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Effects of curcuminoids and resveratrol in micro and nanoformulations on brain-derived neurotrophic factor: A brief review

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ABSTRACT

One of the main investigated neurotrophin proteins in the brain of the mammalian is brain-derived neurotrophic factor (BDNF). Learning, memory, and cognitive function are affected by the decrease of BDNF. Curcuminoids and resveratrol as the main herbal polyphenols, have significant potential in neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. The neuroprotective activities of curcuminoids and resveratrol and its ability to enhance BDNF levels have been reported in several trials. BDNF/tyrosine receptor kinase B (TrkB) signaling pathway is upregulated by curcumin treatment. Nanoformulations of curcuminoids and resveratrol by biocompatible and biodegradable nanomaterials can be considered as a novel strategy with adequate efficacy to improve the bioavailability of these polyphenols. In this way, this mini-review has been tried to address recent progress about both micro and nanoformulations of curcuminoids and resveratrol.

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Introduction

One of the most investigated neurotrophin proteins in the mammalian brain is brain-derived neurotrophic factor (BDNF). The neurogenesis process is stimulated and modulated by these neurotrophins encoded by the *bdnf* gene [1]. Certain neurons expressing tropomyosin receptor kinase B or tyrosine receptor kinase B (TrkB) in the peripheral nervous system and the central nervous system are affected by BDNF [2]. BDNF can also bind to the LNGFR (for low-affinity nerve growth factor receptor) or p75 on the surface of the cell [3]. In addition to the basal forebrain, cortex, and hippocampus, BDNF is expressed in the motor neurons, retina, kidneys, skeletal muscle, and prostate [4]. The function of BDNF is necessary for higher thinking, memory, and learning [5]. Nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) are other neurotrophins similar to BDNF, structurally [6]. The decrease of BDNF impacts on learning, memory, and cognitive function lead to behavioral disorders [7]. Phytocompounds regulate cellular signal pathways related to the expression of antiapoptotic Bcl-2 (B-cell lymphoma 2), BDNF, and glial cell line-derived neurotrophic factor (GDNF) [8]. In this case, curcuminoids and resveratrol are two main polyphenols with potential neuroprotective activities [9, 10]. These two natural compounds can affect BDNF by related signaling pathways, which we explained in this mini-review in detail. Low bioavailability of resveratrol and curcuminoids including curcumin, bisdemethoxycurcumin, and demethoxycurcumin (Figure 1) is the main hindrance for getting effective formulations suitable for physiological conditions. Low bioavailability of these natural metabolites leads to their poor absorption and fast metabolism from the reticuloendothelial system (RES) [11]. Similar to other natural metabolites [12, 13], this property can be improved by nanoformulations by biocompatible and

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biodegradable nanomaterials that have been discussed in this mini-review.

Curcuminoids

Curcumin in two main forms of keto and enol as one of the herbal polyphenols has significant potential in neurodegenerative diseases such as Parkinson's and Alzheimer's diseases [14, 15]. Furthermore, curcumin polyphenol possess promising capacity for the prevention and treatment of age-related disorders via modulating and activating the expression of BDNF [16]. This polyphenol mitigates Alzheimer's diseases-related cognitive deficits by up-regulation of BDNF-extracellular regulated protein kinase (ERK) signaling in the hippocampus [17]. Concentrations of 200 to 1820 mg/d for 8 to 12 weeks were found as curcumin supplementation dose and period range, respectively [18]. In the case of Parkinson's disease, curcumin treatment activated phosphatidylinositol 3 kinase (PI3k)/protein kinase B (Akt) and BDNF signaling pathways. It worth noting that the BDNF and PI3k/ Akt signaling pathways contribute to anti-apoptotic and nerve regeneration activities [19]. Neuroinflammation of traumatic brain injury can be ameliorated by upregulation of BDNF/TrkB signaling pathway upon curcumin treatment [20]. Treatment of forty-four females with metabolic syndrome aged 60–65 by consuming per day of one curcumin capsule (containing 10% nano-curcumin and 2% curcuminoids) and 80 mg of nano-curcumin with a treadmill exercise for 3×12–17 min for 6 weeks showed the increase of interleukin-10 (IL-10) and BDNF concentrations [21]. Heavy metals such as cadmium (Cd) can cause cytotoxicity, specifically neurotoxicity because of its high bioavailability (15–20 years) [22]. In this regard, curcumin at a concentration of 160 mg/kg mitigated the neurotoxicity effect of Cd with the promotion of neurogenesis via increasing of the hippocampal BDNF level [23]. In a combination therapy, low ferrous sulphate (18 mg elemental iron) and 500 mg curcumin for 42 days led to higher serum BDNF level compared to controls and high ferrous sulphate (65 mg elemental iron) and 500 mg curcumin. In this regard, combination of curcumin with low dose iron supplementation increased ferritin formation followed by improved intestinal iron uptake over time [24]. Decreased BDNF levels in depressive state can result in the memory deficits. Curcumin at a dose of 200 mg/kg for one week increased the hippocampal BDNF in model rats [25]. In another combination therapy, curcumin (0.5 mg/kg) and fluoxetine (10 mg/kg) enhanced the cerebral expression of *bdnf* mRNA [26].

