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REVIEW ARTICLE

Neuroprotective Polyphenols: A Modulatory Action on Neurotransmitter Pathways

Elzbieta Rebas[1], Jowita Rzajew[1], Tomasz Radzik[1] and Ludmila Zylinska[1,*]

[1]*Department of Molecular Neurochemistry, Faculty of Health Sciences, Medical University of Lodz, Lodz, Poland*

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Abstract: ***Background*:** Balance in neurotransmission is essential for the proper functioning of the nervous system and even a small, but prolonged disturbance, can induce the negative feedback mechanisms leading to various neuropathologies. Neurodegenerative and mood disorders such as Alzheimer's, Parkinson's or affective disorders are increasing medical and social problems. Among the wide spectrum of potentially destructive events, oxidative stress and disrupted metabolism of some neurotransmitters such as acetylcholine, GABA, glutamate, serotonin or dopamine appear to play a decisive role. Biologically active plant polyphenols have been shown to exert a positive impact on the function of the central nervous system by modulation of metabolism and the action of some neurotransmitters.

***Methods*:** Based on published research, the pharmacological activities of some naturally occurring polyphenols have been reviewed, with a focus on their potential therapeutic importance in the regulation of neurotransmitter systems.

***Results*:** Phytochemicals can be classified into several groups and most of them possess anticancer, antioxidative, anti-inflammatory and neuroprotective properties. They can also modulate the metabolism or action of some neurotransmitters and/or their receptors. Based on these properties, phytochemicals have been used in traditional medicine for ages, although it was focused mainly on treating symptoms. However, growing evidence indicates that polyphenols may also prevent or slow neurological diseases.

***Conclusion*:** Phytochemicals seem to be less toxic than synthetic drugs and they can be a safer alternative for currently used preparations, which exert adverse side effects. The neuroprotective actions of some plant polyphenols in the regulation of neurotransmitters metabolism, functioning of neurotransmitters receptors and antioxidative defense have potential therapeutic applications in various neurodegenerative disorders.

Keywords: Polyphenols, neurotransmitters, neurotransmitter receptors, neuroprotection, neuropathology, central nervous system.

1. INTRODUCTION

Naturally occurring compounds existing in plants and showing the positive or negative effects in the animal's organisms are named as phytochemicals. Their positive actions include antioxidative properties (flavonoids, sulfides, carotenoids, anthocyanins, phytoestrogens), anticancerogenic properties (sulfides, phytoestrogens, saponins, flavonoids, carotenoids, anthocyanins, monoterpenes, phytosterins), antibacterial (flavonoids, glucosinolates, saponins, sulfides, phenolic acid), antithrombotic action (anthocyanins, sulfides, flavonoids) and anti-inflammatory effects (carotenoids, glucosinolates, flavonoids, saponins, sulfides). Some of them can regulate blood pressure, decrease blood cholesterol or stabilize blood glucose concentration [1, 2].

Phytochemicals are frequently used as dietary supplements; however, in some cases, there is also a risk of overdosing. It is well documented that certain types of phytochemicals can disturb various processes when used in high amounts *e.g.* excess of isothiocyanates or resveratrol (3,5,4′ - trihydroxy - *trans* - stilbene) has a negative effect on the thyroid gland and synthesis of thyroid hormones [3-5]. Regardless, phytochemicals are considered to be less toxic than synthetic drugs and can be a safer alternative for currently used preparations, which may exert a lot of adverse side effects.

Among many functions, biologically active plant compounds have been shown to exert a positive impact on the

*Address correspondence to this author at the Department of Molecular Neurochemistry, Faculty of Health Sciences, Medical University: 92-215 Lodz, 6/8 Mazowiecka Street, Lodz, Poland; Tel: +4842 272 5680; Fax: +4842 2725679; E-mail: ludmila.zylinska@umed.lodz.pl

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function of the central nervous system, including modulation of metabolism and action of some neurotransmitters [6]. These properties were used in traditional medicine mainly for treating symptoms, but also for reducing the risk of various neurological diseases. Some neurodegenerative and mood diseases like Alzheimer's (AD), Parkinson's (PD) or affective disorders are caused by disrupted metabolism of glutamate (Glu), γ-aminobutyric acid (GABA), acetylcholine (ACh) or serotonin (5-HT) [6, 7]. It was found that ACh is responsible not only for cholinergic signaling, but is also involved in Aβ plaque distribution in the brain [8]. The sedative and anxiolytic effect of phytochemicals or cognitive enhancement can be caused by direct binding to $GABA_A$ receptor [9]. Polyphenols with antidepressant properties inhibit monoamine oxidase leading to elevation of 5-HT, dopamine (DA) or noradrenaline levels [10].

Here, we review data concerning the effects of the selected plant polyphenols on the regulation of neurotransmitter metabolism, functioning of neurotransmitter receptors as well as antioxidative defense mechanisms.

2. SOURCES, STRUCTURES AND CLASSIFICATION OF POLYPHENOLS

Polyphenols occur naturally in fruits, vegetables and some beverages, like tea and wine. They are found in different parts of the plant: grains, bark, roots, stems, leaves, skins and flowers. As the plant pigments, they are responsible for a specific color of flowers, fruits, leaves and vegetables. For example, flavonoids abundant in various berries give them from orange/red to dark blue or dark violet/purple color, in most cases, more flavonoids mean the darker color [11].

Different groups of phytochemicals usually coexist in foods or plants, *e.g*. berry extracts comprise anthocyanins and other polyphenols, and thereby their individual properties can enhance the total biological effects [12]. Many medicinal plants and herbs have been used for years in traditional medicine in various countries like China, Nepal, India or Mexico. At present, numerous dietary supplements or drugs prepared based on the plant extracts are accessible on the market without prescription. For example, weak sedative effects due to modification of GABA action have been exerted by extracts from *Passiflora caerulea* (blue passion flower), *Passiflora incarnata* (purple passion flower), *Cinnamomum cassia* (Chinese cinnamon), *Salvia officinalis* (sage), *Withania somnifera* (ashwagandha), *Tagetes Lucida* (Mexican tarragon*), Argemone mexicana* (Mexican poppy), *Melissa officinalis* (lemon balm) or others [13-15].

The polyphenols represent a large group of phytochemicals and comprise flavonoids, lignans, aurones, chalconoids, tannins, curcuminoids, stilbenoids and others. More than 8000 polyphenols are known, but only about 500 were studied [2, 16]. Flavonoids, the biggest group of polyphenols, can be divided into several subclasses on the basis of their structures. The common feature of all flavonoids is the 15-carbon atom skeleton (2-phenylchromenone or 3-phenylchromenone) with two aromatic rings A and B and heterocyclic ring C, which can be saturated or non-saturated, and oxidized or non-oxidized. Flavonoids differ in the amount and type of functional groups attached to rings. Most of them possess hydroxyl group/or groups, which can be glycosylated or may possess a ketonic group [7, 17]. Naturally occurring flavones exist in a glycosylated form rather than in aglycone form [11]. The brief characteristics of the main classes of flavonoids are shown in Table **1**.

