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CURCUMIN – A REVIEW ON NEUROPROTECTION

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ABSTRACT: Treatment based on traditional medicine is very popular in the developing world due to inexpensive properties. There is a growing interest in herbal medicine. Curcumin a hydrophobic poly-phenol is derived from turmeric, the rhizome of the herb *Curcuma longa* L. Neurodegenerative diseases have become a major challenge for public health because of their incurable status. Curcumin has an outstanding safety profile and a number of pleiotropic actions with potential for neuroprotective efficacy, including anti-inflammatory, antioxidant, and anti-protein-aggregate activities. Because of its pleiotropic actions on the central nervous system, including preferential binding to amyloid proteins, Curcumin is being touted as a promising treatment for age-related brain diseases. This review article aims at gathering information predominantly on neurodegenerative diseases.

INTRODUCTION: Turmeric is a spice that has received much interest from both the medical/scientific worlds as well as from the culinary world. Turmeric is commonly called as “golden spice” or “spice of life”⁸. *Curcuma longa*, commonly known as turmeric, is a perennial herb that belongs to the Zingiberaceae family, with 133 different species available worldwide. Curcuma has been reported to be used in Ayurveda, Siddha, and Unani system of medicines from Vedic times. Turmeric also has special religious significance in Hinduism. It is used as a cooking spice, cosmetic agent, dying agent, and also in medicinal practice to treat various ailments like skin infections and liver and gastrointestinal disorders⁴⁸.

Curcuma longa has been traditionally used in Asian countries as a medical herb due to its antioxidant, anti-inflammatory²³, anti-mutagenic, antimicrobial³⁶, and anticancer properties⁴⁷. While in India, its average consumption is estimated to be about 4 g/day⁴⁶. Curcumin content in turmeric of turmeric is variable.

Curcumin, a polyphenol, has been shown to target multiple signaling molecules while also demonstrating activity at the cellular level, which has helped to support its multiple health benefits¹⁴. It has been shown to benefit inflammatory conditions¹, metabolic syndrome³³, pain¹⁹, and to help in the management of inflammatory and degenerative eye conditions²⁷. In addition, therapeutic contributions of curcumin in many neurological diseases have been proven in several studies¹³. Lower incidence rate of many neurodegenerative diseases in Indians can be attributed to the regular intake of turmeric in their routine diet¹⁷.

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History of Curcumin: Pelletier and Vogel made the remarkable scientific discovery of curcumin by isolating the yellow-colored pigment from the rhizomes of turmeric in 1815. In 1842 they synthesized pure curcumin. Later in 1973, Roughly and Whiting described its detailed chemical structure. Later, chemists discovered that turmeric paper could be used to test the alkalinity of a substance, as the turmeric's orange-yellow root powder color changed into reddish-brown color when treated with alkaline chemicals. Great enthusiasm for curcumin research started after researchers came to know about the botanical history of *Curcuma longa* from the book, "Maude Greve's book—A Modern Herbal". Though various Indian medical systems use turmeric from ancient times, German scientists started detailed research in the early 1920s, as they identified the therapeutic potential of oils extracted from the roots of *Curcuma* herb in 1926. Curcumin is extracted from turmeric by column chromatography, Soxhlet apparatus, pulse ultrasonic, and microwave-based extraction methods³⁴.

Curcumin is being recognized and used worldwide in many different forms for multiple potential health benefits. For example, in India, turmeric containing curcumin has been used in curries; in Japan, it is served in tea; in Thailand, it is used in cosmetics; in China, it is used as a colorant; in Korea, it is served in drinks; in Malaysia, it is used as an antiseptic; in Pakistan, it is used as an anti-inflammatory agent and in the United States, it is used in mustard sauce, cheese, butter, and chips, as a preservative and a coloring agent, in addition to capsules and powder forms.

