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Therapeutic Potential of Curcumin in Alzheimer's Disease: A Golden Spice in Medicinal Role

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Abstract:

Alzheimer's Disease (AD) is a chronic, progressive neurodegenerative disorder associated with cognitive impairments; behavioral, social, and work-related dysfunctions; and ultimately causes the death of the individuals. The golden spice, curcumin, is a dietary polyphenol that emerged out from the kitchen to the scientific platform. It is an important component of *Curcuma longa* (Family: Zingiberaceae). It has been reported for the treatment of various diseases, due to its analgesic, antioxidant, anti-inflammatory, antitumor, antiapoptotic, antiproliferative, immunomodulatory, antiepileptic, antidepressant, and neuroprotective effects. Due to these multiple pharmacological effects, it has been explored in the treatment of AD. Despite having excellent safety and efficacy profile, naïve curcumin faces some challenges in proving its therapeutic efficacy during clinical trials due to its poor aqueous solubility, low bioavailability, and reduced blood-brain barrier permeability. Multiple mechanistic pathways through which curcumin elicits its neuroprotective effects and the challenges associated with curcumin that compromise therapeutic efficacy is described in this article. The nanoformulations developed to enhance the bioavailability and therapeutic efficacy of curcumin are also covered with detailed descriptions of research works carried by various researchers to treat AD. Further, some clinical studies conducted for curcumin and its nanoparticles against AD are also enlisted.

1. Introduction

Alzheimer's disease (AD) is one of the most common and challenging global concerns. It belongs to the class of neurodegenerative disorders. It is a geriatric medicinal challenge for scientists, pharmaceutical and biotechnological industries. AD is recognized as the most responsible issue leading to dementia [1, 2]. According to a current statistical report of 2019, about 50 million population of the world are reported to have or suffer from AD or AD-associated dementia [3]. AD is identified as a disease related to age as the risk of the onset of AD exponentially increases with the increase in age of the individuals. It is also reported that it brings disability in aged individuals. By 2050, the occurrence statistics of dementia are predicted to increase by 68% in low- and middle-income countries [2, 4].

Clinical AD can be identified by progressive memory deficits and difficulty in the execution of normal function even daily routine work. The early symptoms of AD include abnormal or alteration thinking, impairment in behavior, the decline in memory, impairment in understanding with respect to new information, and dysfunction in verbal communication i.e. speech and language [5]. In the advanced stage of AD patients suffering increases which ranges from severe memory loss, hallucinations, disorientation to lack of self-sufficiency. In this advanced AD, individuals eventually die due to respiratory syndrome, infection as well as fasting [6, 7]. The biological signatures of AD are the development of Aβ plaques, neurofibrillary tangles (NFTs), which are indicative of primary pathological stages of AD. Development of gliosis, and neuronal loss may be accompanied by cerebrovascular amyloidosis, obesity, inflammation, and other major synaptic changes [8-14]. All the symptoms of AD are caused by changes in proteolytic processing of amyloid precursor protein (APP), and neurofibrillary tangles (NFTs) caused by hyper-

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phosphorylation of the tau protein [15]. Among various risk factors like diet, pollution, obesity, cardiac disorders, oxidative stress has been recognized as the most important contributing factor. This oxidative stress is mainly or mostly found to affect aged individuals. It also causes fast aging and contributes to the progression of multiple neurodegenerative diseases including AD. Increased production of reactive oxygen species (ROS) associated with age- and disease-dependent loss of mitochondrial function, altered metal homeostasis, and reduced antioxidant defense directly affect synaptic activity and neurotransmission in neurons leading to cognitive dysfunction. In addition, molecular targets affected by ROS include nuclear and mitochondrial DNA, lipids, proteins, calcium homeostasis, mitochondrial dynamics and function, cellular architecture, receptor trafficking and endocytosis, and energy homeostasis. Abnormal cellular metabolism in turn could affect the production and accumulation of amyloid-β (Aβ) and hyperphosphorylated Tau protein, which independently could exacerbate mitochondrial dysfunction and ROS production, thereby contributing to a vicious cycle. Epidemiological studies indicate that natural therapy can be adopted for the treatment of AD if they have good antioxidant properties. It is reported that polyphenols, fatty-acids or vitamin-rich aliments, may delay the occurrence of neurodegenerative diseases [16, 17], however, randomized controlled clinical trials are absent to confirm the protective or therapeutic efficacy of such molecules [16-18]. Donepezil and galantamine-like drugs cause improvement in cognition. These drugs provide stoppage of cognitive deterioration but in some cases, patients do not respond to the treatment. Its beneficial effect is restricted to temporal with several adverse effects [19, 20]. It has been also reported that chronic consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) provides a reduction in the risk of AD [21] but its chronic consumption leads to gastrointestinal toxicity which is one of the greatest limitations for its use. Cyclooxygenase is an enzyme getting inhibited by the NSAIDs. While mounting evidence implicates ROS in the AD etiology, clinical trials with antioxidant therapies have not produced consistent results [14, 22-25].

