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Review Article

Bioactive natural products against experimental autoimmune encephalomyelitis: A pharmacokinetics review

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ABSTRACT

Multiple sclerosis (MS) is a central nervous system (CNS) chronic disease in which axons are demyelinated and signal conduction is slowed or blocked. Unfortunately, current drugs that are used to treat MS have limited efficiency and considerable side effects. The use of bioactive natural products for treating neurodegenerative diseases has become of great interest due to their multimodal mechanism of action and potential safety. However, pharmacokinetic parameters such as bioavailability, absorption, metabolic pathways, and elimination routes are essential for evaluating the efficacy and toxicity of herbal medicines and herbal preparations in the clinic. In this review, we have summarized different pharmacokinetic parameters of neuroprotective natural products with anti-experimental autoimmune encephalomyelitis (EAE) effects and recent developments in strategies to improve their bioavailability and effectiveness.

Keywords:
Multiple sclerosis
Demyelination
Natural products
Pharmacokinetics
Experimental autoimmune encephalomyelitis

Introduction

Pharmacokinetics, which characterizes drug absorption, distribution, metabolism, and excretion, is one of the key factors in designing a safe and effective treatment protocol for drugs. Data obtained from pharmacokinetic studies can help us to understand the complex actions of herbal medicines and predict the efficacy and toxicity of herbs and herbal preparations (Liu et al., 2005). Bioactive natural products have opened new horizons in the treatment of neurodegenerative diseases due to their effectiveness, multimodal mechanism of action, and potential safety (Mohtashami et al., 2019). Generally, the use of natural medicines has relied on traditional knowledge that is not completely supported by empirical evidence and it has been a continuing challenge to assess the efficacy and safety of natural medicines. Evaluating bioavailability, absorption, metabolic pathways, elimination routes and the overall kinetics of these compounds are of great importance (Bhattaram et al., 2002) since clinical efficacy of the observed *in vitro* or *in vivo* activities relies on the pharmacokinetic properties of these agents (Kohlert et al., 2000).

Multiple sclerosis (MS) is an inflammatory disease characterized by focal damage to myelin and axons in the

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gray and white matter of the brain and spinal cord (Lassmann, 2018). This autoimmune disorder is believed to result from the activation and migration of peripheral autoreactive CD4 T cells into the CNS and their subsequent attack on the myelin sheath (Baecher-Allan et al., 2018). Several medicinal plants and natural molecules have been reported to be of benefit for the treatment of MS (Emami et al., 2016), however, the magnitude of the effect of a drug is related to the concentration of that drug at the site of receptors. Drug concentrations can be enhanced and reduced due to different absorption, distribution, metabolism, and excretion (ADME). Pharmacokinetic studies deal with these matters to determine the fate of administered drugs in the body (Dowd, 2017). Herein, a comprehensive review regarding the bioavailability and pharmacokinetic parameters of neuroprotective natural phytochemicals has been presented and summarized in tables 1 and 2.

Pharmacokinetic parameters

A typical pharmaceutical company is eager to discover and develop oral active drugs with a suitable potency, selectivity, good oral bioavailability, and good stability. The main reasons for failure during drug development are ineligible efficacy, toxicity, and poor pharmacokinetic parameters (Roberts, 2005).

Absorption

A drug should be soluble at the delivery site so that it can have maximum efficiency. When administered from the oral route, the drug must dissolve in the lumen of the small intestine. After dissolving, it must be absorbed through intestine walls and cross the barriers between blood and the receptor site thereafter. The entrance of many orally administered drugs into the blood circulation depends on their lipophilicity. A lipophilic structure can penetrate more efficiently into the lipid membranes and be transported via blood lipoproteins, however, the urinary excretion of these compounds are lesser in comparison to hydrophilic drugs and they can undergo an extensive metabolism either. Lipophilic compounds mostly cross the plasma membrane through the transcellular route, while hydrophilic compounds mostly cross the paracellular route. However, due to the large surface area of the intestine, even poorly soluble compounds can undergo good absorption (Roberts 2005).

Bioavailability

After absorption, first-pass metabolism can decrease the total exposure of the body to the administered drug. This metabolism is mediated by transmucosal or hepatic routes after absorption and before drug entrance into the systemic circulation. Therefore, bioavailability can be described as the rate and extent of unchanged drugs in the bloodstream after oral administration. This factor is defined as the fraction of maximum levels of drug present in the blood circulation after an intravenous (i.v.) dose that is dependent on the maximum concentration (C_{max}) of the drug, time to reach the maximum concentration (t_{max}), and area under the curve (AUC). Bioavailability can be calculated using the following equation:

$$\text{Bioavailability}=(AUC_1 dose_2/AUC_2 dose_1)100$$

where 1 refers to oral administration and 2 refers to i.v. administration (Roberts 2005).

Distribution

Drug distribution can be described as the reversible transfer of the drug around the body. Administered drugs are usually distributed within the vascular system quickly but distribution into the tissues is variable and depends on factors like perfusion rate, diffusion rate, protein binding, and tissue binding. It is not possible to directly measure the amount of distribution, however, to measure this factor apparent volume of distribution (V_d) can be calculated which is defined as the apparent volume into which the drug is distributed to make the same concentration as in the blood plasma. Distribution can be calculated using the following equation:

$$V_d=dose/C_0$$

where C_0 refers to the plasma concentration that the drug may have if immediately distributed into its final volume after an i.v. dose.

The lower V_d values are usually for hydrophilic compounds, while higher values are for drugs with a high affinity for tissues. The volume of distribution is related to plasma elimination half-life ($t_{1/2}$) and plasma clearance (Cl_p) according to the following equation:

$$t_{1/2}=V_d/Cl_p$$

Where $t_{1/2}$ refers to the time it takes for the amount of drug in the body or the plasma concentration to be reduced by 50% and Cl_p refers to plasma clearance (Roberts 2005).

TABLE 1: Pharmacokinetic parameters of neuroprotective natural products in human studies

Compound	Human model	Administration/ Dose	C_{max}[1] (μM)	t_{max}[2] (h)	$t_{1/2}$[3] (h)	Bioavail-ability (%)	V_d[4] (L)	Cl[5] (mL/min)	Ref.
Hesperetin	Healthy volunteers	Oral/135 mg	0.0027±0.00136	4	3.05±0.91	Low (3.26)	136.38± 68.40	497.42± 138.36	(Kanaze et al., 2007)
Naringenin			0.0074±0.0028	3.5	2.31±0.40	Low (5.81)	51.65± 19.75	258.57± 92.51	
Genistein	Healthy women	Oral/50 mg	1.26±0.27	5.2	6.78±0.84	-	161.1±44.1	1.98±0.34	(Setchell et al., 2001)
Silymarin	Healthy volunteers	Oral/600 mg of milk thistle extract	Free silychristin: not detected	not detected	not detected	Low	-	-	(Wen et al., 2008)
			Conjugated silychristin: 0.08±0.02	3.7±0.6	7.9±1.7	Low	-	-	
			Total silychristin: 0.08±0.02	3.7±0.6	7.9±1.7	Low	-	-	
			Free silydianin: not detected	not detected	not detected	Low	-	-	
			Conjugated silydianin: 0.04±0.01	2.8±1.3	3.3±0.6	Low	-	-	
			Total silydianin: 0.04±0.01	2.8±1.3	3.3±0.6	Low	-	-	
			Free silybin A: 0.05±0.02	1.0±0.4	1.3±0.5	Low	-	-	
			Conjugated silybin A: 0.05±0.01	2.2±0.8	6.0±1.9	Low	-	-	
			Total silybin A: 0.09±0.03	1.3±0.3	5.3±2.3	Low	-	-	
			Free silybin B: 0.03±0.01	0.83±0.1	2.3±0.7	Low	-	-	
			Conjugated silybin B: 0.24±0.04	1.5±0.5	3.5±0.8	Low	-	-	
			Total silybin B: 0.27±0.06	1.3±0.3	3.4±0.8	Low	-	-	
			Free isosilybin A: 0.02±0.01	0.75±0.3	3.2±0.7	Low	-	-	
			Conjugated isosilybin A: 0.22±0.06	2.5±1.3	4.1±0.1	Low	-	-	
			Total isosilybin A: 0.23±0.06	1.7±0.3	4.1±1.3	Low	-	-	
			Free isosilybin B: 0.02±0.01	0.75±0.3	2.4±0.8	Low	-	-	
			Conjugated isosilybin B: 0.11±0.03	2.5±0.9	4.0±1.1	Low	-	-	
			Total isosilybin B: 0.12±0.03	1.5±0.0	4.7±2.3	Low	-	-	

