Insights into the potential benefits of triphala polyphenols toward the promotion of resilience against stress-induced depression and cognitive impairment

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ABSTRACT

In response to environmental challenges, stress is a common reaction, but dysregulation of the stress response can lead to neuropsychiatric disorders, including depression and cognitive impairment. Particularly, there is ample evidence that overexposure to mental stress can have lasting detrimental consequences for psychological health, cognitive function, and ultimately well-being. In fact, some individuals are resilient to the same stressor. A major benefit of enhancing stress resilience in at-risk groups is that it may help prevent the onset of stress-induced mental health problems. A potential therapeutic strategy for maintaining a healthy life is to address stress-induced health problems with botanicals or dietary supplements such as polyphenols. Triphala, also known as Zhe Busong decoction in Tibetan, is a well-recognized *Ayurvedic* polyherbal medicine comprising dried fruits from three different plant species. As a promising food-sourced phytotherapy, triphala polyphenols have been used throughout history to treat a variety of medical conditions, including brain health maintenance. Nevertheless, a comprehensive review is still lacking. Here, the primary objective of this review article is to provide an overview of the classification, safety, and pharmacokinetics of triphala polyphenols, as well as recommendations for the development of triphala polyphenols as a novel therapeutic strategy for promoting resilience in susceptible individuals. Additionally, we summarize recent advances demonstrating that triphala polyphenols are beneficial to cognitive and psychological resilience by regulating 5-hydroxytryptamine (5-HT) and brain-derived neurotrophic factor (BDNF) receptors, gut microbiota, and antioxidant-related signaling pathways. Overall, scientific exploration of triphala polyphenols is warranted to understand their therapeutic efficacy. In addition to providing novel insights into the mechanisms of triphala polyphenols for promoting stress resilience, blood brain barrier (BBB) permeability and systemic bioavailability of triphala polyphenols also need to be improved by the research community. Moreover, well-designed clinical trials are needed to increase the scientific validity of triphala polyphenols' beneficial effects for preventing and treating cognitive impairment and psychological dysfunction.

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1. Introduction

Changes in diet and lifestyle habits, as well as an increase in life expectancy, are contributing to an increase in chronic diseases, including psychiatric disorders, which have evolved into major global public health issues that seriously threaten human health and sustainable socioeconomic development (Sun et al., 2022). Especially, when chronic or improperly managed, stress is known to negatively affect people's health and well-being on a global scale (Cenat et al., 2021). The concept of resilience has been receiving increasing attention in recent years, the ability to maintain normal psychological and physical functioning and avoid serious mental illness despite extreme stress or trauma (Sher, 2019). However, evidence is mounting that overexposure to a wide range of stressors such as sleep deprivation induces a pathophysiological response in the body that may precipitate or worsen medical conditions of a wide variety (Lopresti, 2020). Indeed, 75%–90% of diseases are closely associated with chronic psychosocial stress, including depression, mood disorders, and a variety of other stress-related conditions (Liu et al., 2017). Resilience under stressful conditions is poorly understood (Unno et al., 2018), and it is imperative to identify and target the mechanisms that contribute to this resilience.

Intriguingly, natural medicines, especially traditional Chinese medicine, have long been used in clinical practice to prevent and treat myriad diseases such as neurological disorders (Sharma et al., 2022). In addition, it is pertinent to note natural products or nutritional compounds that play an influential role in preventing or slowing cognitive decline, such as acetyl-L-carnitine and caffeine (Fisicaro et al., 2021; Pennisi et al., 2020). A recent study reported that daily consumption of mocha coffee was associated with better cognition and mood status in non-smokers subjects with mild vascular cognitive impairment (Fisicaro et al., 2022). Importantly, as a result of their extensive pharmacological effects, lower cost, higher bioavailability, and less toxicity, natural plant ingredients such as polyphenols are gaining increasing attention in the scientific community (Bernstein et al., 2021; Shah et al., 2021; W. Wang et al., 2023).

Triphala, also known as Zhe Busong decoction in Tibetan, is a well-recognized *Ayurvedic* polyherbal medicine comprising dried fruits from three different plant species in equal proportions, namely *Phyllanthus emblica* Linn. (also known as *Emblica officinalis* Gaertn. in the *Ayurvedic* pharmacopeia of India, Family *Euphorbiaceae*), *Terminalia bellerica* (Gaertn) Roxb. (Family *Combretaceae*), and *Terminalia chebula* Retz. (Family *Combretaceae*) (Peterson et al., 2017; Sharma et al, 2020; Sharma et al., 2019). Triphala originated in India, which was first recorded in the *Ayurvedic* text *Charaka Samhita* (X. Li et al., 2022). Thereafter, as a complementary and alternative medicine for chronic diseases, triphala was introduced to China via the Silk Road, and is now extensively used throughout East Asia as a complementary and alternative medicine (Tiwana et al., 2020). Nowadays, it is the most common basic prescription in Tibetan medicine. Moreover, triphala has been described by traditional healers as a powerful health tonic that purifies, rejuvenates, and balances the body's elements (Ahmed et al., 2021). As a multipurpose therapeutic drug, modern studies have revealed that triphala has many pharmacological activities, as shown in Fig. 1.

Among the many phytochemicals found in triphala are phenolic acids, ascorbic acid, flavonoids, alkaloids, and carbohydrates (Jantrapirom et al., 2021). In general, polyphenols are the main components of triphala. Interestingly, polyphenols have recently attracted major attention as one of the most attractive molecules for drug discovery and application in the pharmacological setting (Ullah et al., 2022; Wu et al., 2021). Furthermore, a growing number of scientific publications have been published about triphala in recent years. Researchers have been encouraged by the health benefits of triphala and their characteristic polyphenols for preventing diseases and promoting health, as evidenced by their publication record (Fig. 2). In spite of this, there has not been a comprehensive review of recent experimental studies and the mechanisms of action of triphala polyphenols toward the promotion of resilience against stress-induced depression and cognitive impairment. This review focuses on triphala, providing information on its classification,
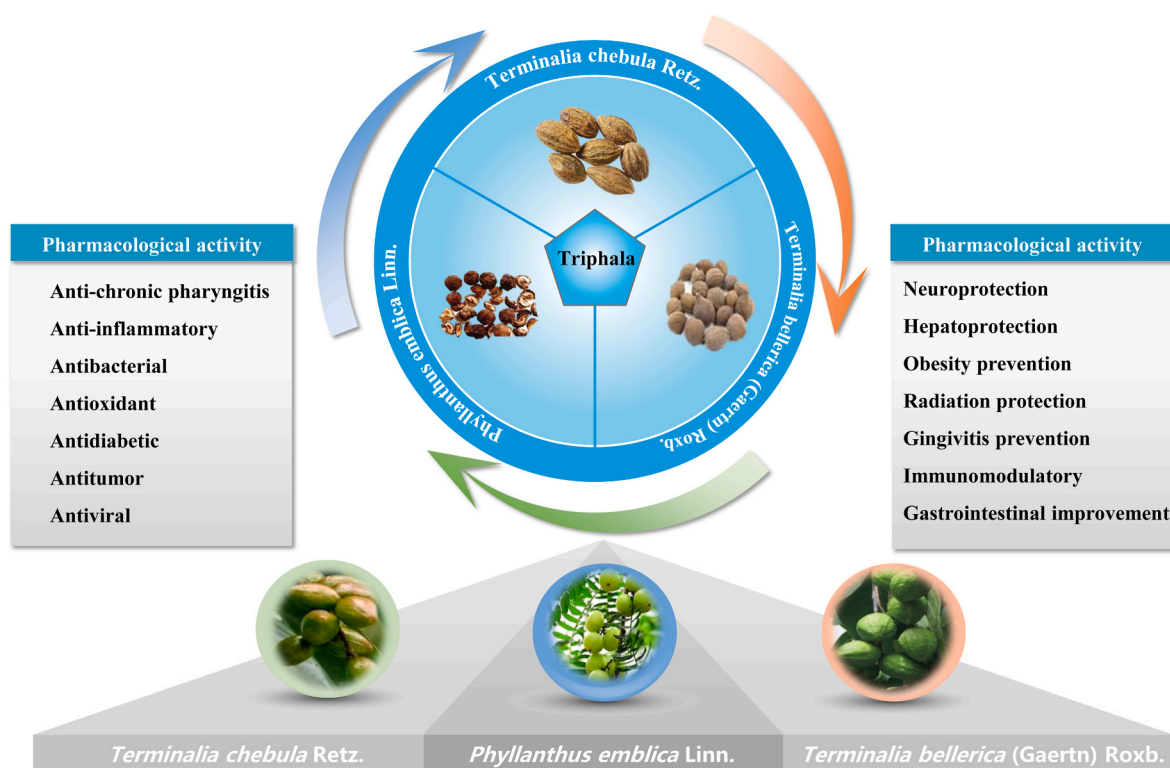
Fig. 1. Overview of the composition and pharmacological action of triphala. Triphala is a well-recognized *Ayurvedic* polyherbal medicine that consists of dried fruits from three different plant species that possess many pharmacological activities, such as antioxidant, anti-inflammatory, and neuroprotective properties.
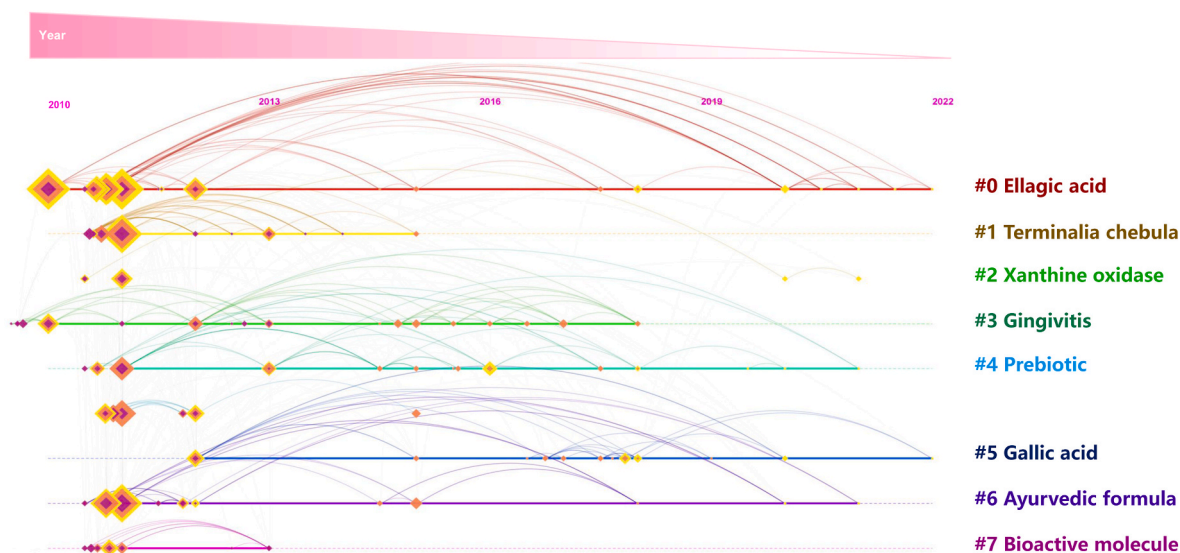
Fig. 2. Timeline and clustering view of triphala polyphenols, which visually shows the phased hotspots and development directions of research on triphala polyphenols from the time dimension.

safety, pharmacokinetics, and health benefits, as well as providing a strategic framework for developing triphala polyphenols as therapeutic agents to therapeutically promote resilience and prevent psychological dysfunction and cognitive impairment.

