SPANDIDOS PUBLICATIONS WORLD ACADEMY OF SCIENCES JOURNAL 8: 34, 2026

Bioactive compounds that enhance dopamine levels in the brain, with their challenges and future prospects (Review)

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Received December 3, 2024; Accepted February 19, 2026

DOI: 10.3892/wasj.2026.449

Abstract. The dopamine molecule serves as a neurotransmitter, functioning as an amine that is formed by removing a carboxyl group from L-DOPA. This essential molecule ($C_8H_{11}NO_2$) is produced by neurons to transmit information to other neurons in both the brain. The present review discusses the mechanisms through which the bioactive molecules such as naringenin, cyanidin, uridine, luteolin, rutin, caffeine and morphine can enhance dopamine synthesis, modulate its pathways and support brain health. Dopamine deficiency is a major risk factor for neurodegenerative disorders, and it is imperative to explore the relationship between dopamine level and neurodegenerative disorders. Bioactive molecules provide promising avenues for enhancing dopamine signaling and preventing neurodegenerative disorders; challenges remain in maximizing dopamine bioavailability using bioactive molecules. The present review highlights the various benefits of bioactive molecules in enhancing dopamine synthesis, preventing neurodegenerative disorders, and ensuring safety for brain health, as well as opportunities for future research.

Contents

1. Introduction

Natural bioactive compounds that originate from plants, animals, fungi and their bioactive compounds have been extensively examined and researched for their use as treatments for multiple conditions, such as neurological disorders, cardiovascular diabetes, hypertension, reproductive disorders and cancer (1). A number of studies have comprehensively covered a variety of different natural bioactive components utilized effectively for neurodegenerative disorders (NDDs) such as memory loss, Huntington's disease, Parkinson's disease and amyotrophic lateral sclerosis (1,2). Natural substances are being studied as possible neuroprotective agents for the treatment of NDDs (3). Since natural treatments are less costly and more culturally appropriate, and may aid in reducing the risk of developing neurodegenerative disorders at an early stage, millions of individuals with age-related NDDs may benefit from using natural bioactive compounds instead of traditional pharmaceutical products. Several investigations using animals and cells have demonstrated the neuroprotective benefits of a polyphenol-rich diet (3-5). One of the most natural methods used to raise dopamine levels and increase dopamine release, is by the use of bioactive compounds such as, naringenin, cyanidin, uridine; rutin, naringin, caffeine, vitamin D and amino acids. There continues to be a shortage of established procedures for examining the effects of bioactive compounds on dopamine levels in the brain. Some of the current studies systematically cover a number of different natural bioactive compounds which enhance dopamine levels, such as β-phenylethylamine (β-PEA), omega-3 fatty acids and others that have been shown to enhance dopamine levels in the brain (6).

2. Dopamine

Dopamine (3,4-dihydroxyphenethylamine) is an amine formed by removing a carboxyl group from the L-DOPA ($C_8H_{11}NO_2$) molecule (Fig. 1); it is an essential particle produced in the brain, kidneys and in plants, and in the majority of animals. Dopamine functions as a neurotransmitter, a substance produced by neurons to transmit information to other neurons. A recent study focused on how aromatherapy influences the treatment of neuro pathologies, such as Alzheimer's disease (7). The brain chemical, dopamine, affects behavior

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Key words: naringenin, cyanidin, rutin, uridine, caffeine

driven by rewards. The pituitary gland release of prolactin is suppressed by hypothalamic dopamine. There are five known subtypes of dopamine receptors in mammals, namely D1 D2, D3, D4 and D5; there are two groups into which these receptors are separated. In humans, the trace amine-associated receptor 1 has a high affinity for dopamine. Abnormal dopamine synthesis or metabolism has been related to addiction, bipolar disease and attention deficit hyperactivity disorder (8). In a previous study, an *in vitro* neuronal cell line system was employed to examine the possible neuroprotective properties of Aloysia citrovorum-derived essential oils against oxidative stress and amyloid-induced neurotoxicity (9). The main enzyme that converts DOPA into dopamine is known as DOPA decarboxylase. Tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of dopamine, transforms tyrosine into DOPA (9). Considering the intimate association between the hippocampus and memory/learning processes, essential oils may change NDDs via altering the olfactory system. The process of converting L-tyrosine to L-DOPA is facilitated by the enzyme tyrosine hydroxylase (9). Furthermore, essential oils may function directly as therapies by modulating a variety of oxidative stress and inflammatory processes linked to NDDs.

In certain cell types, such as neurons and cells found in the adrenal medulla, dopamine synthesis is achieved through a two-step process (10). The synthesis of dopamine is under the control of homeostasis, which can increase or decrease production depending on the levels of extracellular dopamine (11). The essential components for this reaction are iron (Fe^{2+}), diatomic oxygen (O_2) and tetrahydrobiopterin (BH4).

The conversion of L-DOPA to dopamine is catalyzed by aromatic L-amino acid decarboxylase during neurotransmitter synthesis (12). The rate at which dopamine is synthesized is usually determined by the speed at which TH converts tyrosine into L-DOPA. The function of TH is carefully monitored by different methods, including phosphorylation at four serine residues by several kinases (12):

Dephosphorylation by two phosphatases: The regulation of enzyme activity through response inhibition by catecholamine neurotransmitters, such as dopamine occurs through protein-protein interactions with other enzymes and structural proteins. To create dopamine effectively, the body needs tyrosine, which can be obtained from dietary proteins or converted from phenylalanine. Even though dopamine can be found in certain foods, it is incapable of crossing the brain barrier, requiring the brain to synthesize it for proper neuronal functioning (9).

Degradation: Dopamine undergoes a process of breakdown by specific enzymes to form inactive metabolites. The degradation of dopamine in the striatum is mostly carried out by MAO-A, although both MAO-A and MAO-B are involved in its metabolism (13).

Catechol-O-methyl transferase (COMT). In order to degrade catecholamine neurotransmitters, such as dopamine, norepinephrine and epinephrine, the enzyme COMT transfers a methyl group from s-adenylyl methionine to catechol substrates. The formation of O-methylated metabolites of these neurotransmitters aids in stopping their signaling, particularly in areas of the brain with relatively low dopamine transporter expression, such as the prefrontal cortex (14).

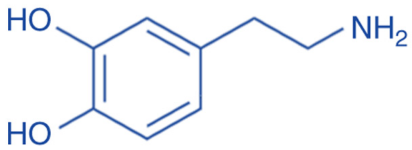

Figure 1. Dopamine (3,4-dihydroxyphenethylamine) is an amine formed by removing a carboxyl group from the L-DOPA ($C_8H_{11}NO_2$) molecule.

Aldehyde dehydrogenase (ALDH): The primary result of dopamine degradation is Homovanillic acid, which is discharged through urine (9).

As regards dopamine receptors, these are classified into two main families: D1-like receptors (D1 and D5) and D2-like receptors (D2, D3 and D4). These receptors are distributed throughout the brain and play crucial roles in various physiological processes. As regards functions, the brain is filled with receptors that are vital for many physiological functions (11): Learning and motivation, memory and focus, pleasure and reward, mood and attention, movement and coordination, sleep regulation, pain processing and cardiovascular function.