Despite an extensive scientific investigation, it was observed that the available disease-modifying treatment strategies have many kinds of limitations [1] and the lack of effective pharmacotherapy has led researchers to seek alternative approaches to prevent AD. In this context, more neurobiological underpinnings are being discovered. Therefore, the urgency is to find new, safer, and (more) effective pharmacological strategies to treat AD.

In recent years, medicinal plants attracted attention due to their potential role in dementia [1]. Curcumin (CRM) has received increased interest due to its unique molecular structure that targets inflammatory and antioxidant pathways as well as (directly) amyloid aggregation; one of the major hallmarks of Alzheimer's disease. Taking into account of all the above concerns measurements of important inflammatory and antioxidant biomarkers, optimal dosages of CRM, food interactions, and duration of treatment would increase our understanding of its promising effects on cognition. In addition, increasing its bioavailability could benefit future research.

1.1. Etiopathogenesis

Alois Alzheimer, a German neurologist discover AD. He gave information that AD is one of the neurodegenerative diseases. He examined Auguste Deter (a 51-year-old lady), who suffered from loss of language, disorientation, memory, and hallucinations. He observed plaques and tangles in the cerebral cortex. It indicated the evidence of typical dementia. His discovery revealed the presence of neuritic amyloid β (Aβ) plaques in dementia patients [26]. Further, the scientists confirm that the disease of prominent protein-conformation leads to neuronal degeneration called AD. It is identified by misfolding of proteins, in which soluble neuronal proteins also undergo altered conformational changes leading to impairment of neuronal functions or loss [27-31]. The underlying cause of AD is Aβ, Neurofibrillary Tangles (NFTs), and synaptic loss but more knowledge about the same is under investigation. Different hypotheses were proposed for neuropathological aspects of AD but among them, impairment in the cholinergic function and diversification of amyloid β-protein production is the most accepted one [32-34]. In the cholinergic concept of AD, there are three important points which are required to understand which includes i.e. (a) In the cerebral cortex, decrease in presynaptic cholinergic markers (b) In basal forebrain, severe neurodegeneration of nucleus basalis of Meynert

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(NBM) (c) Cholinergic antagonists in memory decline compared to the agonists [35-37]. According to the amyloid hypothesis, the degradation of Aβ takes place which is the derived product of amyloid precursor protein (APP) because of the action of an enzyme i.e., β- and γ-secretase. The process of development of AD takes place with the increase in age and it results in the accumulation of Aβ peptides which involve Aβ40 and Aβ42. When the increase in the ratio of Aβ42/Aβ40 takes place it leads to causes Aβ amyloid fibril formation. Consequently, neurotoxicity occurs with the induction of Tau pathology (**Fig.1.)**. Finally in histopathological observation gives a piece of information about neuronal cell death and neurodegeneration as a confirmatory sign of AD [38-40].