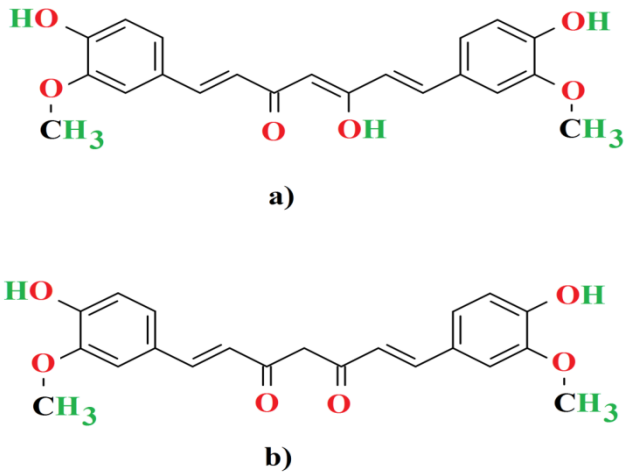

Fig. 1. Chemical strictures of enol (a) and keto (b) form of curcumin.

Resveratrol

Resveratrol ($C_{14}H_{12}O_3$; 3,5,4'-trihydroxystilbene) is a hydroxylated derivative of stilbene (stilbenoid), a type of polyphenols, synthesized by various fruits and plant species such as blueberries, grapes, peanuts, raspberries, and Japanese knotweed (*Polygonum cuspidatum*) [27, 28]. There are two isomers including cis- and trans-reserverarol (Figure 2). Low bioavailability of resveratrol can be ameliorated by several strategies such as using natural bioenhancers. For instance, piperine as an alkaloid can increase astrointestinal absorption and decrease of efflux of resveratrol from the site of action by related mechanisms [29]. Bioenhancer effects of piperine and quercetin as increased intestinal permeability of resveratrol have been illustrated in figure 3. Chronic restraint stress can be ameliorated by resveratrol similar to the effects of fluoxetine. Resveratrol can mitigate chronic restraint stress by increasing phosphorylation of extracellular signal-regulated kinase (pERK), BDNF, and Bcl-2 mRNA expression [28]. Long-term cognitive dysfunction and neuropathological brain changes may result from repeated neonatal exposure to general anesthetics such as sevoflurane. In neurodegenerative diseases, a reduction of sirtuin 1 (SIRT1) can cause cognitive dysfunction. BDNF downregulation regulated via