3. CHOLINERGIC SIGNALING AND POLYPHENOLS

Acetylcholine (ACh) is an abundant neurotransmitter found in both central (CNS) and the peripheral (PNS) nervous systems. It stimulates all motor neurons and is responsible for body movements. In the brain, ACh plays roles in learning, memory and improves cognitive functions. In addition, acetylcholine is known as an anti-Alzheimer agent through the direct interaction with β-amyloid protein (Aβ), one of the main hallmarks of Alzheimer's disease [18]. Both types of acetylcholine receptors, nicotinic ionotropic receptor (nAChR) and muscarinic metabotropic receptor (mAChR), can be involved in pathology or treatment of AD, but α7nAChR subtype seems to be more important. Up-regulation of α7nAChR is a therapeutic goal in AD and schizophrenia since it can form complexes with Aβ slowing down amyloid plaque deposition, thus prevents Aβ-induced cytotoxicity. New evidence indicates that intracellular Aβ accumulates in α7nAChR positive neurons [19, 20]. Other observations confirm a significant decrease in M1mAChR and M4mAChR during various stages of AD [21].

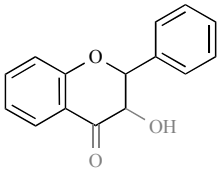
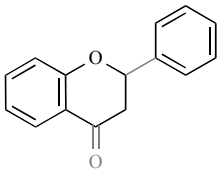
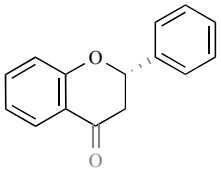
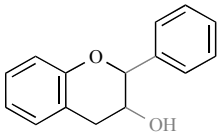
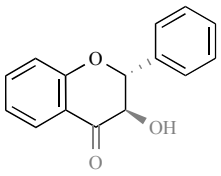
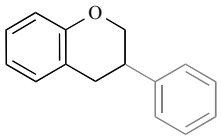
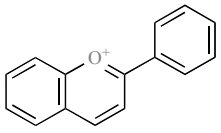
3.1. Effect of Polyphenols on ACh Receptor

It has been documented that some polyphenols can interact with α7nAChR or increase the expression and surface density of mAChR, thereby they could be considered as the potential drugs in the therapy of neurodegenerative diseases. An *in vitro* study demonstrated that human neuroblastoma cells pretreated with curcumin - polyphenol found in *Curcuma longa* - or its metabolites, showed significant potentiation of choline-induced Ca^{2+} transients. This phenomenon took place due to the activation of α7-nicotinic acetylcholine receptors [22]. The α7nAChR subtype, unlike other neuronal nicotinic receptors, exhibits a relatively high permeability to calcium ions [23]. It was also independent of protein kinases A, C, and Ca^{2+}/calmodulin-dependent kinase, which are known to regulate the activity of ligand-gated Ca^{2+} channels. This indicates that the phosphorylation of α7nAChR channel is not required for allosteric action of curcumin [22].

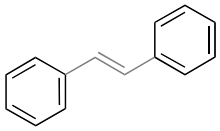
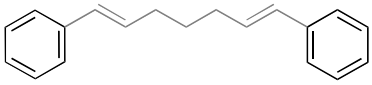
Epigallocatechin gallate (EGCG) is a very promising phytochemical, which is able to suppress Aβ-induced neurodegenerative disorders. The study on rat primary cortical neurons showed that the neuroprotective mechanism of EGCG involved activation of the α7nAChR signaling cascade. In Aβ-treated neurons, EGCG increased cell viability, reduced number of apoptotic cells and decreased reactive oxygen species (ROS) generation [24]. The reduction in nAChR–mAChR receptors and expression of mRNA for the cholinergic receptor (M1, M2 and M4) was detected in the frontal cortex and hippocampus of rats exposed to cadmium, which is known to induce cognitive deficits associated with the cholinergic system [25].

Administration of a flavonoid, quercetin, protected from a cadmium-dependent decrease in mAChR and the mechanism of

Table 1. Characteristics of main classes of polyphenols.

Polyphenols	Structural Formula	Compounds	Sources	Action
Flavonols		Kaempferol, quercetin, myricetin, fisetin, morin, rutin, chrisin, sibelin, galangin	Apple skin, berries grapes, red wine, grapefruit, tea, broccoli, parsley, onions	Antioxidant potential and reduced risk of vascular disease protection of AChR from ROS inhibition of AChE action of $GABA_A$ receptor effect on Glu signaling effect on DA signaling inhibition of MAO
Flavones		Luteolin, apigenin, tangeritin, acacetin, chrysin, diosmetin, linarin, spinosin, baicalin, amentoflavone, nobiletin	Celery, parsley, red peppers, chamomile, mint *Ginkgo biloba* citrus peels	Inhibitors of CYP anticancer impact on AChE expression activation of AChE action on $GABA_A$ receptor effect on Glu signaling effect on 5-HT signaling effect on DA signaling inhibition of MAO inhibition of Cav2.1 and Cav2.2
Flavanones		Fisetin hesperetinnarigin naringenin taxifolin silybin eriodictyol liquiritigenin	All citrus fruits such as oranges, lemons and grapes – fruit and peels	Antioxidant, anti-inflammatory, blood lipid-lowering and cholesterol lowering agents inhibition of AChE action on $GABA_A$ receptor increasing of 5-HT level effect on DA signaling
Flavanols Catechins Theavlavins Proanthocyanidins		Catechin gallocatechin epicatechin epigallocatechin epigallocatechin gallate epicatechin gallate theaflavin-3-gallate	Black tea green tea white tea red wine grapes apple juice cocoa	Antioxidant activation of nAChR signaling inhibition of AChE action on $GABA_A$ receptor inhibition of GDH effect on DA signaling inhibition of COMT inhibition of NMDAR expression
Flavanonols		Taxifolin aromadedrin	*Gordoniachrysandra* wine tea	Chemopreventive antiproliferative antibacterial
Isoflavonoids Isoflavones Isoflavanes Isoflavandiols Isoflavenes Coumestrol		Daidzein genistein glycitein	Soy alfalfa sprouts red clover chickpeas peanuts legumes brussels sprout	Anticancer antioxidant action on $GABA_A$ receptor
Anthocyanins		Cyanidin delphinidin malvidin pelargonidin peonidin petunidin	Berries, cherries, grapes, raspberries, red grapes, red wine, strawberries, tea, fruit peels with dark pigments	Anticancer effect on mAChR

(Table 1) contd….

Polyphenols	Structural Formula	Compounds	Sources	Action
Stilbenoid		Resveratrol	Grapes red wine blueberries	Antioxidant improved activity of AChE and ChAT effect on Glu uptake effect on DA signaling increase serotonin level inhibition of the NMDA receptor inhibition of AMPA receptor expression effect on kainate receptor
Curcuminoids		Curcumin	Curry turmeric	Antioxidant anti-inflammatory effect on Glu signaling inhibition of Cav2.1 and Cav2.2 channels increase 5-HT level inhibition of NMDA receptor expression

action of quercetin is based on its antioxidative properties [25]. In clinical studies, quercetin prevented the inactivation of nAChR and mAChR receptors in AD brain tissue [26]. In the aging rat brain, the increased total amount of M1AChR in rat C1 hippocampal and medial prefrontal cortex cells was observed after oral administration of grape seed proanthocyanidin extract (GSPE) [27]. Additionally, acetylcholine esterase (AChE) was inhibited, and the authors suggested the protective role of proanthocyanidins against cognitive decline. The crucial action of polyphenols on the cholinergic system is shown in Fig. **1**.

