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Chemical and Structural Perspectives of Nutraceuticals in Neurodegenerative and Neurodevelopmental Disorders: From Molecular Design to BBB Delivery

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ABSTRACT:

This article presents a critical evaluation of the increasing prevalence of neurological disorders and the therapeutic limitations imposed by the blood-brain barrier (BBB) in conventional central nervous system (CNS) drug delivery. It emphasizes the strategic integration of nutraceutical compounds, particularly curcumin and resveratrol, due to their multifaceted neuroprotective properties and their capacity to penetrate the BBB. The study investigates their underlying molecular actions, such as antioxidant, anti-inflammatory, and gene-regulatory effects, in the context of major neurodegenerative diseases including Alzheimer's and Parkinson's. Ultimately, this work aims to support the rational design of advanced CNS-targeted delivery systems that leverage nutraceuticals for enhanced clinical efficacy and patient outcomes.

KEYWORDS: Neurological Disorders, Blood-Brain Barrier, CNS Drug Delivery, Curcumin, Resveratrol, Neurodegeneration, Nutraceuticals, SIRT1, NF-κB Pathway, Therapeutic Strategy.

INTRODUCTION:

Overview of neurological disorder:

Neurological diseases (NDs) are a subset of human ailments that refer to disorders affecting the brain. Neurological diseases, sometimes referred to as brain, behavioural, or cognitive problems, impact a person's capacity for movement, speech, learning, and walking [1]. Since the brain is where human nerves are controlled, any damage to it could be fatal. The death rate has decreased as a result of increased awareness of these illnesses; still, certain chronic NDs can result in partial or permanent disability or pain. These conditions were present in 10.2% of the cases worldwide. Moreover, these diseases have an annual incidence rate of 16.8% each. According to these percentages, the rates of disability associated with neurological and neuropsychiatric illnesses are higher than those of other human disorders [3]. Furthermore, one of the most difficult and evolving issues is the diagnosis of neurological disorders. Current diagnostic tools, covered in Section 4, provide vast volumes of data for the diagnosis, tracking, and treatment of neurological illnesses.

Neurological disorders are diseases of the central and peripheral nervous systems. Common symptoms include loss of consciousness, pain, convulsions, muscle weakness, paralysis, and impaired coordination. Brain tumors, Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), epilepsy, dementia, headache disorders, neuro infections, stroke, and traumatic brain injury are among the more than 600 diseases that impact the neurological system. Patients are frequently examined neuropathologically to detect abnormal or atypical neurological conditions. Nonetheless, the majority of persons have neurological anomalies that are typically unrelated to neurological illnesses [19].

Parkinson's Disease	Parkinson's disease is a progressive neurodegenerative disorder that primarily affects movement. It's characterized by the loss of dopamine-producing cells in the brain, leading to a range of motor symptoms like tremors, stiffness, and slow movement, as well as non-motor symptoms such as sleep disturbances and cognitive change
Dementia	Dementia is a syndrome in which cognitive performance, such as thinking, remembering, and reasoning, deteriorates to the point where it conflicts with daily life and tasks. Many dementia patients lose emotional control, and even personality shifts occur. Memory loss, task difficulty, disorientation, language problems, behavioural abnormalities, and lost opportunities for initiative are the most common indications and symptoms of dementia
Alzheimer's Disease	It is a degenerative brain condition characterized by the loss of cognitive function, and hasno proper cure.

Frontotemporal Dementia	Frontotemporal dementia (FTD) is a rare type of dementia that affects behaviour and communication and is detected in individuals aged <60. FTD is associated with aberrant levels or types of tau and TDP-43 proteins
LewyBody Dementia	Lewy body dementia is a type of dementia characterized by Lewy bodies and aggregates of alpha-synuclein. It grows in the nerve cells in the parts of the brain that control thinking, memory, and movement (motor control).
Vascular Dementia	It is a chronic condition encompassing a wide range of cognitive dysfunctions produced by brain tissue damage induced by vascular disease
Mixed Dementia	Mixed dementia is a condition in which the brain displays symptoms of more than one type of dementia.
Multiple Sclerosis	Multiple sclerosis is defined as having scar tissue in various sites. When the myelin sheath is removed or injured in multiple sites, a scar or sclerosis occurs.
Cerebral Palsy	Cerebral palsy is a group of neurological disorders that begin in infancy or early childhood and affect physical movement and muscle coordination for the rest of one's life. Damage or abnormalities in the developing brain cause CP, reducing the brain's ability to control movements, maintain posture, and balance.
Brain Tumor	A brain tumor is a cluster of aberrant neurons that creates a mass. There are numerous different types of brain tumors. Some brain tumors were benign (non-cancerous).
Epilepsy and Seizures	Epilepsy is a neurological disorder marked by recurring seizures. A seizure is a sudden behaviour change induced by a disruption in the brain's electrical activity.[1]