2. Methodology

PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/), Embase (https://www.embase.com/), and Scopus (https://www.scopus.com/) databases were all used to perform this literature review. The following search terms were entered in data collection: triphala, polyphenols, flavonoids, non-flavonoids, tannins, phenolic acids, aromatic acids, resilience, stress, depression, cognitive impairment, pharmacological action, and molecular mechanism. In most cases, English-published research papers and original full-text articles were selected and analyzed until December 2022. As shown

in Fig. 3, all steps involved in selecting the required literature were outlined in the flowchart.

3. Safety of triphala polyphenols

Triphala is composed of three medicinal and food homologous herbs that have been extensively tested in animal experiments and clinical trials and have shown no adverse effects. In addition, polyphenols, the main components of triphala, are also recognized as safe natural ingredient agents. Acute and subacute oral toxicity studies of triphala on rats were conducted by some scholars, and the maximum tolerated dosage of 5000 mg/kg body weight was found to be safe, and importantly, this group conducted a clinical trial and indicated that a dose of 2500 mg/d of triphala for 28 d was considered to be safe when administered to 10 male and 10 female healthy volunteers (Arpornchayanon et al., 2022). Additionally, another clinical trial evaluating
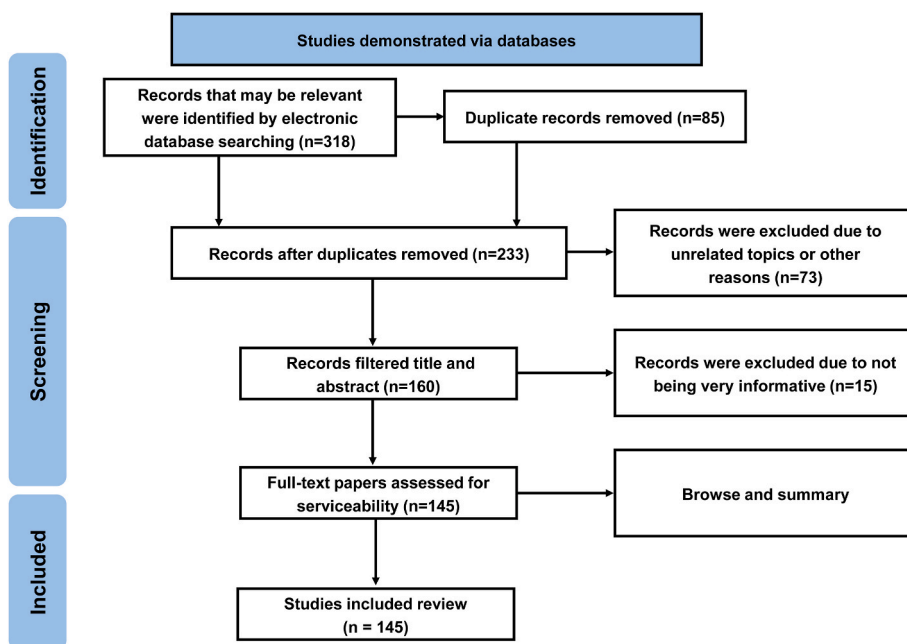

Fig. 3. The stages of selecting data for inclusion in existing research are illustrated in a flow chart (n = number of literature reports).

triphala ethanolic extract found no adverse effects in healthy volunteers taking 1050 mg/d orally for 14 d (Phetkate et al., 2012). All of the evidence suggested that the major polyphenols in triphala, like corilagin and ellagic acid, exert almost no toxicity on normal tissues. Notably, the amounts of ellagic acid in foods have been accepted as existing food additives in Japan, and it has primarily been accepted as an antioxidant with no toxicological data or limitations on its concentration utilization (W. Wang et al., 2022).

Industrially, triphala is processed using reflux extraction in accordance with current pharmaceutical production standards. Furthermore, it is well known that the types of preparation methods for triphala polyphenols affect the polyphenol composition. Particularly, the total polyphenol amounts may be affected by the extraction temperature. Triphala and related plants have previously been extracted using common hot and cold extraction methods, but the extraction temperature affects the chemical composition of the plant (Ran et al., 2021). Actually, macromolecular substances like chebulagic and chebulinic acid could be hydrolyzed into certain small molecules like gallic acid at higher temperatures (Fig. 4). For instance, heat- and reflux-mediated extractions of the *Phyllanthus emblica* Linn. component of triphala showed hydrolytic tannin conversion, such as gallic acid, suggesting that different polyphenols may be produced by different extraction techniques. Remarkably, a relatively low concentration of gallic acid is safe and effective for most cells, whereas a relatively high concentration is toxic (Borchers and Pieler, 2010; Tanaka et al., 2020). Therefore, although the existence of various preparation processes, the preferred extraction method should be selected based on the amounts of polyphenols to meet the consistency requirements and ensure the safety of triphala polyphenols.

4. Chemical properties and classification of triphala polyphenols

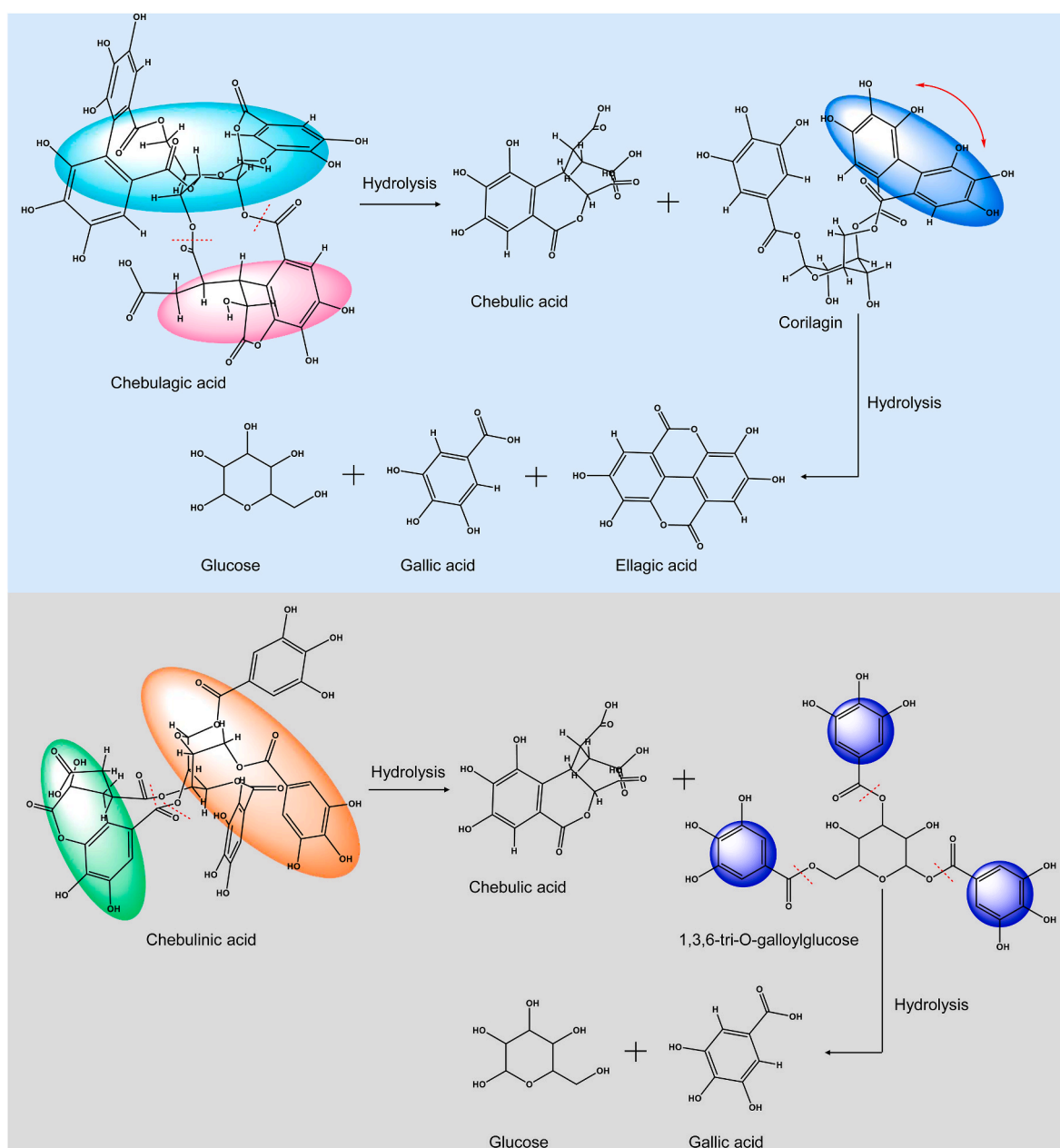Triphala is rich in nutritious and functional ingredients. Particularly,

Fig. 4. Schematic diagram of the hydrolysis of macromolecular substances like chebulagic acid and chebulinic acid into certain small molecules like gallic acid.

many research groups, including our laboratory, focused on the main bioactive chemical components in triphala and some characteristic polyphenols were identified (Table 1). Several polyphenols were demonstrated in triphala, mainly including flavonoids, tannins, phenolic acids and glycosides (W. Wang et al., 2019). Additionally, other saponins, aromatic acids and carbohydrates, amino acids, and fatty acids are also abundant in triphala. In fact, polyphenols can conveniently be categorized as non-flavonoids and flavonoids based on the fact that they are characterized by at least two benzene rings and one or more hydroxyl substituents. Hence, non-flavonoids in triphala are tannins, phenolic acids, and aromatic acids. Some representative components of polyphenols in triphala are shown in Fig. 5. Among these triphala polyphenols, several of these compounds are widely distributed throughout the plant kingdom and have been reported to possess anti-oxidant, anti-apoptosis, anti-inflammatory, and neuroprotective properties (Oesterle et al., 2021).