Curcumin is available in several forms, including capsules, tablets, ointments, energy drinks, soaps, and cosmetics¹⁴. Curcuminoids have been approved by the US Food and Drug Administration (FDA) as "Generally Recognized as Safe" (GRAS)¹⁴ and good tolerability and safety profiles have been shown by clinical trials, even at doses between 4000 and 8000 mg/day² and of doses up to 12,000 mg/day of 95% concentration of three curcuminoids: curcumin, bisdemethoxycurcumin and demethoxy-curcumin²¹. Curcumin has been reported to have a low absorption rate, high biotransformation rate in intestines, and fast elimination rate from the systemic circulation³⁵.

Structure and Synthesis of Curcumin: Turmeric contains 2-9% curcuminoids, depending upon its biological origin and soil fertility and its place of cultivation. Curcuminoids include compounds like curcumin (77%), demethoxycurcumin (17%) and bis-demethoxycurcumin (3%)¹². The chemical structure of curcumin shows symmetry to molecule formula C₂₁H₂₀O₆ (1E, 6E): 1, 7-bis(4-hydroxy- 3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione, with molecular weight of 368.38 g/mol. This molecule has three functional groups attached in its structure: o-Methoxy phenolic groups present in the two aromatic ring systems, associated with a seven carbon attachment comprising α , β -unsaturated β -diketone group, which show keto-enol tautomerism³⁴.

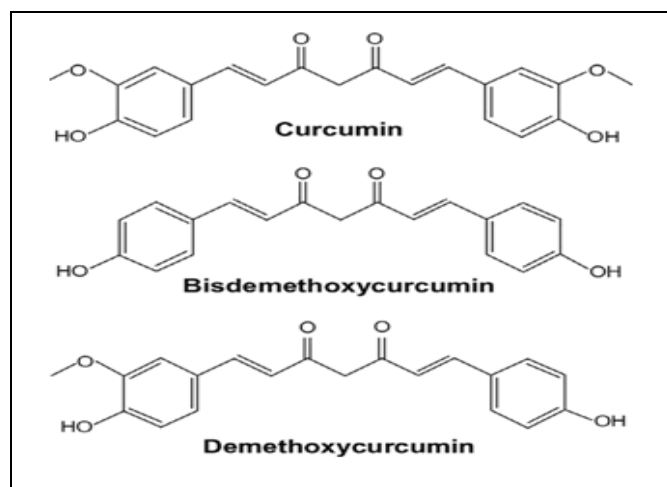


FIG. 1: CHEMICAL STRUCTURE OF CURCUMIN

Chemist Lampe synthesized curcumin using carbomethoxy feruloyl chloride and ethyl acetoacetate²⁰. A new preparatory process of curcumin was developed by Pabon, 2010 using acetylacetone and substituted aromatic aldehydes in the presence of boron trioxide (B₂O₃), trialkyl borate, and n-butylamine and then stabilized the preparatory method with some minor modifications. Pabon's preparatory method has been used extensively and has a good yield. In this method, 2, 4-diketones react with substituted aromatic aldehydes and undergoes Knoevenagel condensation with boron complex to avoid precipitation. In an anhydrous environment, curcumin gets separated easily using polar aprotic solvents. Under a mildly acidic environment, the boron complex breaks into curcumin that can be separated by washing continuously and precipitated by column chromatography³².

Neuroprotective Effects of Curcumin: Many neurodegenerative diseases of aging involve the accumulation of protein aggregates, oxidative damage, and inflammation. Curcumin is a pleiotropic molecule, which not only directly binds to and limits the aggregation of misfolded proteins in many neurodegenerative diseases, Although curcumin corrects dysregulation of several pathways, it may exert multiple effects via a few molecular targets. Curcumin is a drug of interest in the management of various neurodegenerative discussed below.

Alzheimer's Disease (AD): Alzheimer's disease (AD) is a progressive, fatal neurodegenerative disorder involving chronic CNS inflammation leading to significant oxidative^{11, 28, 45}. The classical pathology of AD involves neurodegeneration and the accumulation of protein aggregates to form two major lesions: neurofibrillary tangles (NFTs) extracellularly and senile plaques intra-cellularly along with progressive loss of neurons and dendritic spines in the hippocampal and cortical regions. The most important symptoms in AD include a decline in cognitive and motor performances, dementia, and memory loss⁵.

