

Supplementary Material

Table S1: A survey of the anti-ischemia mechanistic studies reported in the literature for the different plant species and their derived bioactives.

No.	Compound/ Chemical class	Source	Mechanism	Model	Ref
I. Bioactives for management of cerebral ischemia					
1	Totarol (Terpenoid)	<i>Podocarpus totara</i> , F: podocarpaceae	Neuroprotective in cerebral IRI via Activation of Akt/HO-1 pathway.	OGD and tMCAO	[1]
2	Taraxasterol (Terpenoid)	<i>Taraxacum officinale</i> , F: Asteraceae	Neuroprotective in hippocampal neurons via Activation of Nrf2 signalling pathway (ROS↓; MDA↓).	OGD/R	[2]
4	Resveratrol (Terpenoid)	Grape <i>Vitis vinifera</i> , F: Vitaceae	Ref to text.	MCAO	[19]
5	Celastrol (Terpenoid)	<i>Tripterygium wilfordii</i>	Protective effect against cerebral IRI through downregulation of the expression of p-JNK, p-c-Jun and NF-κB.	tMCAO/O GD	[16]
6	Asiatic acid (Terpenoid)	<i>Centella asiatica</i> , F: Apiaceae	Neuroprotective against focal cerebral IRI by suppressing mitochondrial damage and MMP-9 activation.	-pMCAO	[34]
7	11-Keto-β-boswellic acid terpenoid	<i>Boswellia serrata</i> , F: Burseraceae	Neuroprotection and anti- inflammatory against cerebral IRI via regulation of the Nrf2/HO-1 pathway.	MCAO	[112]
8	Acetyl-11-Keto-β- boswellic acid (Terpenoid)	<i>Boswellia serrata</i> , F: Burseraceae	AKBA-loaded o- carboxymethyl chitosan nanoparticles (AKBA-NP) neuroprotection, antioxidant and anti-inflammatory against cerebral IRI via increasing nuclear erythroid 2-related factor 2 and heme oxygenase-1 expression, and decreasing nuclear factor-kappa B and 5-	MCAO	[113]

			lipoxygenase expression.		
9	Andrographolide (Terpenoid)	<i>Andrographis paniculate</i> , F: Acanthaceae	Anti-inflammatory and protective against Cerebral IRI via suppression of NF- κ B and microglial activation, and reducing production of cytokines (TNF- α and IL-1 β) and pro-inflammatory factors (PGE ₂).	pMCAO	[110]
10	Parthenolide (Terpenoid)	<i>Tanacetum parthenium</i> , F: Asteraceae	Protection against cerebral IRI through downregulating NF- κ B, phosho-p38MAPK, and caspase-1 expressions and ameliorating BBB permeability	MCAO	[51]
11	Ursolic acid (Terpenoid)	<i>Ocimum forskolei</i> , F: Lamiaceae	Anti-inflammatory, anti-apoptotic and neuroprotective against cerebral IRI possibly through the HMGB1/TLR4/NF κ B signaling pathway.	MCAO	[129, 130]
12	Bilobalide (Terpenoid)	<i>Ginko biloba</i> , F: Ginkgoaceae	Protection against alterations in mitochondrial respiratory activity in cerebral IRI via protecting complex I and complex III activities and preserving the energetic pool of tissues.	OGD/R	[119]
13	Nomilin (Terpenoid)	<i>Citrus limon</i> , F: Rutaceae	Protective in cerebral IRI via regulation of Nrf2/NQO1 pathway.	OGD MCAO	[80]
14	Paeoniflorin (Terpenoid)	<i>Paeonia lactiflora</i> , F: Paeoniaceae	Inhibition of astrocytic activation in cerebral IRI via regulating the Ca ²⁺ /CaMKII/CREB signaling pathway and reversing the increased expression of astrocyte marker protein GFAP.	tMCAO	[76]
15	Carnosic acid (Terpenoid)	<i>Rosmarinus officinalis</i> , F: Lamiaceae	Protective against After liver IRI, via anti-oxidative, anti-apoptotic -Anti-inflammatory via inactivating NF- κ B signaling	MCAO	[47]

			pathway, leading to down-regulation of pro-inflammatory cytokines releasing.		
16	Linalool terpenoid	<i>Lavandula officinalis</i> , F: Lamiaceae	Neuroprotective in cerebral IRI via reducing pro-inflammatory markers, and caused Nrf2 subcellular redistribution.	MCAO	[82]
17	Senkyunolide I (Terpene)	<i>Ligusticum chuanxiong</i> , F: Apiaceae	Neuroprotective, anti-oxidant and anti-apoptotic against cerebral IRI (activate the Nrf2/ARE pathway by up-regulating the phosphorylation of Erk1/2 and inducing Nrf2 nuclear translocation with enhanced HO-1 and NQO1 expressions).	MCAO	[108]
18	Tanshinone A (Terpenoid)	<i>Salvia miltiorrhiza</i> , F: Lamiaceae	Ref to text. -Suppression of NF-κB expression (MDA↓; SOD↑) - Attenuation of brain oedema formation (ICAM-1↓; MMP-9↓; iNOS↓).	-pMCAO -tMCAO	[7]
19	Ligustrazine (Terpenoid)	<i>Ligusticum chuanxiong</i> , F: Apiaceae	Protection against cerebral endothelial cells injury via the inhibition of the Rho/ROCK signaling pathway (SOD↑; MDA↓; iNOS↓) .	OGD/R	[11]
20	Z-ligustilide (Terpenoid)	<i>Rhizoma Chuanxiong</i> , F: Apiaceae	Ref to text		[1]
21	Triptolide (Terpenoid)	<i>Tripterygium wilfordii</i> , F: Celastraceae	Anticytotoxic and anti-apoptotic against cerebral IRI via inhibiting NF-κB and p38MAPK signaling pathways.	tMCAO/O GD	[17]
22	Safranal (Terpenoid)	<i>Crocus sativus</i> , F: Iridaceae	Protective against skeletal muscle IRI via inhibition of oxidative stress, muscle contractility, I _{Ca-L} and the regulation of Ca ²⁺ homeostasis	ISO-induced	[63]
23	Britanin (Terpenoid)	<i>Inula linearifolia</i> , F: Asteraceae	-Neuroprotective against cerebral IRI via binding Keap1, inhibiting Keap1-mediated ubiquitination of Nrf2 and	OGD/R and MCAO/R	[116]

			inducing Nrf2/ HO-1 pathway		
24	Ginkgolide K (Terpenoid)	<i>Ginkgo pilopa</i> , F: <i>Ginkgoaceae</i>	Anti-oxidant and protective against cerebral muscle IRI via reversed the level of MDA, NO and NOS	MCAO	[43]
25	Salvianolic acid A (Phenolic)	<i>Salvia miltiorrhiza</i> , F: Lamiaceae	Ref to text		[8]
26	Emodin (Phenolic)	<i>Polygonum multiflorum</i> Thunb., F: Polygonaceae	anti-apoptotic against Photothrombotic cortical ischaemia through activation of the PI3K/Akt signaling pathway	glutamate-induced	[9]
27	Magnesium lithospermate B (Phenolic)	<i>Salvia miltiorrhiza</i> , F: Lamiaceae	Anti-apoptosis and attenuation of cerebral excitatory neurotoxicity during IRI through the regulation of miR-107/GLT-1 pathway.	tMCAO	[14]
28	2,3,5,4'-Tetra hydroxystilbene-2-O- β -D-glucoside (Phenolic)	<i>Polygonum multiflorum</i> , F: Polygonaceae	Cytoprotective in focal cerebral IRI via Down-regulation of JNK, SIRT1, and NF- κ B pathways	OGD/R MCAO	[5]
29	Paeonol (Phenolic)	<i>Paeonia suffruticosa</i> , F: Paeoniaceae	Anti-oxidant and anti-apoptotic against brain ischemia injury by increasing antioxidase activity, reducing oxygen-free radicals-induced damage, and inhibiting cell apoptosis -neuroprotective effect by restraining calcium overload and decreasing excitotoxicity	OGD BCCAO	[45]
30	Osthole (Phenolic)	<i>Cnidium monnieri</i> , F: Apiaceae	Anti-oxidant and Neuroprotective against cerebral IRI via activating Nrf2 pathway	BCAO	[117]
31	Tetrahydroxystilbene (Phenolic)	<i>Polygonum multiflorum</i> , F: Polygonaceae	Anti-apoptotic against focal cerebral IRI via inhibition of iNOS mRNA expression and NF- κ B	OGD	[5]
32	Cinnamophilin neolignane (Phenolic)	<i>Cinnamomum Philippinense</i> , F: <i>Lauraceae</i>	Protective against transient focal cerebral ischemia via antioxidant and anti-	(MCAO) OGD	[24]

			inflammatory effects(inhibited (TNF- α), nitrite/nitrate, interleukin-6 (IL-6))		
33	Cinnamophilin (phenolic)	Cinnamon <i>Cinnamomum zeylanicum</i> , F: Lamiaceae	Protective against transient focal cerebral IRI via inhibition of COX-1 and 5-lipoxygenase	OGD/R	[24]
34	Schisandrin B (Phenolic)	<i>Schisandra chinensis</i> , F: Schisandraceae	Neuroprotective against transient focal cerebral ischemia via inhibiting inflammatory markers (TNF- α ↓; IL-1 β ↓; MMP-2↓; MMP-9↓)	tMCAO	[18]
35	Epigallocatechin gallate (Phenolic)	Green Tea <i>Camellia thinensis</i> , F: Theaceae	Ref to text		
36	Shikonin (Phenolic)	<i>Lithospermum erythrorhizon</i> , F: Boraginaceae	Anti-oxidant and protective against cerebral IRI via reducing NDS, MDA and ROS) and upregulating SOD, catalase, GSH-Px activities	MCAO	[44]
37	Paeonol (Phenolic)	<i>Paeonia suffruticosa</i> , F: Paeoniaceae	Anti-oxidant and anti-apoptotic against brain ischemia injury by increasing antioxidase activity, reducing oxygen-free radicals-induced damage, and inhibiting cell apoptosis. Neuroprotective effect by restraining calcium overload and decreasing excitotoxicity.	OGD BCCAO	[45]
38	Curculigoside A (Phenolic)	<i>Curculigo Orchioides</i> , F: Hypoxidaceae	Antiproliferative and protective against cerebral IRI through inducing angiogenesis <i>in vitro</i> via a prograded VCAM-1/Egr-3/CREB/VEGF signaling axis.	MCAO OGD	[78]
39	Theaflavin (Phenolic)	<i>Camellia sinensis</i> , F: Theaceae	Antiproliferative and anti-apoptotic in cerebral IRI decreasing oxidative stress.	MCAO	[74]
40	Salidroside (Phenolic)	<i>Rhodiola rosea</i> , F: Crassulaceae	neuroprotective for cerebral IRI due to inhibitions of RIP140-mediated inflammation	MCAO	[72]

			and apoptosis.		
41	Gastrodin (Phenolic)	<i>Gastrodia elata</i> , F: Orchidaceae	neuroprotective for cerebral IRI via a reduction in glutamate level.	HII	[73]
42	Rosmarinic acid (Phenolic)	<i>Salvia officinalis</i> , F: Lamiaceae	NeuroProtective, anti-oxidant and anti-apoptotic against focal cerebral IRI via inducing Nrf2/HO-1 pathway through the PI3K/Akt signaling.	MCAO	[85, 86]
43	Lyciumamide A (Phenolic)	<i>Lycium barbarum</i> fruits, F: Solanaceae	NeuroProtective, anti-oxidant and anti-apoptotic against focal cerebral IRI via induction of the Nrf2/HO-1 pathway (increasing nuclear Nrf2 and cytoplasmic HO-1 levels).	MCAO	[87]
44	Mangiferin Xanthone, (Phenolic)	<i>Mangifera indica</i> , F: Anacardiaceae	Anti-inflammatory and protective against cerebral IRI via enhancing Nrf2/HO-1 pathway.	MCAO	[88]
45	Procyanidin B2 (Phenolic)	Grapes <i>Vitis vinifera</i> , F: Vitaceae	Neuroprotection against cerebral IRI via activation of NF-E2-related factor pathway.	MCAO	[89]
46	Chlorogenic acid (Phenolic)	<i>O. forskolei</i> , F: Lamiaceae	Anti-apoptotic and anti-inflammatory against cerebral IRI via mediating Nrf2 pathway.	MCAO	[91, 92]
47	Corilagin (Phenolic)	<i>Phyllanthus emblica</i> , F: Phyllanthaceae	Anti-apoptotic and anti-inflammatory against cerebral IRI via attenuating oxidative stress and enhancing angiogenesis via activation of Nrf2 signaling pathway.	MCAO	[100]
48	Alpha tocopherol (Phenolic)	<i>Rosmarinus officinalis</i> , F: Lamiaceae	Anti-oxidant and neuroprotective from cerebral IRI via reduction of cleaved caspase-3 and LC3-II.	tMCAO	[93]
49	Gallic acid (Phenolic)	<i>Camellia sinensis</i> , F: Theaceae	protected against cerebral IRI via activate Nrf2, modulating mitochondria dysfunction, reducing oxidative stress and suppressing neural cell apoptosis.	MCAO	[74]
50	Honokiol	Magnolia	Protective against renal IRI via	Bilateral	[54]