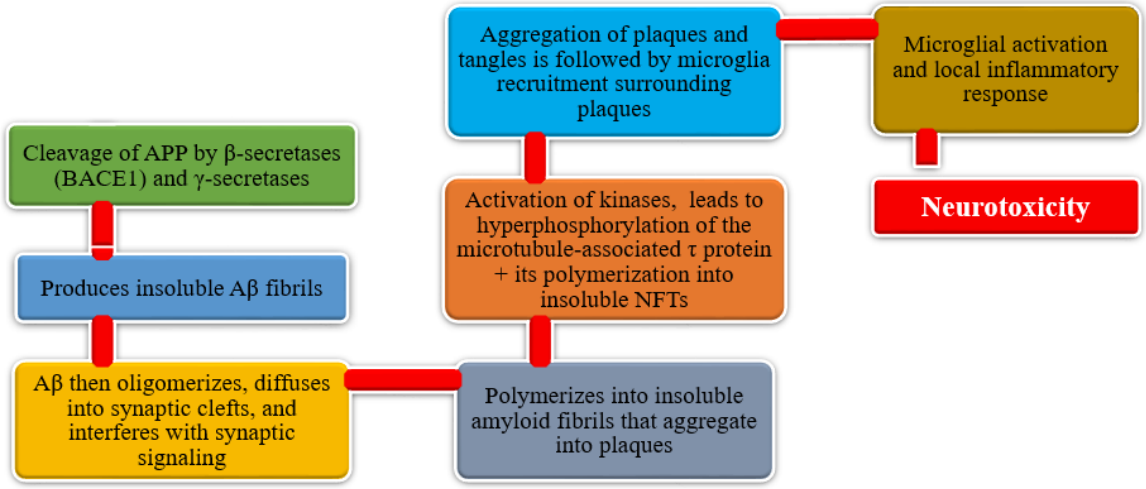

Figure.1. Amyloid and neurotoxicity: Alzheimer's disease

This is very important to note that this hypothesis is most accepted to date. Degradation and synthesis of Aβ are affected by different risk factors associated with AD as well genetic mutations like mutations in APP, Presenilin-1 (PSEN-1), and Presenilin-2 (PSEN-2). It results in a speedy accumulation of Aβ. It is well known that accumulated Aβ causes progression of neurodegeneration [38-40].

1.1.1. Risk factors of AD

The major segment of the brain affected with AD is Hippocampus, Locus coeruleus, Amygdala, Subiculum, Nucleus basalis Meynert, Cingulate cortex, Nucleus accumbens, Entorhinal cortex, Perirhinal cortex, Orbito-frontal Cortex, Prefrontal cortex, and raphe [41]. In critical cases of AD, it was also observed that Aβ is found available throughout the mesencephalon, lower brain stem, as well as cerebellar cortex region. This concentration of Aβ triggers the formation of τ-tangle in the locus coeruleus and transentorhinal and entorhinal areas. Gradually, it spreads to the hippocampus and neocortex region, hence Aβ and NFTs are considered the major players in the progression of AD [42]. Many cases of AD cases are sporadic. Mutation, genetic factors, environmental exposure, age, sex, and mitochondrial haplotypes are the risk factors that can affect AD [43-45]. The risk factors in AD are:

1. Familial mutation and genetics factors

It is one of the important cases which accounts for 1% of the cases of AD. Here, the genes that encode either a transmembrane amyloid-β protein precursor (AβPP) or PSEN1 and PSEN2, which are directly involved in the AβPP processing. Cleavage of AβPP takes place at the plasma membrane by the α-secretase without formation of pathologic amyloid-β (Aβ) peptides, but the cleavage with β- and γ-secretases causes the release in the extracellular space of Aβ peptides with 40 or 42 residues. It is well reported that $A\beta_{42}$ is more prone to aggregation and it constitutes the major component of extracellular amyloid plaques. These extracellular aggregates, Aβ peptides are located in neurons [31, 46-48]. It was evident in multiple research projects that intracellular accumulation of Aβ takes place before the development of extracellular plaques. It further affects

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synaptic function leading to a profound memory deficit [49, 50]. Besides the plasma membrane, AβPP is present at trans-Golgi network, endoplasmic reticulum (ER), and endosomal, lysosomal, and mitochondrial membranes where Aβ could be generated via β- and γ-secretase cleavage [22, 51, 52]. In addition, secreted Aβ peptides could be internalized via receptor-mediated or/and receptor-independent endocytosis [23, 25]. Dominant genes such as *APP*, PSEN-1, *PSEN-2*, and apolipoprotein E (ApoE) are prominently associated with AD.