Compound	Human model	Administration/Dose	C_{max}[1] (μM)	t_{max}[2] (h)	$t_{1/2}$[3] (h)	Bioavail-ability (%)	V_d[4] (L)	Cl[5] (mL/min)	Ref.
Silymarin	Healthy vol-unteers	Oral/175 mg of milk this-tle extract 3 times daily for 28 days	Silybin A: 0.28±0.15	2 (0.5-3)	-	-	-	-	(Zhu et al., 2013)
			Silybin B: 0.09±0.06	1 (0.5-3)					
			Isosilybin B: 0.05±0.04	2 (0.5-3)					
		Oral/175, 350 or 525 mg of milk thistle extract	Silychristin (175 mg): not detected	not detected	not detected	Low	not detected	-	
			Silychristin (350 mg): 0.01±0.002	1.5	not detected	Low	not detected	-	
			Silychristin (525 mg): 0.018±0.007	1.5	2.7 ± 1.5	Low	11079.9±5506.1	-	
			Silydianin (175 mg): not detected	not detected	not detected	Low	not detected	-	
			Silydianin (350 mg): not detected	not detected	not detected	Low	not detected	-	
			Silydianin (525 mg): 0.013±0.008	1.5	not detected	Low	not detected	-	
			Silybin A (175 mg): 0.22±0.1	1.5	1.6 ± 0.5	Low	244.5 ± 108.2	-	
			Silybin A (350 mg): 0.416±0.2	1	1.8 ± 0.5	Low	281.8 ± 130.9	-	
			Silybin A (525 mg): 0.62±0.21	1	1.9 ± 0.5	Low	259.4 ± 127.0	-	
			Silybin B (175 mg): 0.063±0.034	1.5	2.4 ± 0.7	Low	1944.0 ± 1307.7	-	
			Silybin B (350 mg): 0.154±0.094	1	2.6 ± 0.8	Low	1945.4 ± 1171.3	-	
			Silybin B (525 mg): 0.251±0.11	1	2.2 ± 0.8	Low	1190.8 ± 676.4	-	
			Isosilybin A (175 mg): 0.012±0.006	1	not detected	Low	not detected	-	
			Isosilybin A (350 mg): 0.038±0.028	1	3.2 ± 1.5	Low	3781.1 ± 1961.4	-	
			Isosilybin A (525 mg): 0.051±0.024	1	2.8 ± 1.3	Low	2883.4 ± 2281.9	-	
			Isosilybin B (175 mg): 0.046±0.022	1.5	1.9 ± 0.6	Low	662.0 ± 430.5	-	
			Isosilybin B (350 mg): 0.096±0.064	1	2.0 ± 0.7	Low	677.2 ± 353.9	-	
			Isosilybin B (525 mg): 0.157±0.067	1	1.9 ± 0.6	Low	506.4 ± 251.4	-	

Compound	Human model	Administration/Dose	C_{max}[1] (µM)	t_{max}[2] (h)	$t_{1/2}$[3] (h)	Bioavailability (%)	V_d[4] (L)	Cl[5] (mL/min)	Ref.
THC[6]	Men with prior experience of marihuana use	Smoking/13 mg	0.245	0.05	-	18±6	-	-	(Ohlsson et al., 1980)
		Oral/20 mg	0.02	1 or 1.5	-	6±3	-	-	
		i.v.[7]/5 mg	-	-	-	100	-	-	
THC	Volunteers with a history of occasional cannabis consumption	Oral/10 mg THC once a week for 3 weeks	0.01±0.005	1.06±0.59	-	-	-	-	(Nadulski et al., 2005)
		Oral/Cannabis extract (10 mg THC) with 5.4 mg cannabidiol once a week for 3 weeks	0.013±0.007	0.93±0.3	-	-	-	-	
Huperzine A	Healthy volunteers	Oral/0.4 mg	0.01±0.001	0.97±0.06	11.94±2.17	-	0.061±0.015	0.5±0.1	(Li et al., 2007)
Artemisinin	Healthy volunteers	Oral/400 mg	0.92±0.33	1.0±0.5	1.9±0.6	-	-	-	(Titulaer et al., 1990)
		i.m.[8]/400 mg	0.74±0.34	3.4±2.0	7.44±3.83	-	-	-	
Artemisinin	Patients with falciparum malaria	Oral/500 mg per day for 5 days	Day1: 0.86±0.71	2.9±1.9	1.3±1.1	-	-	-	(Gordi et al., 2002)
			Day 5: 0.19±0.17	2.6±1.2	1.4±2.4	-	-	-	
		Oral/100 mg per day for 2 days, then 250 mg per day for 2 days and then 500 mg on the fifth day	Day1: 0.655±0.687	2.8±1.5	1.1±0.7	-	-	-	
			Day 5: 0.20±0.15	2.5±1.0	1.1±0.8	-	-	-	
Oleanolic acid	Healthy volunteers	Oral/40 mg	0.027±0.015	5.2±2.9	8.73±6.11	-	-	-	(Song et al., 2006)

TABLE 2:. Pharmacokinetic parameters of neuroprotective natural products in animal studies

Compound	Animal species	Administration/Dose	C_{max}[1](μM)	t_{max}[2] (h)	$t_{1/2}$[3] (h)	Bioavail-ability	V_d[4] (L or L/kg)	Cl[5] (mL/min)	Ref.
Genistein	Sprague-Dawley rats	i.v.[6]/10 mg/kg	Blood 3.7±1.11	0	0.2±0.03	100	-	642.5±75.2 (mL/min/kg)	(Tsai 2005)
			Brain: not detected	0	not detected	-	-	-	
			Bile: 1.37±0.19	0	0.21±0.09	-	-	-	
		i.v./30 mg/kg	Blood: 4.07±0.37	0	0.27±0.03	100	-	980.7±179.8 (mL/min/kg)	
			Brain: 0.26±0.07	0	0.24±0.05	-	-	-	
			Bile: 10.77±1.55	0	0.09±0.01	-	-	-	
Genistein	FVB mice	Oral/20 mg/kg	0.71±0.22	1.25±0.29	46.37±30.56	23.4	55.6±16.54	21.671±16.67	(Yang et al., 2010)
		i.v./20 mg/kg	57.70±21.84	0	14.2±9.87	100	16.05±10.47	14.5±6	
Baicalin	Sprague-Dawley rats	i.v./24 mg/kg	Blood: 2.8±1.4	0.5	0.95±0.51	100	16.98±12.5 (L/kg)	188±63 (mL/(min kg))	(Huang et al., 2008)
			CSF: 0.77±0.16	0.5	0.65±0.173		30.4±10.69 (L/kg)	534±103 (mL/(min kg))	
Baicalin	Sprague-Dawley rats (MCAO and sham-operated)	Oral/pure baicalin (400 mg/kg) or Huang-Lian-Jie-Du-Tang decoction (equivalent to 400 mg/kg of baicalin)	MCAO (baicalin): 15.43±2.91	0.35±0.14	17.71±9.60	-	-	-	(Zeng et al., 2010)
			Sham-operated (baicalin): 11.16±2.15	0.40±0.11	20.28±9.88	-	-	-	
			MCAO (decoction): 11.36±1.46	0.35±0.14	15.86±2.66	-	-	-	
			Sham-operated (decoction): 8.2±3.02	0.82±0.47	23.50±12.98	-	-	-	
Baicalin	Sprague-Dawley rats	Oral/Xianchaihu Tang (equivalent to 265.4 mg/kg of baicalin)	C_{max1}: 3.67±2.22	0.13±0.046	3.60±0.90	-	-	-	(Zhu et al., 2010)
			C_{max2}: 5.44±1.03	6.4±1.67					
		Oral/*Radix Scutellariae* extract (equivalent to 249.6 mg/kg of baicalin)	C_{max1}: 12.68±4.52	0.2±0.07	5.64±1.67	-	-	-	
			C_{max2}: 7.12±3.72	5.6±0.89					

Compound	Animal species	Administration/Dose	C_{max}[1](μM)	t_{max}[2] (h)	$t_{1/2}$[3] (h)	Bioavail-ability	V_d[4] (L or L/kg)	Cl[5] (mL/min)	Ref.
Baicalin	Sprague-Dawley rats (MCAO)	i.n.[7]/9.6 mg/kg	Baicalin: 2.75±1.12	0.45±0.11	1.83±0.3445	31.69	-	83.05±19.14 (mL/(min kg))	(Xiang et al., 2020)
			Baicalin liposome: 4.03±1.07	0.6±0.22	3.34±1.12	46.18		51.75 ± 6.65 (mL/(min kg))	
Icariin	Wistar rats	i.v./10 mg/kg	-	-	0.562±0.2	100	1.037±0.631 (L/kg)	335.07±96.69 (mL/(min kg))	(Cheng et al., 2007)
Icariin	Sprague-Dawley rats	Oral/*Herba Epimedi* extract	3.56±0.29	1.56±0.53	5.59±2.22	-	0.10±0.53	0.5 (mL/(min kg))	(Li et al., 2009)
		Oral/GKG	4.63±0.43	2.06±0.15	5.37±0.58	-	0.12±0.08	0.5 (mL/(min kg))	
Icariin and icariside II	Sprague-Dawley rats	Oral icariin/30 mg/kg	Icariin: 0.04±0.008 Icariside II: 0.043±0.01	Icariin: 0.25 Icariside II: 2.45±0.285	Icariin: 1.79±1.23 Icariside II: 4.36±3.1	0.1	-	-	(Cheng et al., 2015)
		Oral icariside II/30 mg/kg	0.153±0.043	0.153±0.043	2.25±2.12	4.1±1.4	-	-	
		i.v. icariin/30 mg/kg	Icariin: 52.35±15.16 Icariside II: 0.12±0.03	Icariin:0.083 Icariside II: 0.083	Icariin: 5.65±5.33 Icariside II: 1.97±0.95	100	-	-	
		i.v. icariside II/30 mg/kg	6.34±2.01	0.083	5.37±4.7	100	-	-	
Icariin	Sprague-Dawley rats	Oral/0.69 g/kg of total flavonoid extract from *Herba Epimedii* (equivalent to 42mg/g of icariin)	-	0.46±0.25	3.15±2.36	Low	-	6485.3±3408.5 (mL/(min kg))	(Xu et al., 2017)
Epimedin C	Sprague-Dawley rats	Oral/100 mg/kg	0.484±0.1	0.29±0.1	2.43±0.26	0.58	-	3628±605 (mL/(min kg))	(Lee et al., 2014)
		i.v./1 mg/kg	5.84±0.36	-	1.43±0.4	100	-	22±2 (mL/(min kg))	
		Oral/*Herba Epimedii* extract (equivalent to 41.1 mg of epimedin C)	0.065 ± 0.012	0.23±0.075	2.53±0.53	0.13	-	337995±58510 (mL/(min kg))	