As regards diseases and disorders, there is a correlation between dopamine dysfunction and multiple medical conditions (10). i) Parkinson's disease: Due to the degeneration of dopaminergic neurons in the substantia nigra, motor symptoms and impulsivity control disorders manifest (15). ii) Schizophrenia: The dysregulation of dopamine signaling affects the pathways of both the mesolimbic and mesocortical regions. iii) Attention deficit hyperactivity disorder: Related to changes in dopamine signaling that impact focus and self-control. iv) Addiction: The presence of dopamine is essential for the brain to engage in rewarding activities that can become addictive. v) Tourette syndrome: Related to disruptions in dopamine signaling influencing motor function. vi) Bipolar disorder: Results in an imbalance of dopamine and other neurotransmitters impacting mood and behavior. Exploring the complex functions of dopamine in the brain and body is a vital research goal, potentially paving the way for groundbreaking therapies for various neurological and psychiatric conditions (15).

3. Bioactive compounds that enhance dopamine levels in the brain

Naringenin. Naringenin (molecular formula: $C_{15}H_{12}O_5$) is the glycoside portion of the molecule Naringin that protects the nigrostriatal dopaminergic projection in neurotoxin models of Parkinson's disease, and it has a typical chemical structure (16). These characteristics are a basic flavonoid structure with 15 carbon atoms and three rings, two of which are benzene rings that connect the three carbon chains (17). Naringenin, chemically known as 4,5,7-trihydroxyflavone, has a molar mass of 272.3 and a melting point of 251°C (18). In nature, naringenin is solid and nearly insoluble in water, although it is soluble in organic solvents such as ethanol, ether, dimethyl form amide and dimethyl sulfoxide. Naringenin occurs primarily in citrus fruits such grapes, oranges, blood oranges, lemons and grapefruit, with some research demonstrating a high concentration in citrus peel (19) (Fig. 2A).

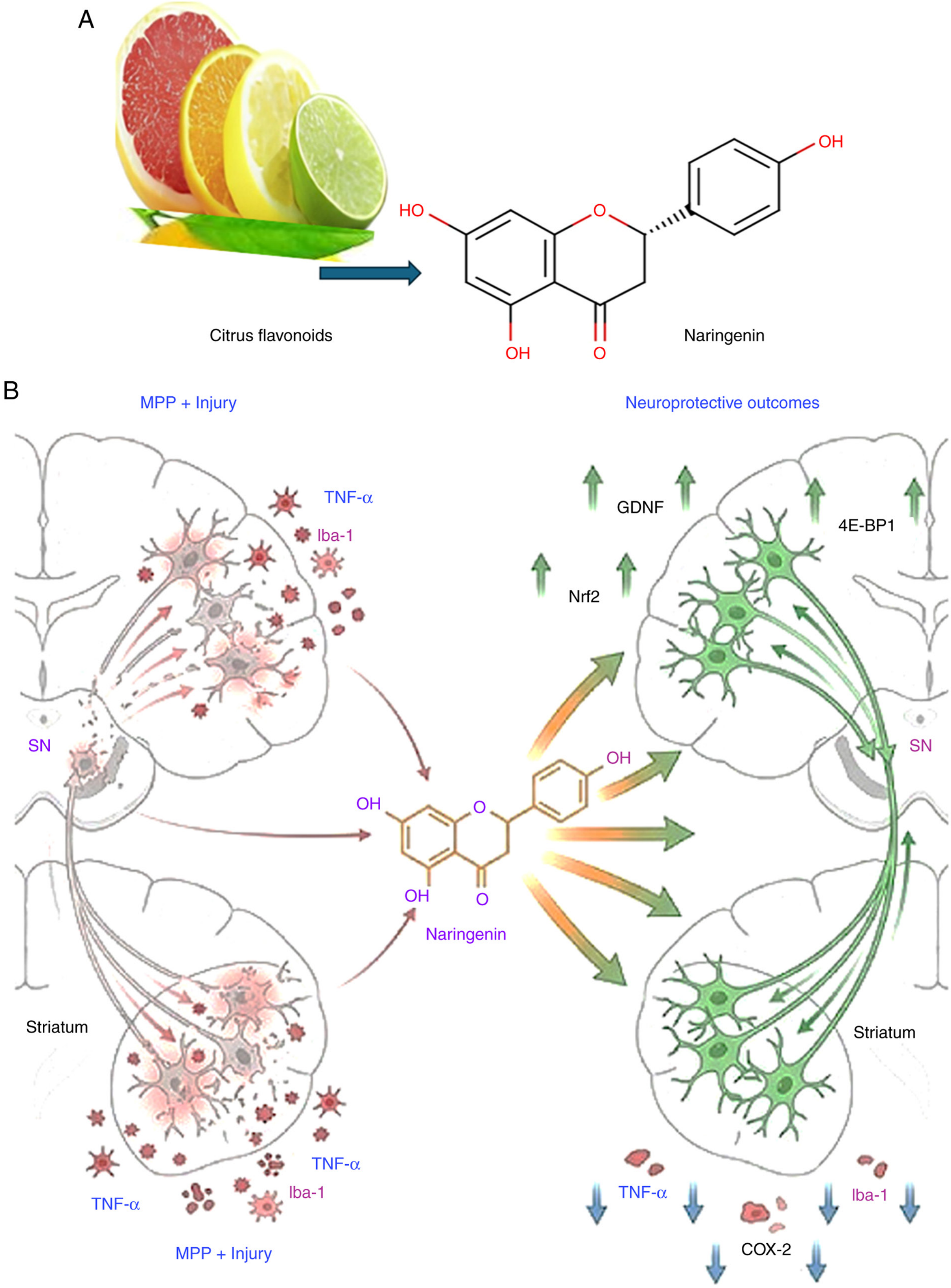

Figure 2. (A) Naringenin (molecular formula: $C_{15}H_{12}O_5$) in citrus fruits such grapes, oranges, oranges, lemons and grapefruit. (B) Neuroprotective mechanisms of naringenin ($C_{15}H_{12}O_5$) in an experimental model of Parkinson's disease: Regulation of dopaminergic survival, GDNF expression, and TNF-α/COX-2-driven neuro inflammation. GDNF, glial cell line-derived neurotrophic factor; 1-methyl-4-phenylpyridinium (MPP+) selectively targets dopaminergic neurons by uptake via the dopamine transporter (DAT), inhibiting mitochondrial complex I (NADH dehydrogenase) to disrupt electron transport, deplete ATP, and generate reactive oxygen species (ROS). This produces oxidative stress, apoptosis, and energy failure, emulating PD nigrostriatal degeneration.

Recent experimental evidence indicates that naringin and naringenin demonstrate extensive pharmacological activity, with specific focus on neurodegenerative diseases including Alzheimer's and Parkinson's, along with other neurological disorders, such as anxiety, depression, schizophrenia and chronic hyperglycemic peripheral neuropathy.

Neurodegeneration is a complex process influenced by various factors, including oxidative stress, dopamine depletion, and neuro inflammation. Naringenin, a compound found in citrus fruits, has been shown to boost dopamine levels and possess anti-inflammatory properties that can aid in reducing inflammation within the brain (20).