a. APP

It is a type I transmembrane protein after cleavage it releases Aβ and other proteins and is encoded by the APP gene on chromosome 21. Out of 30 mutations, 25 kinds of mutations are associated with causing AD as it brings an increased accumulation of Aβ [53, 54]. All mutations surround the secretase cleavage site. The supportive study for the same is, the KM670/671NL mutation in mouse models has shown an increasing level of amyloid plaques in the hippocampus as well as cortex without NFTs. Cortical and hippocampal atrophy was recorded in A673V, D678H, D678N, E682K, and K687N mutations respectively Li et al., 2019; Tcw and Goate, 2017). On the other hand, E682K has exhibited hippocampal atrophy. A673V mutation has shown a presence of NFTs and Aβ, activation of microglia and astrocytes, and neuronal loss, compared to the rest of the mentioned mutations [55]. An increase in the Aβ42/Aβ40 ratio occurs with the mutation such as T714I, V715A, V715M, V717I, V717L, L723P, K724N, and I716V [55-57].

b. PSEN1 and PSEN2

These genes are the autosomal dominant form of early-onset AD (EOAD) located on chromosomes 14 and 1, respectively[34]. It is known to play an important role in the production of Aβ from APP. With more than 200 mutations in the PSEN1 gene is more common, on the other hand, less than 40 mutations were identified in the PSEN2 gene [58, 59]. Knockout studies of PSEN1 showed synaptic dysfunction and memory impairment in preclinical studies performed in mice [56]. Mutations in the PSEN1 gene increase the ratio of Aβ42/Aβ40 by decreasing Aβ40 levels. In contrast, PSEN2 mutations are rare and play a minor role in Aβ production. Any mutation in PSEN2 might have a severe effect on the Aβ 42/40 ratio, causing familial AD in the presence of normal PSEN1 alleles [60-62].

c. Apolipoprotein E (ApoE)

ApoE protein is a glycoprotein expressed highly in the liver, brain astrocytes, and some microglia are responsible for the production of myelin and normal brain function. The ApoE gene is located on chromosome 19 and has three isoforms (ApoE2, ApoE3, and ApoE4) [34]. The ApoEε4 allele is a strong risk factor for both EOAD and late-onset AD (LOAD). Lower risk and protective effect exhibited by ApoEε2 and ApoEε3 respectively. ApoEε4 is potentially responsible to cause Aβ deposition and is also associated with vascular damage in the brain. Senile plaque and cerebral amyloid angiopathy (CAA) is a contributing biological signature to developing AD [63-65].

d. ATP Binding Cassette Transporter A1 (ABCA1)

It regulates cholesterol efflux in the circulation, maintains the stability of ApoE lipidation, and serves as a mediator for high-density lipoprotein (HDL) generation. Hence, it is known to control cardiovascular diseases. Scientific reports suggest that deficiency of ABCA1 reduces amyloid plaques as well as removes lipidation of ApoE[34]. In humans, Tangier disease is reported to occur with a mutation in ABCA1. This disease is characterized by decreases in high-density lipoprotein (HDL) and ApoAI in plasma, and an increase in cholesterol in tissues AD pathogenesis [66, 67].

e. Clusterin Gene (CLU)

In 2009, Genome-Wide Association Studies (GWAS) identified the CLU gene located on chromosome 8, which is upregulated in the cortex and hippocampus of AD brains. CLU interacts with Aβ and promotes its clearance hence, may provide a protective role while it can be neurotoxic when it reduces Aβ clearance. Finally, the ratio of Aβ determines the neuroprotective or neurotoxic potential of CLU[34, 68].

f. Bridging Integrator 1 (*BIN1*)

BIN1 is a Bin-Amphiphysin-Rvs (BAR) adaptor protein that is involved in the production of membrane curvature. These isoforms are found in the brain and interact with clathrin, synaptojanin, and amphiphysin 1.

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Recently, BIN1 is identified as the second most important risk factor for LOAD [34, 69, 70].

g. Evolutionarily Conserved Signaling Intermediate in Toll pathway (ECSIT)

ECSIT gene is located on chromosome 19 and is associated with increasing the risk of AD. It encodes the adapting protein that functions as a cytoplasmic and signaling protein. It is responsible for stabilizing the mitochondrial respiratory complex and is also involved in the activation of nuclear factor (NF)-κB, interferon regulatory factors (IRFs), activating protein-1 and in the coupling of immune toll-like receptor (TLR), homeostatic bone morphogenetic pathway (BMP), and transforming growth factor-beta (TGF-b) pathways [71, 72].