Compound	Animal species	Administration/Dose	C_{max}[1](μM)	t_{max}[2] (h)	$t_{1/2}$[3] (h)	Bioavailability	V_d[4] (L or L/kg)	Cl[5] (mL/ (min	Ref.
Curcumin	C57BL/6 mice	i.n./Curcumin solution (2 mg/kg)	0.014±0.006	1.00±0.00	-	Low	-	-	Zhang et) (al., 2020
		i.n./ Curcumin-encapsulated chitosan-coated PLGA[8] nanoparticles (equivalent to 2 mg/kg of curcumin)	0.011±0.003	0.83±0.17	-	Low	-	-	
		i.n./ hydroxypropyl-β-cyclodextrin-encapsulated curcumin complexes (equivalent to 2 mg/kg of curcumin)	0.026±0.005	0.75±0.14	-	Increased bioavailability in comparison to other formulations	-	-	
Curcumin	Zebra fish	Oral/Curcumin solution (25 mg/kg curcumin)	(μmol/brain) 0.0002	0.083	1.64	-	-	-	More and) Pawar (2020
		Oral/Curcumin-loaded turmeric oil microemulsion(equivalent to 25 mg/kg of curcumin)	(μmol/brain) 0.0007	0.083	0.69	-	-	-	
Arctigenin	Sprague-Dawley rats	Oral/1.61 μmol	-	-	-	Low	-	--	(Gao 2014)
		Oral/3.22 μmol	-	-	-	Low	-	-	
		Oral/8.06 μmol	-	-	-	Low	-	-	
		i.v./0.32 μmol	0.74±0.23	0.04±0.02	0.15±0.03	100	0.46±0.11	40±20	
		i.v./0.64 μmol	1.45±0.33	0.03±0.00	0.22±0.04		0.65±0.09	30±0.00	
		i.v./1.61μmol	4.57±0.69	0.03±0.001	0.22±0.03		0.57±0.13	30±10	

Compound	Animal species	Administration/Dose	C_{max}[1](μM)	t_{max}[2] (h)	$t_{1/2}$[3] (h)	Bioavailability	V_d[4] (L or L/kg)	Cl[5] (mL/min)	Ref.
Resveratrol	Sprague-Dawley rats	Oral/Resveratrol (50 mg/kg/d) for 14 days	0.77	0.25	5.5	19.9	-	-	(Kapetanovic et al., 2011)
		Oral/Resveratrol (150 mg/kg/d) for 14 days	2.16	2	1.8	17.5	-	-	
		i.v./Resveratrol (10 mg/kg)	C_0: 15.11	-	Not calculated	100	-	183.37 (mL/(min kg))	
		Oral/Pterostilbene (56 mg/kg) for 14 days	9.95	2	1.6	73.2	-	-	
		Oral/Pterostilbene (168 mg/kg) for 14 days	21.69	8	1.9	80.8	-	-	
		i.v./ Pterostilbene (11.2 mg/kg)	C_0: 28.64	-	2.9	100	-	45 (mL/(min kg))	
Resveratrol	Wistar rats	Oral/Free resveratrol (20 mg/kg)	19.95±2.1	15	2.37±0.12	-	-	56.67±0.57	(Pandita et al., 2014)
		Oral/Resveratrol-loaded SLN[9] (equivalent to 20 mg/kg of resveratrol)	32.17±4.99	60	11.51±1.16	-	-	6.9±0.12	
Resveratrol	Wistar rats	i.v./Free resveratrol (200 mg/kg)	12004.4±297.9	0	-	-	-	-	(Ahmad et al., 2016)
		i.v./Resveratrol-loaded non-PEG[10] SLN (equivalent to 200 mg/kg of resveratrol)	10208.1±271.6	2	-	Increased bioavailability in comparison to free resveratrol	-	-	
		i.v./Resveratrol-loaded PEG SLN (equivalent to 200 mg/kg of resveratrol)	7535.6±184	2	-	Increased bioavailability in comparison to free resveratrol	-	-	
Resveratrol	Charles Foster rats	i.v./Free resveratrol (2 mg/kg)	-	-	0.53±0.31	100	1.43±0.22 (L/kg)	31.58±6.37 (mL/(min kg))	(Vijayakumar et al., 2016)
		i.v./ Resveratrol-loaded liposome (equivalent to 2 mg/kg of resveratrol)	-	-	2.34±0.35	100	1.23±0.06 (L/kg)	6.16±1.2 (mL/(min kg))	
		i.v./ Resveratrol-loaded TPGS[11] coated liposome (equivalent to 2 mg/kg of resveratrol)	-	-	15.72±2.96	100	1.32±0.42 (L/kg)	0.96±0.13 (mL/(min kg))	

Compound	Animal species	Administration/Dose	C_{max}[1](μM)	t_{max}[2] (h)	$t_{1/2}$[3] (h)	Bioavailability	V_d[4] (L or L/kg)	Cl[5] (mL/min)	Ref.
Resveratrol	Wistar rats	Oral/Free resveratrol (20 mg/kg)	0.657±0.022	0.5±0.04	0.27±0.08	-	-	-	(Singh et al., 2014)
		Oral/Resveratrol-loaded polymeric nanoparticle (equivalent to 20 mg/kg of resveratrol)	0.889±0.048	10±0.01	18.22±0.93	Increased bio-availability in comparison to free resveratrol	-	-	
Plumbagin	Sprague-Dawley rats	Oral/100 mg/kg	1.86±0.53	2.5±0.76	17.13±5.38	38.7±5	-	-	(Hsieh et al., 2006)
		i.v./3 mg/kg	1.01±0.425	0	1.8±1.07	100	-	-	
Plumbagin	C57BL/6J mice	i.m.[12]/Free plumbagin (6 mg/kg)	21.79±3.77	1.33±0.58	3.64±2.17	-	-	6.61±1.04	(Mandala Rayaband-la et al., 2010)
		i.m./Plumbagin micro-spheres (equivalent to 6 mg/kg of plumbagin)	13.66±0.8	3.34±1.16	81.12±0.014	-	-	0.73±0.19	
Salvianolic acid B	Sprague-Dawley rats	Oral/ 500 mg/kg	2.09±1.11	-	4.13±0.18	2.3	-	-	(Wu et al., 2006)
		i.v./100 mg/kg	1266.3±528.8	0	1.75±0.32	100	-	-	
Caffeic acid phenethyl ester	Sprague-Dawley rats	i.v./5 mg/kg	-	0	0.35±0.04	100	5.21±2.31 (L/kg)	172±79.8 (mL/(min kg))	(Wang et al., 2009)
		i.v./10 mg/kg	-	0	0.38±0.07	100	3614±1759 (L/kg)	107±42.3 (mL/(min kg))	
		i.v./20 mg/kg	-	0	0.45±0.15	100	1555±461.6 (L/kg)	42.1±12.4 (mL/(min kg))	
Osthole	Wister rats	Oral/20 mg/kg	Normal: 1.5±0.36	0.61±0.09	4.94±1.84	-	-	0.01±0.003 (mL/(min kg))	(Zhou et al., 2011)
			Cerebral ischemia hy-poperfusion: 1.52±0.31	0.64±0.18	8.57±2.52	-	-	0.007±0.002 (mL/(min kg))	
Osthole	Sprague-Dawley rats	Oral/10 mg/kg of 8 coumarins including osthole	8.35±0.61	0.64±0.04	2.22±0.99	-	3.66±0.38 (L/kg)	13.67±1.67 (mL/(min kg))	(Zhao et al., 2013)

Compound	Animal species	Administration/Dose	C_{max}[1](μM)	t_{max}[2] (h)	$t_{1/2}$[3] (h)	Bioavailability	V_d[4] (L or L/kg)	Cl[5] (mL/min)	Ref.
Huperzine A	Sprague-Dawley rats	Oral/500 μg/kg	Blood: 0.29±0.1	0.85±0.38	2.47±0.77	-	-	-	(Yue et al., 2007)
			CSF: 0.087±0.03	1.70±0.45	3.55±0.29	-	-	-	
		i.v./ 167 μg/kg	Blood: 0.55±0.13	0.033	1.80±0.76	-	0.34±0.10	10.5±2	
			CSF: 0.15±0.03	0.07±0.03	1.11±0.32	-	-	23.1±6.83	
		i.v./ 500 μg/kg	Blood: 1.18±0.43	0.04±0.02	2.03±0.75	-	0.45±0.26	10.5±2.66	
			CSF: 0.32±0.04	0.12±0.07	1.71±0.43	-	-	12.33±4.67	
		i.n./ 167 μg/kg	Blood: 0.25±0.08	0.26±0.13	1.44±0.61	-	-	-	
			CSF: 0.1±0.02	0.63±0.26	1.97±0.66	-	-	-	
		i.n./ 500 μg/kg	Blood: 0.43±0.14	0.38±0.14	1.82±0.23	-	-	-	
			CSF: 0.17±0.05	0.67±0.26	1.96±0.66	-	-	-	
Matrine	Beagle dog	Oral/Matrine (6 mg/kg)	1.88±0.26	1.58±0.38	5.21±0.67	-	-	-	(Wang et al., 2007a)
		Oral/Kushen formula granule (equivalent to 6 mg/kg of matrine)	7.21±0.46	0.63±0.21	3.30±0.38	-	-	-	
Berberine	Wistar rats	i.v./*Coptidis rhizoma* extract (10.2 mg/kg equivalent to 3 mg/kg of berberine)	Blood: -	0	1.13±0.18	100	2.4±0.3 (L/kg)	106.67±3.33 (mL/(min kg))	(Wang et al., 2005b)
			Hippocampus (μg/g): 0.272±0.012	3.67±0.48	12.0±1.5	-	-	-	
Sinomenine	Sprague-Dawley rats	Oral/90 mg/kg	42.19±13.97	0.66±0.147	5.54±3.96	79.6	17.07±12.83 (L/kg)	43.0±15.4 (mL/(min kg))	(Liu et al., 2005)
		i.v./50 mg/kg	521.87±252.07	-	4.48±2.45	100	35.94±37.74 (L/kg)	269.8±73.5 (mL/(min kg))	
Thymoquinone	Vole rabbits	Oral/20 mg/kg	21.19±0.73	2	4.58±0.14	58	L/) 4.88±0.26 (kg	mL/) 12.3±0.3 (((min kg	Alkharfy) et al., (2015
		i.v./5 mg/kg	45.61±1.46	0	1.06±0.18	100	L/) 0.646±0.101 (kg	mL/) 7.19±0.83 (((min kg	