Naringenin may aid in the recovery of dopaminergic neurons following injury if it is administered shortly after the damage has occurred. Dopaminergic neurons are preserved, and glial cell line-derived neurotrophic factor (GDNF) is restored in the substantia nigra (SN), and the number of neurons immune reactive for calcium-binding adaptor molecule 1 (Iba-1) and necrosis factor α (TNF-α) are also resorted (21). In the striatum was reduced as indicators of inflammation in the brain after pre-treatment with naringenin in rats with unilateral 1-methyl-4-phenylpyridinium (MPP+) injury. Eukaryotic initiation factor 4E-binding protein 1 (4E-BP1), and growth differentiation factor and GDNF were upregulated in the cerebellum following a single injection of naringin. Naringin then decreases TNF-α and cyclooxygenase-2 (COX-2) levels and raises the transcription factor nuclear factor 2 (Nrf2) (20).

The potential of naringin as an antioxidant shows promise in the treatment of neurology and diabetes. The decline of nerve cells and dopamine levels in the striatum and substantia nigra pars compacta eliminates dopamine-producing cells, paving the way for the development of Parkinson's disease (Fig. 2B).

Changes in the brain's dendritic arborization and synaptic architecture have been shown to be associated with psychological and neurological disorders such as depression, anxiety and memory loss. Naringenin, a dietary flavanone found in citrus fruits, vegetables, berries and nuts, may play a significant role in addressing these issues (22).

Cyanidin. Cyanidin has been shown to protect SH-SY5Y human neuroblastoma cells from MPP+-induced toxicity, which serves as a model for Parkinson's disease. This finding highlights the potential therapeutic benefits of cyanidin in combating neurodegenerative diseases (23).

Cyanidin belongs to the flavonoid family of polyphenolic natural compounds. The molecular structure of cyanidin is illustrated in Fig. 3. It is commonly found in fruits and vegetables, as well as in leaves, petals, flowers and red fruits. Several vegetables and fruits including blackberries, red onions, grapes, cherries, apples, raspberries, peaches, plums, beans, red cabbage and cranberries contain cyanidin (24).

Cyanidin have been shown to have potential therapeutic effects on a variety of disorders and are commonly recommended as medicines in several countries (25). Consumption cyanidins provide health benefits against the development of obesity and diabetes, as well as suppressing inflammatory. Cyanidin and its metabolites have higher absorption and bioavailability, and interaction with gut microbes may enhance their health benefits. Several *in vitro* studies have demonstrated the ability of cyanidin to reduce reactive oxygen species (26). Despite current reports indicating the various health benefits of cyanidin, its antioxidant potential through modulation of the Nrf2 pathway is still less defined in modulating oxidative stress against DNA damage, apoptosis, carcinogenic toxicity and inflammatory conditions (26). The administration of cyanidin shows promise as a potential pharmacological or functional food therapy for combating oxidative stress and protecting against Alzheimer's disease. Cyanidin possesses potent antioxidant properties and unique characteristics that render it a promising candidate for further research and development as a therapeutic agent. Therefore, it is imperative to conduct further *in vivo* studies to explore its potential benefits in greater detail (27). To further elucidate the molecular mechanisms underlying the neuroprotective effects of cyanidin, a previous study investigated the effects of cyanidin on neuroinflammation in human neuroblastoma cells (27). Although these findings indicate the potential benefits of cyanidin for neurological health, further research is necessary to establish a direct association between cyanidin consumption and dopamine production or regulation in humans.

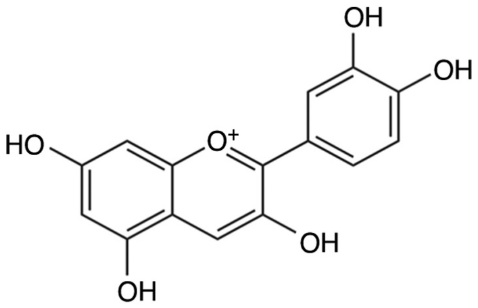

Figure 3. Molecular structure of cyanidin.

Rutin. Rutin, a flavonoid quercetin glycoside and the disaccharide rutinose (α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranose) (Fig. 4), is found in numerous plants and fruits, partiuclarly buckwheat, apricots, cherries, grapes, grapefruit, peaches and oranges (28). Pharmacological studies have reported the beneficial effects of rutin in several disease states, and its therapeutic potential in several models of non-communicable diseases has aroused great enthusiasm. The present review summarized the currently available knowledge on the mechanisms of action of rutin in different experimental models of diseases of the central nervous system. Rutin has been shown to upregulate the tyrosine hydroxylase (TH) gene, a crucial component in the biosynthesis of dopamine (28) The mechanisms of action reviewed herein include reducing pro-inflammatory cytokines, improving antioxidant enzyme activities, activating mitogen-activated protein kinase cascade, downregulating mRNA expression of Multiple Sclerosis (MS)-related and pro-apoptotic genes, upregulating ion transport and anti-apoptotic genes and restoring mitochondrial complex enzyme activities. These findings suggest that rutin may be a promising neuroprotective compound for the treatment of atypical neurological disorders (29).

Rutin has been found to upregulate the TH gene, a crucial component in dopamine biosynthesis (28). This discovery suggests that rutin may play a role in increasing dopamine production within the body. In a study utilizing a rat model of 6-hydroxydopamine (6-OHDA)-induced Parkinson's disease, pre-treatment with rutin was shown to protect against the reduction in dopamine content and its metabolite 3,4-dihydroxyphenyl acetic acid (30). These results indicate that rutin could

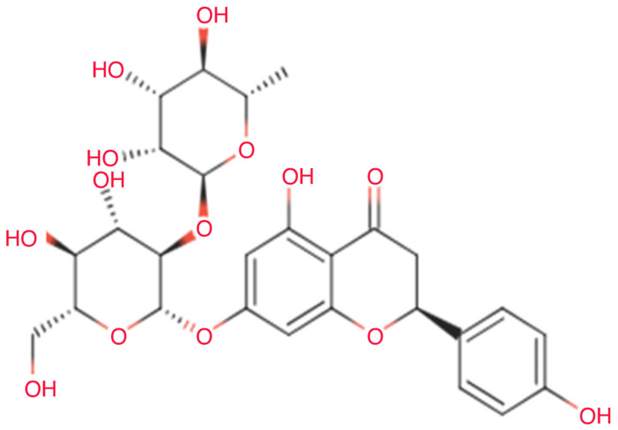

Figure 4. Molecular structure of rutin.

Figure 5. Natural products rich in uridine.

potentially help in maintaining optimal dopamine levels in the brain. Furthermore, rutin has exhibited neuroprotective properties on dopaminergic neurons. In a previous study, in an animal model of Parkinson's disease, rutin was able to shield neurons in the substantia nigra from the detrimental effects of 6-OHDA, indirectly supporting dopamine function (30). When combined with levodopa, a common medication used for Parkinson's disease, rutin was shown to mitigate the peripheral adverse effects of dopamine, such as nausea and hypotension (28). This suggests that rutin may enhance the efficacy of dopamine-related treatments. Moreover, rutin has demonstrated antioxidant and anti-inflammatory characteristics, which could contribute to its neuroprotective effects (31). By reducing oxidative stress and inflammation, rutin may aid in the preservation of dopaminergic neurons and the maintenance of dopamine levels. While these findings are promising, it is important to acknowledge that the majority of studies have been conducted using animal models or *in vitro*. Further research, particularly human clinical trials, is necessary to fully comprehend the effects of rutin on dopamine levels and its potential therapeutic applications in neurodegenerative disorders. Rutin, a flavonoid present in numerous plants and fruits, has demonstrated promising effects on dopamine levels and neuroprotection in several studies (31).