CHALLENGES IN CNS DRUG DELIVERY SYSTEM:

The Blood-Brain Barrier (BBB) is a physiological mechanism that limits the entry of most molecules from the bloodstream into the brain. This concept was first introduced by Paul Ehrlich, who observed that water-soluble dyes injected into the circulatory system stained all body tissues except the brain and spinal cord [32,33]. Later, Edwin Goldmann expanded on this finding by injecting trypan blue directly into the cerebrospinal fluid (CSF). His study showed that the dye stained the brain and central nervous system but did not reach the surrounding tissue of the body [33]. These observations led to the idea that a physical barrier separates the bloodstream from the central nervous system (CNS). This barrier is now understood to result from tight junctions between the endothelial cells of the brain's microvasculature [34]. These tight junctions, made up of proteins such as claudin and occludin, form a highly restrictive seal between blood and brain tissue [35].Further research revealed that the BBB is not only a physical barrier but also functions as an active chemical and metabolic barrier. Specific mechanisms, like P-glycoprotein (P-gp) and multidrug resistance-associated proteins, actively prevent certain substances from entering the brain [36]. Additionally, BBB cells contain high levels of metabolizing enzymes, including various cytochrome enzymes [37,38].Because of these features, it is believed that drugs intended to cross the BBB should have a molecular weight of no more than 500 Daltons, contain fewer than 10 hydrogen bond donors or acceptors, and lack strong affinity for BBB enzyme systems, efflux transporters, or plasma proteins [39]. The BBB is the main barrier between the CNS and systemic circulation, making it a critical focus in developing CNS-targeted drug delivery systems.

The Blood–Cerebrospinal Fluid (CSF) Barrier refers to the selective barrier between the bloodstream and the cerebrospinal fluid. Like the BBB, it regulates the passage of substances into the CNS. It acts as a selective filter, allowing only certain molecules to enter the CSF. This barrier is formed by tight junctions between the epithelial cells of the choroid plexus, rather than by tight junctions in the supplying capillaries. The capillaries of the choroid plexus have fenestrae (small openings) that allow substances to move freely out of the bloodstream. However, the tight junctions of the epithelial cells prevent these substances from entering the CSF.

An important difference between the blood–CSF barrier and the BBB is their relative surface areas — the blood–CSF barrier has 1,000 times less surface area compared to the BBB [40]. Therefore, in terms of drug delivery, the blood–CSF barrier represents a much smaller obstacle than the BBB.(2)

BASIS OF NUTRACEUTICALS:

Any product made from food sources that offers additional health advantages over the fundamental nutritional value is referred to as a nutraceutical (Gul et al., 2016). Terms like "nutraceuticals," "functional food," "herbal remedies," and "health food" frequently have conflicting and unclear definitions.

The legal systems of various nations, marketing (market presence and dosages), and public opinion all contribute to their definitions and differences (Lockwood, 2007; Aronson, 2017). The term "nutraceutical" is still not included in Directive 2002/46/EC on food supplements and novel foods (most recently amended by the new European Parliament and Council Regulation (EU) 2015/2283), which defines new food categories and the classification of food supplements.