Compound	Animal species	Administration/Dose	C_{max}[1](μM)	t_{max}[2] (h)	$t_{1/2}$[3] (h)	Bioavailability	V_d[4] (L or L/kg)	Cl[5] (mL/min)	Ref.
β-elemene	Sprague-Dawley rats	i.v./50 mg/kg	-	0	0.98±0.14	100	-	58±5 (mL/(min kg))	(Wang et al., 2005a)
		i.v./75 mg/kg	-	0	0.98±0.30	100	-	56±4 (mL/(min kg))	
		i.v./100 mg/kg	-	0	1.085±0.098	100	-	46±4 (mL/(min kg))	
Triptolide	Sprague-Dawley rats	Oral/0.6 mg/kg	0.70±0.13	0.18±0.04	0.36±0.05	72.08	-	-	(Shao et al., 2007)
		Oral/1.2 mg/kg	1.24±0.31	0.17±0.00	0.28±0.09	-	-	-	
		Oral/2.4 mg/kg	1.49±0.40	0.17±0.00	0.34±0.06	-	-	-	
		i.v./0.6 mg/kg	-	0	0.25±0.07	100	-	-	
Andrographolide	Wistar rats	i.v./5 mg/kg	1.57±0.49	0	6.72±1.81	100	53.65±16.34 (L/kg)	94.99±29.02 (mL/(min kg))	(Yang et al., 2013)
Andrographolide	Wistar rats	Oral/30 mg/kg	0.33±0.05	0.75±0.29	2.45±0.44	-	-	-	(Bera et al., 2014)
Diosgenin	Sprague-Dawley rats	Oral/100 mg/kg	Normal: 0.66±0.18	5.81±1.15	5.72±1.06	-	-	380±69.8 (mL/(min kg))	(Xu et al., 2009)
			Hyperlipidemic: 2.13±0.61	9.69±1.9	8.35±2.42	-	-	75.83±20.83 (mL/(min kg))	
Astragaloside IV	Sprague-Dawley rats	Oral/20 mg/kg	0.48	0.43	4.65	-	0.56 (L/kg)	7.17 (mL/(min kg))	(Gu et al., 2004)
Astragaloside IV	Sprague-Dawley rats	Oral/20 mg/kg	1.32	0.75	3.8	3.66	-	102.67 (mL/(min kg))	(Du et al., 2005)
		i.v./2 mg/kg	-	0	3.01	100	-	3.83 (mL/(min kg))	

Compound	Animal species	Administration/Dose	C_{max}[1](μM)	t_{max}[2] (h)	$t_{1/2}$[3] (h)	Bioavailability	V_d[4] (L or L/kg)	Cl[5] (mL/min)	Ref.
Astragaloside IV	Sprague-Dawley rats	i.v./0.75 mg/kg	Male: 4.83	0	1.63	100	0.39 (L/kg)	5 (mL/(min kg))	(Zhang et al., 2006)
			Female: 6.6	0	0.57	100	0.14 (L/kg)	5 (mL/(min kg))	
		i.v./1.5 mg/kg	Male: 8.89	0	1.12	100	0.43 (L/kg)	7 (mL/(min kg))	
			Female: 6.11	0	1.11	100	0.16 (L/kg)	3 (mL/(min kg))	
		i.v./3 mg/kg	Male: 9.92	0	1.2	100	0.38 (L/kg)	6 (mL/(min kg))	
			Female: 9.22	0	21.19	100	0.21 (L/kg)	3 (mL/(min kg))	
	Beagle dogs	i.v./0.25 mg/kg	Male: 1.41±0.36	0	0.87±0.14	100	0.23±0.05 (L/kg)	4±1 (mL/(min kg))	
			Female: 1.44±0.05	0	1.05±0.37	100	0.22±0.01 (L/kg)	4±1 (mL/(min kg))	
		i.v./0.5 mg/kg	Male: 5.59±3.31	0	1.0±0.14	100	0.14±0.07 (L/kg)	4±1 (mL/(min kg))	
			Female: 4.43±2.04	0	1.12±0.13	100	0.16±0.07 (L/kg)	4±1 (mL/(min kg))	
		i.v./1 mg/kg	Male: 10.09±4.71	0	1.15±0.35	100	0.14±0.07 (L/kg)	4±1 (mL/(min kg))	
			Female: 11.29±3.18	0	0.84±0.22	100	0.12±0.04 (L/kg)	3±1 (mL/(min kg))	

[1] maximum serum concentration, [2] time to reach to the maximum serum concentration, [3] plasma elimination half-life, [4] volume of distribution, [5] clearance, [6] intravenous, [7] intranasal, [8] poly (lactic-co-glycolic acid), [9] solid lipid nanoparticle, [10] polyethylene glycol, [11] D-α-tocopheryl polyethylene glycol succinate, [12] intramuscular

Elimination

Drug elimination is the irreversible transfer of a drug from plasma or blood by different routes like biliary, renal, pulmonary, hepatic, sweating, and milk. Clearance is a crucial factor in drug development processes and can be described as the volume of blood from which the drug is removed completely in a unit of time. The total clearance (Cl_{TOT}) is the sum of clearances in all body organs. Cl_p can be calculated by the dose and AUC obtained from i.v. administration using the following equation:

Cl_p= dose/AUC (Roberts 2005)

Pharmacokinetic characteristics of neuroprotective compounds

Flavonoids

Hesperidin and naringenin

Hesperidin is a flavonoid glycoside which is isolated from the rinds of some *Citrus* species like lemon and sweet orange (Sun et al., 2017). Previous pharmacological studies have indicated that oral administration of hesperidin can reduce the severity and clinical score of experimental autoimmune encephalomyelitis (EAE) which is a well-known animal model for investigating different aspects of MS *in vivo*. Hesperidin can inhibit leukocyte infiltration into the CNS and reduce inflammatory cytokines like interleukin 17 (IL-17), tumor necrosis factor α (TNF-α), and IL-6 (Haghmorad et al., 2017). Naringenin can attenuate EAE by lowering demyelination and infiltration of inflammatory cells into the spinal cord and decreasing T helper (Th) 1, Th9, and Th17 cells (Wang et al., 2018). Unfortunately, hesperidin has a limited bioavailability due to the presence of the rutinoside moiety. To be absorbed by colonocytes, hesperidin is converted to its aglycone, hesperetin, by the microflora of the colon (Roohbakhsh et al., 2014). Kanaze et al. investigated the pharmacokinetic properties of hesperetin and naringenin following oral administration of 135 mg of each compound in six healthy volunteers under fasting conditions. Both hesperetin and naringenin were rapidly absorbed and their concentrations in plasma peaked at 4.0 and 3.5 h, respectively. Elimination half-lives were found to be 3.05±0.91 h for hesperetin and 2.31±0.4 h for naringenin. Due to extensive first-pass metabolism, both flavanone aglycones have low bioavailability (Kanaze et al., 2007), however, both hesperidin and naringenin demonstrated promising anti-EAE activity when administered orally (Haghmorad et al., 2017; Wang et al., 2018) or subcutaneously (s.c.) (Ciftci et al., 2015). In another study, hesperetin, but not its conjugates, was detected in the rat brain, especially the striatum after i.v. administration (Tsai and Chen, 2000).

Genistein

Genistein is an isoflavone that can decrease disease severity in the early phase of EAE by reducing IL-12, interferon-gamma (IFN-γ), and TNF-α (Razeghi Jahromi et al., 2014) and enhancing IL-10 (Razeghi Jahromi et al., 2014; Razeghi et al., 2009). It has been reported that low concentrations of genistein were detected in rats that received this compound at three different time intervals, as a fetus, neonate that was being fed by maternal milk, and as adults (Chang et al., 2000). Yang et al. showed that after both i.v. and oral administrations of genistein, more than 80% of the compound was converted to glucuronide and sulfate conjugates in mice. The bioavailability of genistein aglycone was 23.4% (Yang et al., 2010). Clinical pharmacokinetics studies revealed that genistein is extensively metabolized in the human body, and the unconjugated genistein concentration in plasma was very low. Following oral administration of 50 mg genistein, its aglycone accounted for only 3.7% in the first 2 hours and 1.6 % at steady state in women (Setchell et al., 2001). ADME studies suggested that genistein has low oral bioavailability due to two important factors, extensive metabolism and high expression level of efflux transporters (Yang et al., 2012). The results of an HPLC–UV combined with the microdialysis method to detect unbound genistein in rat blood, brain, and bile demonstrated that this compound goes through hepatobiliary excretion after i.v. administration (10 or 30 mg/kg) and a small ratio of genistein pass through the blood-brain barrier (BBB) (Tsai, 2005).

Silymarin

Silymarin is found in the seeds of *Silybum marianum* (L.) Gaertn. and is a mixture of flavanolignans silibinin, isosilibinin, silicristin and silidianin. Silymarin has shown immunosuppressive effects by suppressing the secretion of inflammatory cytokines like IFN-γ, IL-2, and TNF-α (Esmaeil et al., 2017; Gharagozloo et al., 2010). Zhu et al. investigated the pharmacokinetics of *S. marianum* extract in healthy volunteers after oral ad-

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ministration of single doses of either 175 mg, 350 mg, or 525 mg of the extract on three separate study visits. Pharmacokinetic parameters of the extract were determined following the administration of 175 mg thrice daily for 28 consecutive days. The results showed that all six flavonolignans were rapidly absorbed and eliminated (Zhu et al., 2013). Following oral administration, silymarin is quickly metabolized to its conjugates, mainly glucuronides, which are primary components present in human plasma (Wen et al., 2008). However, silymarin flavonolignans have been shown to possess remarkable neuroprotective activities after oral use in animal models (Nencini et al., 2007; Toklu et al., 2008).