Uridine. Uridine occurs primarily in blood and brain fluid, where it helps to maintain fundamental cellular activities that are influenced by enzyme activity, dietary patterns and ATP depletion. Certain mushrooms may have distinct synergistic effects with uridine, and antioxidants, potentially improving brain function (32,33). Uridine is contained in infant formulae as its monophosphate, UMP, which is bioavailable (34,35).

Uridine is known to play a crucial role in modulating neurotransmitter systems, specifically dopamine and serotonin. This nucleoside has been shown to potentially produce an anti-epileptic effect by disrupting the dopaminergic system. Giant oyster mushrooms, lion's mane and tiger milk mushroom (a lesser-known variation) promote neurite outgrowth, which regenerates nerve cells. They boosted nerve growth factor in both cells and animals.

Several foods contain uridine in the form of RNA (36). Although it is claimed that virtually none of the uridine in this form is bioavailable, as demonstrated by Gasser *et al* (36) in 1981, it is destroyed in the liver and gastrointestinal tract, and no food, when consumed, has ever been reliably shown to elevate blood uridine levels. A previous study found that plasma uridine levels increased 1.8-fold at 30 min following the consumption of beer, indicating at the very least inconsistent evidence (37). On the other hand, ethanol which is found in beer raises uridine levels, which may explain the increased Uridine plasma concentration rises due to pyrimidine breakdown after purine degradation by ethanol and fructose (38).

A number of natural products rich in uridine (Fig. 5), such as milk and dairy products from goats and sheep, tomatoes (0.5-1.0 g uridine per kg/dry weight) (39), sugarcane extract, broccoli and beer (40), meats (such as the liver and pancreas) and Brewer's yeast (1.7% uridine, dry weight) (39). Uridine metabolism consists of three stages: *De novo* synthesis, salvage synthesis path and catabolism and homeostasis, which is closely related to glucose homeostasis, and the breakdown of amino acids (40). Uridine contributes to the glycolysis pathway of galactose (41). There is no metabolic mechanism that converts galactose. As a result, galactose is converted to glucose and metabolized by the common glucose pathway. Uridine is absorbed by the brain to generate CDP-choline, a well-known memory enhancer, as well as other phospholipids. In a study on healthy individuals who underwent brain imaging, uridine supplements boosted their brain levels of phosphor ethanolamine (PE), a key phospholipid-building component (42). Uridine is produced by the liver and is released during regular cell and RNA breakdown in humans, particularly during fasting from fat cells. As a result, uridine is constantly present in the circulation (43). Recently produced or recycled uridine engages in several critical activities in the brain and nervous system, including maintaining the lipid membranes of neural cells and creating connections between neurons, as it can pass the blood-brain barrier (44). Additionally, it appears to bind to P2Y2, P2Y4, P2Y6 and P2Y14 receptors in the brain. However, it may also potentially be attached to other, yet unidentified receptors (45). Uridine is deemed to be a promising molecule for further research; however, there are presently few human clinical trials evaluating its effects and there is insufficient information available on its metabolism (Fig. 6) and its function in the brain (45).

Vitamin D and sunlight. Human skin produces vitamin D, a fat-soluble vitamin, when it is exposed to sunlight. However, the majority of individuals do not receive sufficient levels of sun-induced vitamin D. Researchers estimate that 50% of individuals may not have sufficient levels vitamin D (46). Vitamin

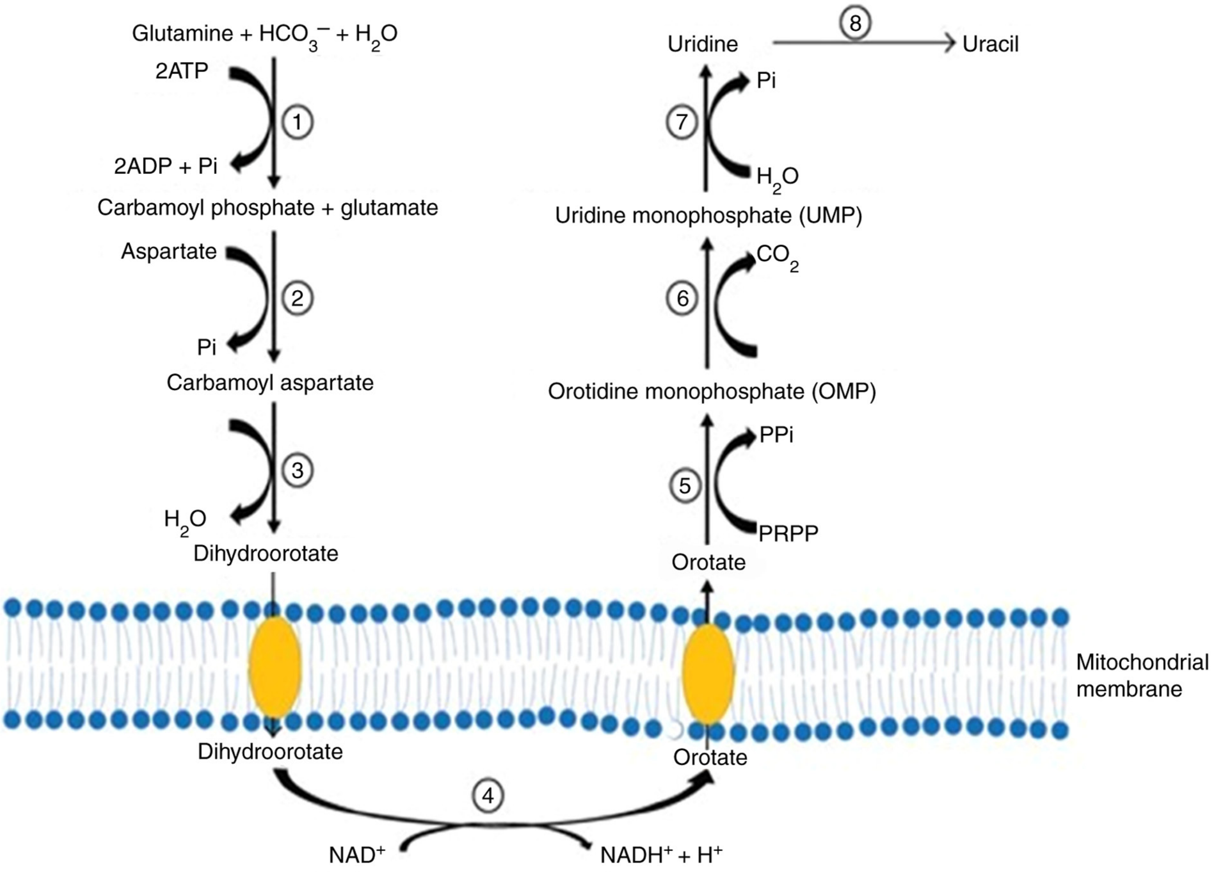

Figure 6. Uridine metabolism phases and its function in the brain.