AD is characterized by the deposition of senile plaques consisting of β-amyloid that can aggregate into a number of forms of Aβ peptides. It was reported that an endogenous, low molecular weight inhibitor (LMW) from Alzheimer's brain inactivated the human brain mAChR probably by the generation of ROS. Moreover, the naturally occurring antioxidants including bilirubin, biliverdin, carnosol, and flavonoids - myricetin and quercetin- can protect the mAChR from free radical damage in brain cells [28].

3.2. Effect of Polyphenols on AChE

Degradation of acetylcholine by AChE serves to terminate cholinergic synaptic transmission. Some flavonoids can act directly as competitive or noncompetitive inhibitors of AChE [6] and indirectly by changes in gene expression or changes in AChE inhibitors' activity [29, 30]. Synthetic or natural inhibitors of AChE (*e.g.* caffeine, Rivastigmine, Galantamine, Donepezil generally in doses 8-10 mg/day) are widely used in the treatment of neurological diseases such as AD, but evoke the adverse effects like vomiting, decreased appetite, weight loss, nausea, diarrhea and bradycardia or heart arrhythmias [31]. Naturally occurring plant compounds can be less toxic. AChE inhibition by polyphenols and the rise of ACh level may improve the therapy of AD, PD as well as dementia.

Rats with impaired brain by carotid artery stenosis showed that animals had a highly reduced expression and mRNA level of AChE, choline acetyltransferase (ChAT) and vesicular acetylcholine transporter (vAChT) [29]. Treatment with resveratrol, a stilbene known for its antioxidative properties, increased the expression of these three key proteins in the cholinergic system. Additionally, resveratrol improved the activity of AChE and ChAT and thereby, cognitive function. Another flavonoid, spinosin was demonstrated to have an impact on AChE expression levels in the pathological state. Mice with impaired memory induced by amyloid β1-42 oligomers showed the reduced expression of AChE in the hippocampus, but spinosin administration reversed this effect [30].

It was reported that extracts from various plants can inhibit the activity of AChE [32]. This direct action was observed using, among others, polyphenols obtained from Black chokeberry extract (quercetin), *Paulownia tomentosa* fruits (quercetin), *Maclura tinctoria* stem (quercetin), *Paulownia barbatus* leaves (rosmarinic acid), *Cistus laurifolius* leaves (derivatives of quercetin), *Alpiniae officinarum* rhizome (galangin), *Linaria sp.* aerial parts (linarin) [6]. *In vitro* studies confirmed the inhibition of AChE by extracts from some Korean plants used for rejuvenation or improving memory, especially from *Prunella vulgaris* and *Oenothera biennis* [33]. The similar anti-AChE activity was observed using polyphenol catechin from *Rhizophora mucronata* [34]. Additionally, epigallocatechin gallate (EGCG) enhanced the action of huperzine A, an AChE inhibitor, and improved cognitive functions in Alzheimer's disease [35]. Also, catechins from green tea can inhibit AChE, thereby preventing neuronal damage by blocking the aggregation of Aβ peptides [34]. This inhibitory action of polyphenols is supported by their antioxidant properties [34, 36]. AChE activity could also be suppressed by other flavonoids like naringenin [37, 38], liquiritigenin [39] and acacetin, O-methylated flavone found (among other species) in *Clerodendrum inerme* [26]. An opposite effect on AChE activity has been reported for luteolin. This flavonoid possesses the potential anti-oxidant, anti-inflammatory, apoptosis-inducing and chemopreventive activities. *In vitro* studies on the PC12 cell line showed that luteolin can modulate AChE by increasing the enzyme activity in a time- and dose-dependent manner. The mechanism responsible for this phenomenon is probably related to the activation of extracellular signal-regulated kinase 1/2 (ERK1/2) and PI3K/Akt signaling pathways. In addition, luteolin increased total choline and ACh release [40]. Activa-

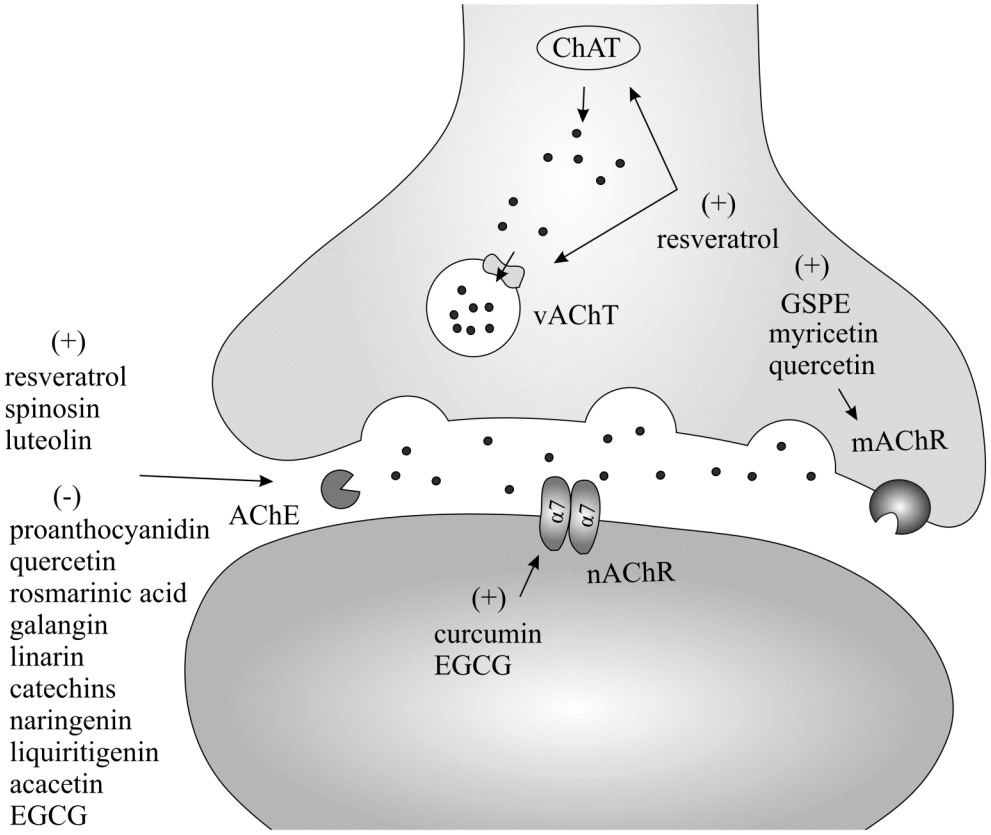


Fig. (1). The effect of polyphenols on cholinergic system components. AChE - acetylcholine esterase, ChAT - choline acetyltransferase, EGCG - epigallocatechin gallate, GSPE - grape seed proanthocyanidin extract, vAChT- vesicular acetylcholine transporter, AChR - acetylcholine receptor, mAChR- muscarinic acetylcholine receptor, (+) - enhancement or activation of system component, (-) - inhibition or blocking of system component. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

tion of AChE is associated with neuronal differentiation, thus luteolin can play a neuroprotective role by promoting neurite outgrowth.

4. GABA-ERGIC SIGNALING AND POLYPHENOLS

GABA is a primary inhibitory neurotransmitter in mammalian CNS. It plays a crucial role in maintaining balance in the nervous system. Disturbances in the GABA-ergic system are observed in AD, schizophrenia, anxiety or mood disorders. In medicine, benzodiazepine derivatives *e.g*. diazepam or barbiturates are commonly used as drugs modulating GABA-ergic signaling, but many unwanted side-effects are associated with this type of treatment including impairment of long-term memory, cognitive decline and addiction [41].