cAMP response element-binding protein (CREB) and methyl-cytosine-phosphate-guanine–binding protein 2 (MeCP2) leads to the SIRT1 inhibition in hippocampi. Resveratrol increased the expression of hippocampal SIRT1 and BDNF in mice exposed to sevoflurane [30]. Resveratrol has potential antidepressant-like activity. In this regard, resveratrol has an action similar to desipramine by increasing BDNF, phosphorylated pERK, and CREB [31]. Lipopolysaccharides can induce depressive-like behavior and inflammatory response [32]. Reduction of BDNF expression and lipopolysaccharide-induced nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation in the hippocampus and prefrontal cortex has been indicated for resveratrol [33]. In another study, serum BDNF levels in male Wistar rats after 2 and 4 weeks of treatment with 10 mg/kg resveratrol were found to values of 1.52 and 1.64 ng/mL, respectively [34]. The therapeutic effects of resveratrol on learning and memory can result from the induction of BDNF expression in the hippocampus by resveratrol. The expression levels of BDNF exons III, IV, and IX were increased at a concentration of 120 mg/kg BW/day in adult rats. However, the concentration of pro-BDNF protein has not shown changes in the hippocampal tissues in embryonic and adult rats [35]. A single dose of resveratrol at a concentration of 180 mg/kg in 300 µL encapsulated in sunflower oil increased the level of BDNF in the frontal cortex of rat model [36].

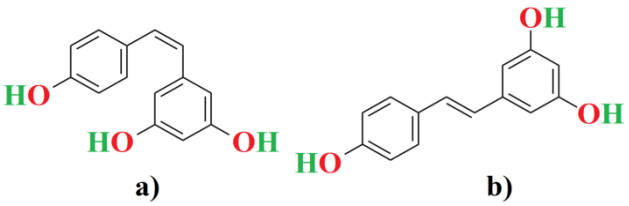

Fig. 2. Chemical strictures of cis- (a) and trans-resveratrol (b).