2. Aging

Aging is a complex and irreversible process. It involves all the cellular as well as multiple organ systems which can be indicated by the reduction in the brain volume and weight, a prominent loss of synapses, Senile Plaques (SP) deposition, and Neurofibrillary Tangles (NFTs). Glucose hypometabolism, cholesterol dyshomeostasis, mitochondria dysfunction, depression, and cognitive decline occur with aging [73-75]. Hence it becomes difficult to distinguish the cases in early AD. AD can be divided based on the age of onset. The first one can be early-onset AD (EOAD), which is rare and are familial AD (30–60 or 65 years). The second type is the late-onset AD (LOAD). It is common (above 65 years). Both types may occur in people who have a family with a positive history of AD and families with a late-onset disease [73-75].

3. Environmental factors

It includes multiple things like metals, diet, air pollution, and air pollution. copper, zinc, and iron are a kind of biological metals as they are useful for human beings but metals like aluminum and lead do not possess biological functions hence, they are called as toxicological metals. Aluminum is bound to plasma transferrin and to citrate molecules which leads to the transfer of it to the brain. Neuropharmacological studies reported that aluminum accumulates and interacts with the protein in the cortex, hippocampus, and cerebellum areas. This harmful interaction leads to develop misfolded, aggregated, and highly phosphorylated proteins like tau protein, which is one of the signs of AD [76]. Lead competes with e calcium and can cross the blood-brain barrier (BBB) rapidly, where it can cause neural differentiation and synaptogenesis, which can cause massive damage. On the other hand, cadmium which can also cross BBB, and responsible to bring aggregation of Aβ plaques and the self-aggregation of tau in the AD brain [77, 78].

4. Diet

Various nutritious supplements can reduce the risk of AD like antioxidants, poly phenolic compounds, vitamins, and fish. But saturated fatty acids and high caloric food can lead to developing cardiac disorders, obesity, and AD. Such food causes a decrease in water volume in our body, decreases heat-sensitive micronutrients like vitamin C and folates, and the formation of toxic end products from non-enzymatic glycation of free amino groups in proteins, lipids, and nucleic acids. The AGEs are capable of the formation of reactive oxygen species and cause oxidative stress and inflammation. Cognitive decline and development of AD occur with the elevation of AGEs levels in serum. Malnutrition, eating, and swallowing problem is the other major contributing factor of AD [34, 76].

5. Infection and diseases

Scientific shreds of evidence indicate that Ads can occur due to infection of the brain. Chronic infections of the central nervous system can an accumulation of Aβ plaques and NFTs [34]. Syphilitic dementia is caused by *Treponema pallidum*, which is accumulated in the cerebral cortex, and produced lesions similar to NFTs, and it is well known that it leads to devastating neurodegenerative disorders i.e AD. *Chlamydia pneumonia* bacterium can trigger late-onset AD by activation of astrocyte and cytotoxic microglia, disrupt calcium regulation and apoptosis, resulting in deterioration of cognitive function, and increase the risk of AD [79-81].

Chronic hyperglycemia can induce cognitive impairment as a result of increasing amyloid-beta accumulation, oxidative stress, mitochondrial dysfunction, and neuroinflammation. Alteration in insulin action can result in Aβ accumulation and reduce the tau protein degradation associated with AD [43, 82-85]. Cardiovascular diseases like atherosclerosis, peripheral artery disease, hypo-perfusion, and emboli are all related to increased risk of AD [86, 87]. Obesity is a well-known risk factor for type 2 diabetes, CVDs,

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and cancer, which are identified as risk factors for dementia and AD [43, 82-85].

1.1.2. Biological signatures for neuropathology of AD

Synaptic damage and neurodegeneration in AD may occur due to the development of Aβ monomers, oligomers, and other Amyloid precursor protein (APP) metabolites. Still, the investigations are under process to find out exact possibilities or the reason behind the neuropathology of AD. Formation and development of pore-like structures associated with channel activity; modification in glutamate receptors, excitotoxicity, signaling pathways correspond to synaptic plasticity, neuronal cell death and neurogenesis; circuitry hyper-excitability and mitochondrial dysfunction [88-96]. Previous reports have shown that fyn kinase [97-101], glycogen synthase kinase-3β [GSK3β and cyclin-dependent kinase-5 [CDK5], members of the MAPK family such as ERK and JNK as well as other pathways such as p21-activated kinase are found to involved in the neurodegenerative progression of AD [102-107]. Abnormal activation of signaling pathways might lead to synaptic failure and altered neurogenesis by promoting abnormal Tau phosphorylation and aggregation, cytoskeletal abnormalities, activating caspase pro-apototic pathways, and activating calcium and calpain dependent proteolysis [108-110]. Many of the biological signatures are discussed below.