A large number of flavonoids can modulate $GABA_A$ receptors by two separate mechanisms (Fig. **2**). The first one uses a flumazenil-sensitive high-affinity benzodiazepine binding site. Flumazenil is a known selective benzodiazepine $GABA_AR$ antagonist acting through competitive inhibition [42]. The second mechanism uses a flumazenil-insensitive low-affinity benzodiazepine site. Critical for the particular type of action is α, β and γ subunits composition of $GABA_A$ receptor [43, 44].

In most cases, flavonoids directly act on benzodiazepine site exerting anxiolytic actions [43, 45, 46]. This effect was reported for naringenin-dihydro derivative of apigenin found in citrus products, genistein (an isoflavone from soybeans), wogonin and andoroxylin (O-methylated flavones found in S*cutellaria baicalensis)*, p-coumaric acid (hydroxy derivative of cinnamic acid occurring in *Gnetum cleistostachyum)*, dihydromyricetin (ampelopsin, flavanonol present in some *Ampelopsis species, Hoveniadulcis, Cercidiphyllum japonicum* or *Rhododendron cinnabarinum)* [43, 45-49].

Epigallocatechin gallate, flavan abundantly found in green tea, exhibited neuroprotective, anxiolytic, sedative-hypnotic and amnesic properties [43, 50]. Also, a number of lipophilic flavonoids isolated from *Leptospermum scoparium* induced sedative and anxiolytic effects by interaction with the benzodiazepine binding site [43].

Baicalein and baicalin, the components of Scutellaria baicalensis showed both, neuroprotective and anticonvulsant effects *in vivo* [43]. They acted through the benzodiazepine site on $GABA_A$ receptor subtypes comprising the α2 and α3 subunits [51]. Anxiolytic and sedative effects of baicalein may also be exerted by its interaction with GABAergic non-benzodiazepine sites [52].

Apigenin, found in chamomile tea, is well known for its anti-anxiety properties due to agonistic action on $GABA_A$-R [43, 45, 46]. Biflavone amentoflavone is a negative modulator of $GABA_A$ receptors *in vitro,* which binds to benzodi-

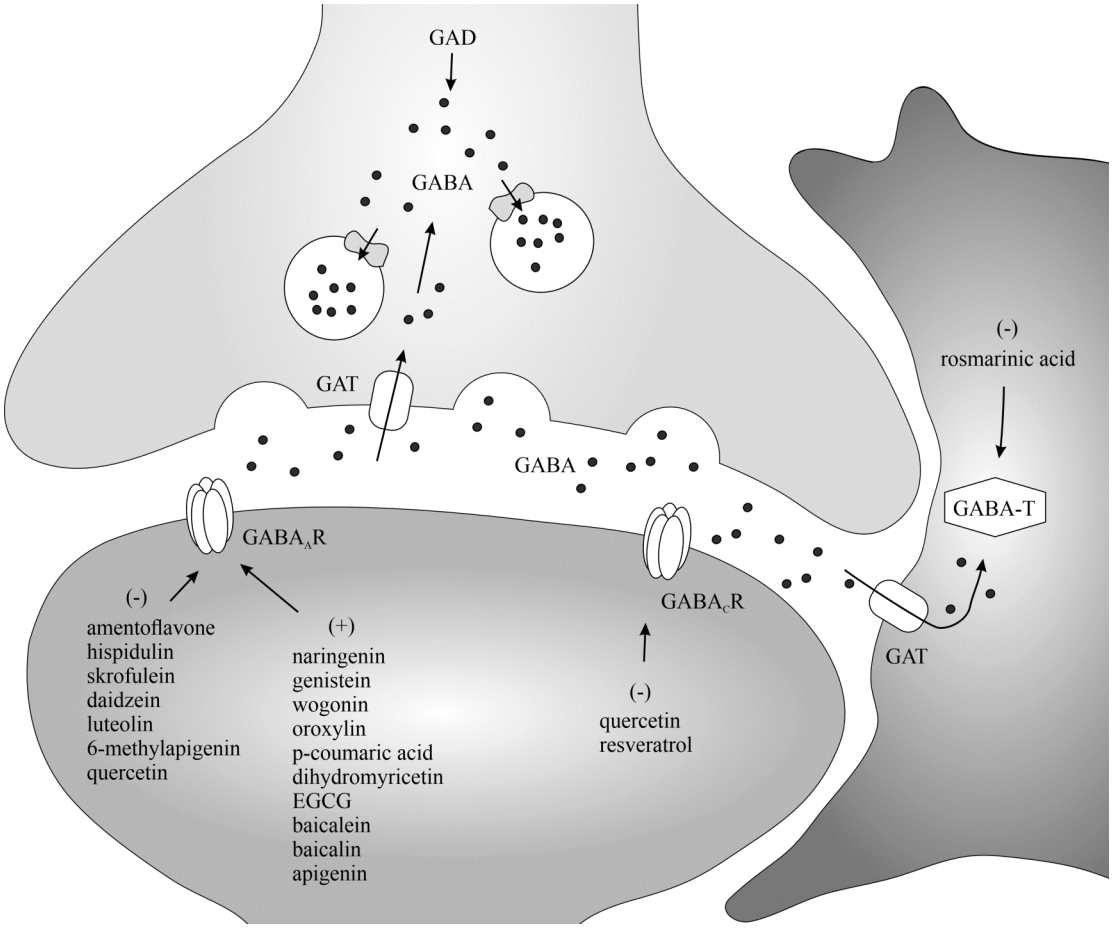


Fig. (2). The effect of polyphenols on GABA-ergic signaling components. GABA-γ-aminobutyric acid, $GABA_AR$-$GABA_A$ receptor, $GABA_CR$-$GABA_C$ receptor, GABA-T-GABA transaminase, GAD-glutamate decarboxylase, GAT-glutamate transporter, (+) - enhancement or activation of signaling component, (-) - inhibition or blocking of signaling component. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

azepine site with an affinity similar to diazepam [43]. It can act *via* classical flumazenil-sensitive benzodiazepine binding sites, as well as independently of flumazenil [42, 44, 53]. This effect is dependent not only on subunits composition but also on amentoflavone doses. Amentoflavone is always a negative modulator, but it acts as a benzodiazepine antagonist at low nM concentration and as a flumazenil-insensitive modulator of GABA action at a higher concentration [44, 53].

Plant-derived compounds, which act as agonists of the $GABA_A$ receptor, could be used instead of synthetic drugs for the therapy of anxiety [54]. Agonists of $GABA_A$ receptors can also show anticonvulsant properties. Such an effect has been observed for two flavones - hispidulin and skrofulein - found in *Artemisia herba-alba*. They acted as weak partial agonists of the benzodiazepine binding site of the receptor [42]. Moreover, hispidulin exhibited positive allosteric modulatory effects on α1,3,5,6β2γ2S $GABA_A$ receptor subtype [55].

Daidzein - isoflavone isolated from *Puerariae radix* inhibits the binding of flunitrazepam (drug from benzodiazepine group) to benzodiazepine receptors. Luteolin, flavonoid aglycon, was found to displace flunitrazepam binding, although with low affinity [42, 56]. A derivative of apigenin, 6-methylapigenin, isolated from the roots and rhizomes of *Valerianawallichii,* exhibits similar properties [42].