5. Pharmacokinetics of triphala polyphenols in the body

It is the chemical structure of triphala polyphenols that determines its pharmacokinetics, absorption capacity, and urinary excretion in humans. Generally, a small amount of digestion and absorption is carried out in the stomach after polyphenols are partially deconjugated in the mouth (Fig. 6) (Rajha et al., 2022). Meanwhile, an extensive amount of polyphenol is extensively metabolized in the intestine through deglycosylation, methylation, and glucuronidation *etc.* (Luca et al.,

2020; Mithul Aravind, Wichienchot, Tsao, Ramakrishnan and Chakkaravarthi, 2021). Actually, a significant percentage of macromolecular polyphenols consumed cannot be absorbed by the upper gastrointestinal track (Luca et al., 2020). By contrast, these macromolecular polyphenols can be metabolized in the colon into phenolic metabolites and low molecular weight compounds by the gut microbiota (N. Zhou et al., 2020), which are more readily absorbed by the gastrointestinal epithelium (Fig. 6). Among the polyphenols in triphala, chebulagic acid, corilagin, and chebulinic acid monomers are relatively well-assimilated polyphenols, whereas a comparison is made between gallic acid and ellagic acid, which show poor absorption, low bioavailability, and easy saturation. There is evidence for chebulinic and chebulagic acids being present in tissues that are abundant in blood (C_{max}, peak concentration) is 605.8 ± 35.6 ng/mL and 1327.1 ± 118.6 ng/mL, respectively), and the kidney had the highest concentrations (chebulinic acid, 462.6 ± 138.5 ng/g and chebulagic acid, 1651.7 ± 167.7 ng/g), followed by the heart, liver, spleen and lung (Lu et al., 2019). Furthermore, the gastrointestinal tract absorbs a significant amount of gallic acid, which is then distributed primarily in the kidneys, followed by other organs (X. Chen et al., 2018). An LC-MS/MS study on plasma pharmacokinetics of oral gallic acid in rats found that the parameters of the mean time to peak concentration (T_{max}, peak time), C_{max}, and terminal elimination half-life ($T_{1/2}$) are 1.5 h, 0.83 μg/mL, and 2.56 h, respectively (Yu et al., 2018). There is also evidence that the gut microbiome modulates the bioconversion and bioavailability of bioactive phenolic metabolites obtained from oral consumption of polyphenol-rich botanical supplements,

Table 1

Physicochemical and pharmacokinetic parameters of triphala polyphenols. The information is from TCMSP (https://old.tcmsp-e.com/tcmsp.php). Adapted from (Ru et al., 2014).

Molecule Name	MW	AlogP	Hydrogen bond donor (Hdon)	Hydrogen bond acceptor (Hacc)	Oral bioavailability (OB, %)	Caco-2 permeability (Caco-2)	Blood-brain barrier (BBB)	Drug-likeness (DL)
Phyllanemblinin A	616.47	1.42	9	17	72.44	−2.28	−3.14	0.33
Chebulic acid	356.26	−0.26	6	11	72	−1.4	−1.75	0.32
Quinic acid	191.18	−3.07	4	6	55.92	−1.79	−4.38	0.06
(+)-catechin	290.29	1.92	5	6	54.83	−0.03	−0.73	0.24
Sennoside E	524.5	3.91	6	9	50.69	−0.74	−1.56	0.61
Quercetin	302.25	1.5	5	7	46.43	0.05	−0.77	0.28
Phyllaemblicin A	582.61	−1.19	6	14	45.63	−2.37	−2.62	0.77
Ellagic acid	302.2	1.48	4	8	43.06	−0.44	−1.41	0.43
Kaempferol	286.25	1.77	4	6	41.88	0.26	−0.55	0.24
Teresautalic acid	166.24	1.42	1	2	41.42	0.94	1.26	0.09
Emblicanin B	780.53	1.89	12	22	37.08	−2.22	−3.6	0.07
β-sitosterol	414.79	8.08	1	1	36.91	1.32	0.99	0.75
Luteolin	286.25	2.07	4	6	36.16	0.19	−0.84	0.25
Chebulinic acid	956.72	1.83	13	27	33.48	−3.24	−4.28	0.13
Phyllanthin	418.58	4.11	0	6	33.31	1.06	0.57	0.42
Gallic acid	170.13	0.63	4	5	31.69	−0.09	−0.54	0.04
(−)-epicatechin	290.29	1.92	5	6	28.93	−0.03	−0.58	0.24
Brevifolin	196.22	1.27	1	4	27.19	0.82	0.77	0.06
Progallin A	198.19	1.23	3	5	25.61	0.33	0.11	0.06
Epigallocatechin	306.29	1.65	6	7	24.18	−0.22	−0.82	0.27
Arjunolic acid	488.78	4.36	4	5	23.22	−0.32	−1.01	0.72
Phyllanemblinin D	518.42	−2.16	9	16	21.95	−3.09	−3.64	0.69
Myristic acid	228.42	5.46	1	2	21.18	1.07	0.99	0.07
Palmitic acid	256.48	6.37	1	2	19.3	1.09	1	0.1
Punicalagin	1084.75	3	17	30	18.17	−3.44	−4.46	0
Maslinic acid	472.78	5.46	3	4	15.54	0.1	−0.55	0.74
Phyllanemblinin E	518.42	−2.16	9	16	14.94	−3.01	−3.84	0.69
Melissic acid	452.9	12.75	1	2	13.22	1.31	0.9	0.49
Emblicanin A	782.55	2.21	12	22	12.36	−2.4	−3.17	0.22
Phyllanemblinin C	1254.94	1.17	19	36	12.08	−4.34	−4.98	0.04
Phyllaemblicin B	744.77	−2.94	9	19	9.3	−3.45	−3.77	0.35
Phyllanemblinin F	518.42	−2.16	9	16	4.11	−2.94	−3.51	0.69
Sennoside C	848.82	0.1	12	19	3.99	−3.54	−4.8	0.09
Phyllaemblicin C	876.9	−4.18	11	23	3.04	−4.48	−5.03	0.16
Punicafolin	938.7	3.38	15	26	3.01	−2.85	−3.91	0.12
Phyllanemblinin B	634.49	0.9	11	18	3.01	−2.36	−3.31	0.47
Pentagalloylglucose	940.72	3.69	15	26	3.01	−3.08	−4.17	0.21
Corilagin	634.49	0.9	11	18	3.01	−1.79	−2.58	0.44
Chebulagic acid	954.7	1.52	13	27	3.01	−3.79	−4.44	0.03
Gallocatechin	306.29	1.65	6	7	2.26	−0.27	−1.11	0.27

Non-flavonoids

① Ellagic acid
② Gallic acid
③ Chebulinic acid
④ Corilagin
⑤ Phyllanthin
⑥ Chebulic acid
⑦ Phyllaemblicin A
⑧ Phyllanemblinin A
⑨ Punicalagin
⑩ Chebulagic acid

Flavonoids

① Epicatechin
② Catechin
③ Kaempferol
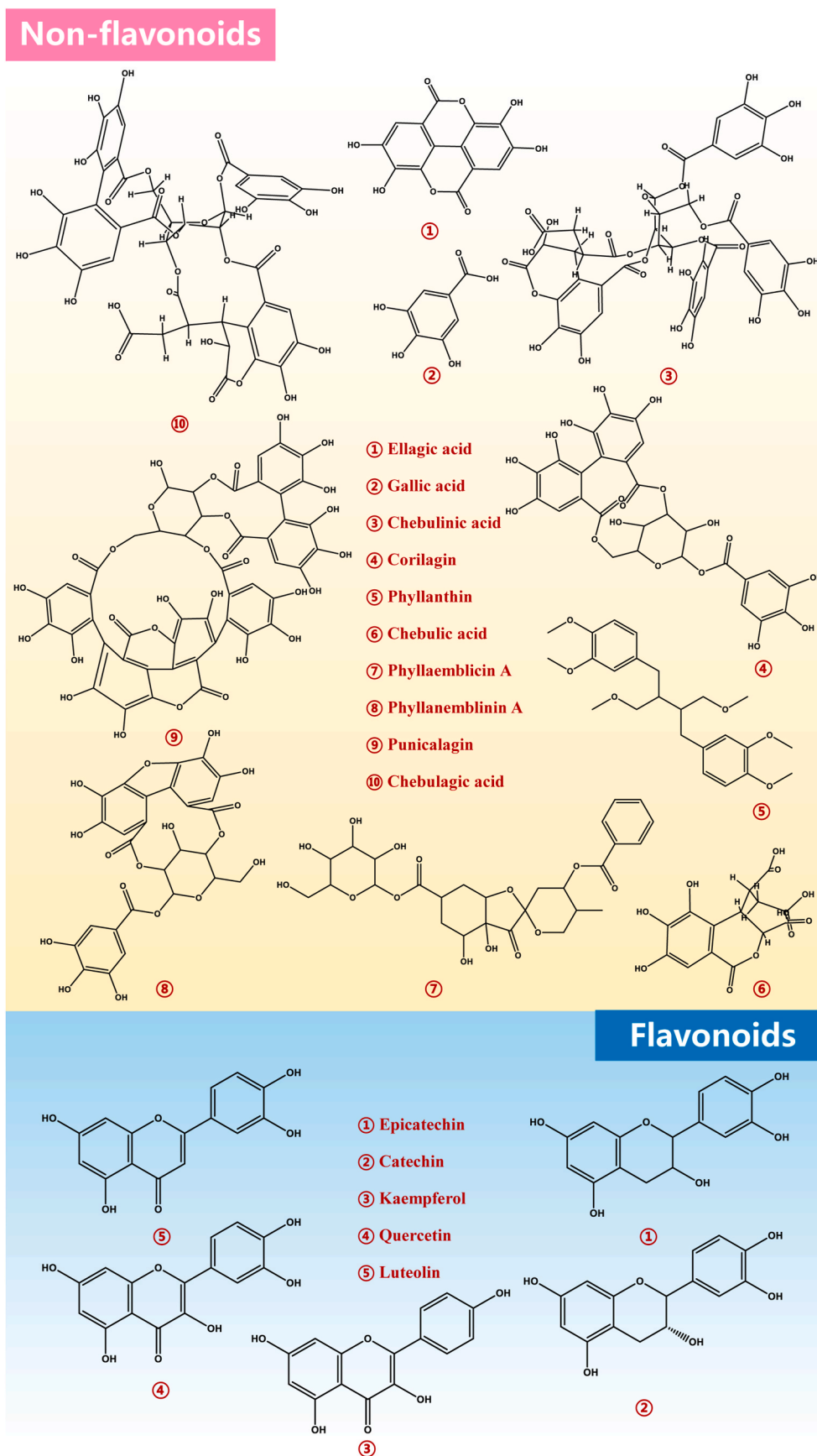④ Quercetin
⑤ Luteolin