Baicalin

Isolated from the roots of *Scutellaria baicalensis* Georgi, baicalin has shown an effective inhibitory effect against EAE development by reducing IFN-γ, inducing IL-4 (Zeng et al., 2007b), increasing the apoptosis of inflammatory cells in the spinal cord (Xu et al., 2011), and regulating the differentiation of Th1 and Th17 cells (Zhang et al., 2015). After oral administration of baicalin in rats, only the glucuronide and sulfate derivatives were detected in plasma (Lai et al., 2003) and the absolute oral bioavailability of this compound has been reported to be very low (Zhang et al., 2016). Thus, its clinical efficacy is remarkably weakened (Xiang et al., 2020). Zeng et al. compared the pharmacokinetics of baicalin after oral administration of pure baicalin at 400 mg/kg and Huang-Lian-Jie-Du-Tang decoction (at a dose equivalent to 400 mg/kg baicalin) in both middle cerebral artery occlusion (MCAO) and sham-operated rats. The results indicated a better absorption of pure baicalin than decoction in both groups (Zeng et al., 2010). In another study, pharmacokinetic parameters like $t_{1/2}$, C_{max}, and t_{max} for baicalin were different after oral administration of "Minor *Radix Bupleuri* decoction" and *Radix scutellariae* extract (Zhu et al., 2010). Therefore, it can be concluded that interactions between the constituents of different herbal preparations can lead to a significant difference in the pharmacokinetic parameters of this compound. After i.v. administration, baicalin can be detectable in the brain cerebrospinal fluid of rats, suggesting that this compound can cross BBB (Huang et al., 2008).

Intranasal (i.n.) administration of baicalin phospholipid complex to rats resulted in the transfer of 52.36 %–100 % of baicalin to the brain via the olfactory pathway. C_{max} for BP in plasma, olfactory bulb, cortex, striatum and cerebellum were 0.831±0.072, 38.34±6.06, 2.821±0.952, 2.658±0.288 and 1.555± 0.285 g/mL g, respectively. While the C_{max} value for i.v. administration of BP was 1.093±0.2170, 0.886±0.074, 1.053±0.122 and 0.972±0.199 g/mL g, respectively. Similarly, the $AUC_{0\sim480}$ for i.n. administration of BP in the cortex, striatum, and cerebellum was far higher than i.v. administration showing that baicalin absorption into the CNS is much better through i.n. route in comparison to i.v. route. Thus, i.n. administration of phospholipid complex might be a promising approach to transfer baicalin to the brain (Li et al., 2011). Similar results were obtained by baicalin liposomes as well because brain biodistribution of baicalin liposomes in cerebral ischemia-reperfusion injury rats was shown to be higher in i.n. administration in comparison to i.v. administration. Also, i.n. administration could remarkably ameliorate neurological deficits in these rats (Xiang et al., 2020).

Icariin

This flavonoid glucoside compound is isolated from *Epimedium* spp. (Shen et al., 2015) and exerts neuroprotective and estrogen-like effects (Becher et al., 2002). It has been reported that icariin decreases the expression of IFN-γ and IL-17 in the CNS and peripheral lymphoid organs, alleviates inflammatory infiltration, reduces BBB leakage of paracellular tracer (Shen et al., 2015), promotes oligodendrogenesis, and increases remyelination of axons (Zhang et al., 2017). Cheng et al. investigated the pharmacokinetic parameters of icariin in Wistar rats when administered i.v. The results showed that $t_{1/2}$ was 0.562±0.200 h, indicating that icariin distribution and elimination in rats is rapid (Cheng et al., 2007). Pharmacokinetic investigation of icariin and icariside II, a hydrolysis product of icariin in the intestine, in rats demonstrated that 91.2% of icariin is transformed into icariside II after oral administration, while only 0.4% of icariin was transformed into icariside II after i.v. administration. C_{max} and $AUC_{0\text{-}t}$ of oral icariside II were 3.8 and 13.0 times higher than those of oral icariin while after i.v. administration, the C_{max} and $AUC_{0\text{-}t}$ of icariside II were 12.1% and 4.2% of those of icariin. This indicates that after oral administration, icariside II is absorbed faster and metabolizes slower than icariin. However, after i.v. administration, icariside II metabo-

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lizes faster, whereas icariin is not metabolized into icariside II. Altogether, it can be suggested that icariin and its metabolite icariside II have distinct pharmacokinetic properties (Cheng et al., 2015). It has been reported that pharmacokinetic parameters of icariin are improved when administered in the form of composite formulations. Gan-kang granules (GKG) is an icariin-containing traditional Chinese composite used to treat hepatitis. B. Li et al. reported that icariin release from GKG is different from *Herba Epimedii* extract after intragastric (i.g.) administration to Sprague-Dawley rats. This may result from a pharmacokinetic interaction between icariin and other ingredients of GKG. Higher C_{max} and $AUC_{0-\infty}$ and longer t_{max} and $t_{1/2}$ were observed when administering GKG. A higher AUC suggests that icariin absorbs better than GKG in comparison to *Herba Epimedii* extract. Also, longer t_{max} and $t_{1/2}$ indicate delayed absorption and slow elimination (Li et al., 2009). Unfortunately, the $AUC_{0-\infty}$ of icariin in the brain is very low which shows that icariin cannot pass the BBB efficiently (Xu et al., 2017). Therefore, to get good MS/EAE-healing effects, it is necessary to perform more studies for improving icariin penetration into the CNS.

Epimedium flavonoids

Epimedium flavonoids, derived from *Epimedium brevicornu* Maxim., seem protective against EAE. Accordingly, these compounds could decrease EAE clinical score, inhibit astrocyte activation, alleviate demyelination (Yin et al., 2012), and decrease myelin breakdown in the corpus callosum of C57BL/6 mice (Liang et al., 2015). Lee et al. evaluated the pharmacokinetic profile of epimedin C following administration of *Herba Epimedii* (the dried leaves of *Epimedium* L.) in rats. The resulting data revealed rapid distribution and slow elimination after i.v. administration of epimedin C. The bioavailability of this compound after oral administration of pure compound and *Herba Epimedii* were approximately 0.58% and 0.13%, respectively. This suggests that other compounds of *Herba Epimedii* may decline the oral bioavailability of epimedin C (Lee et al., 2014). After a single oral administration of *Herba Epimedii* extract, the tissue concentrations of epimedin B in rats was in the following order: liver > ovary > uterus > lung > kidney > spleen > heart > brain. This indicates that epimedin B could pass through BBB to reach the brain (Feng et al., 2017).

Polyphenols

Curcumin

Curcumin is isolated from the rhizomes of *Curcuma longa* L. and has been used as a flavoring and coloring agent in foods for centuries. Curcumin has ameliorated EAE by lowering IL-6 and IL-21 and reducing the differentiation of Th17 cells (Xie et al., 2009). It has decreased IL-12, IL-17, IL-23, and IFN-γ (60), and up-regulated IL-10 and peroxisome proliferator-activated receptor gamma (PPAR-γ) in the CNS and lymphoid organs (Kanakasabai et al., 2012). Tsai et al. evaluated the ability of curcumin and its nano-formulation for penetrating the organs and different regions of the brain. Curcumin and curcumin-loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles were distributed in the liver, spleen, heart, lungs, kidneys, and brain. Nano-formulation could significantly increase AUC, $t_{1/2}$, and mean residence time (MRT) of curcumin in all these organs, except the heart. Distribution levels in regions of the brain showed that both formulations of curcumin accumulated in the hippocampus. The retention times of curcumin in the cerebral cortex and hippocampus were significantly extended by PLGA nanoparticle encapsulation (Tsai et al., 2011).

Another method to improve the brain delivery of curcumin is i.n. administration of curcumin-cyclodextrin complex that has resulted in higher bioavailability and brain distribution of this compound (Zhang et al., 2020). Also, in a study by More and Pawar, curcumin encapsulated turmeric oil microemulsion could increase *ex vivo* oral absorption and improve *in vivo* brain pharmacokinetics by enhancing $AUC_{(0-\infty)}$ to a value of 3.97 fold higher in comparison to curcumin solution in a zebrafish model (More and Pawar, 2020).

Arctigenin

Arctigenin is isolated from *Arctium lappa* L. and exerts its protective effects against EAE through inhibiting IL-17A, IL-17F, and IFN-γ, as well as Th1, and Th17 cells. This compound can activate 5' AMP-activated protein kinase (AMPK), up-regulate PPAR-γ, and inhibit phosphorylated p38 which results in suppression of Th17 cells differentiation (Li et al., 2016). It has been shown that arctigenin is widely distributed throughout body tissues following hypodermic injection in rats. At 0.5 h after injection, low concentrations of this compound were detected in the brain. Notably, the brain

level of arctigenin increased after 1 h to 3 h, indicating that it could pass through the BBB. However, 6 h after treatment, arctigenin was not detectable in the brain, but it was still present in the intestine and liver (Gao, 2014).