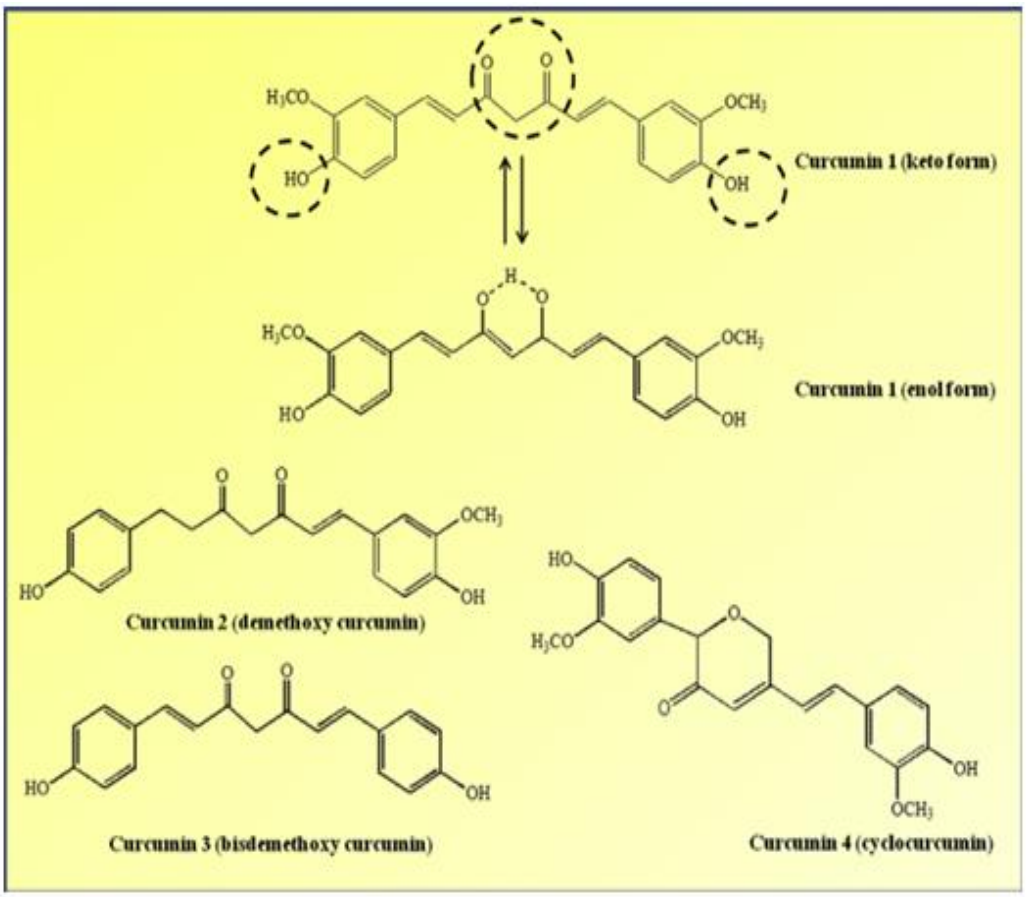
The founder and chairman of the Foundation for Innovation in Medicine (FIM), located in Cranford, New Jersey, Dr. Stephen DeFelice, MD, coined the term "nutraceutical" in 1989. According to DeFelice (2002), a "nutraceutical" is "a food (or portion of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease." Since this term has frequently been used interchangeably with functional foods or dietary supplements to refer to foods that promote health or the components that are derived from them, Kalra attempted to distinguish between these three categories and redefine them in 2003. Accordingly, functional foods that help prevent and/or treat conditions other than anemia are referred to as nutraceuticals (Kalra, 2003).[3]

NUTRACEUTICAL MEDICINE:

CURCUMIN: Curcumin is the primary biologically active phytochemical found in turmeric, a plant belonging to the *Curcuma* genus of the Zingiberaceae family. Curcumin has the ability to cross the blood-brain barrier (BBB) [17,18], allowing it to exert neuroprotective effects in various neurological conditions such as stroke, spinal cord injury, traumatic brain injury (TBI), Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and epilepsy [19]. These protective effects are mainly attributed to its antioxidant, anti-inflammatory, anti-amyloidogenic, antidepressant, antidiabetic, and antiaging properties [20–22].

On a molecular level, curcumin reduces the expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, an enzyme involved in the production of reactive oxygen species (ROS) and advanced glycation end products (AGEs) [23]. It also alleviates neuroinflammation, thereby delaying the onset of neurological disorders and certain types of cancers [19]. Furthermore, curcumin inhibits the activation of microglia and astrocytes, suppresses nuclear factor-kappa B (NF-κB) activity, and lowers the production of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-8.