Fig. 5. Classification and some representative components of triphala polyphenols. Triphala polyphenols are primarily divided into flavonoids and non-flavonoids. Some representative components are shown in the figure.
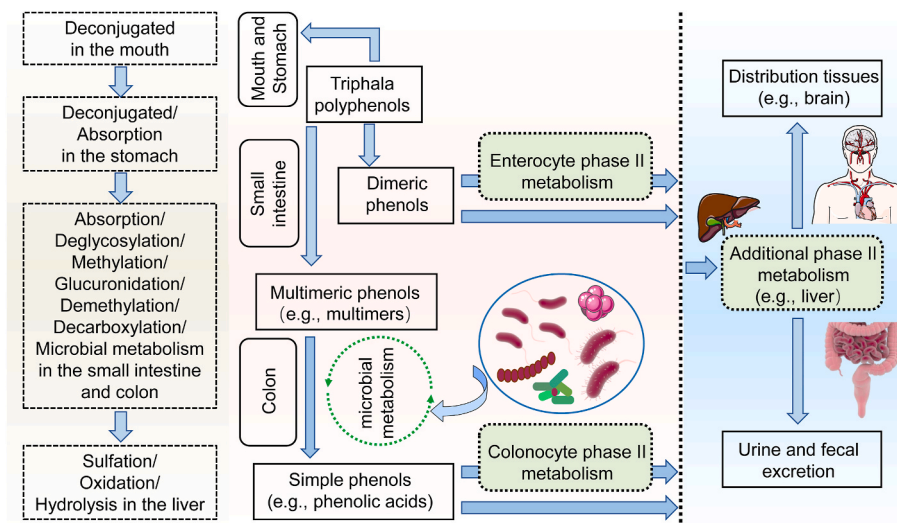
Fig. 6. Digestion and absorption of triphala polyphenols in the human body.

particularly phenolic acids such as ellagic acid (D'Amico et al., 2021). There is a very small amount of ellagic acid in the peripheral tissues and systemic circulation, and the C_{max} value ranges from 0.1 μmol/L to 0.4 μmol/L, whereas its metabolites urolithins and conjugates can reach concentrations that are as high as micromolar in the human body (Gupta et al., 2021). Additionally, a metabolic hydrolysis of macromolecules ellagitannin-rich triphala like punicalagin in the gastrointestinal tract could result in the release of free ellagic acid that can either be absorbed in the body or undergo a massive metabolic process to produce urolithins. It should also be mentioned that the blood brain barrier (BBB) prevents many potential therapeutic macromolecular agents from entering the brain, and is a major obstacle to drug delivery into the brain (Mignani et al., 2021). But happily, certain small molecules of triphala polyphenols like epicatechin can cross the BBB and reach the central nervous system (Shimazu et al., 2021). Detailed pharmacokinetics of triphala polyphenols information such as oral bioavailability, drug-likeness, intestinal epithelial permeability was obtained from Traditional Chinese Medicine Systems Pharmacology (TCMSP) (https://old.tcmsp-e.com/tcmsp.php) (Ru et al., 2014), as outlined in Table 1.

6. Triphala polyphenols toward the promotion of resilience against stress-induced depression

As one of the major mental disorders, depression is characterized by a triad of symptoms, including low mood, anhedonia, and low energy levels (McCarron et al., 2021). There is no doubt that depression disorders are highly chronic illnesses that have a significant adverse impact on an individual's functioning and well-being as well as on their family (Monroe and Harkness, 2022). In addition, depression has become a public health concern due to its high prevalence, mortality, suicide rates, and recurrence rates, and it has become a significant economic burden on society as well (Disease, G. B. D. et al., 2018). The problem is that there is no effective proven strategy to prevent depression caused by stress. In fact, despite the fact that a large number of antidepressant drugs that act on the central monoaminergic system are available for the treatment of depression, in particular 5-hydroxytryptamine (5-HT) and noradrenergic synaptic neurotransmissions, such as benzodiazepines, and these drugs provide improvement in the clinical condition of patients, their slow onset of action and adverse effects are major concerns (Sharma et al., 2018). Henceforth, there is an urgent need for new, more selective therapeutics that target stress-induced depression's underlying mechanisms. Additionally, in view of the fact that stress-related anxiety and depression often coexist in patients (Dolan et al., 2022), it would be beneficial to develop drugs that act as both anti-depressants and

anti-anxiety agents. Hence, the promotion of resilience against stress-induced depression and anxiety is a promising line of research using bioactive and bioavailable triphala polyphenols. As a matter of fact, there is compelling clinical evidence to suggest that polyphenols, such as luteolin, gallic acid, and quercetin, are effective in relieving and treating depression and anxiety in patients (Ferianec et al., 2020; Taliou et al., 2013). Exploration of the recent advances in the use of triphala polyphenols in stress-induced depression and anxiety has revealed several common mechanisms, including the receptors of 5-HT and brain-derived neurotrophic factor (BDNF), that alter neuronal and synaptic functions (Fig. 7, Table 2).

6.1. Non-flavonoids

Gallic acid is not only the most abundant in triphala, but also one of the most abundant phenolic acids in the plant kingdom (Ahmed et al., 2021; Bai et al., 2021; Pereira et al., 2020). Actually, gallic acid is nontoxic to mammals at pharmacological doses and exhibits potent neuroprotective effects (Al Zahrani, El-Shishtawy and Asiri, 2020). A study based on histopathology in rats found that gallic acid administration ameliorated anxiety and depression in the behavioral tests, as well as altered cellular loss in the CA1, CA2, CA3 (CA, cornu ammonis) and dentate gyrus (DG) hippocampal subdivisions (Moghadas et al., 2016). Ulteriorly, Samad and colleagues suggested that gallic acid has protective effects on anxiety and depression-like behaviors in male rats via its antioxidant potential (Samad et al., 2019). Mechanistically, Salehi et al. found that gallic acid treatment significantly reduced elevated levels of serum and brain malondialdehyde (MDA) and increased total antioxidant capacity to ameliorate anxiety-like behaviors induced by chronic restraint stress (Salehi et al., 2018). Homoplastically, Chhillar and Dhingra examined gallic acid treatment in Swiss young male albino mice subjected to chronic unpredictable mild stress, showing that gallic acid demonstrated antidepressant-like effects in stressed mice as a result of its antioxidant activity and its ability to reduce oxidative-nitrosative stress and inhibit monoamine oxidase-A (MAO-A), as well as decreased hypothalamic-pituitary-adrenal axis hyperactivity as indicated by a decrease in plasma corticosterone levels (Chhillar and Dhingra, 2013). Interestingly, a new study by Chinese scientists showed that gallic acid inhibits the expression of the P2X7 receptor in the hippocampus, spinal cord, and dorsal root ganglion, which can alleviate comorbid visceral pain and depression (Wen et al., 2022). Additionally, a preclinical study has demonstrated that gallic acid increases levels of both serotonin and catecholamine in synaptic clefts of the central nervous system in a dual antidepressant way, and the
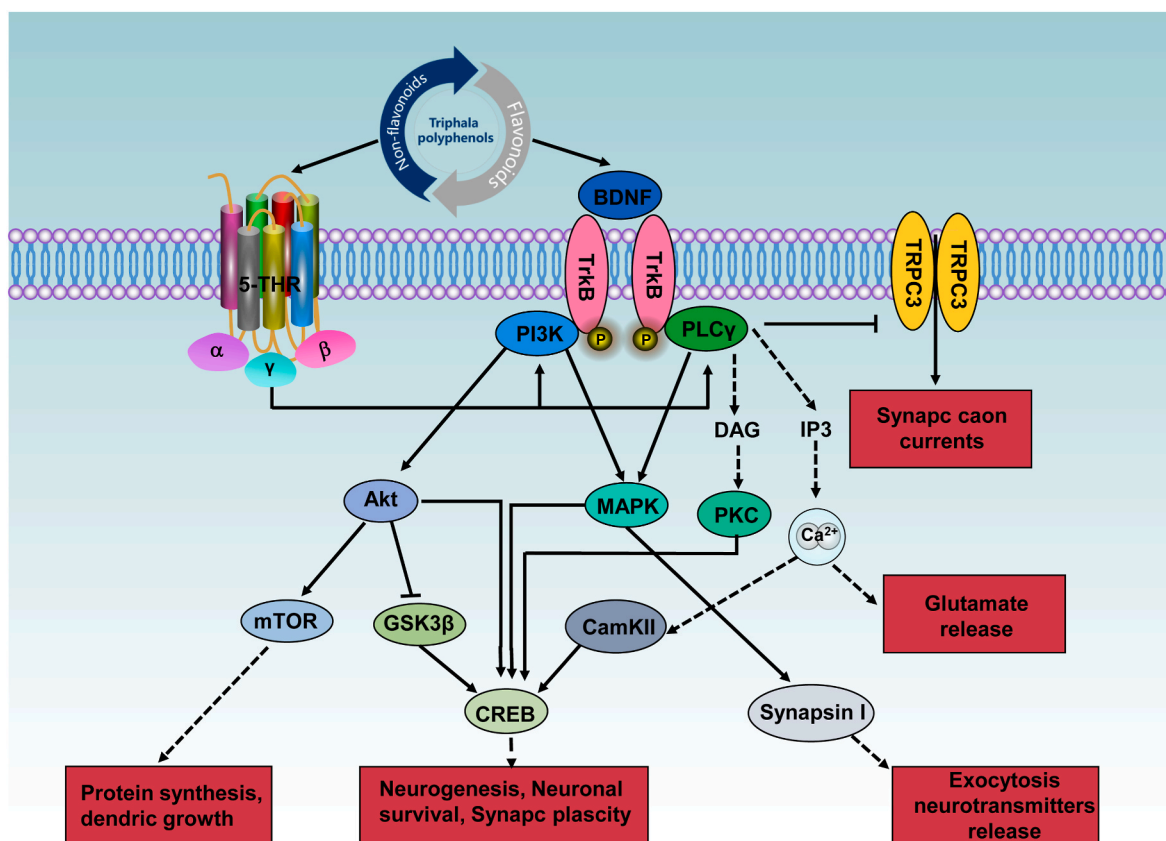
Fig. 7. Triphala polyphenols improve stress-induced depression and anxiety by activating the receptors of 5-HT and BDNF, which in turn alter neuronal and synaptic functions. 5-HT, 5-hydroxytryptamine; Akt, protein kinase B; BDNF, brain-derived neurotrophic factor; CamKII, Calcium/Calmodulin Dependent Protein Kinase II; CREB, cAMP responsive element binding protein; DAG, diacylglycerol; GSK3β, glycogen synthase kinase 3β; 5-HTR, 5-hydroxytryptamine receptor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide-3-kinase; PLCγ, phospholipase C γ; TrkB, tyrosine receptor kinase B; TRPC3, transient receptor potential canonical subfamily 3.

effects of gallic acid are further mediated by the modulation of alpha adrenergic receptors, 5-HT2A/2C and 5-HT3 serotonergic receptors, and dopaminergic receptors D1, D2, and D3 (Can et al., 2017).