Stilbenoids

Resveratrol

Resveratrol has exerted several pharmacological activities such as anti-cancer, anti-inflammatory, anti-oxidant, and anti-microbial (Wang et al., 2016). The neuroprotective effects of resveratrol are mediated through lowering inflammatory cytokines such as IL-2, IL-6, IL-8, IL-12, TNF-α, and IFN-γ (Ghaiad et al., 2017; Imler and Petro, 2009). This compound inhibits EAE development by suppressing the development of Th1 and Th17 cells (Wight et al., 2012). SIRT1, a member of the sirtuin family proteins, is a deacetylase enzyme which has a pivotal role in innate immunity by inhibiting the production of proinflammatory cytokines in dendritic cells and macrophages (Jia et al., 2018). A pharmaceutical formulation of resveratrol (SRT501) has shown neuroprotective activity in optic nerves and spinal cords of the EAE model that may result from the activation of SIRT1 accompanied by improvement of neuronal survival (Shindler et al., 2010). On the contrary, it has been reported that resveratrol can exacerbate inflammation and demyelination in the CNS of EAE models by increasing inflammatory infiltration across the BBB (Sato et al., 2013). Resveratrol's biological activity is restricted by first pass metabolism. Low plasma concentrations of resveratrol are seen after oral administration and metabolism to sulfate and glucuronide conjugates is rapid (Walle et al., 2004; Wenzel and Somoza, 2005). Kapetanovic et al. compared the pharmacokinetic profiles of resveratrol and pterostilbene in male rats after a single i.v. dose, a single oral dose, and daily oral doses administered over 14 days. Following i.v. administration, Cl_{TOT} of resveratrol (11 L/h/kg) was greater than that of pterostilbene (2.7 L/h/kg) which may at least partially, be responsible for the lower plasma levels and exposure of resveratrol in comparison to pterostilbene (Kapetanovic et al., 2011). The use of different nano-systems namely solid-lipid nanoparticles (SLNs) (Ahmad et al., 2016; Jose et al., 2014; Pandita et al., 2014), liposomes (Vijayakumar et al., 2016), and polymeric nanoparticles (Singh et al., 2014) as drug carriers has increased the bioavailability of this compound. As an example, resveratrol-loaded SLNs result in a high accumulation of this compound in the brain tissue, making this formulation suitable for brain delivery (Jose et al., 2014).

Some researchers believe that the metabolism of resveratrol to its conjugates may be a protective mechanism against the high concentration of bolus nutraceutical doses (Calabrese et al., 2010). Sulfate metabolites can produce the parent compound intracellularly through a hydrolysis mechanism (Chung et al., 2012; Gescher et al., 2013). Also, resveratrol conjugates possess bioactivity potential (Aires et al., 2013; Patel et al., 2013). Thus, circulating concentrations of resveratrol at a given time point are not an indicator of actual exposure and are possibly a wrong target for expected efficacy (Chachay et al., 2014).

Cannabinoids

Tetrahydrocannabinol

Delta-9-tetrahydrocannabinol (THC) is a psychoactive constituent of *Cannabis* that was shown to ameliorate the ratings of spasticity in patients with MS at doses of more than 7.5 mg (Ungerleider et al., 1987). Cannabidiol which is another active compound of *Cannabis* may regulate the undesirable effects of tetrahydrocannabinol (McPartland and Russo, 2001), however, the ameliorative effects of cannabidiol on MS have not been investigated in clinical studies. Leuschner et al. studied the pharmacokinetics of THC in rabbits 8-10 days after a single i.v. dose of 1 mg/kg or 26 days after treatment with the same dose for 22 days. The results showed that plasma Cl values were high, but a large amount of drug was sequestered in tissues as evidenced by a large V_d. Fat tissue was the major site of sequestration. The relative concentrations of THC in the various tissues were similar to those of lipophilic compounds, suggesting that the distribution of THC is mainly controlled by its physicochemical properties (Leuschner et al., 1986).

Δ1-tetrahydrocannabinol (Δ1-THC) and its major metabolite (7-hydroxy-Δ1-THC) could rapidly penetrate the CNS after i.v. administration in mice with a t_{max} value of 20 min (Gill and Jones, 1972). 14C-Δ8-tetrahydrocannabinol intramuscular (i.m.) injection resulted in a C_{max} value of 0.06% of the administered dose in the brain. After chronic administration (for two weeks), the cannabinoid level in the brain remained unchanged which shows the efficiency of BBB in limiting the uptake and accumulation of cannabinoids (Nahas et al.,

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1981).

Intravenous administration and smoking of THC in 11 healthy subjects resulted in similar plasma profiles whereas oral administration caused low and irregular plasma levels, indicating the slow and erratic oral absorption of THC. The systemic availability of THC after smoking and oral use was found to be 18±6% and 6±3%, respectively. The time courses of plasma levels and clinical "high" were similar for i.v. injection and smoking, with the prompt onset and steady decline over a 4 h period. The appearance of "high" lagged behind the rise in plasma levels, demonstrating that brain concentration of THC increased as plasma levels declined. After oral administration, the onset of THC effects was much slower and lasted longer, but occurred at much lower plasma concentrations than i.v. administration and smoking (Ohlsson et al., 1980).

It has been found that the instant uptake and unlimited storage of THC by neutral fat could limit its plasma concentration. Slow release of THC from fat tissue can lead to a rate-limited uptake of this compound into the brain which would protect brain function from prolonged exposure to THC (Nahas, 2001).

Cannabidiol

Cannabidiol, a non-psychoactive cannabinoid, is the major non-CB1/CB2 receptor ligand derived from *Cannabis* (Showalter et al., 1996) and possesses immunomodulatory activities (Kozela et al., 2011). Cannabidiol could ameliorate clinical signs, retard disease progression, and reduce axonal damage and inflammatory infiltration in the spinal cord (Kozela et al., 2011). It has been shown that topical administration of cannabidiol cream lowers axonal loss and demyelination in the spinal cord and decreases the expression of inflammatory cytokines such as TNF-α, and IFN-γ (Giacoppo et al., 2015). Pretreatment of mice with cannabidiol could remarkably increase AUC and $t_{1/2}$ values of all THC metabolites in the brain, with a modest increase in AUC of THC (Bornheim et al., 1995). However, these increases in pharmacokinetic parameters of THC were found to be too small in human studies (Nadulski et al., 2005).

Naphtoquinones

Plumbagin

This bicyclic naphthoquinone is found in the roots of *Plumbago zeylanica* L. Plumbagin can control EAE severity and demyelination via suppressing the production of IFN-γ and IL-17 and inhibiting the differentiation of Th1 and Th17 (Jia et al., 2011). It has been reported that Plumbagin can prevent the differentiation, maturation, and function of dendritic cells (DCs) derived from human monocytes and restricts the expression of Th1- and Th17-polarizing cytokines in mature DCs (Zhang et al., 2014).

The oral bioavailability of plumbagin was evaluated in rats and found to be 38.7±5%. Due to its high lipophilicity, plumbagin was widely distributed in the body tissues creating a third, deep compartment model with slow elimination. This study also indicated that 49% of plumbagin was excreted through feces following a single oral dose in mice (Hsieh et al., 2006). Interestingly, the elimination half-life of plumbagin from chitosan-based plumbagin microspheres was 22-fold higher than free plumbagin (Mandala Rayabandla et al., 2010).

Phenolic acids

Salvianolic acid B

This major water-soluble component of *Salvia miltiorrhiza* Bunge has several notable treating effects including anti-oxidant and anti-inflammatory. Intraperitoneal administration of salvianolic acid B after EAE onset can decrease disease severity by downgrading inflammatory infiltration into the CNS, limiting astrogliosis, and restricting peripheral Th1 responses (Dong et al., 2016). The oral bioavailability of salvianolic acid B was calculated to be 2.3% in rats (Wu et al., 2006). After oral administration, this compound can distribute into the brain, indicating its potency to cross the BBB. However, its concentration was below the quantification limit, suggesting that salvianolic acid B might bind to some target proteins in the brain. This compound was rapidly absorbed and readily distributed in the liver, kidney, lung, and spleen. The amount of the salvianolic acid B in tissues was in the descending order of kidney, liver, lung, and spleen and was too small to detect at 150 min. This represents that there was no long-term accumulation in the four tissues studied (Xu et al., 2007).

Caffeic acid phenethyl ester

This compound is an active component of honeybee propolis. It can reduce EAE severity by decreasing inflammatory infiltration, suppressing glial activation, inhibiting ROS (Ilhan et al., 2004), and increasing regula-

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tory T cells (Treg) in the CNS (Zhou et al., 2020). The pharmacokinetic profile of caffeic acid phenethyl ester (CAPE) was evaluated in rats after i.v. administration of 5, 10, or 20 mg/kg CAPE. The AUC was increased in a ratio higher than the increase in doses from 5 to 20 mg/kg. Cl_{TOT} values for CAPE ranged from 42.1 to 172 mL/(min kg) and decreased as the dose increased. Similarly, by dose increase, V_d value, ranging from 1.55 to 5.21 L/kg, decreased. The $t_{1/2}$ which ranged from 21.2 to 26.7 min was dose-independent (Wang et al., 2009). CAPE could pass through the BBB after intraperitoneal injection of 10 μmol/kg for five consecutive days in rats (Barros Silva et al., 2013). No pharmacokinetics data for oral administration of this compound was available.

Coumarins

Osthole

The anti-inflammatory, neuroprotective and immuno-modulatory activities of this compound were previously shown in diseases like hepatitis and arthritis (Li et al., 2014). Chen et al. have demonstrated that osthole can delay EAE onset, improve its clinical severity, reduce nerve growth factor (NGF), and inhibit IFN-γ expression (Chen et al., 2010). In another study, transplantation of bone marrow-derived neural stem cells (BM-NSCs) transplantation plus osthole pre-treatment suppressed EAE and showed significant advantages over conventional BM-NSC therapy (Gao et al., 2014). After oral administration of the root of *Angelica dahurica* (Hoffm.) Benth. & Hook.f. ex Franch. & Sav. in rats, the plasma concentration of osthole and other eight coumarins present in the plant was very low (Zhao et al., 2013). In a rat model of Alzheimer's disease, following intracerebroventricular injection of β-amyloid, the rats were treated with osthole (12.5 or 25 mg/kg, i.p.) for 14 successive days. The results showed that osthole treatment significantly improved cognitive impairment and protected hippocampal neurons of rats with Alzheimer's disease. This suggests that osthole could cross BBB to reach the brain (Dong et al., 2012).

The pharmacokinetic profile of osthole after oral administration in cerebral ischemia hypoperfusion and normal rats was studied by Zhou et al. Significant differences in pharmacokinetic parameters in two groups were observed. Following oral administration, osthole could be detected in plasma after 5 min in both normal and cerebral ischemia hypoperfusion rats, with $t_{1/2}$ of 4.94 h and 8.57 h, respectively. The plasma levels of osthole in cerebral ischemia hypoperfusion rats were consistently higher compared to the normal animals and showed a lower clearance and a longer mean retention time (Zhou et al., 2011).