	(Phenolic)	<i>officinalis</i> , F: <i>Magnoliaceae</i>	activation of nuclear factor erythroid 2-related factor 2, via PI3K/Akt and protein kinase C signaling.	renal model	
51	Salvianolic acid B, (phenolic)	<i>Salviae miltiorrhizae</i> , F: Lamiaceae	Ref to text.		[57]
52	4-OH-benzyl alcohol (Phenolic)	<i>Gastrodia elata</i> , F: Orchidaceae	Antagonize cerebral ischemia by increasing Bcl-2 expression, inhibiting caspase-3 activity and modulating cytoprotective genes (Nrf2, PDI, and neurotrophic factors).	MCAO	[58]
53	Theaflavin (Phenolic)	<i>Camellia sinensis</i> (black tea), F: Theaceae	Neuroprotective and Anti-inflammatory against cerebral IRI via reducing expression of STAT-1 (inflammation-related genes such as ICAM-1, VCAM-1, E-selectin, IL-6, IL-8, and cyclooxygenase-2)	MCAO	[48]
54	4'-geranyloxyferulic acid. (Phenolic)	<i>Acronychia baueri</i> , F: Rutaceae	Anti-inflammatory agents used to treat cerebral IRI via regulation of PPAR γ and NF- κ B pathway.	MCAO	[49, 50]
55	Hydroxysafflor yellowA (Phenolic)	<i>Carthamus tinctorium</i> , F: Asteraceae	Anti-inflammatory against cerebral IRI by suppressing p38 phosphorylation and NF-B signaling .	OGD	[75]
56	Schizandrin A (Phenolic)	<i>Schisandra chinensis</i> , F: Schisandraceae	Anti-oxidant and neuroprotective against Cerebral IRI via regulating the AMPK/Nrf2 pathway and suppressing inflammation and oxidative stress.	MCAO	[109]
57	Forsythiaside A (Phenolic)	<i>Forsythia suspensa</i> , F: Oleaceae	Anti-apoptotic and anti-inflammatory against cerebral IRI via mediation of the activation of Nrf2 and ER stress pathways.	MCAO	[111]
58	Trilobatin (Phenolic)	<i>Lithocarpus polystachyus</i> , F: Fagaceae	protective, antioxidant and anti-inflammatory in astrocytes and cortical neurons in cerebral IRI via upregulation of nuclear	MCAO and OGD	[74]

			Nrf2, NQO1, and HO-1 expression, increasing Sirt3 expression and the reduction of Keap1.		
59	Ferulic acid (Phenolic)	<i>Ligusticum chuanxiong</i> , F: Apiaceae	- anti-apoptotic against cerebral IRI via regulation of Bax/cytochrome c/Smac/DIABLO/XIAP/ caspase-3- (or Bax/AIF-) and Beclin-1/LC3A/B-II/Atg5-mediated signaling, respectively, in penumbral cortex.	pMCAO	[118]
60	Lithospermic acid (Phenolic)	<i>O. forskoleoi</i> , F: Lamiaceae	Anti-oxidant and Protective against mesenteric IRI by decreasing oxidative stress (increasing tissue SOD and GPx activities and decreasing MDA and MPO levels).	Intestinal ischemia	[92, 132]
61	Epicatechin (Flavonoid)	Black tea <i>Camellia sinensis</i> , F: Theaceae	Neuroprotective against cerebral IRI through activation of Nrf2 and an increase in the neuroprotective HO1 enzyme.	pdMCAO	[79]
62	Isoliquiritigenin (Flavonoid)	<i>Glycyrrhiza glabra</i> , F: Fabaceae	- protective against cerebral IRI due to the amelioration of cerebral energy metabolism and its antioxidant property and protecting brain Na ⁺ K ⁺ ATPase activity.	MCAO	[64]
63	Gardenin (Flavonoid)	<i>Ocimum forskolei</i> , F: Lamiaceae	Protective against focal cerebral IRI via regulatory effect on the gene expression.	LCAO	[66]
64	Scutellarin (Flavonoid)	<i>Erigeron breviscapus</i> , F: Asteraceae	Anti-oxidant and Protective against cerebral IRI via augmentation of cellular antioxidant defense capacity.	MCAO	[67]
65	Icaritin (Flavonoid)	<i>Epimedium grandiflorum</i> , F: Berberidaceae	Anti-apoptotic and neuroprotective against cerebral IRI in SH-SY5Y cells via regulation of Nrf2/Keap1 signaling pathway.	H ₂ O ₂ -induced	[70]
66	Nobiletin (Flavonoid)	<i>Citrus nobilis</i> , F: Rutaceae	Anti-apoptotic and anti-inflammatory against cerebral	pMCAO	[81]

			IRI via modulating the MAPK signaling pathway (upregulating Bcl-2 and downregulating Bax, caspase3, p-p38 and MAPKAP-2.		
67	Apigenin-7-O- β -D-(-6''-p-coumaroyl)-glucopyranoside (Flavonoid)	<i>Clematis tangutica</i> , F: Ranunculaceae	Anti-apoptotic and cardioprotective against myocardial IRI Via activating PKC ϵ (reduces mitochondrial oxidative stress and promotes Nrf2/HO-1-mediated anti-apoptosis signaling).	ligation of the left anterior descending coronary artery	[106]
68	Myricetin (Flavonoid)	<i>Tomatoes Solanum lycopersicum</i> , F: Solanaceae	Neuroprotection against cerebral IRI via decreasing reactive oxygen species.	MCAO	[90]
69	Silibinin-C-2',3-bis hydrogensuccinat (Flavonoid)	Milk thistle <i>Silybum marianum</i> , F: Asteraceae	Anti-oxidant and protective against skeletal muscle IRI via reduction of reactive oxygen species (prevent ROS lipid peroxidation).	-	[41]
70	Butein (Flavonoid)	<i>Rhus verniciflua</i> (Cashew), F: Anacardiaceae	Protective against renal IRI via activating sirt1 .	Open and close of peritoneum	[48]
71	Wogonin (Flavonoid)	<i>Scutellaria baicalensis</i> , F: Lamiaceae	Anti-inflammatory, attenuated the death of hippocampal neurons by transient global ischemia via suppression of NF κ B activity (diminishing LPS-induced TNF- α , IL-1 β , and NO production).	OGD	[44]
72	Isoquercetin (Flavonoid)	<i>Mangifera indica</i> , F: Anacardiaceae	Antioxidant, anti-apoptotic and protective against cerebral IRI via inducing the translocation of Nrf2 into the nucleus, and inhibiting NOX4/ROS/NF-B pathway.	MCAO OGD	[99]
73	6''-O-succinylapigenin (Flavonoid)	<i>Matricaria chamomilla</i> , F: Asteraceae	Active against cerebral IRI via activating the ERK/Nrf2/HO-1 pathway.	MCAO	[101]
74	Luteoloside (Flavonoid)	<i>Cynara scolymus</i> , F: Asteraceae	Antineuro-inflammatory against focal cerebral IRI via inhibiting NF- κ B signaling	MCAO	[102]

			pathway.		
75	Biochanin A (Flavonoid)	Glycine max, F: Fabaceae	Protective against myocardia IRI through blocking TLR4/NF-kB/NLRP3 signaling pathway.	transient coronary ligation	[96]
76	Xanthohumol (Flavonoid)	<i>Humulus lupulus</i> , F: Cannabaceae	Anti-apoptotic, anti-oxidant and anti-inflammatory against cerebral IRI via the inhibition of phosphorylation of p38- MAPK and the mediation of nuclear Nrf2 activation.	MCAO and OGD	[97]
77	Galuteolin (Flavonoid)	<i>Lonicera Japonica</i> , F: Caprifoliaceae	Neuroprotective against cerebral IRI-through the down- regulation of autophagy-related indicators in I/R Anti-apoptotic, anti-oxidant and anti-inflammatory (reduced pro-inflammatory factors IL-1 β and TNF- α and inhibited VEGF expression).	MCAO/R	[103]
78	Isoquercetin (Flavonoid)	<i>Mangifera indica</i> , F: Anacardiaceae	- antioxidant, anti-apoptotic and protective against cerebral IRI via inducing the translocation of Nrf2 into the nucleus, and inhibiting NOX4/ROS/NF-B pathway.	MCAO OGD	[99]
79	Baicalein (Flavonoid)	<i>Scutellaria baicalensis</i> , F: Lamiaceae	protective against cerebral IRI by inhibition of 12/15- lipoygenase pathway.	tMCAO	[1]
80	Baicalin (Flavonoid)	<i>Scutellaria baicalensis</i> , F: Lamiaceae	protect against cerebral IRI via inhibiting TLR2/4 signaling pathway and reducing the expression of TLR2/4, NF κ B, COX-2 and iNOS (Li <i>et al.</i> , 2017).	pMCAO	[19]
81	Xanthohumol (Chalcone, flavonoid)	<i>Humulus lupulus</i> , F: Cannabaceae	Protective against renal IRI via ROS scavenging and an anti- inflammatory effect mediated by the inhibition of the JAK- 2/STAT-3 pathway.	MCAO	[35]
82	Naringenin (Flavonoid)	<i>Ocimum sanctum</i> , F: Lamiaceae	Neuroprotective against cerebral IRI by suppressing NF- κ B-mediated	tMCAO	[36]