Corilagin, as a gallotannin, is a major active component of *Phyllanthus emblica* Linn. in triphala (W. Wang et al., 2019). It is also isolated as one of the main polyphenols in certain ethnopharmacological plants, such as *Phyllanthus amarus* Schumm & Thonn. (Family *Euphorbiaceae*) and *Phyllanthus tenellus* Roxb. (Family *Phyllanthaceae*) (Chopade and Sayyad, 2015; Hou et al., 2020). Scientists from Brazil discovered that corilagin acts as selective inhibitors of the enzymes prolyl oligopepti-dase (POP) and acetyl cholinesterase (AChE), particularly, a dose-dependent inhibitor of POP (IC$_{50}$ value is 19.7 ± 2.6 μg/mL) (Dos Santos et al., 2021). Additionally, this study also found that corilagin had a moderate ability to pass through the phospholipid membrane (presenting effective permeability of 1.26×10^{-7} cm/s and membrane retention of 1.8%), which indicates that corilagin can cross the BBB and reach the central nervous system in order to act directly against brain POP. Analogously, there is also evidence that corilagin has potential clinical applications in the treatment of anxiety, and the mechanism of action may be due to its interaction with the γ-aminobutyric acid (GABA) type A receptor (Chopade et al., 2021).

Consistent with the above observations of gallic acid and corilagin, ellagic acid has a very strong effect on improving stress-induced depression and anxiety. Using the forced swimming test and tail sus-pension test, Girish et al. found that ellagic acid exhibited an antide-pressant effect in mice, but no effect on locomotor activity, suggesting that ellagic acid interacts with the monoaminergic system rather than the opioid system to produce its effects (Girish et al., 2012). Subse-quently, this research team further verified that ellagic acid plays an

anxiolytic effect by involving in the GABAergic neurotransmitter system (Girish et al., 2013). In addition, a possible role for excitatory amino acids in depression pathophysiology has also been proposed. Increased hippocampal glutamatergic activity via N-Methyl-D-aspartic acid (NMDA) receptors has been implicated in the pathophysiology of depression and affects hippocampus plasticity. It was determined that ellagic acid has an antidepressant-like effect in mice through mediating the NMDA-nitric oxide (NO) pathway (Lorigooini et al., 2019). There is a correlation between depression and a reduction in brain and plasma concentrations of BDNF, which may be used to treat mental disorders such as depression. There is evidence that ellagic acid's antidepressant-like effects are mediated by an increase in BDNF levels in the hippocampus of mice (Bedel et al., 2018). Actually, there has been a proliferation of research showing that the pathophysiology of human depression goes beyond neuroendocrine function to include inflamma-tion and oxidative stress injury as well. A recent study based on serum metabolomics found that ellagic acid attenuated chronic unpredictable mild stress (CUMS)-induced depression by regulating the neurotrans-mitter levels like BDNF and 5-HT, suppressing the inflammation by inhibiting tumor necrosis factor α (TNF-α) and iterleukin (IL)-1β or promoting IL-10 expression in the serum, and protecting the integrity of the hippocampal tissue (Huang et al., 2020). Mechanistically, Ferreres et al. verified the anti-depressant effect of ellagic acid and its derivatives in vitro experiments and found they have strong anti-oxidant and that anti-cholinesterase (AChE, butyrylcholinesterase and MAO-A) activities (Ferreres et al., 2013).

In fact, phyllathin, chebulagic acid, chebulic acid, and chebulinic acid are also widely enriched in triphala (Akter et al., 2022), possessing multiple biological benefits that might contribute to the promotion of

Table 2
Animal behavioral tests representing triphala polyphenols toward the promotion of resilience against stress-induced depression.

Triphala polyphenols	Animal model	Behavioral tests	Molecular mechanisms	Reference
Non-flavonoids				
Gallic acid	UCMS in male Swiss albino mice	FST and SPT	↓MAO-A; ↓MDA; ↑CAT; ↓plasma corticosterone	Chhillar and Dhingra (2013)
Gallic acid	CRS in male BALB/c mice	EPM and OFT	↓Serum and brain MDA; ↑total antioxidant capacity	Salehi et al. (2018)
Ellagic acid	UCMS in male C57BL/6 mice	SPT, TST, and FST	↑BDNF; ↑5-HT; inflammatory cytokines levels (↓TNF-α, ↓IL-1β, ↑IL-10)	Huang et al. (2020)
Flavonoids				
Quercetin	UCMS in male Swiss albino mice	TST, FST, and OFT	↑5 HT; ↑SOD; ↑GSH; ↓Glutamate; ↓TNF-α; ↓IL-6	Khan et al. (2019)
Quercetin	UCMS in male Swiss albino mice	EPM, OFT, SPT, and PAST	↓TBARS; ↓NO; ↑total Thiol; ↑CAT; ↓IL-6; ↓TNF-α; ↓IL-1β; ↓COX-2	(V. Mehta et al., 2017)
Quercetin	UCMS in male Sprague-Dawley rats	SPT	antioxidant enzymes (↑Cu–Zn, ↑SOD,↑CAT,↑GPx); ↓MAO; ↑GSH; ↓TNF-α; ↓IL-1β	(Guan et al., 2021)
Quercetin	UCMS in male ICR mice	SPT, OFT, and TST	Promoting adult hippocampal neurogenesis via FoxG1/CREB/BDNF signaling pathway	(Z. X. Ma et al., 2021)
Quercetin	UCMS in male Swiss albino mice	TST, FST, and PAST	Modulating hippocampal insulin signaling and neurogenesis; ↓insulin; ↓IR; ↑GLUT-4; ↑DCX	(V. Mehta et al., 2017)
Quercetin	Immobilization stress in male Swiss albino mice	Light-dark activity test, EPM, FST, MWM	Antioxidant enzymes (↑SOD,↑CAT,↑GPx); ↓AChE; ↑Ach; ↑5-HT; ↑5-HIAA	Samad et al. (2018)
Quercetin	UCMS in male Kunming mice	OFT, SPT, and FST	Upregulation of hippocampal PI3K/Akt/Nrf2/HO-1 signaling pathway	(Guan et al., 2021)
Quercetin	CSDS in male mice	OFT, SPT, FST, and EPM	Inhibiting astrocyte reactivation	(J. Zhang et al., 2020)
Luteolin	Noise in male Kunming mice	SPT, OFT, TST, and FST	Improving neuroinflammation and synaptic Plasticity Impairments	Cheng et al. (2022)
Kaempferol	Contextual fear conditioning in Wistar rats	EPM	Inhibition of fatty-acid amide hydrolase	Ahmad et al. (2020)
Epicatechin	Chronic mild stress in male C57BL/6 mice	SPT and OFT	↑Muscle kynurenine aminotransferases	Martinez-Damas et al. (2021)
Epicatechin	Stress in male C57BL/6 mice	OFT and EPM	↑Hippocampal monoamine and BDNF	Stringer et al. (2015)
Catechin	UCMS in male Sprague Dawley rats	SPT and FST	↑CAT; ↑GSH; ↑SOD	Rai et al. (2019)

5-HIAA, 5-hydroxyindole acetic acid; 5-HT, 5-hydroxytryptamine; ACh, acetylcholine; AChE, acetylcholine esterase; Akt, protein kinase B; BDNF, brain-derived neurotrophic factor; CAT, catalase; CRS, chronic restraint stress; CSDS, chronic social defeat stress; COX-2, cyclooxygenase-2; CREB, cAMP responsive element binding protein; DCX, doublecortin; EPM, elevated plus maze; FST, forced swim test; FoxG1, forkhead box G1; GLUT-4, glucose transporter 4; GPx, glutathione peroxidase; GSH, glutathione; HO-1, heme oxygenase 1; IL-10, interleukin-10; IL-1β, interleukin-1β; IL-6, interleukin-6; IR, insulin receptor; MAO, monoamine oxidase; MAO-A, monoamine oxidase-A; MDA, malondialdehyde; MWM, Morris water maze; NO, nitric oxide; Nrf2, nuclear factor-E2-related factor 2; OFT, open filed test; PAST, passive avoidance step-through task; PI3K, phosphatidylinositol3-kinase; SPT, sucrose preference test; SOD, superoxide dismutase; TST, tail suspension test; TBARS, thiobarbituric acid-reactive substances; TNF-α, tumor necrosis factor α; UCMS, unpredictable chronic mild stress.

resilience against stress-induced depression. According to Tao et al., phyllatin mitigates epileptic convulsions and kindling associated post-ictal depression in mice by balancing excitatory glutamate and inhibitory GABA molecules in the brain as well as by inhibiting the activation of the nuclear factor kappa-B (NF-kB)/Toll-like receptor 4 (TLR4) pathway in the brain (Tao et al., 2020). Song and coworkers demonstrated that chebulinic acid is a potent neuroprotectant via inhibiting reactive oxygen species (ROS) production, Ca^{2+} influx, and phosphorylation of mitogen-activated protein kinases (MAPKs), as well as reducing the ratio of Bcl-2-assaciated X protein (Bax) to B-cell lymphoma-2 (Bcl-2), which contribute to glutamate-induced neuronal cell death and oxidative stress injury (Song et al., 2018). Coincidentally, chebulagic acid and chebulinic acid have been shown to have the ability to suppress ferroptosis by regular antioxidant pathways, including iron chelation and ROS scavenging (Yang et al., 2021). An in vitro-study was performed to determine the neuroprotective properties of chebulagic acid, and results indicated that this compound increased autophagy in human neuroblastoma SH-SY5Y cells via the main control factors of Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK), mammalian target of rapamycin, Beclin-1, and microtubule-associated protein 1 light chain 3 (LC3) (Kim et al., 2014).