Alkaloids

Huperzine A

Huperzine A, isolated from *Huperzia serrata* (Thunb.) Trevis., is a sesquiterpene alkaloid with EAE ameliorating activities. This compound can down-regulate mRNA levels of proinflammatory chemokines and up-regulate anti-inflammatory cytokines like IL-4 and IL-10 in the spinal cord and as a result reduce inflammation (Wang et al., 2012). The pharmacokinetics of huperzine A was investigated in twelve healthy volunteers after administration of a single dose of 0.4 mg in tablet form. Huperzine A appeared in the plasma 5-10 min after oral administration and reached the peak concentration at 58.33±3.89 min. Pharmacokinetic parameters of huperzine A could be described by two-compartment open model. The mean values of $t_{1/2\alpha}$ and $t_{1/2\beta}$ were 21.13±7.28 min and 716.25±130.18 min respectively, showing a biphasic profile with rapid distribution and slower elimination rate (Li et al., 2007). It was found that i.n. administration of huperzine A significantly increased its distribution into the rat brain tissues, especially into cerebrum and hippocampus in comparison to i.v. and i.g. routs (Tao et al., 2006).

Matrine

Matrine can decrease inflammation and demyelination of EAE by inhibiting the production of proinflammatory cytokines like IL-17, IL-23 (Zhao et al., 2011), IL-6, and TNF-α (Chu et al., 2021). It can improve BBB integrity (Zhang et al., 2013), protect oligodendrocytes against apoptosis (Wang et al., 2019; Zhu et al., 2016), alleviate astrogliosis (Ma et al., 2020), and induce the production of immunomodulatory molecules like IL-10, IL-27, and IFN-β (Chu et al., 2020). Until now, various pharmacokinetic studies have been performed for matrine and oxymatrine. It has been reported that, after oral administration of oxymatrine to humans or animals, this compound is converted to matrine by the gastrointestinal tract and liver (Xie et al., 1983). In a study by Wang et al., the plasma levels of oxymatrine and matrine were assayed after oral administration of oxymatrine, matrine,

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and Kushen formula granule (a traditional Chinese medicine) solutions to beagle dogs. The results showed that C_{max} and $AUC_{0-\infty}$ for matrine and oxymatrine were increased after Kushen formula granule (KFG) administration in comparison to oral solutions of oxymatrine and matrin. It can be concluded that other ingredients in the KFG may help the better absorption of oxymatrine and matrine (Wang et al., 2007a).

Berberine

Berberine is isolated from many Berberidaceae species like *Coptis* and *Berberis*. Berberine consumption at the disease onset is effective in reducing the severity and EAE clinical score. Studies have shown that It inhibited the enhanced expression of matrix metallopeptidase 9 (MMP-9) in the brain of EAE mice by improving BBB permeability (Ma et al., 2010). Berberine regulates the differentiation and activation of Th1 and Th17 cells, suppresses IL-6 production (Qin et al., 2010), inhibits gelatinase activity, and decreases laminin degradation (Jiang et al., 2013).

Wang et al. reported that after i.v. administration of *Coptis chinensis* Franch. rhizoma (containing 3 mg/kg of berberine) to rats, berberine passes through BBB and distributes to the hippocampus with $t_{1/2\alpha}$= 0.215 h and a peak concentration of 272 ng/g at 3.67 h. Berberine is rapidly eliminated from plasma ($t_{1/2\beta}$= 1.13 h) while $t_{1/2\beta}$ from the hippocampus is 12.0 h (Wang et al., 2005b).

Sinomenine

Derived from *Sinomenium acutum* (Thunb.) Rehder & E.H.Wilson, sinomenine can improve EAE by lowering the expression levels of IFN-γ and TNF-α in the spinal cord (Zeng et al., 2007a), reducing the production of inducible nitric oxide synthase (iNOS) (Gu et al., 2012), decreasing tissue level of IL-6, IL-18, and IL-17A, and enhancing IL-10 (Kiasalari et al., 2021). As the oral bioavailability of sinomenine has been reported at approximately 80% following a single dose of 90 mg/kg in rats, So, oral administration would be appropriate for sinomenine. After 40 min, sinomenine is extensively distributed in the body tissues. Tissue concentrations decrease in the following order: kidneys, liver, lungs, spleen and heart, brain, and testicles (Liu et al., 2005).

Terpenoids

Thymoquinone

This compound is isolated from the seed oil of *Nigella sativa* L. Thymoquinone administration results in a significant improvement of EAE symptoms by decreasing oxidative stress in the spinal cord (Mohamed et al., 2003). Alkharfy et al. investigated the pharmacokinetic profile of thymoquinone following i.v. (5 mg/kg) and oral (20 mg/kg) administration of this compound in Vole rabbits. Compartmental analysis revealed that $t_{1/2\alpha}$ and $t_{1/2\beta}$ values were approximately 8.9 min and 86.6 min, respectively. The absolute bioavailability of thymoquinone was calculated to be about 58% and its protein binding was more than 99%. These results indicated that after oral administration, thymoquinone undergoes a rapid elimination and a relatively slower absorption (Alkharfy et al., 2015).

β-elemene

Elemene is derived from the ginger plant *Curcuma zedoaria* (Christm.) Roscoe. Elemene is a mixture of α, β, and δ isoforms in which the β isoform is the main compound (Zhang et al., 2010). β-elemene can improve EAE by inhibiting the production of IL-6 and IL-23, preventing the differentiation of Th17 cells, and promoting the expansion of Treg cells (Zhang et al., 2011). The tissue distribution study of elemene after i.g. (200 mg/kg) or i.v. (100 mg/kg) administration in rats revealed that elemene can pass through the BBB; however, higher concentrations of elemene could be detected in the lungs, spleen, and liver (Wu et al., 2009). After a single i.v. administration of β-elemene in rats, the metabolites were mainly eliminated. Cumulative fecal, biliary, and urinary excretion were 0.61%, 0.06%, and 0.003% of the administered dose after 32 h of administration, respectively (Wang et al., 2005a). High protein binding was also observed for β-elemene in rats (Wang and Su, 2000).

Artemisinin

Artemisinin and its analogs are best known for exerting anti-malarial activity, however, it has been shown that they are beneficial in treating immune-related diseases (Yao et al., 2016). It has been shown that SM933 which is a derivative of artemisinin could prevent the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and inhibit the proliferation of encephalitogenic T cells (Wang et al., 2007b). Also, SM934 which is another derivative of artemisinin could

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ameliorate EAE by increasing the differentiation of Treg cells (Li et al., 2013). Oral administration of artemisinin results in rapid and incomplete absorption (mean absorption time: 0.78 h). But as it has been reported, MRT of i.m. administration of artemisinin oil suspension is 3 times higher than that of the oral formulation. However, i.m. and rectal administration of the aqueous artemisinin suspension results in a low and variable serum level which may demonstrate the erratic absorption of this compound (Titulaer et al., 1990). In a double-blind, comparative, parallel-group study by Gordi et al., 77 male and female adults with uncomplicated falciparum were chosen and categorized into 2 groups. The first group received a certain dose of artemisinin and the second group received increasing doses until the fifth day. The final dose was the same as the first group. It was shown that the average parasite clearance time was more for the second group. The concentration of artemisinin in saliva, measured on days 1 and 5, demonstrated that the average oral clearance in the second group was two-fold higher than the first group on day 1. Besides, there were no differences in drug half-lives, demonstrating a saturable first-pass metabolism. The pharmacokinetic parameters were similar in both groups on day 5, however, there was a significant increase in oral clearance from day 1 to 5. It can be concluded that artemisinin may have dose- and time-dependent pharmacokinetics (Gordi et al., 2002).

Triptolide

Triptolide administration can protect against demyelination and inflammation of the CNS by inhibiting the expression of Th2 cytokines in the spinal cord, preventing nuclear translocation of NF-κB (Wang et al., 2008), reducing IFN-γ, and lowering the expression of IL-6 and IL-12 (Chitnis and Khoury, 2003; Powell et al., 1990; Samoilova et al., 1998). However, further medical and clinical applications of this compound are limited due to its toxicity (Hikim et al., 2000; Huynh et al., 2000). LLDT-8, a derivative of triptolide suppresses the production of IL-6 and TNF-α (Zhou et al., 2005; Zhou et al., 2006). This product is lesser cytotoxic than triptolide (Zhou et al., 2005). Shao et al. investigated ADME of triptolide in rats following a single oral or i.v. dose administration. After administration of oral doses (0.6, 1.2, and 2.4 mg/kg), t_{max} was detected to be 15 min and declined rapidly with $t_{1/2\beta}$ from 16.81 to 21.70 min. Triptolide followed the kinetics of the one-compartment model after i.v. administration and showed a high oral absolute bioavailability of 72.08% at the dose of 0.6 mg/kg. This compound was also rapidly distributed and eliminated in all selected tissues (Shao et al., 2007). In one study, after i.g. and i.v. administration of 3H-triptolide to rats, the concentration found in the brain was lower than those observed in the liver, spleen, lung, kidney, intestine, and heart (Shusen et al., 1991). Data on the CNS distribution of triptolide is scarce.