$GABA_A$ receptors containing α1-β2-γ2 subunits or $GABA_A$, composed entirely of ρ1 subunits (formerly known as a $GABA_C$) are inhibited by quercetin. A recent study demonstrated that quercetin was able to reduce GABAergic synaptic transmission in cortical neurons *in vitro* [57]. Resveratrol showed a little effect on $GABA_A$α1-β2-γ2 subtypes, but it can exert antagonistic effects on the rho subunit-containing $GABA_A$ receptors [3, 58]. Rosmarinic acid is an example of polyphenol, which modulates GABAergic signaling not through the GABA receptor, but by increasing the total amount of GABA due to the inhibition of GABA transaminase (GABA-T), the enzyme responsible for the breakdown of GABA [59].

5. GLUTAMATERGIC SIGNALING AND POLYPHENOLS

Glutamic acid (Glu, glutamate, L-glutamate) plays a pivotal role in maintaining proper functions of CNS and is responsible for synaptic plasticity, learning and memory. Disturbances in metabolism or action of this main excitatory neurotransmitter, including excessive Glu releasing, are as-

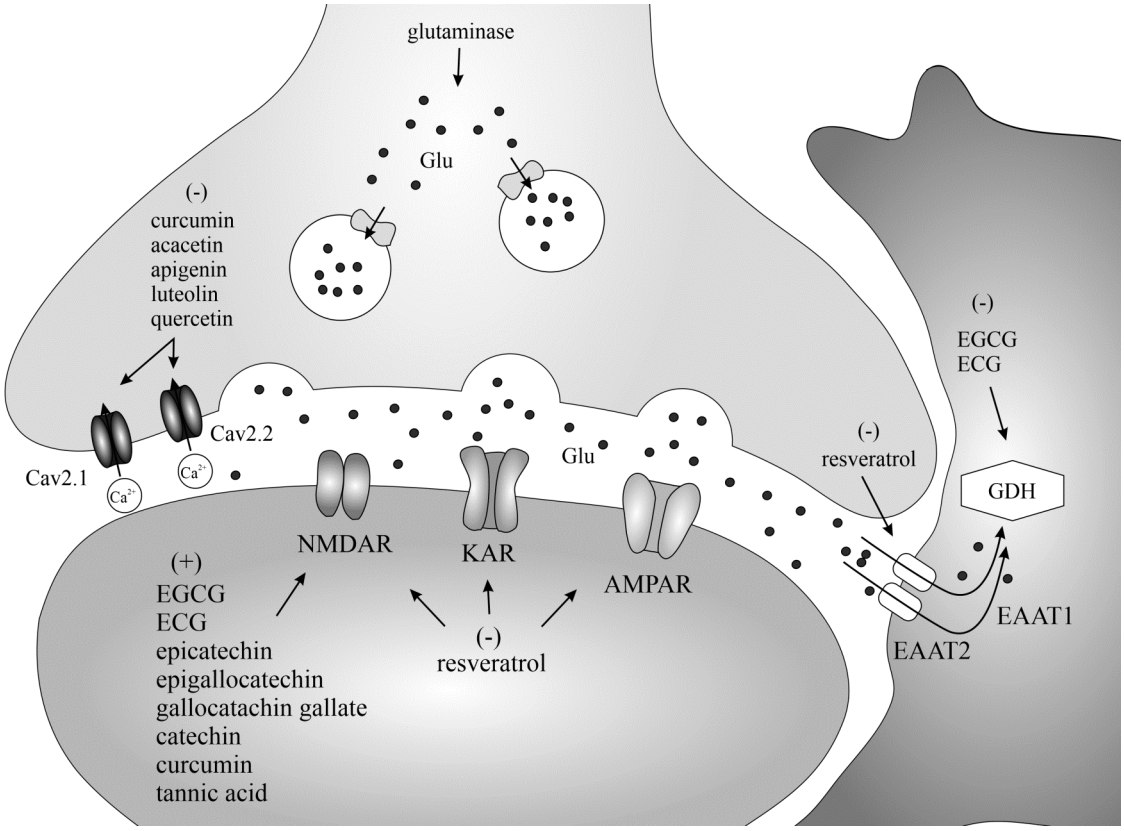


Fig. (3). The effect of polyphenols on glutamatergic signaling components. ECG - epicatechingallate, EGCG - epigallocatechin gallate, Glu - glutamic acid, GDH - glutamate dehydrogenase, NMDAR - N-methyl-D-aspartate receptor, KAR - kainate receptor, AMPAR - α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor, (+) - enhancement or activation of signaling component, (-) - inhibition or blocking of signaling component. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

sociated with affective disorders, epilepsy, AD and PD. Glutamate activates the excitatory glutamate receptors; thus compounds that block glutamic acid receptors or inhibit Glu release could be neuroprotective, when used in therapy of these diseases. Presynaptic Glu secretion depends on Ca^{2+} influx through voltage-gated Ca^{2+} channels Cav2.1 and Cav2.2. Some flavonoids were identified as inhibitors of both subtype of channels, subsequently decreasing Glu release (Fig. **3**).

Curcumin, acacetin and apigenin showed to inhibit Glu release in rat hippocampal synaptosomes [60-62]. Similar effect has been described for luteolin, which significantly decreased Glu release in rats' synaptosomes evoked by 4-aminopyridine, K^+ channel blocker. This effect was reversed by blocking of Cav2.1 and Cav2.2 channels [63]. Another compound - quercetin - was also shown to prevent depolarization-evoked Glu release from rat synaptosomes and, comparable to luteolin, decreased presynaptic voltage-dependent Ca^{2+} entry by blocking Cav2.1 and Cav2.2. Moreover, this mechanism involved the simultaneous inhibition of both PKC and PKA activities, which by phosphorylation, regulate the activity of Ca^{2+} channels [64].

Resveratrol has been shown to affect Glu uptake in cultured cortical astrocytes in a dose-dependent manner, and while lower concentration increased Glu uptake, higher dose exerted an opposite effect [65]. Excess of glutamate could also be removed by glutamate dehydrogenase (GDH) – an enzyme responsible for the reversible oxidative deamination of L-glutamate to α-ketoglutarate. It has been demonstrated that epigallocatechin gallate and epicatechin gallate can inhibit GDH by binding to its adenosine diphosphate (ADP) site [66, 67].

Excess of glutamate and over-stimulation of glutamate receptors – N-methyl-D-aspartate receptors (NMDAR), kainate receptors (KAR) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPAR), lead to excitotoxicity due to more intensive calcium influx, and is frequently reported in various neurological (*e.g.* epilepsy) or neurodegenerative diseases. On the other hand, too low amount or decreased activation of NMDA or AMPA receptors can disturb long-term potentiation (LTP) in the hippocampus, impairing learning and memory functions.

Some polyphenols exert neuroprotective effects *via* modulation of glutamate receptors activity or expression. For instance, glutamate-induced excitotoxicity was reduced in the presence of resveratrol [68]. In hippocampal CA1 neurons, this polyphenol (10 - 100 μM) inhibited amplitude and frequency of postsynaptic currents mediated by Glu receptors. Interestingly, NMDA and KA receptors were more sensitive to the resveratrol than AMPA receptors [69, 70]. Using selective inhibitors of Glu receptors, another study showed that in hippocampal slices, resveratrol exhibited a strong

antioxidant/scavenger activity that prevented NMDA, AMPA/KA and intracellular Ca^{2+} activation, thereby protected neurons against glutamate-induced neuronal damage [68].