			neuroinflammation.		
83	Puerarin (Flavonoid)	<i>Pueria Radix</i> , F: Fabaceae	Neuroprotection against cerebral IRI associated with erythropoietin (EPO) elevated expression and decreased COX-2 level.	MCAO OGD	[19]
84	Calycosin (Favonoid)	<i>Astragalus membranaceu</i> , F: Fabaceae	Neuroprotective against cerebral IRI via anti-autophagic, anti-apoptotic and anti-inflammatory actions (upregulated the expression of p62, NBR1 and Bcl-2, and downregulated the level of TNF- α).	Focal cerebral IRI	[126]
85	Calycosin-7-o- β -d-glucoside (Flavonoid)	<i>Astragalus membranaceus</i> , F: Fabaceae	Anti-oxidant and anti-apoptotic against cerebral IRI via the SIRT1/FOXO1/PGC-1 α signaling pathway. (upregulated the expression of SIRT1, FOXO1, PGC-1 α , and Bcl-2 and downregulated the expression of Bax).	OGD/R	[127]
86	Lutein (Flavonoid)	<i>Citrus limon</i> , F: Rutaceae	Protective against ovarian IRI by its antioxidative and anti-inflammatory activities.	Vascular clips	[123]
87	Apigenin (Flavonoid)	<i>Matricaria recutita</i> , F: Asteraceae	Anti-apoptotic and anti-oxidant for cerebral IRI via mitochondrial activation (improved MMP in PC12 cells with CoCl ₂ -induced injury).	MCAO	[131]
88	Breviscopine (Flavone)	<i>Scutellaria barbata</i> , F: Lamiaceae	anti-apoptotic and neuroprotective against cerebral IRI via regulating the protein expression related to apoptosis (inhibited the expression caspase-3 and up-regulated the expression of bcl-2).	MCAO	[134]
89	Silibinin (Flavonoid)	<i>Silybum marianum</i> , F: asteraceae	Ref to text.		[137]
90	5,7,3',4',5'-pentahydroxy	<i>Anogeissus Pendula</i> , F:	Anti-apoptotic and anti-oxidant against cerebral IRI via	MCAO	[139]

	dihydroflavanol-3O-(2''-O-galloyl)- β -D-glucopyranoside (Flavonoid)	Combretaceae	reduced lipid peroxidation and inhibited cyclooxygenase activity.		
91	Anthocyanin (Flavonoid)	<i>Lycium ruthenicum</i> , F: Solanaceae	Anti-inflammatory and protective against cerebral IRI via regulation of Nuclear factor-kappa B (NF- κ B) and the NLRP3 inflammasome pathway.	MCAO/R	[140]
92	Genistein (Flavonoid)	<i>Ocimum sanctum</i> , F: Lamiaceae	Neuroprotective in transient focal cerebral IRI via increasing endogenous antioxidant mechanisms and reducing oxidative stress.	MCAO	[20] [21]
93	Equol (4', 7 isoflavandiol) (flavonoid)	Soybean <i>Glycine max</i> , F: Fabaceae	Neuroprotection against focal cerebral IRI by inhibiting oxidative stress.	MCAO	[20]
94	Luteolin (Flavonoid)	<i>Ixeris sonchifolia</i> , F: Asteraceae	Neuroprotective against <i>ischemia-induced cerebral injury</i> via activation of Nrf-2.	MCAO	[23]
95	Polygalasaponin F (Saponin)	<i>Polygala japonica</i> , F: Polygalaceae	Anti-apoptotic and protective against cerebral IRI via activation of PI3K/Akt signalling	OGD/R-	[61]
96	Ruscogenin (Saponin)	<i>Ophiopogon Japonicas</i> , F: Asparagaceae	Neuroprotection against focal cerebral IRI via inhibition of NF- κ B p65 expression and activation of NF- κ B Signaling pathway .	MCAO	[29]
97	Dioscin (Saponin)	<i>Dioscorea opposita</i> , F: Dioscoreaceae	Inhibited cerebral IRI-induced inflammation through inhibition of the TLR4/MyD88/NF- κ B.	MCAO	[37]
98	Diosgenin (Saponin)	<i>Dioscorea rhizome</i> , F: Dioscoreaceae	Neuroprotective against cerebral IRI .	(MCAO)	[46]
99	Glycyrrhizin (Saponin)	<i>Glycyrrhiza glabra</i> , F: Fabaceae	NeuroProtective against cerebral IRI via inhibiting HMGB1 and IL-17A .	MCAO	[77]
100	S-allyl cysteine (Sulphur containing	Garlic <i>Allium sativum</i> ,	Cytoprotective of astrocytes in cerebral IRI via increasing in	MCAO	[83]

	compound)	F: Amaryllidaceae	Nrf2 and its targets and decreased phosphorylated JNK and p38 levels.		
101	(DATs) di-allyl trisulfide (Sulphur containing compound)	Garlic <i>Allium sativum</i> , F: Amaryllidaceae	Protective against Cerebral IRI Via Nrf2 induction (reduced MMP9 levels, MDA levels).	MCAO	[84]
102	3H-1,2-dithiole-3- (Sulphur containing compound)	Broccoli <i>Brassica oleracea</i> , F: Brassicaceae	Neuroprotective from cerebral IRI via inducing Nrf2 expression in the brain which suppresses microglia activation.	tMCAO	[94]
103	Sulforaphane (Sulphur containing compound)	Broccoli <i>Brassica oleracea</i> , F: Brassicaceae	Anti-oxidant and protective against Intestinal and liver IRI through Nrf2-ARE pathway (increased level of liver Nrf2 and HO-1 expression).	clamping the superior mesenteric artery	[95]
104	Lipoic acid (Sulphur containing compound)	Peas <i>Pisum sativum</i> , F: Fabaceae	Anti-oxidant and protective against cerebral IRI through activation of the BDNF-PI3K/Akt-ERK1/2 pathway.	MCAO	[98]
105	Allicin (Sulphur containing compound)	<i>Allium sativa</i> L., F: Amaryllidaceae	Anti-apoptotic and neuroprotective against cerebral IRI via increasing the activities of (CAT, SOD, GPX, GST) and promoting the angiogenesis in the peri-infarct zone .	MCAO	[133]
106	Guattegaumerine (Alkaloid)	<i>Guatteria gaumeri</i> , F: Annonaceae	protective against cerebral IRI via anti-oxidant anti-inflammatory and anti-apoptotic.	H2O2	[53]
107	Spiramin T (Alkaloid)	<i>Spiraea japonica</i> var. <i>acuta</i> , F: Rosaceae	NeuroProtective against global cerebral IRI. Via modulation of endogenous antioxidant enzymes and reduction of calcium accumulation.	MCAO	[40]
108	Huperzine A (Alkaloid)	<i>Huperzia serrata</i> , F: Lycopodiaceae	Neuroprotective and anti-inflammatory against focal cerebral IRI via inhibition of NF-κB translocation and	MCAO	[31]

			reduced iNOS and COX-2 expression in cortex and striatum.		
109	Sinomenine, (alkaloid)	<i>Sinomenium Acutum</i> , F: Menispermaceae	Neuroprotective action on infarction size increased due to ischemia and recovered the neurological function.	cerebral ischemia- reperfusion	[32]
110	Leonurine (Alkaloid)	<i>Leonotis leonurus</i> , F: Lamiaceae	Neuroprotective in cerebral IRI via Inhibition of mitochondrial ROS production (SOD↑; GPx↑; MDA↓).	MCAO	[3]
111	Neferine (Alkaloid)	<i>Nelumbo nucifera</i> , F: Nelumbonaceae	Neuroprotective against cerebral IRI via inducing autophagy and regulating the p62/Keap1/Nrf2 pathway which activated Nrf2/HO-1.	pMCAO	[115]
112	Ephedrine (Alkaloid)	<i>Ephedra sinica</i> , F: Ephedraceae	Anti-apoptotic and neuroprotective against cerebral IRI via reducing inflammatory responses, associating with decreasing the protein expression of p-NF-κB.	MCAO	[136]
113	Swertiamarin (Iridoid)	<i>Gentiana macrophylla</i> , F: Gentianaceae	Anti-oxidant, anti-apoptotic and neuroprotective against cerebral IRI via -suppressing oxidative stress by activation of the Nrf2/ HO-1 pathway.	MCAO	[114]
114	Cornel (Iridoid)	<i>Cornus officinalis</i> , F: Cornaceae	Promoted neurogenesis and angiogenesis and improved neurological function after cerebral ischemia via modulating CIG's increasing VEGF and Flk-1 in the brain.	MCAO	[59]
115	Cornin (Iridoid)	<i>Cornus florida</i> , F: Cornaceae	Neuroprotective in cerebral IRI via Stabilization of mitochondrial function (SOD↑; GPx↑; MDA↓).	MCAO	[4]
116	Jasminoidin (Iridoid)	<i>Salvia miltiorrhiza</i> , F: Lamiaceae	Protective against focal cerebral IRI via, repressing the expression of tumor necrosis factor-alpha and interleukin 1 beta as well as	OGD/R	[38, 39]

			vonWillebrand factor.		
117	Beta carotene (Carotenoid)	<i>Daucus carota</i> , F: Apiaceae	Protective against cerebral IRI via significantly enhancing the expression levels of genes (including apo E) related to cholesterol regulation and promoting neuronal repair after brain injuries.	MCAO	[120]
118	b-cryptoxanthin (Carotenoid)	<i>Citrus reticulata</i> , F: Rutaceae	Protective against myocardial IRI via -inhibiting NF-κB-mediated inflammatory signalling in rats (decreasing p-p38 MAPK levels).	Left anterior descending coronary artery ligation	[121]
119	Zeaxanthin (Carotenoid)	<i>Lycium</i> Chinese berries, F: Solanaceae	NeuroProtective against retinal IRI by increase in visual acuity due to optical reasons and enhance in the survival of RGC.	cannulation	[124]
120	Astaxanthin (Carotenoid)	<i>Nicotiana tabacum</i> , F: Solanaceae	Protective against renal IRI via Anti-apoptotic, anti-oxidant and anti-inflammatory.	Renal IRI	[125]
121	Dihydrocapsaicin (Carotenoid)	<i>Capsicum annum</i> , F: solanaceae	Anti-oxidant and Protective against focal cerebral IRI via increasing the expression of Nrf2 and NQO1 and decreasing NADPH oxidase (NOX2, NOX4), p65 subunit of NF-κB, and MMP9 levels.	MCAO	[85]
122	Crocin (Carotenoid)	<i>Crocus sativus</i> , F: Iridaceae	Ref to text.		[42]
123	Polysaccharides (Miscellaneous)	<i>Momordica charantia</i> , F: Cucurbitaceae	Inhibition of intracerebral hemorrhage-induced brain injury via Inhibition of JNK3 signalling cascade.	OGD/R, MCAO	[6]
124	Ginkgolide B (Miscellaneous)	<i>Ginco biloba</i> , F: Ginkgoaceae	Protective and anti-apoptotic against cerebral IRI via modulation of the PI3K signalling pathway.	OGD	[65]
125	Oleuropein (Miscellaneous)	<i>Olea europaea</i> , F: Oleaceae	neuroprotective against cerebral IRI via a reduction in anti-apoptotic markers	MCAO	[10]
126	Embelin	<i>Embelia ribes</i> , F:	Neuroprotective against	BCCAO	[12]