D is produced in the skin following exposure to UVB rays but without burns. In addition to the liver and kidneys, where 1,25(OH)2D is produced in a paracrine/autocrine function, additional tissues also receive vitamin D subsequent metabolism to produce its primary circulating form, 25(OH)D, and hormonal form, 1,25(OH)2D. The immune system, intestinal epithelium, parathyroid gland, prostate gland and breast are a few types of these tissues (46).

Lower dopamine levels are caused by a vitamin D deficiency, while dopamine release is enhanced by vitamin D3 therapy (47,48). One of the most natural methods to raise dopamine levels in the brain is to spend time in the sun. Studies have revealed that exposure to sunshine increases dopamine release (49,50).

Dopamine levels in the brain can rise following exposure to sunlight. To support dopamine, release, exposure to sunlight during the spring and summer seasons is mandatory. It is vital to expose the top of the face and head to sunlight to promote dopamine levels. It is therefore recommended that no head and face cover or sunglasses be used to increase the level of dopamine in the brain (51).

Dopamine D1 receptor (Drd1) signaling within the superchiasmatic nucleus (SCN) is essential for resynchronizing activity rhythms in time with phase-shifting light-dark cycles and that raising the Dopamine (DA) tone through the selective activation of dopaminergic neurons in the ventral tegmental area VTA accelerates photic stimulation (51). (Fig. 7), illustrates the functional connection between dopaminergic neurons in the ventral tegmental area (VTA) and neurons in the SCN that express Drd1 receptors, demonstrating their direct neuroanatomical and functional link. Stimulating these neurons while recording SCN activity allows for functional assessment and real-time study of the VTA-SCN circuit dynamics, accelerating the response to light stimulation.

There are several natural products rich in vitamin D. According to studies, 25(OH)D appears to be roughly 5-fold more potent than the parent vitamin in terms of increasing blood 25(OH)D concentration (52,53). Further research discovered that when the 25(OH)D content of beef, pig, chicken, turkey and eggs is taken into consideration, the overall quantity of vitamin D in the meal is 2- to 18-fold greater than the amount in the parent vitamin alone, depending on the food (52).

Vitamin B9 and magnesium (Mg). Vitamin B9 (folate) is a primary vitamin B that plays a key role in methyl-group transfer reactions and is one of the most critical vitamins required for the optimal performance of energy and nervous system functions. The connection between mental health signs and B vitamins must be understood. Mental symptoms can be suppressed, and the disease duration may decrease with the use of vitamins B6, B8 and B12; individuals with low folate levels in their blood are at an increased risk of suffering from depression (54). One of the reasons for this is that folate is necessary for the production and enhancement of dopamine in the brain (54,55). When there are low folate blood levels, there will also be lower levels of dopamine as the body cannot

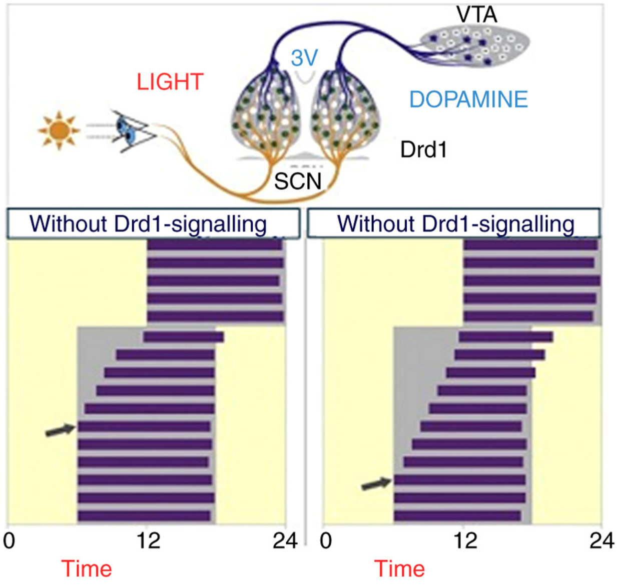

Figure 7. The image illustrates the functional connection between dopaminergic neurons in the VTA and neurons in the SCN that express Drd1 receptors, demonstrating their direct neuroanatomical and functional link. Stimulating these neurons while recording SCN activity allows for the functional assessment and real-time analysis of the VTA-SCN circuit dynamics, accelerating the response to light stimulation. VTA, ventral tegmental area; SCN, suprachiasmatic nucleus.

produce dopamine efficiently, contributing to depression (56). Another condition among depressed individuals is folate deficiencies; aproximately one-third of depressive patients have an absolute deficiency. Water-soluble vitamin folate is required for the correct production of dopamine, adrenaline and serotonin neurotransmitters (55). Natural folate sources include leafy greens, asparagus, brussels sprouts, avocado, beef liver, seeds and nuts (57). Natural compounds, such as magnesium are an essential mineral. Unfortunately, many individuals are deficient in it. This is unfortunate as it plays a role in >300 biochemical reactions in our body and is essential for optimal neurotransmitter activity. Magnesium has antidepressant effects, one reason being that it increases dopamine activity in the brain (58).

There are ample foods that are high in magnesium and the consumption of these foods on a regular basis can ensure adequate levels. Such foods include spinach, watercress, pumpkin seeds, almonds, avocados and nuts (58).

Amino acids

Phenylalanine (Phe) and tyrosine (Tyr). The only other known activities of aromatic amino acids in the brain, previously being parts of protein, are as precursors to the catecholamine (dopamine, norepinephrine and adrenaline) and the monoamine neurotransmitter, serotonin. This latter biochemical association is critical due to brain concentrations of catecholamine [tryptophan as (5HT), Phe and Tyr] and other precursor amino acids, which are in turn regulate the synthesis and release of these neurotransmitters (59).

The large neutral amino acids and other amino acids that compete with them for a shared transporter across the blood brain barrier, as well as physiological and pathophysiological variables that affect the blood concentrations of these amino acids predictably alter the concentrations of aromatic amino acids in the brain, the production and release of certain monoamine transmitters, and subsequently the way in which the brain functions (59,60).

With an emphasis on the Tyr-catecholamine association, the present review takes into account the research demonstrating that precursor availability affects monoamine synthesis, as well as the physiological variables that affect the connection. The hypothesis that Phe functions as a substrate with Tyr for Tyr hydroxylase and is not an inhibitor of this enzyme *in vivo* at normal and even high concentrations, is supported by the consideration of the role of Phe in catecholamine production. The present review also discusses how Tyr-mediated modifications to catecholamine production affect brain activities (61).

The enzyme TH catalyzes the first step, which is hydroxylation to DOPA. Aromatic L-amino acid decarboxylase rapidly converts DOPA to dopamine after it is produced. In neurons that employ dopamine as a transmitter, enzymatic alteration stops there. An extra enzyme called dopamine-by-hydroxylase is present in neurons that employ norepinephrine as a transmitter, and it transforms dopamine into norepinephrine. Phenylethanolamine N-methyltransferase is an extra enzyme found in neurons that use epinephrine as a transmitter. It catalyzes the conversion of norepinephrine to epinephrine. Tyr hydroxylation, the first step in the route, is rate limiting, which means that it regulates the rate of synthesis throughout the whole pathway (61,62). Initial research has revealed that the enzyme is susceptible to end-product inhibition (63).