Andrographolide

Andrographolide can decrease the incidence and clinical severity of EAE in the early phase via lowering IFN-γ and IL-2 and reducing the efficiency of DCs maturation (Iruretagoyena et al., 2005), and interfering with NF-κB activation in DCs of EAE mice (Iruretagoyena et al., 2006). The pharmacokinetic profile of andrographolide in rats and human volunteers after oral administration of *Andrographis paniculata* (Burm.f.) Nees extract or fixed combination tablet was investigated by Panossian et al. This compound is quickly and almost entirely absorbed into the blood after oral administration of the extract. However, the bioavailability was reduced four-fold after administration of a ten times higher dose. This may be due to the high protein binding of andrographolide. Prescribing four tablets (equal to 20 mg of andrographolide) to human volunteers resulted in a maximum plasma concentration of 393 ng/mL after 1.5-2 hours and a $t_{1/2}$ of 6.6 h. The calculated steady-state plasma level of this compound after multiple doses of tablets (the normal therapeutic dose regimen is 4 tablets three times a day) was approximately 660 ng/mL which is adequate to demonstrate the anti-platelet-activating factor (PAF) effect (Panossian et al., 2000).

In a recent study, UPLC-ESI/MS method was used to determine the content of andrographolide and its phase one metabolite 14-deoxy-12-hydroxy-andrographolide in the serum of rats. The pharmacokinetic parameters of the metabolite such as distribution and elimination rate constants, $t_{1/2,}$ and MRT, were remarkably less than those of andrographolide after a single i.v. dose of 5 mg/kg. However, the $AUC_{0\text{-}720\ min}$ was 17.71 times higher than that of andrographolide. These results show that the pharmacokinetic profile of andrographolide and its metabolite are significantly different when used intravenously (Yang et al., 2013). After oral administration of

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A. paniculata extract and andrographolide at 133.33 and 100 mg/kg/d, respectively, it was shown that the highest concentration of andrographolide was in the kidneys. The plasma and various tissue concentrations were reduced which may be due to a relatively rapid elimination or distribution of andrographolide from the central compartment (Bera et al., 2014).

Boswellic acids

Boswellic acids are pentacyclic triterpenes being isolated from the gum resin of *Boswellia serrata* Roxb. ex Colebr. Acetylboswellic acids have significantly reduced EAE clinical symptoms in guinea pigs. However, inflammatory infiltration into the CNS was not significantly reduced compared with the control group (Wildfeuer et al., 1998). It has been shown that acetyl-11-keto-β-boswellic acid (AKBA) can decrease the differentiation of Th17 cells *in vitro*, thus, it can be considered a potential therapeutic candidate for treating MS (Stürner et al., 2014). Gerbeth et al. determined the permeability, metabolic stability, and brain availability of six major boswellic acids (BAs) namely 11-keto-β-boswellic acid (KBA), 3-acetyl-11-keto-β-boswellic acid (AKBA), β-boswellic acid (βBA), 3-acetyl-β-boswellic acid (AβBA), α-boswellic acid (αBA), and 3-acetyl-α-boswellic acid (AαBA) *in vitro* and *in vivo*. To study permeability, the Caco-2 model was adapted to physiological conditions by the addition of bovine serum albumin to the basolateral buffer and the use of modified fasted state simulated intestinal fluid (FaSSIF) on the mucosal (apical) side of Caco-2 cell monolayers. The results revealed that the four BAs lacking the 11-keto moiety (βBA, AβBA, αBA, and AαBA) have moderate permeability. βBA and αBA were found to be intensively metabolized after incubation with human and rat liver microsomes. Despite high permeability of KBA and AKBA, their plasma levels were rather low. The extensive metabolism of KBA can explain its low plasma concentration, whereas the great distribution of AKBA in different compartments might be the reason for its extremely low plasma levels. The mean concentration of all six major BAs in rat brain 8 hours after oral administration of 240 mg/kg of *B. serrata* gum resin extracts (BSE) in rats was 11.6 ng/g for KBA, 37.5 ng/g for AKBA, 1066.6 ng/g for βBA, 485.1 ng/g for αBA, 163.7 ng/g for AβBA and 43.0 ng/g for AαBA. The higher brain/plasma ratio of βBA compared to KBA and AKBA indicated a facilitated BBB permeability for βBA. The pharmacological actions of BSE are mainly attributed to BAs lacking the 11-keto group, especially βBA (Gerbeth et al., 2013).

The effects of concomitant food intake on the bioavailability of BAs from a BSE dry extract (BSE-018) have been investigated in a randomized clinical trial. Healthy male volunteers received three capsules containing 786 mg dry extract either in the fasted state or concomitant with a standardized high-fat meal. BA plasma levels were analyzed for up to 60 hours after oral administration. The concomitant administration of the extract with a high-fat meal led to a several-fold increase in AUC as well as peak concentrations of βBA, KβBA, and AKβ-BA when compared to the fasted state. Plasma levels of both AαBA and αBA could only be detected when administered together with the high-fat meal (Sterk et al., 2004).

Saponins

Diosgenin

Diosgenin is used as a precursor for the synthesis of diverse steroidal drugs in the pharmaceutical industry (154). Diosgenin improves EAE by activating the differentiation of oligodendrocyte progenitor cells to mature oligodendrocytes leading to accelerated remyelination (Xiao et al., 2012). Xu et al. developed a LC/ESI/tandem mass spectrometry method to detect diosgenin in the plasma of normal and hyperlipidemic rats 60 hours after a single oral administration of 100 mg/kg. The results demonstrated a higher C_{max} and $t_{1/2}$ and a lower clearance of diosgenin in hyperlipidemic rats (Xu et al., 2009). After oral administration of this compound, the absorbed sapogenin was metabolized extensively and several metabolites were detected in the bile of rats or dogs (Cayen et al., 1979).

Astragaloside IV

Astragaloside IV that is isolated from *Astragalus propinquus* Schischkin ameliorates EAE severity by suppressing cytokine secretion of Th1 and Th17, reducing inflammatory infiltration into the spinal cord, improving demyelination and BBB leakage (He et al., 2013), inhibiting iNOS and inflammatory cytokines (He et al., 2014), modulating the differentiation of autoreactive CD4+ T cells (Yang et al., 2019), and suppressing the maturation and function of DCs (Yang et al., 2020). The

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absolute bioavailability of this compound was reported to be 3.66% after oral administration, which is an important limitation of this route (Du et al., 2005). Intravenous administration of this compound in rats has shown its moderate to fast elimination and limited distribution into the brain (Zhang et al., 2006).

Strategies for improving bioavailability and distribution

Assessing the bioavailability and pharmacokinetic characteristics of natural products can provide necessary data for more rational use of these agents. This study provides comprehensive data on pharmacokinetic aspects of neuroprotective phytochemicals for the treatment of EAE, which is a well-known animal model for studying neurodegenerative disorders especially MS. CNS is highly protected by BBB, a continuous endothelial membrane that controls the penetration of exogenous and endogenous molecules into the brain. BBB permeability of a compound is a crucial predictor for achieving effective CNS concentrations (Jeffrey and Summerfield, 2010). Delivery of natural compounds into the CNS may improve their efficacy and reduce side effects. It has been shown that i.n. administration of interferon-β to rats can bypass BBB and deliver this drug to the sites where demyelination mostly occurs in the CNS. Also, intranasal administration may reduce systemic side effects of anti-EAE drugs due to their decreased concentration in blood and peripheral organs (Ross et al., 2004). Intranasal administration of baicalin phospholipid complex in rats has led to similar results since it could transfer 52.36-100 % of baicalin to the brain via the olfactory pathway. The $AUC_{0\sim480}$ for i.n. administration of BP in the cortex, striatum, and cerebellum was higher in comparison to i.v. administration (Li et al., 2011) indicating an effective CNS delivery of this compound. Therefore, i.n. administration may be a promising approach to transfer natural compounds to the brain. Utilizing nanotechnology may be another effective method to increase CNS delivery of natural compounds since a nano-formulation of curcumin has increased curcumin absorption into the brain (Tsai et al., 2011). Also, plumbagin microspheres (Chandrasekaran and Nagarajan, 1981), curcumin-loaded nanoparticles (Arozal et al., 2021; Tsai et al., 2011), and icariin polymeric micelles (Han et al., 2019) could reduce the elimination of these compounds significantly that may lead to increased pharmacological effects. Another method to improve the bioavailability of natural compounds is to synthesize their prodrugs. As an example, a valine carbamate prodrug of naringenin has shown a higher total AUC value and a C_{max} of 4 times higher in comparison to naringenin alone (Xu et al., 2021). Different used methods for better delivery and improving pharmacokinetic parameters of anti-EAE natural compounds have been summarized in Fig. 1. However, good CNS penetration is not always a key factor for anti-EAE activity. Anti-inflammatory effects are usually due to reducing proinflammatory and inflammatory cytokines, suppressing infiltration into the CNS, and up-regulating anti-inflammatory factors (Mohtashami et al., 2019) which can be achieved by systemic administration. Also, in chronic inflammatory conditions of the CNS such as MS or Alzheimer's disease, a transient or permanent deterioration of BBB may occur. Changes in the BBB which may be disruptive at the histological level or non-disruptive at the molecular level can alter its permeability characteristics (Varatharaj and Galea, 2017). Therefore, inflammation-induced BBB changes should be carefully considered in the pharmacokinetic evaluation of neuroprotective compounds used to treat CNS inflammatory disorders.

Conclusion

Pharmacokinetics describes drug absorption, distribution, metabolism, and excretion. Pharmacokinetic studies are crucial in drug discovery and help researchers to assess the efficacy and toxicity of potential drugs. Bioactive natural products with neuroprotective effects can revolutionize treatment protocols for neurodegenerative diseases like MS, however, the magnitude of the effect of a drug is related to the concentration of that drug at the site of receptors. Considering the results of this study, pterostilbene, sinomenine, thymoquinone, and triptolide have good bioavailability and can be considered as potential anti-EAE/MS compounds for further clinical studies. It should be mentioned that good bioavailability cannot be considered the sole important factor in determining a suitable drug candidate because low bioavailability of drugs can be overcome by i.v. or i.n. administrations or utilizing nanoparticles like liposomes or SLNs. In conclusion, more pharmacological and pharmacokinetic studies on EAE animals and patients with MS are essential to determine the potential

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anti-MS drug candidates for further clinical studies.

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Conflict of interest

The authors declare that there is no conflict of interest.

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