1. Amyloid precursor protein (APP)

Amyloid precursor protein (APP) is a type I transmembrane protein containing a large N-terminal ectodomain which contains part of the Aβ sequence, and a short intracellular C-terminal domain. Processing of APP always commences with the cleavage of the ectodomain by the secretase to generate a large N-terminal fragment (NTF). It takes part in the amyloidogenic pathway and non-amyloidogenic pathway where, APP cleavage by β-secretase and α-secretase respectively [111]. β and α-secretase result in the secretion of an exclusive NTF, sAPPβ, and cleavage within the Aβ domain respectively [46, 48, 112-114].

2. Senile Plaques (SP)

Extracellular deposits of Aβ with different morphological forms having neuritic, diffuse, dense-cored, or classic and compact nature are called Senile Plaques (SP) [115]. It is well established that β-secretase and γ-secretase are causative enzymes to synthesize Aβ deposits from APP [116]. These enzymes cause cleavage of APP into six fragments of amino acids which include 43, 45, 46, 48, 49, and 51 amino acids. Finally, it appears in Aβ40 and Aβ42 as a final form [21, 34, 117]. Large and insoluble amyloid fibrils accumulate to form amyloid plaques throughout the brain to cause damage to axons, dendrites, and loss of synapses, in addition to cognitive impairments [32, 118-120].

3. Neurofibrillary Tangles (NFTs)

Neurofibrillary Tangles (NFTs) are abnormal filaments of the hyperphosphorylated tau protein it can form paired helical filament (PHF) when it undergoes twisting. It accumulates in neuralperikaryal cytoplasm, axons, and dendrites to cause a loss of cytoskeletal microtubules and tubulin-associated proteins. The hyperphosphorylated tau protein is the major constituent of NFTs in the brains of AD patients [121]. Morphological NFTs stages are: (1) Phosphorylated tau proteins are accumulated in the somatodendritic compartment without the formation of PHF, (2) mature NFTs, having filament aggregation of tau protein with the displacement of the nucleus to the periphery part of the soma, and (3) it results from a neuronal loss due to large amounts of filamentous tau protein with partial resistance to proteolysis [122].

4. Synaptic Loss

Synaptic damage in the neocortex and limbic system causes memory impairment and generally is observed at the early stages of AD. Synaptic loss mechanisms involve defects in axonal transport, mitochondrial damage, oxidative stress, and other processes that can contribute to small fractions, like the accumulation of Aβ and tau at the synaptic sites.-p.

Synaptic proteins serve as biomarkers for the detection of synapses loss, and severity. These proteins are neurogranin, a postsynaptic neuronal protein, visinin-like protein-1 (VILIP-1), and synaptotagmin-1 [5, 123-126].

5. Tau protein

Intracellularly Tau protein gets accumulated to forms the NFTs and other inclusion bodies. It also aids in the process of microtubule formation by promoting tubulin assembly. Microtubules provide structural support to

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the neuron. In AD, improper folding of the tau protein occurs resulting in its failure to bind with microtubules. It leads to the aggregation of this tau in the form of fibrillary structures inside the neurons [127].

1.2. Treatment Strategies

It is well observed and evident in pre-clinical research antioxidant experimental therapeutics produced promising results in animal models of AD but there is no FDA-approved antioxidant therapy is available for the treatment of AD [128-131]. Currently approved and accepted strategies for the treatments for AD are restricted to cholinesterase inhibitors and a low affinity NMDA receptor antagonist. Donepezil, rivastigmine, and galantamine are belong to the class of cholinesterase inhibitors, and, memantine comes under NMDA receptor antagonists. Many antidepressants are used in depression in AD **(Table.1.)**