	(Miscellaneous)	Primulaceae	transient cerebral IRI through a reduction of oxidative markers (GST↑; MDA↓; total thiol↑)		
127	Phycocyanobilin (Miscellaneous)	<i>Spirulina platensis</i> , F: Microcoleaceae	prevented the H ₂ O ₂ and glutamate-induced PC12 cell injury via a modulation of 19 genes mostly related to a detrimental pro-inflammatory environment and counteracted the oxidative imbalance in the treated BCCAO animals	pBCCAO	[13]
128	Hyperforin (Miscellaneous)	<i>Hypericum perforatum</i> , F: Hypericaceae	- protection against transient focal cerebral IRI via COX-1 and 5-lipoxygenase inhibition.	MCAO	[25]
129	Withaferin A (Miscellaneous)	<i>Withania somnifera</i> , F: Solanaceae	Prevents Myocardial IRI by Upregulating AMP-Activated Protein Kinase-Dependent B-Cell Lymphoma2 Signaling	Reperfusion injury	[69]
130	Carnosine (Miscellaneous)	<i>Ginkgo biloba</i> , F: Ginkgoaceae	Neuroprotective and anti-oxidotoxic in transient and permanent cerebral IRI via a reduction of reactive oxygen species	pMCAO, tMCAO	[33]
131	Phycocyanobilin (Miscellaneous)	<i>Arthrospira platensis</i> , F: Microcoleaceae	Protective against PC12 cell injury in cerebral IRI via modulating 190 genes (93 up- and 97 down-regulated) associated to several immunological and inflammatory processes	pBCCAO	[13]
II. Bioactives for management of myocardial ischemia					
132	Astragaloside (Terpenoid)	<i>Astragalus membranaceus</i> , F: Leguminosae	Cardioprotective against IRI via suppression of NF-κB, MMP-9, ICAM-1, and TNF-α in the parenchyma of brain	MCAO	[30]
133	Protocatechualdehyde (Phenolic)	<i>Salvia miltiorrhiza</i> , F: Lamiaceae	Anti-apoptotic and anti-inflammatory Against IRI in cultured neonatal rat cardiomyocytes-via inhibiting the NF-κB signaling pathway.	ligation of the left anterior descending coronary artery	[105]

134	Cyanidin-3-O-D-glucopyranoside (Phenolic)	<i>Morus albus</i> , F: Moraceae	Protective against myocardial IRI. suppressed the expressions of USP19, Beclin1, NCOA4, and LC3II/LC3I. relieved oxidative stress, downregulated LC3II/LC3I, TfR1 expression, and upregulated the expressions of FTH1 and GPX4.	OGD	[68]
135	Tetrandrine (Phenolic)	<i>Sephania tetrandra</i> , F: Menispermaceae	Protective against myocardial IRI through reducing the harmful cytokine TNF- α and IL-6, IL-1 β .	Left anterior descending coronary artery ligation	[138]
136	Fisetin (Flavonoid)	<i>Salvia Rosmarinus</i> , F: Lamiaceae	Protected against myocardial IRI via inhibiting expression of NF- κ B, decreased the loss of MMP-9 and reduced nuclear translocation of NF- κ B.	HII	[60]
137	Palmatine, (Flavonoid)	<i>Coptis chinensis</i> , F: Ranunculaceae	Protective against myocardial IRI via reducing oxidative stress and modulating inflammatory mediators.	HII	[56]
138	Isorhamnetin (Flavonoid)	<i>Ginkgo biloba</i> , F: Ginkgoaceae	Anti-apoptotic and protective effect against myocardial IRI via the attenuation of apoptosis and oxidative stress (decreased expression of Bax and cleaved-caspase-3, increased expression of Bcl-2).	Langendorf f-perfused hearts.	[107]
139	Pinocembrin (Flavonoid)	<i>Pinus densiflora</i> , F: pinaceae	Protective against myocardial IRI via direct stimulation of cardiac glycolysis through promoting the expression of the glycolytic enzyme, PFKFB3.	Global IR	[141]
140	Berberine (Alkaloid)	<i>Rhizoma coptidis</i>	Reduced myocardial apoptosis in myocardial I/R via activating AMPK and PI3K–Akt–eNOS signaling in diabetic rats.	HII (hypoxia ischemic injury)	[55]
141	Cyclobuxine (Alkaloid)	<i>Buxus microphylla</i> , F: Buxaceae	Neuroprotective against myocardial IRI via inhibiting the release of ATP metabolites, and preventing the release of creatine phosphokinase during reperfusion.		[135]

142	Picroside II (Iridoid)	<i>Picrorhiza kurroa</i> , F: Scrophulariaceae	Protective and anti-apoptotic against myocardial IRI via upregulating the phosphoinositide 3-kinase/Akt/endothelial NOS pathway (increase NO production and regulate Bcl-2 and Bax expressions).	Global ischemia	[128]
143	Lycopene (Carotenoid)	<i>Solanum lycopersicum</i> , F: Solanaceae	Protective against myocardial IRI via inhibition of ROS accumulation and consequent inflammation in mice (suppressed JNK phosphorylation).	1 Left anterior descending coronary artery ligation	[122]
III. Bioactives for management of both cerebral and myocardial ischemia					
144	Thymoquinone (Phenolic)	<i>Nigella sativa</i> , F: Ranunculaceae	Ref to text.		[62]
145	Hesperetin (Flavanone)	<i>Citrus genus</i> , F: Rutaceae	Ref to text.		[52]
146	Quercetin (Flavonoid)	<i>Citrus reticulatus</i> , F: Rutaceae	Ref to text.		[22]
147	Ginsenoside Rb1 (Saponin)	<i>Panax ginseng</i> , F: Araliaceae	Ref to text.		[26]
148	Ginsenoside Rg3 (Saponin)	<i>Panax ginseng</i> , F: Araliaceae	Ref to text.		[27]
149	Ginsenoside Rh2 (Saponin)	<i>Panax ginseng</i> , F: Araliaceae	Ref to text.		[27]
150	Ginsenoside Rd (Saponin)	<i>Panax ginseng</i> , F: Araliaceae	Ref to text.		[28]
151	Notoginsenoside R1 (Saponin)	<i>Panax ginseng</i> , F: Araliaceae	Ref to text.		[104]
152	Ginsenoside Rg1 (Saponin)	<i>Panax ginseng</i> , F: Araliaceae	Ref to text.		[71]
153	Curcumin (Carotenoid)	<i>Curcuma longa</i> , F: Zingiberaceae	Ref to text.		[19]

Table S2. All collected ischemia-related targets (407 targets) from literature and GeneBank database.

Gene Symbol	Description
MTHFR	Methylenetetrahydrofolate Reductase
F2	Coagulation Factor II, Thrombin

F5	Coagulation Factor V
ACE	Angiotensin I Converting Enzyme
NOS3	Nitric Oxide Synthase 3
NOTCH3	Notch Receptor 3
IL6	Interleukin 6
GP1BA	Glycoprotein Ib Platelet Subunit Alpha
AGTR1	Angiotensin II Receptor Type 1
AGT	Angiotensinogen
PON1	Paraoxonase 1
ENG	Endoglin
CST3	Cystatin C
ALOX5AP	Arachidonate 5-Lipoxygenase Activating Protein
NPPA	Natriuretic Peptide A
MAPT	Microtubule Associated Protein Tau
CRP	C-Reactive Protein
TNF	Tumor Necrosis Factor
FBN1	Fibrillin 1
GLA	Galactosidase Alpha
TLR4	Toll Like Receptor 4
LDLR	Low Density Lipoprotein Receptor
PRKCH	Protein Kinase C Eta
MT-TL1	Mitochondrially Encoded tRNA-Leu (UUA/G) 1
APOE	Apolipoprotein E
ADAMTS13	ADAM Metalloproteinase With Thrombospondin Type 1 Motif 13
PON2	Paraoxonase 2
TH	Tyrosine Hydroxylase
EDNRA	Endothelin Receptor Type A
GNB3	G Protein Subunit Beta 3
VKORC1	Vitamin K Epoxide Reductase Complex Subunit 1
PLAT	Plasminogen Activator, Tissue Type
PROZ	Protein Z, Vitamin K Dependent Plasma Glycoprotein
PSEN1	Presenilin 1
SELP	Selectin P
EPOR	Erythropoietin Receptor
APP	Amyloid Beta Precursor Protein
COL4A1	Collagen Type IV Alpha 1 Chain
PTGIS	Prostaglandin I2 Synthase
TNFRSF1A	TNF Receptor Superfamily Member 1A
SERPINE1	Serpin Family E Member 1
MMP9	Matrix Metalloproteinase 9
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
VWF	Von Willebrand Factor
NPPB	Natriuretic Peptide B
SERPINC1	Serpin Family C Member 1

HTRA1	HtrA Serine Peptidase 1
PDE4D	Phosphodiesterase 4D
BDNF	Brain Derived Neurotrophic Factor
APOH	Apolipoprotein H
IL10	Interleukin 10
ACSL4	Acyl-CoA Synthetase Long Chain Family Member 4
INS	Insulin
TREX1	Three Prime Repair Exonuclease 1
JAK2	Janus Kinase 2
TP53	Tumor Protein P53
ELN	Elastin
MT-ND4	Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 4
ACTA2	Actin Alpha 2, Smooth Muscle
VEGFA	Vascular Endothelial Growth Factor A
F3	Coagulation Factor III, Tissue Factor
LPA	Lipoprotein(A)
APOB	Apolipoprotein B
ADA2	Adenosine Deaminase 2
ALB	Albumin
CASP3	Caspase 3
THBD	Thrombomodulin
FGA	Fibrinogen Alpha Chain
PLA2G7	Phospholipase A2 Group VII
TGFB2	Transforming Growth Factor Beta 2
REN	Renin
SOD2	Superoxide Dismutase 2
F7	Coagulation Factor VII
ENO2	Enolase 2
CXCL12	C-X-C Motif Chemokine Ligand 12
MYLK	Myosin Light Chain Kinase
TTR	Transthyretin
HMGCR	3-Hydroxy-3-Methylglutaryl-CoA Reductase
TGFBR2	Transforming Growth Factor Beta Receptor 2
IL1B	Interleukin 1 Beta
CDKN2B-AS1	CDKN2B Antisense RNA 1
NOS2	Nitric Oxide Synthase 2
ACVRL1	Activin A Receptor Like Type 1
ADM	Adrenomedullin
SOD1	Superoxide Dismutase 1
ALOX5	Arachidonate 5-Lipoxygenase
LMNA	Lamin A/C
EDN1	Endothelin 1
HSPA4	Heat Shock Protein Family A (Hsp70) Member 4

MYH11	Myosin Heavy Chain 11
OLR1	Oxidized Low Density Lipoprotein Receptor 1
PRKG1	Protein Kinase CGMP-Dependent 1
NOTCH1	Notch Receptor 1
F10	Coagulation Factor X
PF4	Platelet Factor 4
SERPINA3	Serpin Family A Member 3
PECAM1	Platelet And Endothelial Cell Adhesion Molecule 1
COG2	Component Of Oligomeric Golgi Complex 2
ABCA1	ATP Binding Cassette Subfamily A Member 1
F2R	Coagulation Factor II Thrombin Receptor
MT-TK	Mitochondrially Encoded TRNA-Lys (AAA/G)
ANGPT1	Angiopoietin 1
CCL2	C-C Motif Chemokine Ligand 2
MAP2	Microtubule Associated Protein 2
ADORA1	Adenosine A1 Receptor
AVP	Arginine Vasopressin
PLG	Plasminogen
LOX	Lysyl Oxidase
ADRB2	Adrenoceptor Beta 2
SH2B3	SH2B Adaptor Protein 3
PPBP	Pro-Platelet Basic Protein
MT-ND1	Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 1
CREB1	CAMP Responsive Element Binding Protein 1
RETN	Resistin
GUCY1A1	Guanylate Cyclase 1 Soluble Subunit Alpha 1
MBP	Myelin Basic Protein
P2RY12	Purinergic Receptor P2Y12
HMGB1	High Mobility Group Box 1
SELE	Selectin E
ACE2	Angiotensin I Converting Enzyme 2
MB	Myoglobin
SMAD3	SMAD Family Member 3
PPARG	Peroxisome Proliferator Activated Receptor Gamma
MIR126	MicroRNA 126
SLC1A2	Solute Carrier Family 1 Member 2
AQP4	Aquaporin 4
ADIPOQ	Adiponectin, C1Q And Collagen Domain Containing
PROCR	Protein C Receptor
PIK3C2A	Phosphatidylinositol-4-Phosphate 3-Kinase Catalytic Subunit Type 2 Alpha
HTR2A	5-Hydroxytryptamine Receptor 2A
CASP1	Caspase 1
SELL	Selectin L