A previous *in vivo* study tracked the rate at which 14C-Tyr converted to 14C catecholamine in the brains of rats given a medication to increase endogenous catecholamine concentrations (such as a monoamine oxidase inhibitor) or *in vitro* using enzyme preparations (64). Subsequent research revealed that TH was susceptible to several other regulators, such as an enzyme that is rapidly activated in response to an increase in neuronal activity (i.e., synthesis rises during times of greater neuronal demand (65). Additional research revealed that administering the amino acid to increase brain Tyr concentrations can rapidly accelerate the production of DOPA in rat brains (66). This result implied that Tyr concentrations are at much below saturation levels in the area around TH. This discovery was further refined to demonstrate that neuronal activity was necessary, at least in DA neurons, to detect a precursor-linked stimulation of DA production. For instance, Tyr administration may increase the synthesis of dopamine in the corpus striatum, which is home to a significant terminal projection from DA cell bodies in the substantia nigra. However, to activate the neurons in these rats, pre-treatment with a DA receptor antagonist was necessary (67).

DA neurons in the rat retina provide a physiological illustration of the requirements for neuronal activity. The retina has a large amount of light-sensitive dopamine interneurons, which are quiescent in darkness, but become active in light. Neuronal activity is associated with TH activation (68). If activation is typically necessary for Tyr administration to raise Tyr hydroxylation rate, Tyr injection should increase hydroxylation rate in retinas during the day but not at night, (69,70). DOPA concentrations typically accumulate linearly for 30 min after drug administration, providing an accurate estimate of the

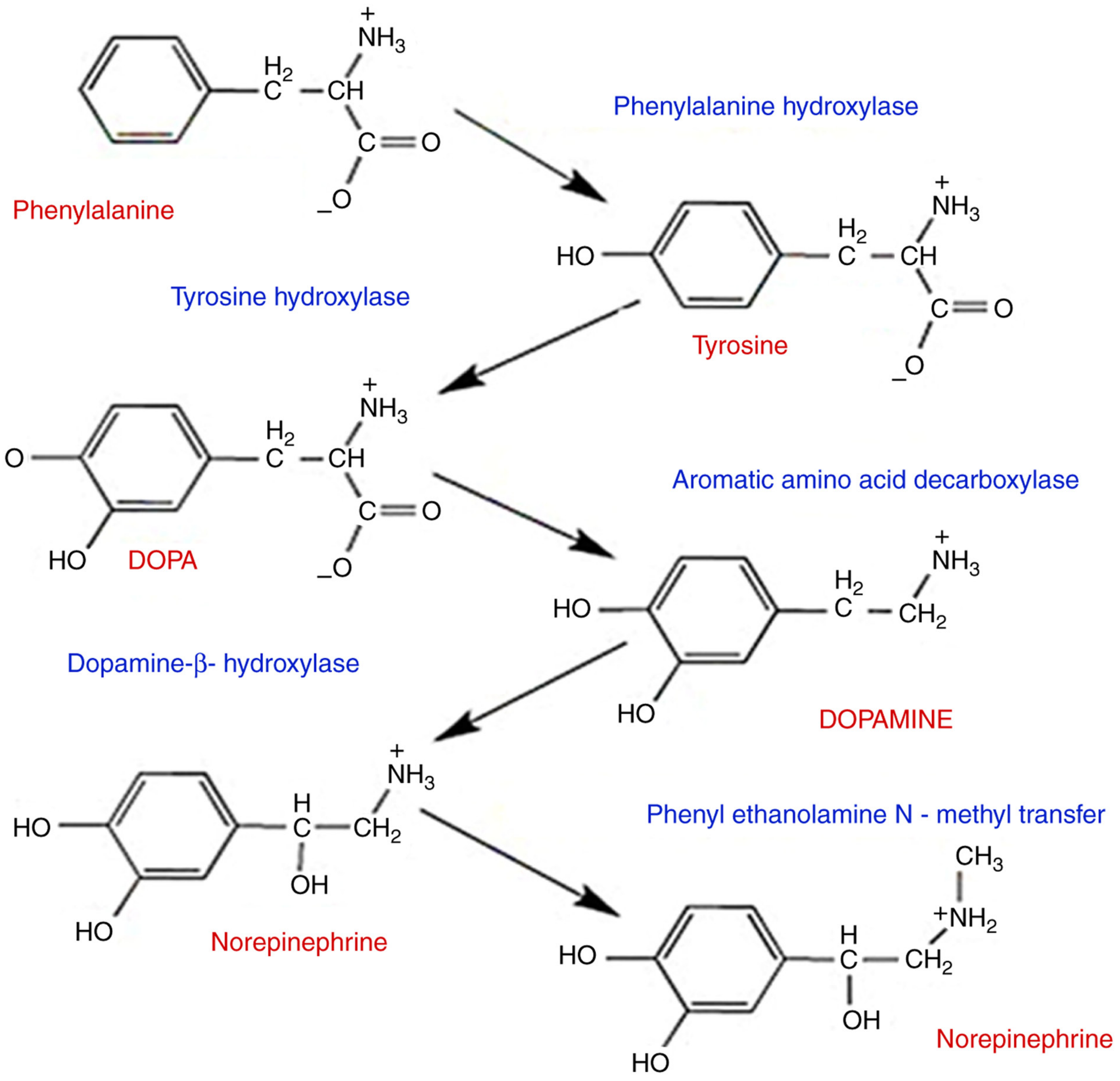

Figure 8. The mechanism of biosynthesis for catecholamine neurotransmitters.

hydroxylation rate and overall rate of catecholamine synthesis, phenylethanolamine N-methyltransferase is a key enzyme in the biosynthesis of catecholamines, specifically catalyzing the conversion of norepinephrine (noradrenaline) into epinephrine (adrenaline), the mechanism of biosynthesis for catecholamine neurotransmitter appearances on (Fig. 8).