6.2. Flavonoids

Luteolin, also called 3´,4´,5,7-Tetrahydroxyflavone, belongs to flavonoids which play an extremely potent neuroprotective activity (Kou et al., 2022). Studies have confirmed that luteolin has strong anxiolytic and antidepressant effects (Achour et al., 2021; Gadotti and Zamponi, 2019). A previous study has shown that luteolin has antidepressant-like

effects in mice, partly due to the suppression of endoplasmic reticulum stress (Ishisaka et al., 2011). Similarly, a latest study also indicated that luteolin ameliorates depression-like behaviors by preventing endoplasmic reticulum stress to suppress microglial activation in the brain (Tana and Nakagawa, 2022). According to Cheng and colleagues, luteolin administration protects against noise-induced depression and other mental disorders by improving synaptic plasticity and neuroinflammation in the brain (Cheng et al., 2022). Like the flavone luteolin, its glycoside luteolin-7-O-glucuronide also elicits anti-stress and antidepressant effects. Recently, a team from Korea reported that luteolin-7-O-glucuronide mitigates depression-like behavior and stress coping in a sleep deprivation stress model by activating the BDNF signaling pathway (Ryu et al., 2022).

One of the most common plant flavonoids, quercetin (3,3′,4′,5,7-pentahydroxyflavone), has been found to reduce anxiety and depressive behavior in rodents. In a study carried out on mice, quercetin was found to prevent the impairment of antioxidant enzymes, regulate 5-HT and cholinergic neurotransmission, produce an antianxiety effect, antidepressant effect, and enhance memory following a 2-h immobilization period (Samad et al., 2018). The antidepressant effects of quercetin were also studied by Khan et al. using a mouse model of CUMS-induced depression. They concluded quercetin had antidepressant-like effects by enhancing antioxidant, anti-inflammatory, excitotoxic (glutamate) levels and enhancing 5-HT levels, resulting in antidepressant-like effects (Khan et al., 2019). In the same study, Guan et al. found quercetin to be antidepressant in a rat model of depression induced by UCMS, and that quercetin regulates serum elements through the inhibition of inflammation, reduction of oxidative stress, and regulation of neurotransmitter systems (Guan et al., 2021). A great deal of information regarding the

mechanisms leading to the development of stress-mediated neurological complications remains unresolved. The comorbidity of oxidative stress and neuroinflammation in the brain, however, has been demonstrated. Specifically, oxidative stress and neuroinflammation interactions in the hippocampus impair neuronal plasticity to a significant degree. The study conducted by Mehta et al. revealed that quercetin alleviates the oxidative and inflammatory stress in the hippocampal area of mice inflicted with CUMS to prevent depressive-like behavior (Mehta et al., 2017). Meanwhile, this team further found that quercetin treatment was effective in alleviating stress-mediated behavioral dysfunction by modulating hippocampal insulin signaling (lowered insulin and insulin receptor expression and significantly enhanced glucose transporter 4) and neurogenesis (enhanced doublecortin expression) in the brain (Mehta et al., 2017). According to Guan et al., quercetin has been shown to reduce depression in CUMS mice by upregulating hippocampal nuclear factor-E2-related factor 2 (Nrf2) and inhibiting inducible nitric oxide synthase, thus restoring balance between oxidative and antioxidant activity and controlling the inflammatory response in the central nervous system (Guan et al., 2021). Prominently, the activated microglia of the brain play an instrumental role in the pathogenesis of depression, which release inflammatory cytokines into the extracellular milieu, carry out neurotoxic effects on surrounding neurons, and secrete inflammatory cytokines into the extracellular milieu. Researchers have studied the mechanisms underlying quercetin's antidepressant activity using electrophysiological and magnetic-activated cell sorting techniques, and quercetin was shown to enhance neuronal activity in the medial prefrontal cortex and hippocampus and improve behavioral performance by inhibiting microglial and astrocyte responses to stress by improving neuronal activity (J. Zhang et al., 2020). Ulteriorly, the latest research has demonstrated quercetin to protect neurons by inhibiting mtROS-mediated activation of the NOD-like receptor protein 3 (NLRP3) inflammasome in microglia through mitophagy, hence providing a potential new therapeutic intervention for stress-induced depression (Han et al., 2021). Intriguingly, neurogenesis has been proposed as a potential mechanism of antidepressant action. A study in vivo suggested that quercetin exerts its antidepressant effects by promoting adult hippocampal neurogenesis through the forkhead box G1 (FoxG1)/cAMP responsive element binding protein (CREB)/BDNF signaling pathway (Z. X. Ma et al., 2021). Additionally, an estrogen-mediated hormone regulator, estrogen receptor of some type, plays a crucial role in protecting against depression. In an article made by Wang et al., the authors proposed quercetin had significant improved estrogen receptor $\alpha^{-/-}$-induced hippocampal dysfunction antidepressant effects via BDNF/tyrosine receptor kinase B (TrkB)/protein kinase B (AKT)/extracellular regulated protein kinases 1/2 (ERK1/2) (G. Wang et al., 2021).

It is of note that kaempferol, known chemically as 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one, is capable of exerting beneficial effects on depression and anxiety. Some studies have demonstrated that kaempferol and other flavonoids like quercetin have shown some anxiolytic activity in studies conducted on male C57BL/6 mice or Swiss albino mice (Aguirre-Hernandez et al., 2010; Grundmann et al., 2009; Vissiennon et al., 2012). Anxiolytic properties of kaempferol have been demonstrated in vivo and in vitro by Ahmad and collaborators. Therefore, in vivo results demonstrated that kaempferol facilitated the extinction of aversive memories along with a reduction of anxiety induced by stress using contextual fear conditioning and elevated plus maze. The in-vitro test revealed that kaempferol can inhibit fatty acid amide hydrolase (IC$_{50}$: 1.064 μM), thus regulating the action time of the endocannabinoid molecular system, regulating complex circuits to take an influential part in anxiety-like states (Ahmad et al., 2020).

Catechin also widely derived from natural sources belongs to a class of flavanols that has been proven to have extensive biological activities including antidepression and antianxiety (Mehta et al., 2021). CUMS-induced depression in rats was studied in India by a research team, and catechin was found to reverse depression by reducing oxidative stress (Rai et al., 2019). Catechin administration improved depression and anxiety-like behaviors in rats by modulating the central noradrenergic system, according to another study from the Republic of Korea (Lee et al., 2013). In the depression model of mice plasma, Geng et al. found catechin to be metabolized primarily by glucuronidation and methylated glucuronidation, and suggested that catechin may be an effective antidepressant candidate targeting the melatonin receptors (Geng et al., 2019).

Epicatechin is an isomer of catechin, which is collectively referred to as catechin compounds together with catechin gallate, epicatechin gallate, epigallocatechin, and epigallocatechin gallate (EGCG) (Borges, Ottaviani, van der Hooft, Schroeter and Crozier, 2018). It has been demonstrated that epicatechin is capable of crossing the BBB and may have a direct effect on neurons and supporting structures (Shimazu et al., 2021). Evidence has implicated that epicatechin mitigates depression and anxiety (Bernatova, 2018). In a murine model exposed to mild chronic stress, Mexican researchers found that epicatechin treatment can induce resilience to depression-like behavior (Martinez-Damas et al., 2021). Importantly, it was indicated that chronic epicatechin administration reduces anxiety in mice by increasing hippocampal monoamine oxidase-A levels and BDNF levels, but does not affect pattern separation in mice (Stringer et al., 2015). EGCG is a polyphenolic catechin. EGCG has been demonstrated to alleviate depressive symptoms in rats by increasing 5-HT levels in the hippocampus and is helpful in regaining lost body weight in depressed rats by protecting intestinal structure (G. Li et al., 2020). Particularly, a pilot study conducted by a Spanish research team suggested that EGCG and coconut oil alleviate multiple sclerosis patients' state of anxiety and functional abilities (Platero et al., 2020). Abdelmeguid et al. recently investigated the antidepressant action of EGCG in mice exposed to CUMS, and demonstrated that the effect of EGCG on depression is related to down-regulation of serum IL-1, up-regulation of BDNF mRNA in the hippocampus, and reduction of lesions in CA3 neurons (Abdelmeguid et al., 2022).

7. Triphala polyphenols toward the promotion of resilience against stress/sleep deprivation-induced cognitive impairment

Sleep is a state of immobility and hypo-responsiveness that renders animals immobile (Figorilli et al., 2021). Sleep facilitates the elimination of metabolic waste products from the brain that accumulate during wakefulness, as demonstrated by countless clinical and experimental evidence (Anafi et al., 2019). In reality, sleep functions as a resilient plastic state that consolidates previously acquired information and prioritizes network activity for optimal brain function, regardless of pathological conditions (Lanza et al., 2022). Unfortunately, insufficient sleep or sleep deprivation deleteriously affects the health of individuals, especially cognitive performance (Mason et al., 2021). There is a noticeable decline in cognitive performance even after just one night of sleep deprivation, defined as less than five uninterrupted hours of sleep (Stout et al., 2021). The prevalence of sleep deprivation in the American adult population has recently been declared a common condition (Gonzalez and Tyminski, 2020). Furthermore, shift workers, including medical professionals, are highly susceptible to sleep deprivation (Shriane et al., 2020). Sleep deprivation or loss impairs cognitive functions, including attention, executive functioning, and risk-taking behaviors (Y. Ma et al., 2020). However, the biological basis for these effects is not entirely understood. Until now, despite considerable advances in pharmacotherapy, more effective therapeutic interventions exist for preventing, halting or healing cognitive impairment caused by sleep deprivation remain limited. Consequently, it is vital to investigate the molecular and cellular effects of sleep deprivation in an effort to find more effective treatments or measures to counteract these impacts. Polyphenols are widely regarded as potential agents that can improve cognitive impairment especially through modulating signaling pathways related to inflammation, oxidative damage, autophagy, and

apoptosis (Arruda et al., 2020). More precisely, recent advances in the application of triphala polyphenols in stress/sleep deprivation-induced cognitive impairment revealed the main common mechanism of antioxidant-related signaling pathways (Fig. 8).