RNF213	Ring Finger Protein 213
ESR1	Estrogen Receptor 1
AKT1	AKT Serine/Threonine Kinase 1
SULT1A3	Sulfotransferase Family 1A Member 3
SPP1	Secreted Phosphoprotein 1
CYCS	Cytochrome C, Somatic
CNR1	Cannabinoid Receptor 1
MT-CYB	Mitochondrially Encoded Cytochrome B
MT-ND6	Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 6
EDNRB	Endothelin Receptor Type B
NES	Nestin
MROS	Melkersson-Rosenthal Syndrome
ICAM1	Intercellular Adhesion Molecule 1
AIF1	Allograft Inflammatory Factor 1
MT-ND5	Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 5
KCNQ1	Potassium Voltage-Gated Channel Subfamily Q Member 1
GDNF	Glial Cell Derived Neurotrophic Factor
CXCR4	C-X-C Motif Chemokine Receptor 4
CD40LG	CD40 Ligand
NGB	Neuroglobin
GJA1	Gap Junction Protein Alpha 1
SERPIN1	Serpin Family I Member 1
GP6	Glycoprotein VI Platelet
MIR21	MicroRNA 21
TBXA2R	Thromboxane A2 Receptor
HBA1	Hemoglobin Subunit Alpha 1
ANXA5	Annexin A5
APOA1	Apolipoprotein A1
COL4A2	Collagen Type IV Alpha 2 Chain
TSPO	Translocator Protein
FABP3	Fatty Acid Binding Protein 3
SRC	SRC Proto-Oncogene, Non-Receptor Tyrosine Kinase
MALAT1	Metastasis Associated Lung Adenocarcinoma Transcript 1
SLC6A4	Solute Carrier Family 6 Member 4
ADORA2A	Adenosine A2a Receptor
BMP7	Bone Morphogenetic Protein 7
SIRT1	Sirtuin 1
AOC3	Amine Oxidase Copper Containing 3
GATA4	GATA Binding Protein 4
COL3A1	Collagen Type III Alpha 1 Chain
SERPINF2	Serpin Family F Member 2
APOC3	Apolipoprotein C3
TNNT2	Troponin T2, Cardiac Type

ATP1A2	ATPase Na ⁺ /K ⁺ Transporting Subunit Alpha 2
ITGB3	Integrin Subunit Beta 3
POMC	Proopiomelanocortin
ENTPD1	Ectonucleoside Triphosphate Diphosphohydrolase 1
AGTR2	Angiotensin II Receptor Type 2
MAPK3	Mitogen-Activated Protein Kinase 3
CALR	Calreticulin
MT-CO1	Mitochondrially Encoded Cytochrome C Oxidase I
IGF1	Insulin Like Growth Factor 1
TGFBR1	Transforming Growth Factor Beta Receptor 1
FGB	Fibrinogen Beta Chain
PRNP	Prion Protein
ARSA	Arylsulfatase A
ADORA3	Adenosine A3 Receptor
POLG	DNA Polymerase Gamma, Catalytic Subunit
DCX	Doublecortin
CXCL8	C-X-C Motif Chemokine Ligand 8
BACE1	Beta-Secretase 1
NFE2L2	Nuclear Factor, Erythroid 2 Like 2
TNFRSF12A	TNF Receptor Superfamily Member 12A
PTGS2	Prostaglandin-Endoperoxide Synthase 2
KNG1	Kininogen 1
VCAM1	Vascular Cell Adhesion Molecule 1
CYP11B2	Cytochrome P450 Family 11 Subfamily B Member 2
F9	Coagulation Factor IX
NR3C1	Nuclear Receptor Subfamily 3 Group C Member 1
MIR15A	MicroRNA 15a
JAG1	Jagged Canonical Notch Ligand 1
CYP2C9	Cytochrome P450 Family 2 Subfamily C Member 9
MIAT	Myocardial Infarction Associated Transcript
NTF3	Neurotrophin 3
CASP9	Caspase 9
GBA	Glucosylceramidase Beta
TGFB1	Transforming Growth Factor Beta 1
PPIG	Peptidylprolyl Isomerase G
SERPIND1	Serpin Family D Member 1
MPL	MPL Proto-Oncogene, Thrombopoietin Receptor
EPO	Erythropoietin
FLT1	Fms Related Receptor Tyrosine Kinase 1
THPO	Thrombopoietin
MMP3	Matrix Metalloproteinase 3
CCM2	CCM2 Scaffold Protein
MT-ATP6	Mitochondrially Encoded ATP Synthase Membrane Subunit 6
GSR	Glutathione-Disulfide Reductase

LPL	Lipoprotein Lipase
RTN4	Reticulon 4
ACTB	Actin Beta
KIT	KIT Proto-Oncogene, Receptor Tyrosine Kinase
CYP2C19	Cytochrome P450 Family 2 Subfamily C Member 19
FGF2	Fibroblast Growth Factor 2
MIR155	MicroRNA 155
TGFB3	Transforming Growth Factor Beta 3
GHRL	Ghrelin And Obestatin Prepropeptide
LIPC	Lipase C, Hepatic Type
IL4	Interleukin 4
ADD1	Adducin 1
RBFOX3	RNA Binding Fox-1 Homolog 3
MPO	Myeloperoxidase
PDE5A	Phosphodiesterase 5A
SMAD4	SMAD Family Member 4
SLC2A10	Solute Carrier Family 2 Member 10
TSPAN33	Tetraspanin 33
F12	Coagulation Factor XII
MMP2	Matrix Metalloproteinase 2
GJA5	Gap Junction Protein Alpha 5
HSPA1A	Heat Shock Protein Family A (Hsp70) Member 1A
LEP	Leptin
HIF1A	Hypoxia Inducible Factor 1 Subunit Alpha
PDE3A	Phosphodiesterase 3A
IL18	Interleukin 18
TET2	Tet Methylcytosine Dioxygenase 2
ADRB3	Adrenoceptor Beta 3
MYBPC3	Myosin Binding Protein C3
GFAP	Glial Fibrillary Acidic Protein
ITGAM	Integrin Subunit Alpha M
DARS2	Aspartyl-TRNA Synthetase 2, Mitochondrial
CP	Ceruloplasmin
NOS1	Nitric Oxide Synthase 1
CALCA	Calcitonin Related Polypeptide Alpha
F8	Coagulation Factor VIII
TTN	Titin
TRPV4	Transient Receptor Potential Cation Channel Subfamily V Member 4
DRD4	Dopamine Receptor D4
CBS	Cystathionine Beta-Synthase
CETP	Cholesteryl Ester Transfer Protein
AMPD1	Adenosine Monophosphate Deaminase 1
MFAP5	Microfibril Associated Protein 5
CYP3A5	Cytochrome P450 Family 3 Subfamily A Member 5

AGER	Advanced Glycosylation End-Product Specific Receptor
HSD11B2	Hydroxysteroid 11-Beta Dehydrogenase 2
KCNA5	Potassium Voltage-Gated Channel Subfamily A Member 5
CAT	Catalase
TNNI3	Troponin I3, Cardiac Type
MT-CO3	Mitochondrially Encoded Cytochrome C Oxidase III
IRS1	Insulin Receptor Substrate 1
ITGA2B	Integrin Subunit Alpha 2b
NGF	Nerve Growth Factor
NPY	Neuropeptide Y
GATA6	GATA Binding Protein 6
MAT2A	Methionine Adenosyltransferase 2A
FOXE3	Forkhead Box E3
CCR2	C-C Motif Chemokine Receptor 2
HMOX1	Heme Oxygenase 1
KCNJ5	Potassium Inwardly Rectifying Channel Subfamily J Member 5
MC4R	Melanocortin 4 Receptor
KRAS	KRAS Proto-Oncogene, GTPase
NEFL	Neurofilament Light
ALDH2	Aldehyde Dehydrogenase 2 Family Member
ECE1	Endothelin Converting Enzyme 1
TIMP1	TIMP Metalloproteinase Inhibitor 1
SCNN1A	Sodium Channel Epithelial 1 Subunit Alpha
HP	Haptoglobin
CSF3	Colony Stimulating Factor 3
ITGA2	Integrin Subunit Alpha 2
ACHE	Acetylcholinesterase (Cartwright Blood Group)
MIR143	MicroRNA 143
PTGS1	Prostaglandin-Endoperoxide Synthase 1
TYR	Tyrosinase
HBB	Hemoglobin Subunit Beta
CYP11B1	Cytochrome P450 Family 11 Subfamily B Member 1
FLNA	Filamin A
PCNT	Pericentrin
ENPP1	Ectonucleotide Pyrophosphatase/Phosphodiesterase 1
PRKAG2	Protein Kinase AMP-Activated Non-Catalytic Subunit Gamma 2
SLC2A4	Solute Carrier Family 2 Member 4
MIR146A	MicroRNA 146a
PKD1	Polycystin 1, Transient Receptor Potential Channel Interacting
IAPP	Islet Amyloid Polypeptide
PROC	Protein C, Inactivator Of Coagulation Factors Va And VIIIa
IL17A	Interleukin 17A
KCNJ11	Potassium Inwardly Rectifying Channel Subfamily J Member 11
WFS1	Wolframin ER Transmembrane Glycoprotein

MIR17	MicroRNA 17
CORIN	Corin, Serine Peptidase
PRL	Prolactin
INSR	Insulin Receptor
MIR145	MicroRNA 145
MIR208A	MicroRNA 208a
KDR	Kinase Insert Domain Receptor
F13A1	Coagulation Factor XIII A Chain
CX3CR1	C-X3-C Motif Chemokine Receptor 1
CPS1	Carbamoyl-Phosphate Synthase 1
TNFRSF11B	TNF Receptor Superfamily Member 11b
XDH	Xanthine Dehydrogenase
NCF1	Neutrophil Cytosolic Factor 1
MYD88	MYD88 Innate Immune Signal Transduction Adaptor
GPT	Glutamic--Pyruvic Transaminase
TLR2	Toll Like Receptor 2
GRIN2A	Glutamate Ionotropic Receptor NMDA Type Subunit 2A
NAGS	N-Acetylglutamate Synthase
ADRB1	Adrenoceptor Beta 1
CDK5	Cyclin Dependent Kinase 5
MIR132	MicroRNA 132
KLKB1	Kallikrein B1
MMP1	Matrix Metalloproteinase 1
OTC	Ornithine Carbamoyltransferase
IL2	Interleukin 2
BRCA2	BRCA2 DNA Repair Associated
ATM	ATM Serine/Threonine Kinase
MTR	5-Methyltetrahydrofolate-Homocysteine Methyltransferase
PLA2G2A	Phospholipase A2 Group IIA
INF2	Inverted Formin, FH2 And WH2 Domain Containing
CELA2A	Chymotrypsin Like Elastase 2A
DRD1	Dopamine Receptor D1
PPARA	Peroxisome Proliferator Activated Receptor Alpha
GNAS	GNAS Complex Locus
SON	SON DNA Binding Protein
FCGR2A	Fc Fragment Of IgG Receptor IIA
CACNA1A	Calcium Voltage-Gated Channel Subunit Alpha1 A
EPHX2	Epoxide Hydrolase 2
MYMY1	Moyamoya Disease 1
MYMY3	Moyamoya Disease 3
CD14	CD14 Molecule
MEN1	Menin 1
COMT	Catechol-O-Methyltransferase
GCKR	Glucokinase Regulator