NMDA receptor is hetero-oligomer consisting of four subunits: essential NR1 subunit, one or two modulatory NR2 subunits (types from A to D) and NR3 subunit. The study using morphine-resistant rat spinal cord showed that resveratrol (intrathecally injected at a dose of 30 μg) reversed the up-regulation of NR1 and NR2B subunits expression in synaptosomal membranes. The reduction of NMDAR expression and following suppression of neuroinflammation by resveratrol maintained the antinociceptive effect of morphine even in rats insensitive to this opioid [71]. NMDAR is involved in processes of learning and memory that can be disturbed by dietary or environmental agents. The extract from green tea containing polyphenols like EGCG, epicatechin gallate, epicatechin, epigallocatechin, gallocatechin gallate and catechin improved memory and attenuated cognitive impairments induced by ethanol, increasing the expression of NR1 subunit in the neurons of CA1 hippocampal region [72].

Exposure to some metals can disrupt brain function and cause brain damage. In the hippocampus of rats exposed to lead and aluminum (administered in drinking water for 16 weeks) curcumin and tannic acid reversed inhibitory action of metals on NR2A and NR2B subunits expression and protein level [73]. Because Al and Pb are antagonists of NMDAR and can inhibit LTP, the protective effect of both polyphenols on learning and memory could be a result of the restored level of NMDAR subunits in the brain [73].

Another glutamate receptor involved in LTP, LTD (long term depression) and synaptic plasticity is AMPA receptor. These homo- or heterotetrameric ion channels are built from combinations of GluA1-4 subunits. It was demonstrated that resveratrol (20 - 40 μM) increased the level of both GluA1 and GluA2/3 subunits in rat cortical and hippocampal neurons *in vitro*. Resveratrol enhanced AMPAR expression *via* the up-regulation of translation involving activation of AMP-activating protein kinase, PI3-kinase and eIF4E/4G translation initiation complex [74].

Resveratrol was also shown to down-regulate hippocampal KAR expression in rats [75]. Particularly, an interesting effect of resveratrol on a kainic acid-induced epilepsy was observed in rat hippocampal slices. Epilepsy is caused by excitatory/inhibitory imbalance in the neuronal network. The results showed that in different phases of epilepsy, resveratrol reversed the harmful action of kainite by decreasing or increasing of KAR expression. Additionally, resveratrol modified expression of $GABA_AR$ in a similar manner and decreased the glutamate/GABA ratio in the hippocampus [76].

6. BIOGENIC AMINES AND POLYPHENOLS

Disturbances in serotonergic and dopaminergic signaling are mostly associated with depression [77]. Many drugs used in medicine acted by the inhibition of 5-HT reuptake. However, there are also evidence that the serotonin receptor can be involved in cognitive impairment and development of AD [78]. DA plays a critical role in behavior and movement control. Dysfunction of the dopaminergic system can lead to various mental and motor disorders. The great loss of dopaminergic neurons is a hallmark of PD.

6.1. Serotonergic Signaling

Another mechanism by which polyphenols can lower depression symptoms is the activation of monoamines synthesis or 5-HT receptors (Fig. **4**). Three subtypes of serotonergic receptors: 5-HT1A, 5-HT1B and 5-HT2C can be affected by curcumin [79]. Recent experiments demonstrated that chronic administration of curcumin significantly increased the 5-HT level in the hippocampus and frontal cortex of olfactory bulbectomy rats [80]. Also, amentoflavone, biflavonoid that has been identified in over 120 natural plants, exhibited agonistic activity to 5-HT1Dα and 5-HT2C receptor subtypes [81]. Additionally, amentoflavone interacted with noradrenergic α1 and α2 receptors, but did not modulate dopaminergic and cholinergic system.

Antidepressant action has been revealed in studies with nobiletin, O-methylated flavon obtained from *Citrus peels* [82]. The mechanism involved the participation of 5-HT1A and 5-HT2 receptors, but also α1-adrenoceptor, DA receptors - D1 and D2 appeared to be the targets for nobiletin. This indicates a strong therapeutic potential of this flavonoid for the treatment of depression. Spinosin is a flavone C-glycoside, which showed an ameliorating effect on scopolamine-induced cognitive impairment in mice. Although this action was antagonized by the 5-HT1A receptor agonist, spinosin may be useful for the treatment of cognitive dysfunction in diseases such as Alzheimer's disease [83].

Naringenin is the predominant flavanone in grapefruit and possesses antidiabetic, antioxidant and memory improving properties. It positively stimulated the serotonergic neurotransmission in the brain by enhancing 5-HT synthesis [84, 85]. In rats exposed to chronic mild stress apigenin, another compound belonging to the flavone class, attenuated the altered 5-HT level in the prefrontal cortex, hypothalamus, hippocampus and nucleus accumbens [86]. Flavonoids can also exert antidepressant and neuroprotective properties by up-regulation of transcription factor - cAMP response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF). As a result, the total increased amount of serotonergic neurons, accelerated maturation and higher 5-HT receptors number were observed, what finally promoted neuronal survival [77].

6.2. DA Signaling

Dopaminergic neurons are found abundantly in the CNS. There are five subtypes of dopamine receptors (D_1 to D_5), which use G protein–mediated second messenger systems [87, 88]. Reuptake of transmitter by the DA transporter (DAT) back into presynaptic neurons serves as the major regulator of DA signaling [89]. This plasma membrane protein is found exclusively on DA neurons, and dysregulation of DAT function results in imbalanced DA levels. Disturbances in the dopaminergic system are implicated in several diseases such as ADHD, Tourette syndrome or multiple sclerosis [88]. Psychotic symptoms can be diminished by drugs