Accumulation of insoluble alpha-beta amyloid protein leads to senile plaques and hyperphosphorylation of tau proteins at multiple sites results in neurofibrillary tangles³⁰. Senile plaques and amyloid fibrils form chaperone protein plaques that damage the neuronal structure and its synaptic connections.

Curcumin, because of its strong anti-inflammatory activity, binds with A β (Amyloid beta), and prevents protein aggregation and also destabilize the preformed fibril by metal binding^{4, 9, 31}. Thus, altogether it reduces the progression of neuronal damage in AD brains⁴³. Curcumin has known to possess potent antioxidant and free radical scavenging activity^{15, 29}. Oxidative stress increases the concentration of metals like copper, zinc, or iron in the brain. When the concentrates of these metals reach more than 1 mM, their affinity toward A β increases. This resulted in an increase in peptide aggregation and enhanced plaque formation, which ultimately leads to disease progression¹⁰. Curcumin, because of its free radical scavenging and protein aggregation

inhibition, could be a potential therapeutic value in AD.

Parkinson's Disease: Parkinson's disease (PD) is one of the major neurodegenerative diseases characterized by progressive loss of dopaminergic neurons in substantia nigra compacta (SNpc), deposition of α -synuclein and Lewy bodies^{26, 26}. High levels of free radicals and compromised mitochondrial functions are found to be the main causes of neuronal death in PD brains⁶. The neurotoxin 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) selectively damages mitochondrial complex I of electron transport chain, triggering oxidative stress, and thereby producing dopaminergic degeneration³⁸. In recent studies, curcumin possesses antioxidant, anti-inflammatory, anti-apoptotic activities, and therapeutic potential in neurodegenerative disorders²⁵. Curcumin shields dopaminergic neurons against MPTP-induced neuronal damage. It also causes an increase of dopamine⁴⁹ and tyrosine hydroxylase (TH), by inhibiting the glial fibrillary acidic protein (GFAP) and iNOS protein expression⁴². In several investigations, the transgenic PD model of *Drosophila* showed that curcumin reduces the levels of lipid peroxidation and protein carbonyl aggregates in the brains⁴⁴.

Huntington's Disease: Huntington's disease (HD) is an inherited, an autosomal, neurological, neurodegenerative disorder, characterized by the choreiform movements⁴⁰, selective degeneration of striatum spiny GABAergic neurons in basal ganglia which leads to motor and cognitive impairments^{24, 18}, mood disorders, psychiatric disturbances¹⁶. HD is primarily characterized by the expansion of a polymorphic cytosine-adenine-guanine (CAG) trinucleotide repeat chain encoding N-terminal region of polyglutamine tract within the huntingtin gene (*htt*)³. Curcumin, because of its ability to cross the BBB,²² has been investigated for its therapeutic effects against various motor neurodegenerative disorders. Curcumin has been shown to reverse the polyQ-induced apoptosis and neuronal dysfunction in motor areas of HD patients³⁹. Thus, curcumin is seen as a potential therapeutic candidate in polyp disease patients⁷.

CONCLUSION: Numerous studies have been conducted to test the potential of Curcumin to

prevent or treat different neurological diseases. However, several reports have raised questions about its safety and efficacy, especially at high doses, which may be harmful. Curcumin has received worldwide attention for its multiple health benefits, which appear to act primarily through its anti-oxidant and anti-inflammatory mechanisms. Neurodegenerative diseases are complicated age-related disorders with complex neuropathological characteristics. Neuronal damage and cognitive deficits or impairment of motor coordination are the major problems in these diseases. Because of its pleiotropic actions on the nervous system, including anti-amyloid, anti-inflammatory, and anti-oxidant properties, Curcumin is a promising candidate for targeting protein misfolding neurological diseases.

Furthermore, it is safe and inexpensive, readily available, and can effectively penetrate the blood-brain barrier and neuronal membranes. We have provided detailed information on the anti-amyloid properties of Curcumin in major neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. Collectively, the information available from reviewing the literature on the therapeutic potential of Curcumin can provide helpful insights into the potential clinical utility of Curcumin for treating neurological diseases.

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