CYBA	Cytochrome B-245 Alpha Chain
ITGB2	Integrin Subunit Beta 2
LCN2	Lipocalin 2
CCND1	Cyclin D1
HSPA5	Heat Shock Protein Family A (Hsp70) Member 5
ATP1A3	ATPase Na ⁺ /K ⁺ Transporting Subunit Alpha 3
CCR5	C-C Motif Chemokine Receptor 5 (Gene/Pseudogene)
ZMPSTE24	Zinc Metallopeptidase STE24
GGT1	Gamma-Glutamyltransferase 1
FOS	Fos Proto-Oncogene, AP-1 Transcription Factor Subunit
IL1RN	Interleukin 1 Receptor Antagonist
PTPN1	Protein Tyrosine Phosphatase Non-Receptor Type 1
SCN1A	Sodium Voltage-Gated Channel Alpha Subunit 1
IRS2	Insulin Receptor Substrate 2
ACAN	Aggrecan
ELP1	Elongator Complex Protein 1
TNFSF4	TNF Superfamily Member 4
STAT3	Signal Transducer And Activator Of Transcription 3
S100B	S100 Calcium Binding Protein B
NLRP3	NLR Family Pyrin Domain Containing 3
GCGR	Glucagon Receptor
COL4A5	Collagen Type IV Alpha 5 Chain
SCNN1B	Sodium Channel Epithelial 1 Subunit Beta
MT-CO2	Mitochondrially Encoded Cytochrome C Oxidase II
BCL2L1	BCL2 Like 1
CTF1	Cardiotrophin 1
VDR	Vitamin D Receptor
ERAP1	Endoplasmic Reticulum Aminopeptidase 1
ASS1	Argininosuccinate Synthase 1
TAC1	Tachykinin Precursor 1
PVALB	Parvalbumin
MTOR	Mechanistic Target Of Rapamycin Kinase
SCNN1G	Sodium Channel Epithelial 1 Subunit Gamma
HHT4	Telangiectasia, Hereditary Hemorrhagic, Type 4
EGF	Epidermal Growth Factor
IFNG	Interferon Gamma
SCN8A	Sodium Voltage-Gated Channel Alpha Subunit 8
ITPR1	Inositol 1,4,5-Trisphosphate Receptor Type 1
NAMPT	Nicotinamide Phosphoribosyltransferase
PDGFRA	Platelet Derived Growth Factor Receptor Alpha
KCNMB1	Potassium Calcium-Activated Channel Subfamily M Regulatory Beta Subunit 1
CYP4F2	Cytochrome P450 Family 4 Subfamily F Member 2
CSF2	Colony Stimulating Factor 2
APOA5	Apolipoprotein A5

SLC1A3	Solute Carrier Family 1 Member 3
BGN	Biglycan
C3	Complement C3
NPR3	Natriuretic Peptide Receptor 3
ADD3	Adducin 3
DES	Desmin
ATP1B1	ATPase Na ⁺ /K ⁺ Transporting Subunit Beta 1
PKD2	Polycystin 2, Transient Receptor Potential Cation Channel
CSTB	Cystatin B
MIR33A	MicroRNA 33a
CYP3A4	Cytochrome P450 Family 3 Subfamily A Member 4
DRD2	Dopamine Receptor D2

Table S3. Ischemia-related targets that were predicted to be inhibited by the reviewed compounds. Interactions with blue-colored targets were validated by MDS and $\Delta G_{\text{binding}}$ calculation.

Compounds	SwissPrediction	Inverse Docking					Literature									
Epigallocatechin gallate	MAPT	PIK3CA (PDB:6GVF)	MAPK3 (PDB:2ZOQ)	MMP1 (PDB:3AYK)	MMP2 (PDB:1HOV)	JAK2 (PDB:3E64)	PIK3CA									
Hesperetin		PIK3CA (PDB:6GVF)	NOS1 (PDB:4D1N)	MAPK3 (PDB:2ZOQ)	JAK2 (PDB:3E64)											
Apigenin	CDK5	PIK3CA (PDB:6GVF)	NOS1 (PDB:4D1N)	XOR (PDB:3B9J)	MAPK3 (PDB:2ZOQ)	JAK2 (PDB:3E64)										
Quercetin		PIK3CA (PDB:6GVF)	NOS1 (PDB:4D1N)	XOR (PDB:3B9J)	MAPK3 (PDB:2ZOQ)	JAK2 (PDB:3E64)	NOS1	XOR								
Hesperidin							PIK3CA									
Resveratrol		PIK3CA (PDB:6GVF)	MAPK3 (PDB:2ZOQ)	JAK2 (PDB:3E64)			MPO	TLR4	TNF	MMP9	HMGB1					
Silibinin		MAPK3 (PDB:2ZOQ)					TNF	SOD								
(Z)-Ligustilide							SOD	HSPA5	MMP2	MMP9						
Thymoquinone							XOR									
Tanshinone IIA		HMGR (PDB:3CCZ)					MPO	TNF	IL1B	IL6	NOS1	MAPK3	IL10	TLR4	TGFB2	
Salvianolic acid A		SQLE (PDB:6C6N)					MMP9	GPX1	TNF	IL1B	IL6					
Salvianolic acid B							TNF	IL1B	SIRT1	TLR4	MAPK3	PIK3CA				
Curcumin							XOR	SOD	NOS1	HSPA5	TLR4	MAPK3				
Crocin							PIK3CA	SOD	GPX1	MAPK3	NOX1	HMGB1				
Picroside II							TLR4	GPX1	SOD	XOR	NOX1	MPO				
Glycyrrhizin							TNF	IL1B	IL6							
Ginsenoside rb1							MMP9	NOS1	NOX1	PIK3CA	SOD					
Ginsenoside Rd							PIK3CA	MMP9								
Ginsenoside RG1							MAPK3	HMGB1	TLR4	RhoA	MPO	SOD	CAT			
Notoginsenoside R1							PIK3CA	IL6	TNF							

Table S4. KEGG signaling pathway enrichment

Description	Number of genes	FDR value	Genes
Blood circulation	14	3.34E-07	PIK3C2A GJA1 MAPK3 OLR1 LEP F2R LPA SERPINF2 ADORA2A ADRB3 PDE4D MTOR ADRB1 SOD
Cardiovascular system disease	10	1.10E-05	MAPT PIK3C2A IL10 TGFB2 IL6 GPX1 IL1B XOR MPO SOD
Vascular disease	9	1.92E-04	TGFB2 XOR MPO PIK3C2A MAPK3 FLT1 S100B LPA MYLK
Regulation of blood vessel diameter	7	1.59E-06	PIK3C2A GPX1 XOR SOD NTF3 MYD88 TRPV4
Aging	7	3.11E-03	NOX1 MPO SOD PRNP BRCA2 NFE2L2 SOD2
Artery disease	7	9.20E-03	MPO IL1B IL6 TGFB2 IL10 ITGA2B LPA
Regulation of blood pressure	7	8.35E-03	ADRB3 PDE4D ADRB1 SOD GJA1 PPARG LEP
Cholesterol metabolism	3	1.46E-02	SQLE HMGCR MAPK3

Table S5: Calculated pharmacokinetics and bioavailability properties of the reviewed compounds

No.	Compound	GIT Absorption	BBB Permeability	Bioavailability score	Lipinski
I. Bioactives for management of cerebral ischemia					
1	Totarol (Terpenoid)	High	Yes	0.55	Yes
2	Taraxasterol (Terpenoid)	High	Yes	0.55	Yes
4	Resveratrol (Terpenoid)	High	Yes	0.55	Yes
5	Celastrol (Terpenoid)	High	Yes	0.55	No
6	Asiatic acid (Terpenoid)	High	Yes	0.55	Yes
7	11-Keto- β -boswellic acid terpenoid	High	Yes	0.55	Yes
8	Acetyl-11-Keto- β -boswellic acid (Terpenoid)	High	Yes	0.55	Yes
9	Andrographolide (Terpenoid)	High	Yes	0.55	Yes
10	Parthenolide (Terpenoid)	High	Yes	0.55	No
11	Ursolic acid (Terpenoid)	High	Yes	0.55	Yes
12	Bilobalide (Terpenoid)	High	Yes	0.55	Yes
13	Nomilin (Terpenoid)	High	Yes	0.55	No
14	Paeoniflorin (Terpenoid)	Low	Yes	0.55	No
15	Carnosic acid (Terpenoid)	Low	Yes	0.55	No
16	Linalool terpenoid	High	Yes	0.55	Yes
17	Senkyunolide I (Terpene)	Low	Yes	0.55	No
18	Tanshinone A	High	Yes	0.55	Yes

	(Terpenoid)				
19	Ligustrazine (Terpenoid)	High	Yes	0.55	Yes
20	Z-ligustilide (Terpenoid)	High	Yes	0.55	Yes
21	Triptolide (Terpenoid)	High	Yes	0.55	Yes
22	Safranal (Terpenoid)	High	Yes	0.55	Yes
23	Britanin (Terpenoid)	High	Yes	0.55	Yes
24	Ginkgolide K (Terpenoid)	Low	No	0.55	No
25	Salvianolic acid A (Phenolic)	Low	No	0.55	No
26	Emodin (Phenolic)	High	Yes	0.55	Yes
27	Magnesium lithospermate B (Phenolic)	Low	No	0.55	No
28	2,3,5,4'-Tetra hydroxystilbene- 2-O - β -D- glucoside (Phenolic)	High	Yes	0.55	Yes
29	Paconol (Phenolic)	High	Yes	0.55	Yes
30	Osthole (Phenolic)	High	Yes	0.55	Yes
31	Tetrahydroxystil bene (Phenolic)	High	Yes	0.55	Yes
32	Cinnamophilin neolignane (Phenolic)	High	Yes	0.55	Yes
33	Cinnamophilin (phenolic)	High	Yes	0.55	Yes
34	Schisandrin B (Phenolic)	High	Yes	0.55	Yes

35	Epigallocatechin gallate (Phenolic)	High	Yes	0.55	Yes
36	Shikonin (Phenolic)	High	Yes	0.55	Yes
37	Paeonol (Phenolic)	High	Yes	0.55	Yes
38	Curculigoside A (Phenolic)	High	Yes	0.55	Yes
39	Theaflavin (Phenolic)	High	Yes	0.55	Yes
40	Salidroside (Phenolic)	High	Yes	0.55	Yes
41	Gastrodin (Phenolic)	High	Yes	0.55	Yes
42	Rosmarinic acid (Phenolic)	Low	No	0.55	No
43	Lyciumamide A (Phenolic)	High	Yes	0.55	Yes
44	Mangiferin Xanthone, (Phenolic)	High	Yes	0.55	Yes
45	Procyanidin B2 (Phenolic)	High	Yes	0.55	Yes
46	Chlorogenic acid (Phenolic)	Low	No	0.55	No
47	Corilagin (Phenolic)	High	Yes	0.55	Yes
48	Alpha tocopherol (Phenolic)	High	Yes	0.55	Yes
49	Gallic acid (Phenolic)	Low	No	0.55	No
50	Honokiol (Phenolic)	High	Yes	0.55	Yes
51	Salvianolic acid B, (phenolic)	High	Yes	0.55	Yes
52	4-OH-benzyl alcohol (Phenolic)	High	Yes	0.55	Yes
53	Theaflavin	Low	No	0.55	No