7.1. Non-flavonoids

Derived from natural phytochemicals have been found to be robust efficacious and non-toxic in treating stress and sleep-related disorders (Hu et al., 2018). Prevailingly, it has been demonstrated that polyphenols have various biological activities related to physiological resilience to cognitive deficits, including modulation of synaptic plasticity, inhibition of oxidative stress injury and inflammatory pathways, as well as promotion of neurogenesis (Caruso et al., 2022; Sharma et al, 2020a). Polyphenolic compounds are increasing in popularity for their potential to attenuate cognitive deterioration and prevent the occurrence of detrimental neuropathology in the brain (Caruso et al., 2022). The promotion of resilience against sleep deprivation-induced cognitive impairment is another promising line of investigation using bioactive and bioavailable triphala polyphenols. Alagan and collaborators have isolated bioactive compounds from *phyllanthus amarus*, including corilagin, ellagic acid, gallic acid, and phyllanthin, for which the rodents
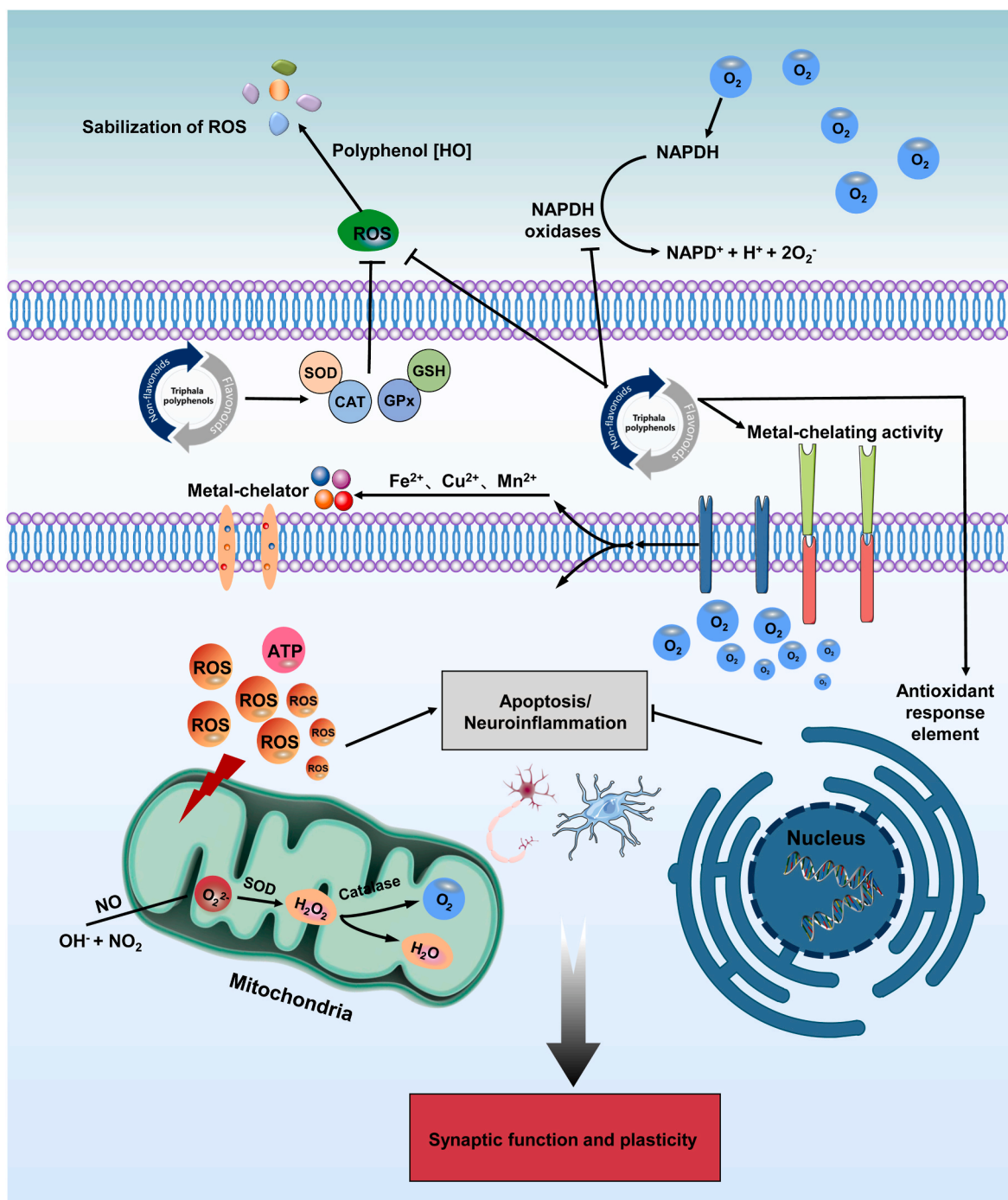

Fig. 8. Triphala polyphenols play a key role in the promotion of resilience against stress-induced cognitive impairment through the activation of antioxidant-related signaling pathways. ATP, adenosine-triphosphate; CAT, catalase; GPx, glutathione peroxidase; GSH, glutathione; ROS, reactive oxygen species; SOD, superoxide dismutase.

were effectively protected from memory deficits (Alagan et al., 2019). Specifically, a great deal of natural products and enriched foods containing corilagin and ellagic acid are available as nutraceuticals and are used to prevent cognitive decline owing to their excellent biological activities in neurodegenerative disorders (W. Wang et al., 2022) For example, previous reports showed that both corilagin and ellagic acid can improve cognitive function in rodents (Farbood et al., 2019; Tong et al., 2016). Studies from our laboratory have shown that corilagin and ellagic acid derived from triphala provide effective protection against sleep deprivation-induced hippocampus-dependent memory impairment, as assessed by novel object recognition, novel object location, and morris water maze tests. Moreover, corilagin and ellagic acid improved memory consolidation and was associated with an increase in dendritic spine density and the number of hippocampal neurons, as well as a decrease in oxidative stress damage and inflammation. As one of the triphala polyphenols, the macromolecule ellagitannin punicalagin also showed strong neuroprotective effects. It was confirmed that punicalagin could ameliorate spatial learning and memory impairments by activating AMPK/peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α)/Nrf2 signaling pathway (Cao et al., 2020). Furtherly, Nasehi and collaborators found that punicalagin showed a tendency of restoring the memory impairment following 24 h of total sleep deprivation using the passive avoidance test in male rats (Nasehi, Mohammadi-Mahdiabadi-Hasani, Zarrindast and Zarrabian, 2021).

Further, polyphenols' biological characteristics are determined largely by their bioavailability, which is heavily influenced by the gut microbiota (Sharma et al, 2020b). Macromolecule polyphenols are therefore broken down by the gut microbiota into low-molecular-weight phenolic metabolites and modified polyphenol conjugates and phenolic acids that can be more readily absorbed (Sorrenti et al., 2020). Increasingly, researchers generally agree that the gut microbiota plays a vital part in promoting the effects of polyphenol-rich diets on cognitive function and resilience (Horn et al., 2022). A team of researchers from the United States has confirmed the existence of bioavailable phenolic metabolites that can restore cognitive function impaired by sleep deprivation (Frolinger et al., 2019). What seems certain is that triphala-derived polyphenols like chebulinic acid and ellagic acid can be converted into bioactive metabolites such as urolithins by the human microbiota (Olennikov et al., 2015; Tarasiuk et al., 2018). Importantly, Punicalagin is also an abundant bioactive compound in triphala. Empirical studies have shown that punicalagin can improve cognitive decline or stress-induced cognitive impairment and anxiety (Cao et al., 2020; Xu et al., 2022). Mohammad Nasehi et al. found that punicalagin has a tendency of restoring the cognitive impairment following 24 h of sleep deprivation in male wistar rats by the passive avoidance test (Nasehi et al., 2021). As a hydrolyzable tannin, punicalagin is the precursor of ellagitannin, which is capable of being hydrolyzed spontaneously into ellagic acid in living organisms. In turn, ellagic acid may be converted into urolithins by the gut microbiota. Furthermore, studies have shown that urolithins can also further ameliorate memory deficits. Some recent studies have shown that urolithin A and urolithin B effectively improve cognitive deficits by inhibiting apoptosis, promoting the survival of neurons, and triggering neurogenesis (P. Chen et al., 2021; Gong et al., 2019). Taken together, these evidences were exciting especially in view of the fact that triphala polyphenols may play a key role in the promotion of resilience against stress/sleep deprivation-induced cognitive impairment through gut microbiota (Fig. 9).

7.2. Flavonoids

There is evidence that stress impairs neuronal functioning, alters insulin signaling, and negatively affects behavioral functioning, which are closely associated with cognitive impairment. According to Vineet Mehta and colleagues, quercetin ameliorates stress-induced memory impairment by reducing insulin resistance and increasing hippocampal glucose transporter 4 levels independently of insulin receptor expression, thus preventing neuronal damage to the regions of the brain responsible for memory (Mehta et al., 2017). Several other researchers have confirmed quercetin's ability to improve cognitive impairment caused by stress, arguing that quercetin works by clearing senescent cells to alleviate chronic unpredictable stress-induced cognitive deficits (Lin et al., 2021). In fact, many scholars have carried out corresponding research on quercetin or its derivatives to improve cognitive impairment caused by sleep deprivation. Brazilian scientists identified quercetin's protective mechanism as its ability to reduce oxidative stress caused by
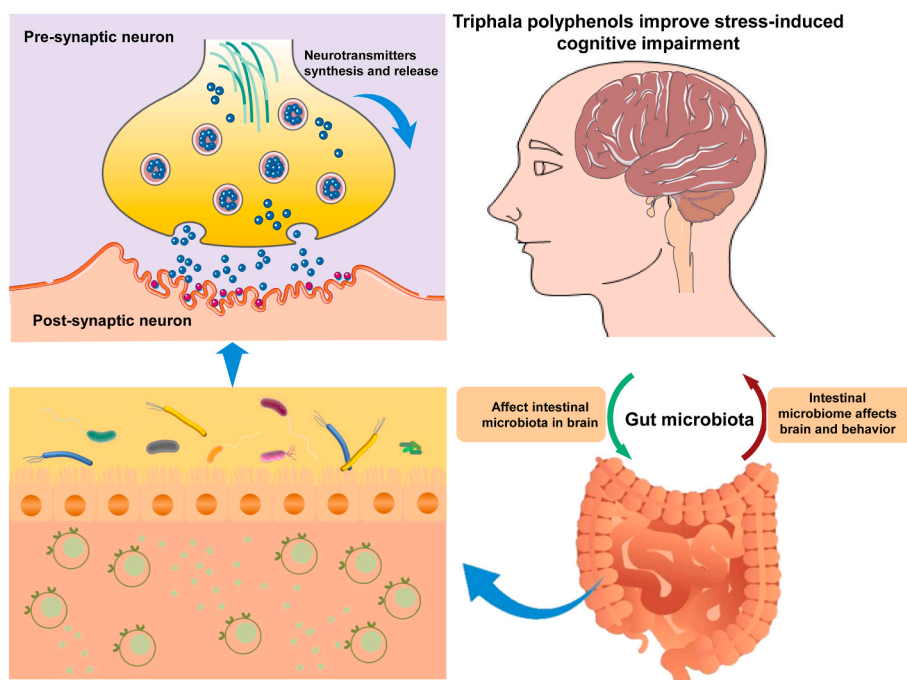

Fig. 9. Triphala polyphenols play a key role in the promotion of resilience against stress-induced cognitive impairment through gut microbiota.

sleep deprivation (Kanazawa et al., 2016). In a recently published study, quercetin was found to suppress the TLR4/myeloid differentiation factor 88 (MyD88)/NF-kB signaling that mediates abnormal microglia activation in the hippocampus in a paradoxical sleep deprivation-related memory impairment model (Y. Zhang et al., 2022). Quercetin-3-O-glucuronide, a quercetin derivative, has shown a significant reduction in sleep deprivation-induced cognitive impairment in mice by activating the CREB pathway (Zhao et al., 2015). In addition, in a recent study by Hairui Zhou and colleagues, it has been demonstrated that isoquercetin improves the learning and cognition of sleep-deprived mice through the suppression of NLRP3-induced pyroptosis of hippocampal neurons (H. Zhou et al., 2022).