This reaction represents the terminal step in catecholamine biosynthesis and is crucial for stress responses and various physiological functions as the hydroxylation step is rate-limited in the pathway (70,71). A previous study examined how L-Tyrosine (TYR), a biological precursor of dopamine believed to improve creativity and cognitive regulation, promotes creativity in both divergent and convergent thinking (72). While TYR did promote convergent (or 'deep') thinking, no evidence could be found that it had any influence on divergent (or 'brainstorming'). That study indicated that TYR may support control-hungry creative processes, since convergent thinking may require more cognitive top-down control. The meals consumed may thus have an impact on thought processes (72). Tyrosine is hydroxylase to L-DOPA by tyrosine hydroxylase, whereas phenylalanine hydroxylase converts tyrosine to tyrosine. The enzyme aromatic amino acid decarboxylase transforms DOPA into dopamine. Dopamine-hydroxylase catalyzes the conversion of dopamine to norepinephrine, and is then methylated to epinephrine by phenylethanolamine N-methyltransferase. The enzyme that limits the rate of the pathway is tyrosine hydroxylase (72). Monoterpene hydrocarbons, particularly pinene, have been shown to be critical components in essential oils, responsible for effects such as metal chelation, free radical scavenging, enhancing reducing power and inhibiting certain enzyme functions (73). Since acute β-PEA administration increased the active psychomotor behaviors of β-PEA-administered mice and produced a positive emotional state, the dopamine concentration and dopamine-related protein expression of rats administered β-PEA was investigated to determine whether β-PEA changes dopaminergic neurotransmission (74). The results revealed that the rats administered acute β-PEA had significantly higher levels of dopamine than the saline control group (74). Moreover, when rats received β-PEA immediately, it significantly improved their tyrosine hydroxylase levels and immune responses relative to the saline control group. The immunological responses of DAT and vesicular monoamine transporter 2 (VMAT-2) levels, however, did not change between the β-PEA-administered rats and the saline control group (74). Acute β-PEA treatment in mice enhanced the level of striatal dopamine, as well as the expression of p-DAT and TH, an enzyme that limits the production of dopamine. According to the findings, acute β-PEA injection is expected to cause p-DAT, reverse DAT function, and ultimately boost dopamine neurotransmission in the striatum. Notably, it was discovered that locomotor activity remained unaltered even after acutely administering 50 mg/kg β-PEA, which increased the striatal dopamine concentration It was revealed that mice treated with β-PEA had higher amounts of striatal dopamine and greater locomotor activity, as well as stereotyped behaviors such as grooming. (74). However, in an alternative investigation, β-PEA at an elevated dose of 50 mg/kg heightened circling, which is recognized as stereotyped behavior, and the head-twitching reaction, which is deemed to be a behavioral indicator of the hallucinogenic effect in humans through the hyper stimulation of dopaminergic neurotransmission (75).

Natural products rich in Phe and Tyr. The following foods are excellent providers of Phe and Tyr: Meats (lamb, venison, hog and beef), fowl (duck, goose, turkey and chicken), seafood (shrimp, lobster, mackerel, salmon, trout and tuna), eggs, dairy products (yoghurt, cheese and milk), nuts (cashews, walnuts, macadamia nuts, pistachios and almonds), pumpkin, squash, hemp and sunflower seeds, nut butters (such as cashew, almond and peanut butter), legumes (beans, black beans, chickpeas and lentils), whole grains (wheat, barley, rye, oats and quinoa), soy goods (edamame, tempeh, tofu, soybeans) and protein supplements (76). Phe is present in a wide variety of high-protein plant and animal foods, such as meat, fish, poultry and legumes. Aspartame, an artificial sweetener frequently added to diet soda and other sugar-free meals, also contains Phe (76). Natural protein or dietary Phe intake is limited by the European Phenylketonuria Guidelines to no >25% of daily intake to maintain target blood Phe concentrations (77). Phenylketonuria (PKU) is an autosomal recessive genetic disorder of phenylalanine metabolism caused by a deficiency of the enzyme hydroxylase, which catalyzes the conversion of phenylalanine to tyrosine (76). The enzyme which regulates the rate of dopamine production is known as tyrosine hydroxylase, or Tyr H. The hydroxylation of tyrosine into L-DOPA is catalyzed through; hormones and neurotransmitters in the central and peripheral nervous systems, catecholamine dopamine, epinephrine and norepinephrine are the end products of the route. In the latter case, the adrenal medulla synthesizes them (78,79). Several brain processes, including attention (80), memory cognition (81) and emotion, are influenced by these catechol monoamines (82,83). The hormone known as the fight-or-flight response, epinephrine, which is generated by the adrenal gland, has an impact on several bodily tissues (84). As a result, variations in catecholamine levels can have a variety of effects, possibly including elevated blood pressure, addiction, dystonia and bipolar disorder (85,86). Tyr H is the slowest enzyme in the process; therefore, its activity is highly relevant to a number of biomedical research disciplines. The complex nature of Tyr H regulation is logical considering the significance of its function. Research on transcription processes controlling its production, as well as the relatively recent topic of its destruction in the proteasome over degradation is extremely active (87).

Omega-3 fatty acids. The main sources of omega-3 fatty acids are cold water fish, such as Salmon, dark-water cod, sailfish, sardines and herring. In a study that nurtured rats with omega-3 adipose acids and a control group that did not receive these acids, the animals fed the omega-3 adipose acids had 40% more dopamine in their frontal brain than rats on the control diet, and more advanced situations of dopamine in the brain than the animals that did not receive the omega-3 adipose acids (88). That study also noted a decrease in the enzyme that breaks down dopamine and increased dopamine binding to dopamine receptors (88). Research also shows that omega-3 adipose acids can help restore normal dopamine release following traumatic brain injury (89). Considering the widespread relevance of marine omega-3 fatty acids, it is recommended to consume fish or other seafood 1-2 times per week, particularly fatty (dark flesh) fish high in eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA) (90). This is paraticularly crucial for women who are pregnant or who wish to become pregnant, as well as nursing mothers. A developing child also needs a consistent supply of DHA from the third trimester to the second year of life to create the brain and other elements of the nervous system, as DHA is the most abundant fatty acid in the brain. While the evidence for harm from a lack of omega-3 fats is significantly more consistent and there is a balance of benefit vs. risk, a number of women avoid eating fish out of fear that mercury and other potential pollutants would harm their future children (91).

The strongest evidence yet for the beneficial effects of omega-3 fats comes from heart disease. These fats appear to help maintain a regular heartbeat as opposed to an irregular one, which may be fatal (92). These arrhythmias account for the majority of the >500,000 cardiac-related deaths that occur in the USA annually. Furthermore, omega-3 fats lower blood pressure and heart rate, while improving blood vessel health. Increased doses lower triglycerides and inflammation, both of which are factors in the development of atherosclerosis (92). Omega-3 fatty acids (omega-3s) include a carbon-carbon double bond that is located three carbons from the methyl end of the chain. Foods high in omega-3s, or n-3s, include fish oil and flaxseed, as well as dietary supplements. The majority of the scientific research focuses on three types of omega-3 fatty acids (Fig. 9): Alpha-linoleic acid (ALA), EPA and DHA. With 20 and 22 carbon atoms, respectively, EPA and DHA are considered long-chain (LC) omega-3s, although ALA only possesses 18 carbon atoms. As a result, linoleic acid and ALA are considered as essential fatty acids, which indicates that they can only be received via food (93). Only a minimal amount of conversion (<15%) has been reported between ALA and EPA and DHA, which occurs mostly in the liver (92). Therefore, the only feasible option to raise levels of these fatty acids in the body is to consume EPA and DHA directly from meals and/or dietary supplements.

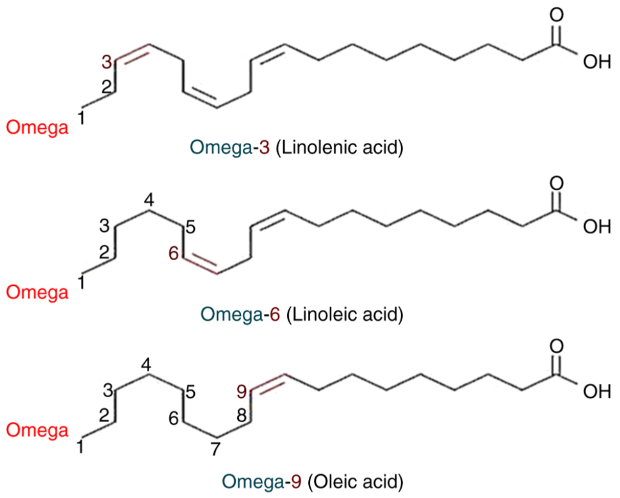

Figure 9. Chemical structure of three types of omega-3 fatty acids.