Table.1. Current Therapeutic approach

Drugs	Class/Target	Funding	Application	References
Donepezil, rivastigmine, and galantamine	inhibitors of cholinesterase and	1st	AD	[132]
Memantamine	uncompetitive antagonist of the N-methyl-D-aspartate (NMDA)		moderate to severe AD	[34, 132]
Sertraline, fluvoxamine, Fluoxetine, Paroxetine, Citalopram, Mirtazapine, Venlafaxine, Duloxetine, Olanzapine, Risperidone, Quetiapine, Ziprasidone, And Aripiprazole	Antidepressants		depression in AD	[133]
Benzodiazepines	Anto-anxiety		Anxiety and agitation associated with AD	[133]
MK-8931, TAK-070, AZD3293	Beta-secretase	β-site amyloid precursor protein cleaving	AD under trial	[134]
AF267B, AF102B, 77-LH-28-1, VU0357017, VU0364572, EVP-6124	Muscarinic (mAChR)/nicotinic (nAChR) receptor	activators of specific mAChR (M_1 & M_4) & nAChR (α_7 & $\alpha_2\beta_4$)	AD under trial	

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It is very important to note that these adopted drug treatments do not provide a "cure" and are not disease-modifying. It is only limited to providing symptomatic treatment for some individuals [14, 135]. Many times, clinical trials fail but now the recent clinical trials are more focused on the Production or clearance of Aβ peptides emphasizes and finding alternative molecular mechanisms that will ameliorate the development of AD [14, 132]. The phytoconstituents alone or in combinations will be a good therapeutic option that can surely help to discover new potent drugs for the effective treatment of AD with lesser side effects than the currently available pharmacological treatment. Recent studies are focused on targeting Aβ, ABB, and tau for treatment and plant-based products provide the best alternative and can be a great boon due to their lesser negative impacts.

1.3. Curcumin (CRM)

*Curcuma longa (*Turmeric) perennial herbs member of Zingeberace family, is an Indian spice [136]. It is widely cultivated in the south and southeast tropical Asia [137] and is used in the form of powdered rhizomes (the root of this plant) in Indian meals as dietary spices for centuries. It is very important to note that 2-5% of turmeric is CRM [138-140]. CRM is the molecule obtained from turmeric and is a hydrophobic phenol. It is represented as (1E,4Z,6E)-5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-hepta-1,4,6-trien-3-one [141, 142]. It is an additive in Indian food [143-145]. In 1910, the feruloylmethane skeleton of CRM was confirmed and synthesized by Lampe [146]. The vibrant yellow color of turmeric is due to the presence of a flavonoid – CRM and it contributes about 70-76% of crude extract of curcuminoids from turmeric [136],[147]. CRM was 1st identified in 1815, and in 1870 it is obtained as crystalline powder and finally recognized as diferuloylmethane [148]. CRM is soluble in ethanol, dimethylsulfoxide (DMSO), and acetone. Its melting point of 183 0C, and have a molecular formula of C21H20O6. Its molecular weight is 368.37 g/mol. Spectrophotometrically, the maximum absorption of CRM was 430 nm and 415-420 nm in methanol and in acetone respectively [149], [150]. 1650 absorbance units are observed in the 1 % solution of CRM.

A reported activity revealed that CRM exhibits a brilliant yellow hue (pH 2.5–7) and red (pH > 7). CRM in solution exists primarily in its enolic form **(Fig.2.)** has an important bearing on the radical-scavenging ability. The stability of CRM in aqueous media improves at high pH (>11.7) [151]. CRM is stable at acidic pH but unstable at neutral and basic pH, under which conditions it is degraded to ferulic acid and feruloylmethane [142, 152]·[153, 154]. More than 90% of CRM is rapidly degraded within 30 min of placement in phosphate buffer (pH 7.2). Degradation of CRM is extremely slow at pH 1–6 [142, 152]·[153, 154] as normally encountered in the stomach. In contrast, one of curcumin's major metabolites (tetrahydrocurcumin, or THC) is quite stable at neutral or basic pH and still possesses antioxidant activities [155, 156].

