-Hz test	Unknown	[160]
TMC-120C (alkaloid)	20 µg/µL	Zebrafish larvae	PTZ	Unknown	[160]
Penicisochroman G (alkaloid)	12.5 µg/µL	Zebrafish larvae	PTZ	Unknown	[160]
Ustusorane B (alkaloid)	12.5 µg/µL	Zebrafish larvae	PTZ	Unknown	[160]
Pseurotin A ₂ (γ-lactams)	12.5 µg/µL 40 mg/kg i.p.	Zebrafish larvae Male NMRI mice	PTZ 6-Hz test	Unknown	[161]
Azaspirofuran A (γ-lactams)	12.5 µg/µL 40 mg/kg i.p.	Zebrafish larvae Male NMRI mice	PTZ 6-Hz test	Unknown	[161]

Table S3. Natural products with potential anti-epileptic activity *via* neuroprotection and anti-inflammatory action.

Compound	Effective dose	Animal model	Seizure-inducing agent	Mechanism	Source
Borneol (monoterpene)	25 mg/kg i.p.	Male Swiss mice	PTZ	Neuroprotective effect	[162]
Thymoquinone (monoterpene)	10 mg/kg i.p., twice	Male Sprague-Dawley rats	Lithium-Pilocarpine model of SE	Protective effect <i>via</i> downregulation of TNF- α and COX-2 in the brain	[56]
<i>ar</i> -Turmerone (sesquiterpene)	50 mg/kg i.p. 46 μ M	Male C57BL/6 mice Zebrafish larvae	PTZ 6-Hz test	Downregulation of <i>c-fos</i> (upregulation of BDNF)	[163]
Bilobalide (sesquiterpene)	5 and 10 mg/kg i.p.	Male Sprague-Dawley rats	Middle cerebral artery occlusion	Neuroprotective effect (\downarrow TNF- α , IL-1 β , p-JNK1/2, and p-p38 MAPK expression)	[62]
Asiatic acid (triterpene)	40 mg/kg/day p.o. (for 7 days)	Male C57BL/6 mice	KA	Neuroprotective effect (\downarrow IL-1 β , TNF- α , PGE ₂ , COX-2, and Bax mRNA expression)	[164]
	5–30 μ M	Hippocampal terminals of male Sprague-Dawley rats	4-AP	Attenuation of the calcium influx via N- and P/Q-type calcium channels, subsequently decreasing glutamate release	[165]
Maslinic acid (triterpene)	40 mg/kg/day p.o. (for 7 days)	Male C57BL/6 mice	KA	Neuroprotective effect (\downarrow IL-1 β , TNF- α , PGE ₂ , COX-2, and Bax mRNA expression)	[164]
Otophyllaside N (steroid)	5 and 10 μ g/mL	Primary cortical neurons			
	2.5 and 5 μ g/kg i.p. (t.i.d. for 7 days)	C57BL/6J mice	PTZ	Upregulation of Bax/Bcl-2 and downregulation of <i>c-fos</i> expression	[166]
	12, 25, and 50 μ g/mL	Zebrafish larvae			
16- <i>O</i> -Acetyl digitoxigenin (steroid)	1.8 mg/kg/day i.p. (for 4 weeks)	Hippocampal neurons of male ICR mice	Pilocarpine	Inhibition of activation of p-mTOR/p-70S6K pathway, inhibition of mTOR signaling pathway, neuroprotective effect	[167]
Corilagin (tannin)	10 and 20 mg/kg i.p. (for 24 days)	Male Wistar rats	PTZ	Anti-inflammatory (\downarrow TNF- α , \uparrow IL-10) Antioxidant (\downarrow ROS production, \downarrow CAI activity)	[168]
Gastrodin (phenolic)	PHT:GD = 1:50 (8.59:429.27 mg/kg)	Male KM mice	Penicillin	Neuroprotective \uparrow NF- κ B for induction of synaptic plasticity	[169]

Arbutin (phenolic)	25 and 50 mg/kg i.p. (for 10 days)	Male NMRI mice	PTZ	Neuroprotective effect (↓ TNF- α , IL-6, and GFAP mRNA expression)	[170]
Vanillyl alcohol (phenolic)	100 mg/kg i.p.	Male Sprague- Dawley Rats	Ferric chloride	Antioxidant activity (↓ lipid peroxide levels)	[171]
Resveratrol (stilbenoid)	20 and 40 mg/kg i.p., three times	Wistar rats of either sex	KA	Antioxidant activity	[172]
	20 mg/kg in liposome i.v.	Male Sprague- Dawley rats	Penicillin	Antioxidant activity (↑ in GST and SOD activity, ↑ GSH and ↓ MDA levels)	[173]
Baicalin (flavonoid)	100 mg/kg i.p.	Male Sprague- Dawley rats	Pilocarpine	Neuroprotective (↓ lipid peroxidation, ↓ NO, ↑ GSH, protects against neuronal apoptosis)	[174]
Chrysin (flavonoid)	10 μ M	BV-2 mouse microglial cell line		Neuroprotective (↓ iNOS, COX-2 expression → ↓ NO, ↓ TNF- α , ↓ IL-1 β) Inhibition of the activation of JNK and NF- κ B	[175]
Fisetin (flavonoid)	10 and 25 mg/kg i.p.	Male Swiss mice	PTZ, STR, INH, MES	↑ GABA Antioxidant activity (↓ NO, ↓ XO)	[176]
	20 mg/kg/day p.o. (for 12 weeks)	Male Wistar rats	FeCl ₃	Antioxidant activity (↓ lipid peroxidation) Restore the activity of the Na ⁺ , K ⁺ -ATPase	[177]
Luteolin (flavonoid)	10 and 20 mg/kg i.p.	Swiss albino mice	PTZ	Antioxidant activity (↑ GSH and ↓ MDA)	[178]
Naringin (flavonoid)	40 and 80 mg/kg i.p., (for 7 days)	Male Wistar rats	KA	Neuroprotective and antioxidant (↓ MDA, ↑ GSH, ↓ TNF- α)	[179]
Berberine (alkaloid)	25, 50, and 100 mg/kg i.g. (for 7 days)	Sprague-Dawley rats	Pilocarpine	Anticonvulsant and neuroprotective effect, block of potassium currents	[180]
Sinomenine (alkaloid)	20, 40, and 80 mg/kg i.p.	Male Sprague- Dawley rats	PTZ	Neuroprotective and anti-inflammatory effect, attenuation of IL-1 β , IL-18, IL-6, TNF- α	[180]