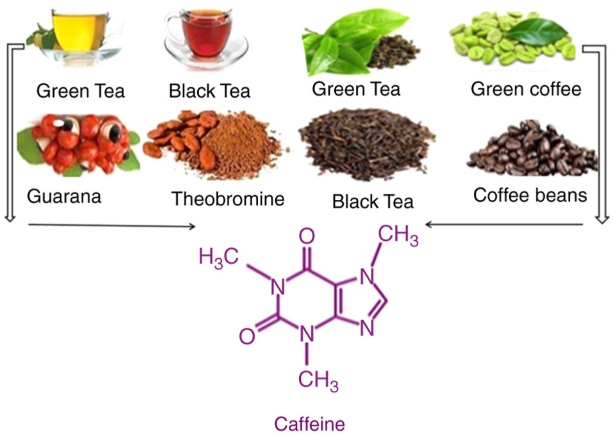

Figure 10. Natural products rich in caffeine.

Natural products rich in omega-3s. Variations exist in fish's omega-3 content. High concentrations of long-chain omega-3 fatty acids (LC omega-3s) are found in cold-water fatty fish, such salmon, mackerel, tuna, herring, and sardines; low-fat fish, like cod, tilapia, and bass, and shellfish, have small concentrations (92). The association between the omega-3 concentration in fish and the makeup of their diet is also evident (94). DHA and EPA levels in farmed fish are typically greater than in wild fish, but this varies depending on the diet (94). The plant oils canola, soybean and flaxseed (linseed) oils are among those that contain ALA, (92,93). Additionally, high in ALA are walnuts and chia seeds. Certain foods are fortified with DHA and other omega-3s, including several types of yogurts, eggs, milk, juices and soy drinks. In the USA, the majority of newborn formulae on the market since 2002 have included DHA and arachidonic acid, which are the two most common LC PUFAs in the brain (95).

Caffeine. Caffeine is the most frequently utilized psychoactive substance (96). Caffeine maintains dopamine levels higher, particularly in brain regions associated with 'attention'. Caffeine enhances sustained attention and attentiveness through this neurochemical interaction and lowers tiredness feelings (97,98). Its pharmacological effects on behavior are comparable to those of stimulants (methylphenidate and amphetamine) and 2-phenyl methyl-sulfinyl acetamide, is the standard IUPAC chemical name for Modafinil, which boost dopamine signaling by augmenting dopamine release from the terminals or inhibiting dopamine transporters (99,101). The stimulating, relaxing and reinforcing effects of these medications are due to their dopamine-enhancing properties (100,102-104). On the other hand, On the other hand, preclinical research suggests that the antagonistic actions of caffeine on adenosine receptors (A1 and A2A subtypes) improves their pharmacological effects (104). Its antagonistic action on striatal A2A receptor (A2AR) has been specifically linked to dopamine effects (105). Similarly, as A2AR mutant animals lack these responses, caffeine-induced increases in locomotor activity and emotion appear to be mediated by A2AR (106,107). Additionally, the effects of caffeine on wakefulness are disrupted when A2AR expression is silenced in the nucleus accumbency using short-hairpin RNA (108).

Other studies have demonstrated that caffeine causes the brain dopamine levels to rise, (109,110); additionally an excellent approach to raising dopamine levels is to drink coffee. It also increases dopamine receptors and improves dopamine signaling (111). Dopamine levels in the brain are increased by coffee and other stimulants. This may be due to the good taste of coffee. However, coffee and caffeine may interfere with sleep; thus, their consumption should be avoided in the evening and before bed. Finally, attempting to consume all the coffee fruit as opposed to simply coffee or pure caffeine may be beneficial. The coffee bean is traditionally removed from the coffee fruit to be roasted. The fruit that surrounds it is thrown away. However, this is problematic since the coffee fruit has several beneficial ingredients that are absent from coffee beans. Furthermore, using whole coffee fruit concentrate has been shown to considerably improve cognitive performance (112). It has also been demonstrated that tea raises dopamine levels in the brain. This includes black tea, as well as green tea (113). The amino acid threonine is present in both black and green tea. Additionally, it has been demonstrated that threonine crosses the blood-brain barrier and markedly increases dopamine release in the brain (114-116). Caffeine naturally occurs in plant leaves, seeds and fruits, substitute, where it acts as a natural herbicide, insect repellent and pollinator attractants Caffeine naturally occurs in plant leaves, seeds and fruits, (117,118). This botanically consequent chemical is the most widely used stimulant globally (119). Caffeine enters the human diet through plant-based foods (Fig. 10), such as coffee beans, tea leaves, guarana, cocoa beans, and kola nuts (120). Coffee is a key caffeine source in the diet (121).

4. Challenges and future prospects

The focus of the present review was to summarize the significance of natural bioactive compounds that contribute to boosting dopamine levels in the brain by influencing the amount of central nerve dopamine. Numerous direct investigations have been conducted in which nerve dopamine levels were gradually boosted, as well as dopamine generation utilizing numerous well-studied plants. Natural bioactive chemicals can enhance neuronal dopamine levels. The study of natural and bioactive compounds has attracted increasing attention due to their direct influence on brain health, physiological activities and medicinal and edible properties. Researchers have conducted numerous studies on bioactive compounds and their biological efficacy for living organisms. However, the extraction process, structure determination, activity and mechanism of these bioactive compounds have not formed systematic theoretical and technical system, which greatly limits their functional application. Therefore, the majority of commercially available natural products are functional foods containing bioactive compounds that affect dopamine levels in the brain. The main reasons for this situation are as follows:

The composition, structure and activity of bioactive compounds in increasing dopamine levels in the culture medium are relatively different, and the association between the source, chemical structure and biological activity is not yet clear. Even for well-studied plant compounds, there are only some preliminary discussions on the relationship of structure to biological activity in humans. However, the majority of studies on biological activity are at the cell and/or animal level; only a limited number of clinical or preclinical studies have been conducted, and the mechanism of biological activity still needs further confirmation. These issues impede the translation of biologically active ingredients that regulate dopamine levels in the human brain.

The industrial production of bioactive chemicals in the human brain suffers by the absence of efficient techniques for extraction, purification, or synthesis, and several small molecular active ingredients remain in the phase of structural elucidation and *in vitro* activity validation.

The advancement of technological systems to maximize the utilization of bioactive compounds in food, healthcare products and clinical medicine is essential for improving brain dopamine levels.

5. Conclusion

In order to develop an effective preventive and therapeutic strategy, it is crucial to possess a thorough understanding of the bioactive compounds that impact brain dopamine levels. These compounds play a vital role in preventing neurodegenerative diseases linked to fluctuations in brain dopamine levels, improving cognitive functions such as memory and focus, heightening feelings of pleasure, regulating mood and attention and managing psychiatric disorders. Researchers need to transition from investigating the antioxidant properties of natural bioactive compounds to determining the ideal brain dopamine levels based on factors such as age, gender, and developmental stages.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

The author (MOE) has confirmed the authenticity of all the raw data and have reviewed and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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