Curcumin also downregulates the activity of enzymes like inducible nitric oxide synthase (iNOS), matrix metalloproteinase-9, cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LOX), and adhesion molecules [19]. On the other hand, it enhances the expression and activity of protective proteins like heme oxygenase-1 (HO-1) and heat shock proteins (HSPs), which assist in preventing protein misfolding and aggregation under stress conditions [24,25].



Studies have shown that direct administration of curcumin into the brains of AD mouse models slows plaque formation [17]. Additionally, curcumin appears to inhibit Aβ oligomerization, though it does not affect fibril formation in vitro at concentrations between 30–300 μM [26]. The exact reason for this difference is unclear, but it may relate to concentration-dependent multiphasic effects on Aβ aggregation [26].

Limited research is available on curcumin's impact on tau aggregation [27]. However, evidence suggests that co-incubation of curcumin with Aβ in PC12 cells reduces tau phosphorylation at serine 202, and curcumin can also modulate tau phosphorylation independently of Aβ [28]. In aged h-tau transgenic mouse models of tauopathy, curcumin has been shown to lower both total and phosphorylated tau dimers and restore altered excitatory synaptic proteins, indicating that tau dimers may significantly contribute to synaptic toxicity in AD pathogenesis [29].

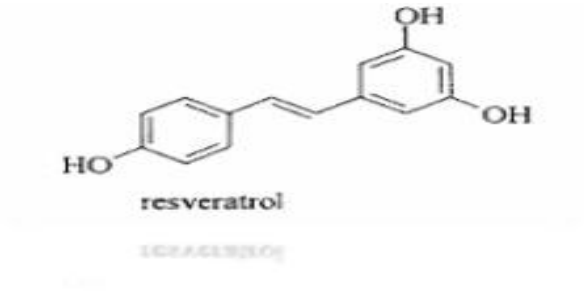
Overall, evidence supports that curcumin's neuroprotective effects—mediated by its anti-amyloid, antioxidant, anti-inflammatory, and tau phosphorylation-modulating activities—make it a promising candidate for treating AD, PD, and other neurological disorders in both animal studies and human trials [30–32].

We have discussed the neurochemical background of these disorders in Chapter 1. In the following sections, we will focus on the specific neuroprotective actions of curcumin in various neurological diseases. (4)

RESERVATROL:

Resveratrol is found in various plants, including vegetables, fruits, grains, roots, flowers, seeds, tea, and wine. It has demonstrated protective effects against several conditions such as cardiovascular diseases, neurodegenerative disorders, and cancer. Several studies have highlighted its antioxidant, anti-inflammatory, and metal-chelating activities [4, 6–8]. Growing evidence also suggests that, in addition to these properties, resveratrol can activate sirtuin 1 (SIRT1), a type of deacetylase enzyme [9]. SIRT1 has recently gained attention as a potential therapeutic target for age-related degenerative diseases. Research on neuronal cells demonstrated that resveratrol, functioning as an SIRT1 activator, protects SK-N-BE cells against oxidative stress and the cytotoxic effects of amyloid beta (Aβ) peptide and alpha-synuclein [9].

Caloric restriction has been shown to prolong lifespan in mammals, a benefit largely attributed to the activation of the SIRT1 gene [10, 11]. Resveratrol seems to replicate the effects of caloric restriction by enhancing SIRT1 activity, promoting deacetylation of proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), and stimulating mitochondrial biogenesis [12]. These enzymes are associated with the regulation of the vitagene network—longevity-related genes that play a critical role in the body's maintenance and repair mechanisms [4, 13–15]. Collectively, these findings indicate that resveratrol could be a promising therapeutic candidate for neurodegenerative diseases [13, 14]. (5)



FACTORS INFLUENCING BBB PENETRATION:

BBB function can be influenced by

a) age
b) sex
c) microRNAs (miRNAs)
d) temperature
e) anaesthetic agents
f) Physical exercise (6)

CONCLUSION:

Neurological disorders are difficult to treat due to the complexity of the brain and the protective nature of the blood-brain barrier. Nutraceuticals like curcumin and resveratrol offer new hope by crossing this barrier and providing antioxidant and anti-inflammatory benefits. When combined with

advanced delivery systems, these compounds may enhance treatment outcomes, offering a promising future for safer and more effective management of CNS disorders.

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