	(Phenolic)				
54	4'-geranyloxyferulic acid. (Phenolic)	High	Yes	0.55	Yes
55	Hydroxysafflor yellow A (Phenolic)	High	Yes	0.55	Yes
56	Schizandrin A (Phenolic)	Low	No	0.55	No
57	Forsythiaside A (Phenolic)	High	Yes	0.55	Yes
58	Trilobatin (Phenolic)	High	Yes	0.55	Yes
59	Ferulic acid (Phenolic)	High	Yes	0.55	Yes
60	Lithospermic acid (Phenolic)	Low	No	0.55	No
61	Epicatechin (Flavonoid)	High	Yes	0.55	Yes
62	Isoliquiritigenin (Flavonoid)	High	Yes	0.55	Yes
63	Gardenin (Flavonoid)	Low	No	0.55	No
64	Scutellarin (Flavonoid)	High	Yes	0.55	Yes
65	Icaritin (Flavonoid)	High	Yes	0.55	Yes
66	Nobiletin (Flavonoid)	High	Yes	0.55	Yes
67	Apigenin-7-O- β -D-(-6"-p-coumaroyl)-glucopyranoside (Flavonoid)	Low	No	0.55	No
68	Myricetin (Flavonoid)	High	Yes	0.55	Yes
69	Silibinin-C-2',3-bis hydrogensuccinate	High	Yes	0.55	Yes

	t (Flavonoid)				
70	Butein (Flavonoid)	High	Yes	0.55	No
71	Wogonin (Flavonoid)	High	Yes	0.55	Yes
72	Isoquercetin (Flavonoid)	High	Yes	0.55	Yes
73	6"-O- succinylapigenin (Flavonoid)	Low	No	0.55	No
74	Luteoloside (Flavonoid)	High	Yes	0.55	Yes
75	Biochanin A (Flavonoid)	High	Yes	0.55	Yes
76	Xanthohumol (Flavonoid)	Low	No	0.55	No
77	Galuteolin (Flavonoid)	High	Yes	0.55	Yes
78	Isoquercetin (Flavonoid)	High	Yes	0.55	Yes
79	Baicalein (Flavonoid)	High	Yes	0.55	Yes
80	Baicalin (Flavonoid)	Low	No	0.55	No
81	Xanthohumol (Chalcone, flavonoid)	High	Yes	0.55	Yes
82	Naringenin (Flavonoid)	High	Yes	0.55	Yes
83	Puerarin (Flavonoid)	High	Yes	0.55	Yes
84	Calycosin (Favonoid)	High	Yes	0.55	Yes
85	Calycosin-7-o- β - d-glucoside (Flavonoid)	Low	No	0.55	No
86	Lutein (Flavonoid)	High	Yes	0.55	Yes
87	Apigenin (Flavonoid)	High	Yes	0.55	Yes
88	Breviscapine	Low	No	0.55	No

	(Flavone)				
89	Silibinin (Flavonoid)	High	Yes	0.55	Yes
90	5,7,3',4',5'- pentahydroxy dihydroflavanol- 3O-(2''-O- galloyl)-β-D- glucopyranoside (Flavonoid)	High	Yes	0.55	Yes
91	Anthocyanin (Flavonoid)	High	Yes	0.55	Yes
92	Genistein (Flavonoid)	Low	No	0.55	No
93	Equol (4', 7 isoflavandiol) (flavonoid)	High	Yes	0.55	Yes
94	Luteolin (Flavonoid)	High	Yes	0.55	Yes
95	Polygalasaponin F (Saponin)	High	Yes	0.55	Yes
96	Ruscogenin (Saponin)	High	Yes	0.55	Yes
97	Dioscin (Saponin)	Low	No	0.55	No
98	Diosgenin (Saponin)	High	Yes	0.55	Yes
99	Glycyrrhizin (Saponin)	Low	No	0.55	No
100	S-allyl cysteine (Sulphur containing compound)	High	Yes	0.55	Yes
101	(DATs) di-allyl trisulfide (Sulphur containing compound)	High	Yes	0.55	Yes
102	3H-1,2-dithiole-	High	Yes	0.55	Yes

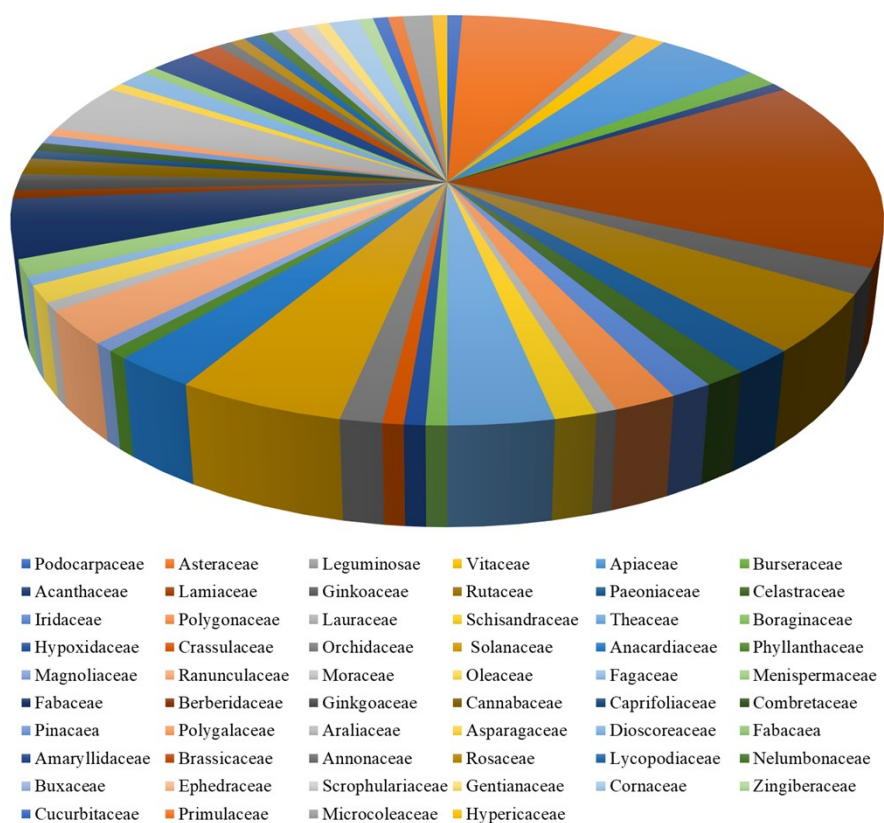
	3- (Sulphur containing compound)				
103	Sulforaphane (Sulphur containing compound)	High	Yes	0.55	Yes
104	Lipoic acid (Sulphur containing compound)	Low	No	0.55	No
105	Allicin (Sulphur containing compound)	High	Yes	0.55	Yes
106	Guattegaumerine (Alkaloid)	High	Yes	0.55	Yes
107	Spiramin T (Alkaloid)	Low	No	0.55	No
108	Huperzine A (Alkaloid)	High	Yes	0.55	Yes
109	Sinomenine, (alkaloid)	High	Yes	0.55	Yes
110	Leonurine (Alkaloid)	High	Yes	0.55	Yes
111	Neferine (Alkaloid)	Low	No	0.55	No
112	Ephedrine (Alkaloid)	High	Yes	0.55	Yes
113	Swertiamarin (Iridoid)	High	Yes	0.55	Yes
114	Cornel (Iridoid)	High	Yes	0.55	Yes
115	Cornin (Iridoid)	High	Yes	0.55	Yes
116	Jasminoidin (Iridoid)	Low	No	0.55	No
117	Beta carotene (Carotenoid)	High	Yes	0.55	Yes
118	b-cryptoxanthin (Carotenoid)	Low	No	0.55	No

119	Zeaxanthin (Carotenoid)	High	Yes	0.55	Yes
120	Astaxanthin (Carotenoid)	High	Yes	0.55	Yes
121	Dihydrocapsaicin (Carotenoid)	High	Yes	0.55	Yes
122	Crocin (Carotenoid)	High	Yes	0.55	Yes
123	Polysaccharides (Miscellaneous)	Low	No	0.55	No
124	Ginkgolide B (Miscellaneous)	High	Yes	0.55	Yes
125	Oleuropein (Miscellaneous)	High	Yes	0.55	Yes
126	Embelin (Miscellaneous)	Low	No	0.55	No
127	Phycocyanobilin (Miscellaneous)	High	Yes	0.55	Yes
128	Hyperforin (Miscellaneous)	High	Yes	0.55	Yes
129	Withaferin A (Miscellaneous)	High	Yes	0.55	Yes
130	Carnosine (Miscellaneous)	High	Yes	0.55	Yes
131	Phycocyanobilin (Miscellaneous)	High	Yes	0.55	Yes
II. Bioactives for management of myocardial ischemia					
132	Astragaloside (Terpenoid)	Low	No	0.55	No
133	Protocatechualdehyde (Phenolic)	High	Yes	0.55	Yes
134	Cyanidin-3-O-D-glucopyranoside (Phenolic)	High	Yes	0.55	Yes
135	Tetrandrine (Phenolic)	Low	No	0.55	No

136	Fisetin (Flavonoid)	High	Yes	0.55	Yes
137	Palmatine, (Flavonoid)	High	Yes	0.55	Yes
138	Isorhamnetin (Flavonoid)	High	Yes	0.55	Yes
139	Pinocembrin (Flavonoid)	High	Yes	0.55	Yes
140	Berberine, (Alkaloid)	High	Yes	0.55	Yes
141	Cyclobuxine (Alkaloid)	High	Yes	0.55	Yes
142	Picroside II (Iridoid)	Low	No	0.55	Yes
143	Lycopene (Carotenoid)	High	Yes	0.55	Yes

1A

No. of compounds extracted from each plant source



1B

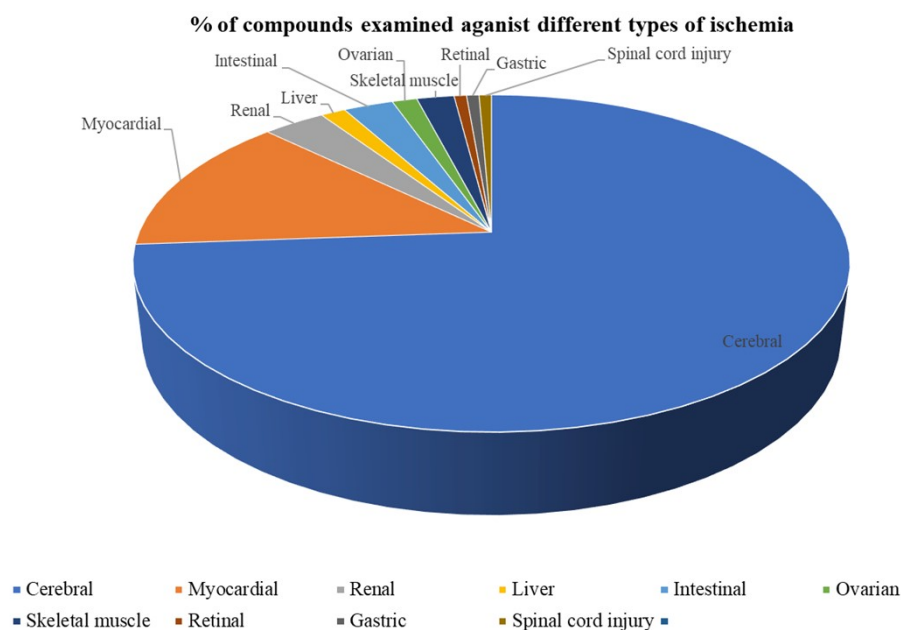


Figure S1 Plant families reported to contain anti-ischemic bioactives (A) and the relative number of bioactives examined against different types of ischemia (B).