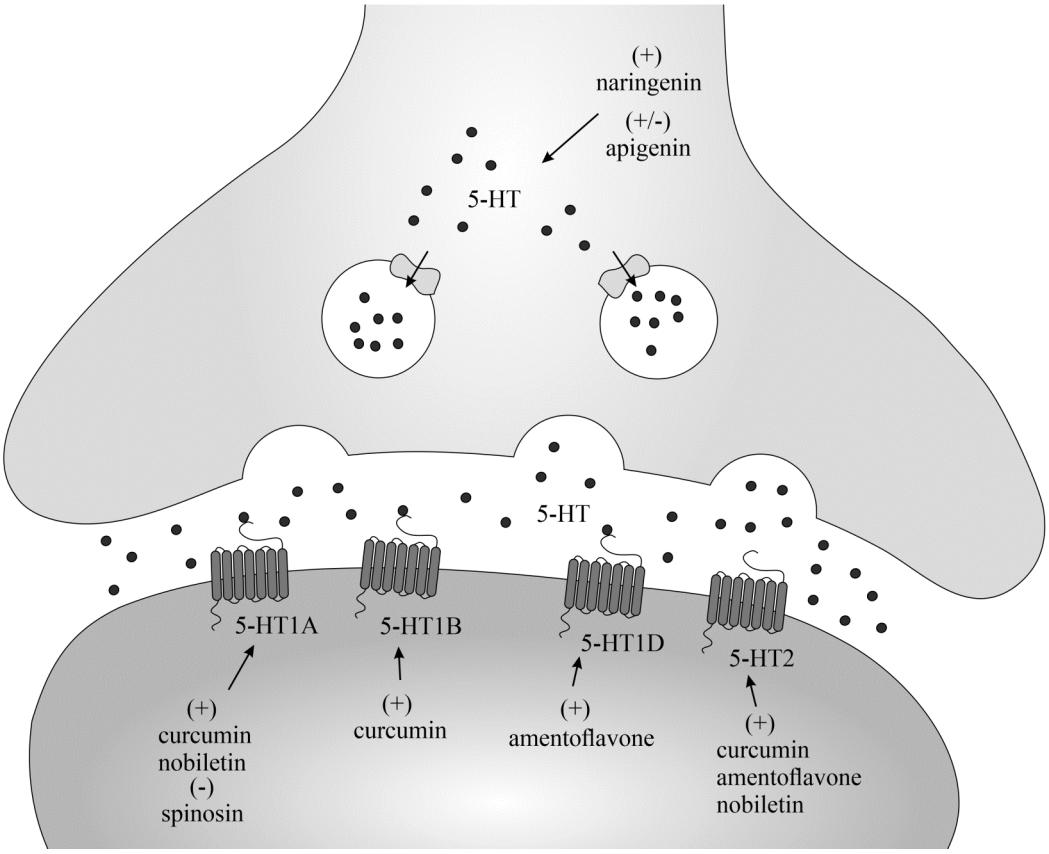


Fig. (4). The effect of polyphenols on serotonergic signaling components. 5-HT - serotonin, 5-HT1A, 5-HT1B, 5-HT1D, 5-HT2 - serotonin receptors, (+) - enhancement or activation of signaling component, (-) - inhibition or blocking of signaling component. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

acting as dopamine antagonists, while drugs increasing DA concentration alleviated depression symptoms.

Similar to other neurotransmitters, the DA level may be modulated by several flavonoids. The crucial polyphenols acting on the dopaminergic system, including DA catabolism, are shown in Fig. **5**. Rats exposed to chronic mild stress had noticeably increased DA level in frontal cortex and nucleus accumbens, which was lowered by the administration of apigenin [86]. Also, resveratrol was able to significantly augment dopamine level in the frontal cortex of mice [10].

DAT is responsible for the removal of dopamine from the synaptic cleft. Inhibition of this uptake by flavan-3-ols can affect neurotransmission by increasing dopamine in the synaptic cleft [90, 91]. However, naringenin, hesperetin and quercetin have been reported to increase DA uptake [92]. The ability of curcumin and naringenin to exhibit neuroprotection in the 6-OHDA-induced model of PD may be related to their antioxidant potential and their capability to penetrate the brain. An *in vitro* experiment on rat striatum showed that naringenin significantly enlarged the content of dopamine [92]. On the contrary, *in vitro* studies demonstrated that oroxylin A selectively suppressed dopamine reuptake, perhaps through the inhibition of dopamine transporter [93]. In DAT-overexpressed PC12 cell line, EGCG inhibited dopamine uptake in a dose-dependent manner and the mechanism was based on the induction of DAT internalization in the cell membrane. EGCG inhibitory effect probably involved protein kinase C, since it was diminished by the inhibitor of PKC [94].

Some classes of flavonoids can regulate the function of DA receptors. A comprehensive *in vitro* study has proved that amentoflavone can markedly inhibit rats' D3-dopamine receptor subtype [95]. In addition, it selectively inhibited the DA transporter.

6.3. Polyphenols and Monoamine Oxidase

Most of the antidepressant drugs (*e.g.* phenelzine) act as inhibitors of monoamine oxidase (MAO), the enzyme responsible for the oxidative deamination of monoamines, but severe side-effects have been noticed during such therapy [77, 96]. MAO inhibitors are often administered at inadequate doses (maximum dose is 90 mg/day, doses range 40 - 90 mg/day) due to many early effects like hypotension, dizziness, insomnia, nausea or late adverse effects such as weight gain, edema, muscle pains, myoclonus, paresthesia, sexual dysfunction. Overdose of MAO inhibitors leads to CNS excitation. Additionally, many interactions with other drugs have been observed (*e.g.* with proton pump inhibitors and inhibitors of CYP2C19). Therapy with MAO inhibitors also requires a specific diet [96].

Mild to moderate depression can be treated by plant-derived compounds and herbals [77]. Flavonoids with antidepressant

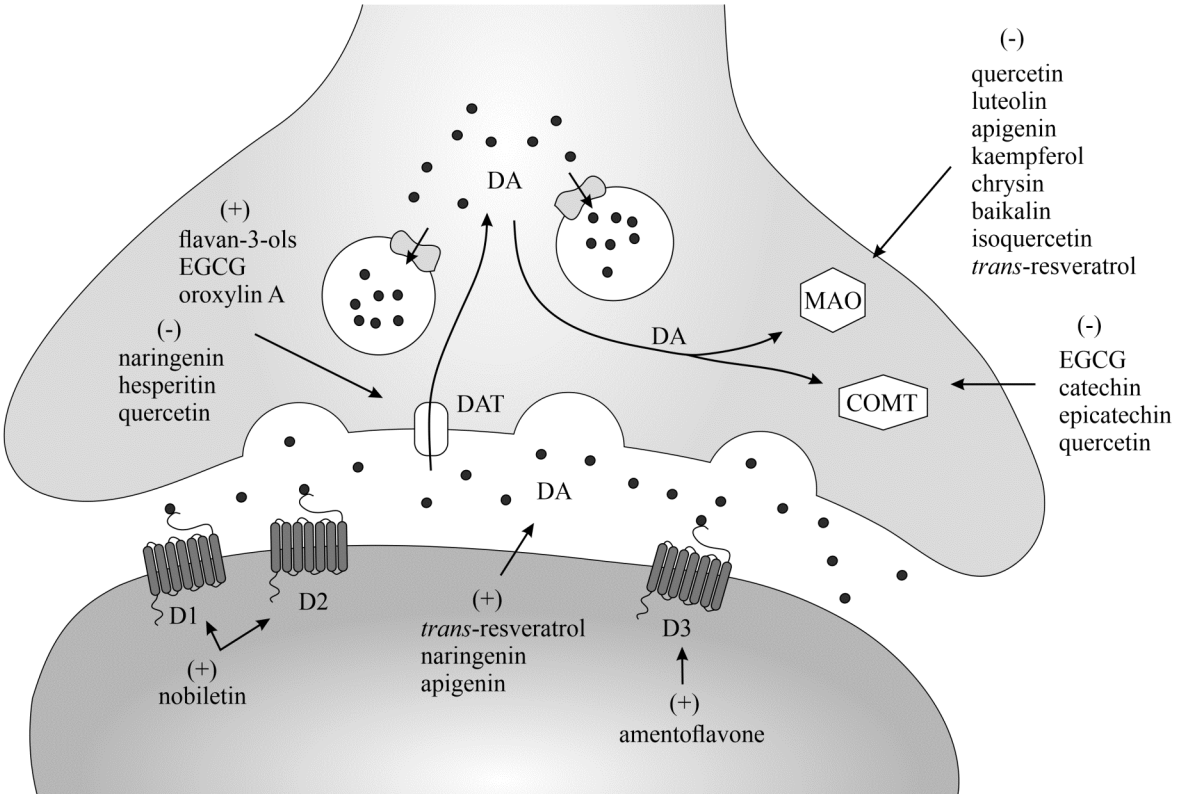


Fig. (5). The effect of polyphenols on MAO, COMT and dopaminergic signaling components. COMT - catechol-O-methyltransferase, D_1 to D_3 - dopamine receptors, DA - dopamine, DAT - dopamine transporter, EGCG - epigallocatechin gallate, MAO - monoamine oxidase, (+) - enhancement or activation of signaling component, (-) - inhibition or blocking of signaling component. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. Serum concentration of selected polyphenols after administration of single dose and effective concentrations, which exert biological effects.