Interestingly, it is clear from preclinical, clinical, and epidemiological studies that consuming other specific flavanols, such as epicatechin, kaempferol, and catechin, can help improve cognitive function (Alemany-Gonzalez et al., 2020; Lei et al., 2012; Navarrete-Yanez et al., 2020). An in-vivo experiment suggested that kaempferol protects against cognitive impairment through attenuation of oxidative stress, in addition to the stimulation of BDNF/TrkB/CREB signaling (Yan et al., 2019). Luteolin permeated the BBB in vivo and attenuated scopolamine-induced amnesia in rats (Ionita et al., 2018). Forouzanfar and collaborators evaluated the effects of catechin and EGCG on sleep deprivation-induced spatial memory impairments using male Wistar rats, and the authors observed that catechin and EGCG could prevent sleep deprivation-induced cognitive deficits in rats through normalizing the hippocampal antioxidant thiol defense system (Forouzanfar et al., 2021).

8. Conclusion and future perspectives

Pharmaceutical and medical industries have made considerable progress and efforts to develop therapeutics for the prevention and treatment of mood disorders, such as anxiety and depression, and sleep deprivation-induced cognitive impairments. The currently available approaches, however, still have a lot of side effects and adverse drug reactions, as well as undesirable interactions between drugs and foods. There is therefore an urgent need to demonstrate the efficacy and safety of novel phytotherapy in order to overcome the prevailing and failing treatment by the pharmaceutical industry. The exciting news is that triphala polyphenols are capable of promoting resilience against depression and cognitive impairment caused by stress. Aside from this, triphala polyphenols are recognized as safe natural ingredient agents that have been extensively tested in animal experiments and clinical trials and have not been found to cause adverse effects. Exploration of
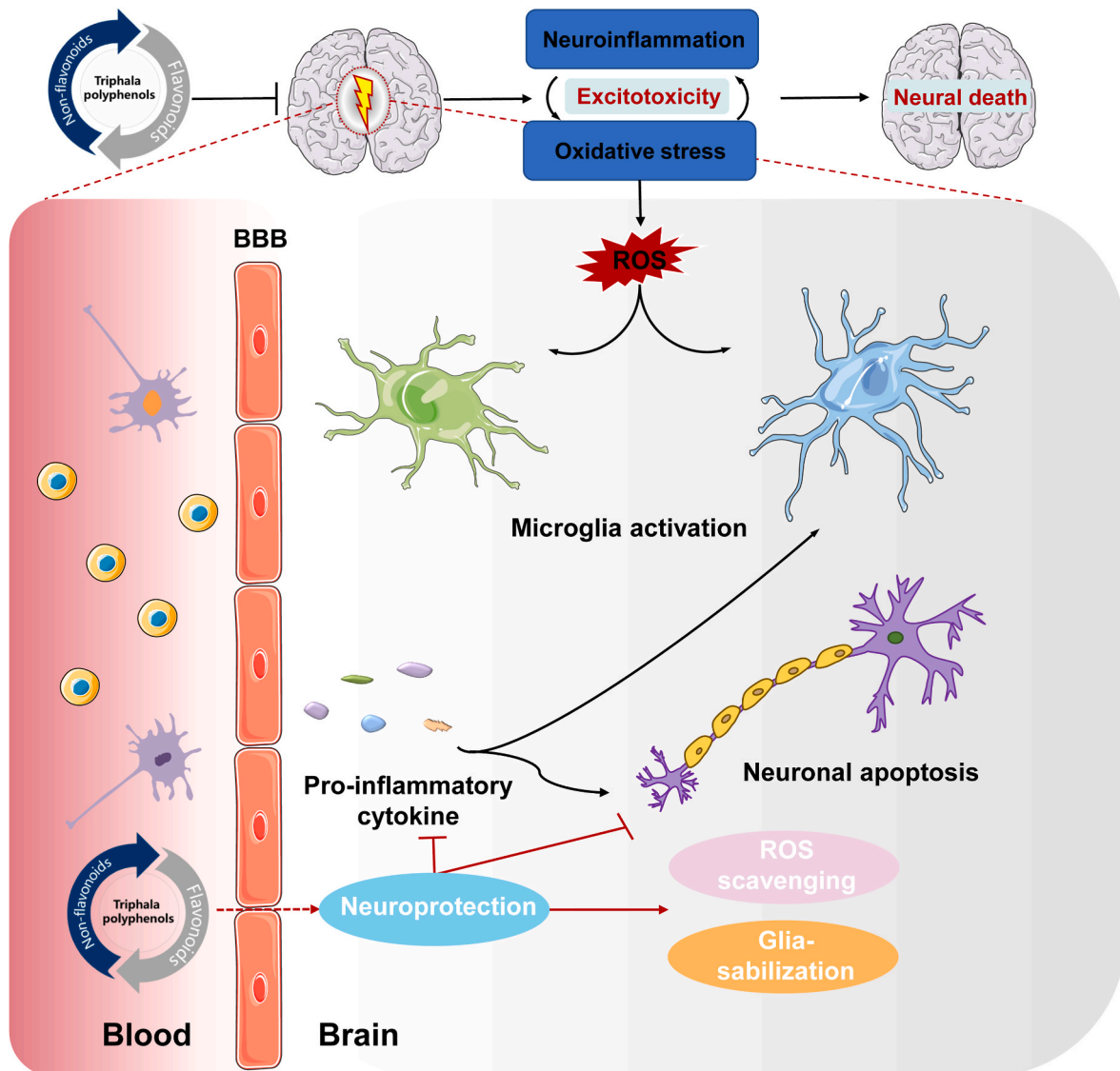

Fig. 10. Some triphala polyphenols can cross the blood brain barrier (BBB) and promote resilience against stress-induced depression and cognitive impairment.

the recent advances in the use of triphala polyphenols in stress-induced depression and cognitive impairment has demonstrated related mechanisms including the regulation of 5-HT and BDNF receptors, gut microbiota, and activation of antioxidant-related signaling pathways. Additionally, several triphala polyphenols like corilagin and epicatechin can cross the BBB and promote resilience against stress-induced depression and cognitive impairment (Fig. 10). Of concern, since most triphala polyphenols are commonly administered orally, no clear evidence exists that all of these triphala polyphenols are capable of reaching the central nervous system from the systemic circulation. The BBB permeability and systemic bioavailability of triphala polyphenols need to be improved, therefore future research should focus on improving these aspects.

Clinical trials need to be thoroughly investigated on the basis of preclinical discussions, as they are an essential component of medical research. Although triphala polyphenols have been studied in animals, fewer clinical studies have been conducted on the effect of triphala polyphenols on stress-induced depression and cognitive impairment in humans. For example, a pilot study confirmed that a supplement containing polyphenols, especially ellagic acid and gallic acid, is effective in improving fatigue, mood disorders, and insomnia in patients suffering from high levels of oxidative stress (Belcaro et al., 2018). Nevertheless, a small sample size clinical study or pilot study has limitations in terms of methodological validity, so there is no guarantee that conclusions will be completely conclusive. Therefore, it is necessary to conduct more rigorous clinical studies, including the use of better study design types, large sample sizes, high quality outcome measurements, and the selection of the correct endpoint, to overcome these methodological constraints. Most importantly, for the purpose of determining whether triphala polyphenols, whether single or mixed, promote resilience to stress-induced depression and cognitive impairment, a comprehensive understanding of the biological mechanisms of triphala polyphenols along with large multicenter clinical trials is also needed.

CRediT authorship contribution statement

Wenjun Wang: Investigation, Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Olufola Oladoyin Ige:** Investigation, Conceptualization, Methodology. **Yi Ding:** Writing – review & editing, Visualization. **Mengshan He:** Investigation, Writing – original draft. **Pan Long:** Investigation, Visualization. **Shaohui Wang:** Writing – review & editing, Visualization. **Yi Zhang:** Conceptualization, Methodology, Supervision. **Xudong Wen:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

Abbreviations

5-HT	5-hydroxytryptamine
AChE	acetylcholinesterase
AKT	protein kinase B
AMPK	Adenosine 5'-monophosphate (AMP)-activated protein kinase
Bax	Bcl-2-assaciated X protein
Bcl-2	B-cell lymphoma-2
BBB	blood brain barrier
BDNF	brain-derived neurotrophic factor
CA	cornu ammonis
C_{max}	peak concentration
CUMS	chronic unpredictable mild stress
CREB	cAMP-response element-binding protein
EGCG	epigallocatechin gallate
ERK1/2	extracellular regulated protein kinases 1/2
DG	dentate gyrus
GABA	γ-aminobutyric acid
IL	iterleukin
iNOS	inducible nitric oxide synthase
LC3	microtubule-associated protein 1 light chain 3
MAO-A	monoamine oxidase-A
MAPKs	mitogen-activated protein kinases
MDA	malondialdehyde
MyD88	myeloid differentiation factor 88
NF-kB	nuclear factor kappa-B
NLRP3	NOD-like receptor protein 3
NMDA	N-Methyl-D-aspartic acid
NO	nitric oxide
Nrf2	nuclear factor-E2-related factor 2
PGC-1α	peroxisome proliferator-activated receptor-gamma coactivator-1alpha
POP	prolyl oligopeptidase
ROS	reactive oxygen species
$T_{1/2}$	half-life
T_{max}	peak time
TLR4	Toll-like receptor 4
TNF-α	tumor necrosis factor α
TrkB	tyrosine receptor kinase B

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