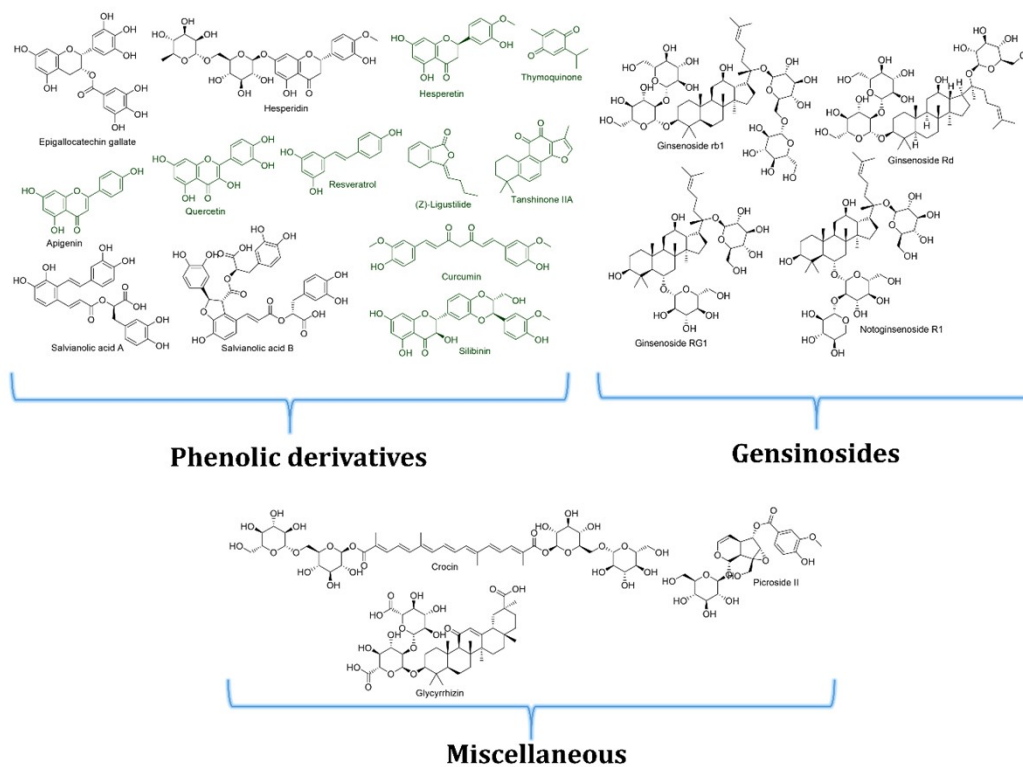


Figure S2. Anti-ischemic natural products collected from literature in the present review. Green-colored compounds have drug-like properties according to Lipinski's and Veber's rules of drug-likeness.

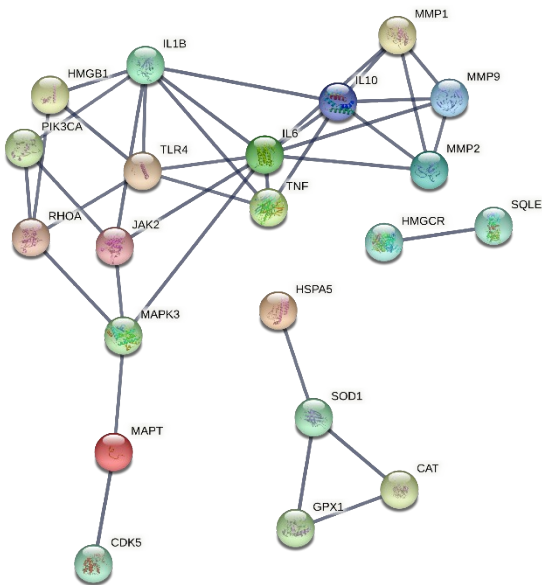


Figure S3. Sub-PPI network constructed from proteins predicted and/or reported to be targeted by the collected natural products in the present investigation. This network consists of 21 nodes and 37 edges with an average node degree of 2.47.

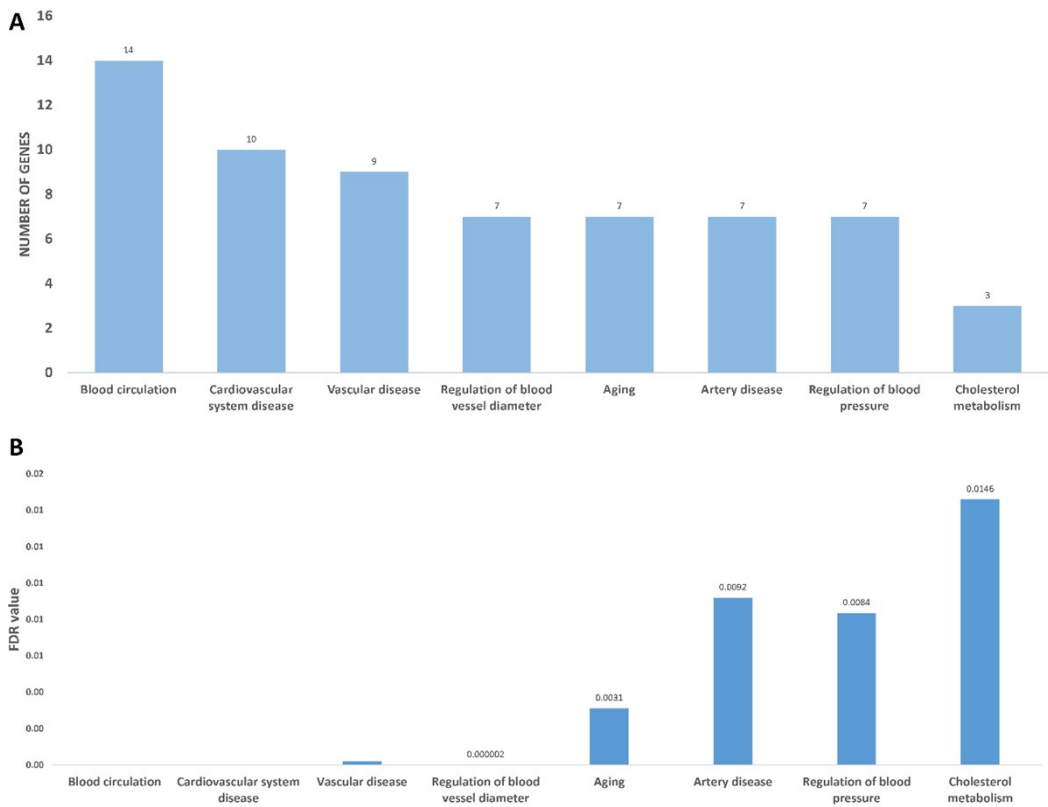


Figure S4. KEGG pathway enrichment. (A) *X*-axis is enrichment gene count, *Y*-axis is KEGG pathway. (B) False discovery rate (FDR) of each annotated pathway.

Experimental

1. Target Proteins of ischemia

Ischemia-related target proteins (**Table S2**) were retrieved from the publicly available databases: GeneCards (<https://www.genecards.org/>; accessed on 22 August 2021) [142]. The words “myocardial ischemia, and cerebral ischemia” were used as the keywords, and the species was set as “*Homo sapiens*”. Additionally, literature from 1990 until 2021 were reviewed for additional targets related both myocardial and cerebral ischemia. Google scholar was used for this literature review- based search using the same keywords: myocardial ischemia, and cerebral ischemia.

2. Determination of the Potential Protein Targets for the most prominent 20 compounds

The potential protein targets for the most prominent 20 compounds were proposed by subjecting all of these compounds structures to inverse docking against all proteins hosted in the Protein Data Bank (PDB; <https://www.rcsb.org/>). The idTarget platform (<http://idtarget.rcas.sinica.edu.tw/>) was used for this task. This structure-based screening software applies a unique docking approach called divide-and-conquer docking that adaptively builds small overlapping grids to make the searching space on the protein surfaces more constrained. Hence, it can run a huge number of accurate docking experiments in a much-reduced time [143]. The retrieved results were obtained as a list of binding affinity scores arranged from the highest negative to the lowest. We set a binding affinity score of -7 kcal/mol as a cut-off value to select the best targets for each compound structure. Considering the collected human myocardial and cerebral ischemia-related proteins, 9 protein targets were obtained for the selected 20 compounds.

Another pharmacophore-based virtual screening platform called SwissTargetPrediction (<http://www.swisstargetprediction.ch/>) [144] was used to predict potential targets for the same

compounds. The species was set as “*Homo sapiens*” and a probability score of 100% was set as a cut-off value.

3. Networks Construction and Functional Enrichment Analysis

Three types of networks were generated: (i) a network of compound-protein-pathway interactions (CPPI) based on the prediction results. Links between the selected 20 compounds and ischemia-related target proteins were generated in this network; (ii) a protein-protein interaction (PPI) network summarizing interactions between ischemia-relevant proteins. The proteins that were predicted to be probable targets for the selected compounds were submitted to the STRING database (<https://string-db.org/>) [145] for protein-protein interaction (PPI) analysis, where “*Homo sapiens*” was set as the search species, the interaction score was set to 0.9 (the maximum confidence), and the rest of the parameters were selected according to the default setting; (iii) a protein-pathway interaction network that showed the interactions between ischemia-related proteins and their associated signaling pathways. This network was constructed after KEGG pathway enrichment analysis. All the aforementioned networks were built using the Cytoscape 3.9.2 (<https://www.cytoscape.org/>) [146] network visualization and analysis software tool. The pre-installed tools carried out functional enrichment analysis and KEGG pathway annotation for ischemia-relevant targets in Cytoscape 3.9.2.

4. Molecular Dynamics Simulation

Desmond v. 2.2 software was used for performing MDS experiments [147–149]. This software applies the OPLS force field. Protein systems were built using the System Builder option, where the protein structure was embedded in an orthorhombic box of TIP3P water together with 0.15 M Na⁺ and Cl⁻ ions in 20 Å solvent buffer. Afterward, the prepared systems were energy minimized and equilibrated for 10 ns. Desmond software automatically parameterizes inputted ligands during the system building step according to the OPLS force field. Metal-containing proteins like MMPs that contain histidine-Zn⁺² complex in the active site should be parameterized during the protein preparation step. To do so, a hetero state should be generated for hetero atoms like Zn (Generate Hetero States). This function is a part of the maestro's Protein Preparation wizard. This step will enable the formation of a suitable hetero state or co-ordinate covalent state for the heteroatom (i.e. Zn⁺²) in complex with the protein so that force fields like OPLS can easily recognize the zinc atom. For simulations performed by NAMD [150], the parameters and topologies of the compounds were calculated either using the Charmm27 force field with the online software

Ligand Reader and Modeler (<http://www.charmm-gui.org/?doc=input/ligandrm>) [151] or using the VMD plugin Force Field Toolkit (ffTK). Afterward, the generated parameters and topology files were loaded to VMD to readily read the protein–ligand complexes without errors and then conduct the simulation step. For MMPs, harmonic Tcl forces were applied to keep Zn⁺² in place.

5. Binding Free Energy Calculations

Binding free energy calculations (ΔG) were performed using the free energy perturbation (FEP) method [150]. This method was described in detail in the recent article by Kim and coworkers [150]. Briefly, this method calculates the binding free energy $\Delta G_{\text{binding}}$ according to the following equation: $\Delta G_{\text{binding}} = \Delta G_{\text{Complex}} - \Delta G_{\text{Ligand}}$. The value of each ΔG is estimated from a separate simulation using NAMD software. Interestingly, all input files required for simulation by NAMD can be papered by using the online website CharmmGUI (<https://charmmgui.org/?doc=input/afes.abinding>). Subsequently, we can use these files in NAMD to produce the required simulations using the FEP calculation function in NAMD. The equilibration was achieved in the NPT ensemble at 300 K and 1 atm (1.01325 bar) with Langevin piston pressure (for “Complex” and “Ligand”) in the presence of the TIP3P water model. Then, 10 ns FEP simulations were performed for each compound, and the last 5 ns of the free energy values was measured for the final free energy values [150]. Finally, the generated trajectories were visualized and analyzed using VMD software.

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