Polyphenol	Single Dose	Peak Level*	Time to Reach Peak Level	Elimination Half Time	Effective Concentration/dose	Target	Refs.
Daidzein (aglycon) or unconjugated daidzein	50 mg	0,76 µM or 0,07 µM	2 h	9 h	15,43 µM	BZ1, BZ2 binding site of GABA-R	[52, 100]
Genistein (aglycon) or unconjugated genistein	50 mg	1,26 µM or 0,05 µM	9 h	6 h	100 µM	$GABA_A$	[44, 46, 100]
Quercetin (aglycon)	151 mg	5 µM	37 min	18 h	100 mg/kg	AChR	[57, 101]
					10-100 µM	GABA-A	
Epicatechine	137 mg	260 nM	2h	6 h	5-10 µM or 500 mg/kg	COMT	[99, 102]
Curcumin conjugated (glucuronide or sulfate)	10 g 12 g	2,04 or 1,57 µg/ml (3,74 µM or 3,5 µM) # 1,4 or 0,87 µg/ml (2,7 µM or 1,78 µM) #	4,3 h or 3,7 h	10 h or 8,8 h	1-100 µM	7αnAChR	[23, 79, 80, 103]
					100 mg/kg	5-HT	
Resveratrol (free or sulfated)	500 mg	71 ng/ml (0,03 µM) # or 1515 ng/ml (4,8 µM) #	1,3 h or 2,7 h	5,11 h or 8,3 h	40-80 mg/kg	MAO	[10, 29, 58, 65, 104]
					20 mg/kg	AChE, ChAT	
					25 µM, 250 µM	Glu uptake	

*The highest concentration detected in blood serum. #own calculation.

activity are similar in structures, but the position of the hydroxyl group(s) on the A-ring can modify antidepressant effects. The flavonoids with the highest inhibitory action on MAO include quercetin, luteolin, apigenin, kaempferol, chrysin and baicalin [77, 95, 97]. All of them are inhibitors of both the enzyme isoforms, MAO-A and MAO-B. Derivatives of quercetin, like isoquercetin or quercetrin, can abolish only MAO-B activity [77].

A study performed in rodents suggested that *trans*-resveratrol exhibited an antidepressant-like effect by increasing serotonin level. In addition, at 80 mg/kg dose, it also inhibited the activity of MAO-B [10]. Generally, inhibition of monoamine oxidase by polyphenols can increase the concentration of serotonin, dopamine and noradrenaline, thereby reducing symptoms of depression and eliminating the potential side-effects.

6.4. Polyphenols and Catechol-O-methyltransferase

The hallmark of PD is the loss of nigrostriatal dopaminergic neurons and a subsequent decrease in striatal DA content. The precursor of DA, levodopa (L-DOPA), is commonly used to reduce PD symptoms. L-DOPA is a substrate for two enzymes: DOPA decarboxylase and catechol-O-methyltransferase (COMT). Because peripheral DOPA decarboxylase is inhibited by drugs administrated during PD treatment, it is important to suppress the conversion of L-DOPA into methylated metabolites by COMT. Some catechins from tea, such as epigallocatechin-3-gallate, catechin, epicatechin and flavonol quercetin, are strong inhibitors of human COMT. The effects of catechins together with their potent antioxidant properties make the tea flavonoids a very effective group of neuroprotectors [98, 99].

The serum concentration of selected polyphenols after administration of a single dose and their effective concentrations, which exert biological effects, are presented in Table **2**. In most cases, a higher single dose is required to reach effective polyphenol concentration in the serum. On the other hand, half time of polyphenols elimination is rather long and repeated doses or daily intake of food containing these compounds may be sufficient to maintain safe, but stable, effective level in the serum. It should be noted that no adverse effects have been observed for polyphenols presented in Table **2**, in contrast to the drugs used in the therapy of psychical diseases (*e.g*. MAO or AChE inhibitors). Additionally, compounds naturally occurring in food can bind reversibly to neurotransmitter signaling components (in opposite to *e.g*. irreversible binding of MAO blockers) and are easily removed from the organism.

CONCLUSION

There are many polyphenols showing anti-degenerative and protective properties acting *via* changes in neurotransmission. This review presents only selected mechanisms of neuroprotection evoked by plant compounds. According to the given examples, some polyphenols (apigenin, quercetin, lutein, naringenin) can exhibit multifaceted action, simultaneously modulating pathways for different neurotransmitters. This phenomenon is frequently accompanied by overlapping effects. Considering the lack of toxicity of polyphenols, the final result is positive for the brain and these chemicals can make an alternative to the classical treatment of neurodegenerative diseases and/or provide support to the therapy. Elucidation of molecular mechanisms underlying synergistic or antagonistic action of polyphenols could also enable their prophylactic application to prevent neurodegeneration or slow down the progression of diseases. However, taking into account that plant extracts could contain a mixture of different polyphenols with sometimes contradictory impact on particular signaling pathways, usage of polyphenols as dietary supplements without control should be considered with caution.

LIST OF ABBREVIATIONS

5-HT	=	Serotonin
Aβ	=	β-amyloid protein
ACh	=	Acetylcholine
AChE	=	Acetylcholine esterase
AD	=	Alzheimer's disease
AMPAR	=	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor
BDNF	=	Brain-Derived Neurotrophic Factor
ChAT	=	Choline acetyltransferase
CNS	=	Central Nervous System
COMT	=	Catechol-O-methyltransferase
CREB	=	cAMP response element-binding protein
DA	=	Dopamine
DAT	=	Dopamine transporter
ECG	=	Epicatechingallate
EGCG	=	Epigallocatechin gallate
ERK1/2	=	Extracellular signal–regulated kinases 1/2
GABA	=	γ-aminobutyric acid
$GABA_AR$	=	$GABA_A$ receptor
GABA-T	=	GABA transaminase
GAT	=	Glutamate transporter
GDH	=	Glutamate dehydrogenase
Glu	=	Glutamic acid
GSPE	=	Grape seed proanthocyanidin extract
KAR	=	Kainate receptors
L-DOPA	=	Levodopa
LMW	=	Low molecular weight inhibitor
LTD	=	Long term depression
LTP	=	Long-term potentiation
mAChR	=	Muscarinic metabotropic receptor

MAO	=	Monoamine oxidase
nAChR	=	Nicotinic ionotropic receptor
NMDAR	=	N-methyl-D-aspartate receptors
PD	=	Parkinson's disease
PKA	=	Protein kinase A
PKC	=	Protein kinase C
PNS	=	Peripheral nervous system
vAChT	=	Vesicular acetylcholine transporter

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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