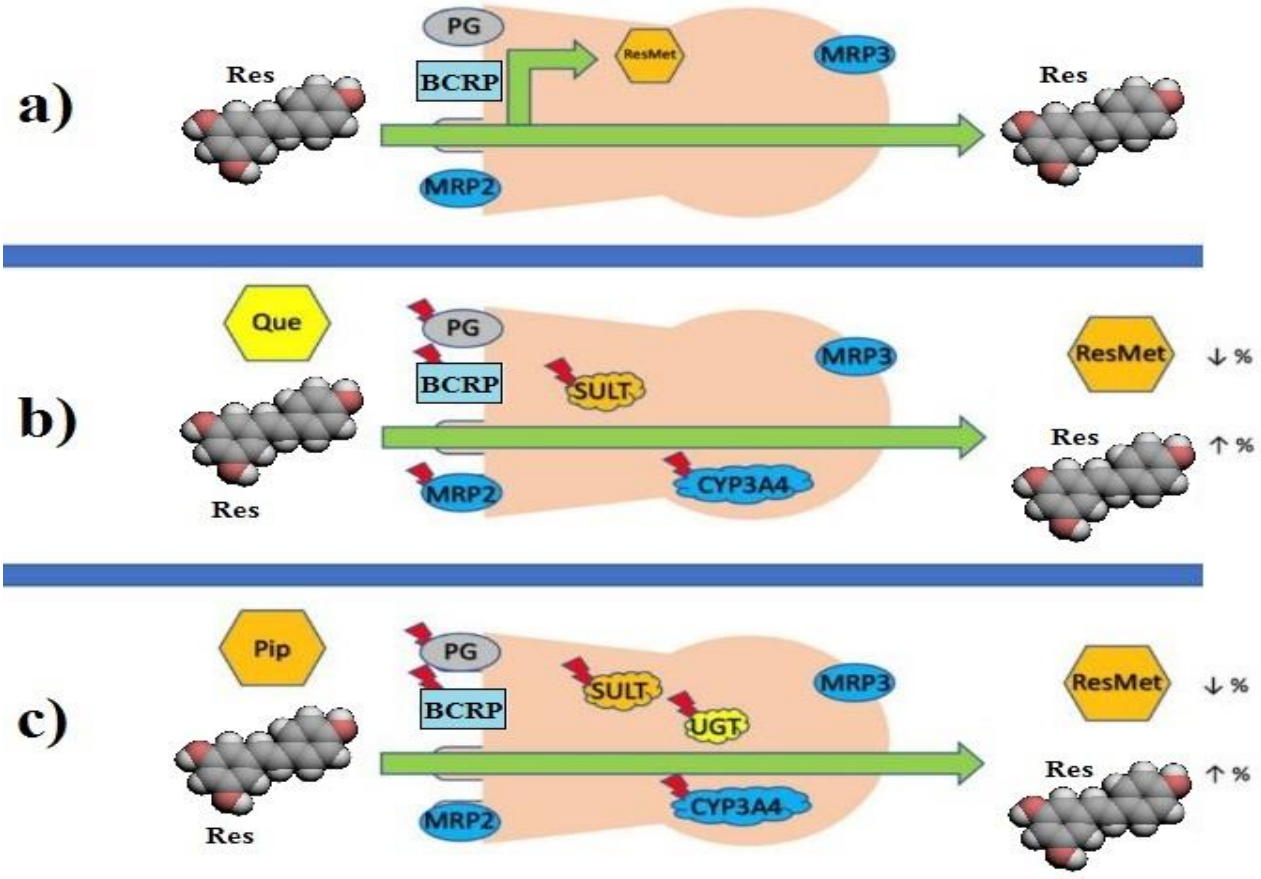

Fig. 3. Changes in intestinal permeability with (a) resveratrol alone, (b) quercetin, and (c) piperine. Multidrug resistance protein 2 (MRP2), P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), sulfotransferase (SULT), glycosyltransferases (UGT), cytochrome P450 3A4 (CYP3A4) (Extracted and modified from [29]).

Conclusions

BNDF is a molecule related to neuroprotection in most neurodegenerative disorders. The application of bioenhancers such as piperine may be a suitable strategy to ameliorate the bioavailability of curcuminoids and resveratrol in novel drug delivery systems. Curcumin at a concentration of 160 mg/kg reduces the neurotoxicity effect of heavy metals such as Cd with induction of neurogenesis via increasing of the hippocampal BDNF level. The combination of curcumin with low-dose iron supplementation enhanced ferritin formation and BDNF levels. In addition, curcumin in combination with fluoxetine drug augmented the cerebral expression of *bdnf* mRNA. Resveratrol can increase BDNF serum amounts in brain parenchyma. The induction of BDNF expression in the hippocampus by resveratrol has exhibited a vital role in the therapeutic effects of this metabolite on the memory and learning. Anti-depressant-like properties, anti-inflammatory, and antioxidants have been found for resveratrol. Similar to fluoxetine, resveratrol can mitigate chronic restraint stress by increasing pERK, BDNF, and Bcl-2 mRNA expression. Resveratrol can increase the expression of hippocampal SIRT1 and BDNF in mice with long-term cognitive dysfunction and neuropathological brain changes. Resveratrol can be considered an effective therapeutic agent with lipopolysaccharide-induced depressive-like properties and anti-inflammatory activity via regulating BDNF and pCREB expression in the hippocampus and prefrontal cortex.

Study Highlights

- Curcumin at a concentration induces neurogenesis via increasing of the hippocampal BDNF level.
- The combination of curcumin with low-dose iron supplementation enhances ferritin formation and BDNF levels.
- Curcumin in combination with fluoxetine drug increases the cerebral expression of *bdnf* mRNA.
- Resveratrol augments BDNF serum amounts in brain parenchyma.
- Resveratrol increases the expression of hippocampal BDNF in mice having neuropathological brain changes.
- Resveratrol shows anti-inflammatory activity via regulating BDNF.

Abbreviations

Akt: Protein kinase B
Bcl-2: B-cell lymphoma 2
BDNF: Brain-derived neurotrophic factor
CREB: cAMP response element-binding protein
GDNF: Glial cell line-derived neurotrophic factor
MeCP2: Methyl-cytosine-phosphate-guanine–binding protein 2
NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells
NGF: Nerve growth factor
NT-3: Neurotrophin-3
NT-4: Neurotrophin-4
pERK: Phosphorylation of extracellular signal-regulated kinase
PI3k: Phosphatidylinositol 3 kinase
RES: Reticuloendothelial system
SIRT1: Sirtuin 1
TrkB: Tyrosine receptor kinase B

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Author Contributions

All authors: conceptualization, preparing the first draft, and editing.

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