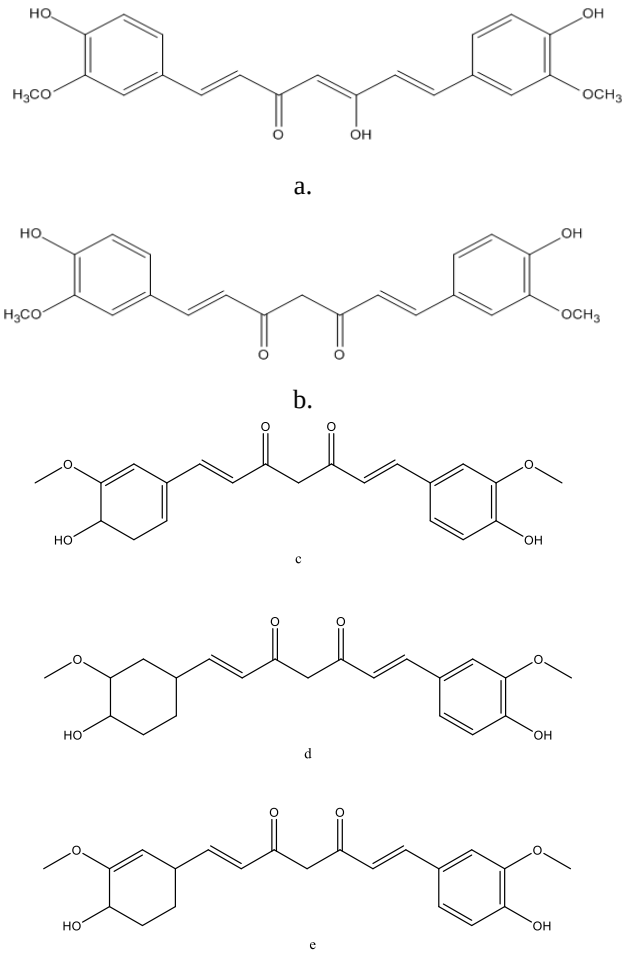

Figure.2. Chemical structures of CRM a. enol form, b. keto form, and metabolites in rats c. Hexahydrocurcumin, d. Dihydrocurcumin and e. Tetrahydrocurcumin

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CRM is soluble in 0.1 M sodium hydroxide, although it remains stable for only 1–2 h. In comparison, CRM is more stable in cell culture medium containing 10% fetal calf serum and in human blood, <20% of CRM being degraded within 1 h and approximately 50% by 8 h [157-159].

The Indian solid gold curcumin (Turmeric) obtained from the plant *Curcuma longa is* used in the Indian continent not only as spices but also known as an auspicious ingredient for cultural heritage[139]. In industries, CRM is also known to be useful as a dye for yellow color as well used as a food preservative. Since the ancient time of Ayurveda, numerous therapeutic potentials have been assigned to turmeric for a wide variety of diseases and conditions. It was first discovered by Vogel and Pelletier from the rhizomes of turmeric (*Curcuma longa*) [160]. Structurally, it can exist in at least two tautomeric forms, keto and enol and they possess antioxidant, anti-inflammatory, anticancer, antiviral, antibacterial, and antidiabetic properties [138, 142, 148, 161-166]. These traits can be attributed to the methoxy, hydroxyl, α, β-unsaturated carbonyl moiety, or diketone groups present in CRM [167]. It has been reported to possess antioxidant, anti-inflammatory, immunomodulatory, cancer chemo-preventive, and neuro-protective activities [143, 168-175].

CRM is considered safe at its higher doses and can be tolerated well [139, 140, 170, 175, 176]. This drug is not only acting in the treatment of neurological disorders like neuropathic pain but also acts as a nutritious supplement [139, 140, 170, 175, 176]. In medical science also is assured drug treatment for various pathological states due to its diverse pharmacologic activities and multiple therapeutic targets. It is also known to have anticancer efficacy when used as a single agent and/or in combination with conventional radio chemotherapy [140]. Among the numerous natural remedies, turmeric has gained considerable attention due to its profound medicinal values [177]. This agent possesses antioxidant, anti-inflammatory, anticancer, antigrowth, antiarthritic, antiatherosclerotic, antidepressant, antiaging, antidiabetic, antimicrobial, anti-hyperalgesic effects [178, 179], wound healing, and memory-enhancing activities [164]. Moreover, it exerts chemopreventive, chemosensitization, and radiosensitization effects as well [138, 180]. In traditional Indian medicine, this spice has been also used to treat different ailments such as gynecological problems, gastric problems, hepatic disorders, infectious diseases, blood disorders, acne, psoriasis, dermatitis, rash, and other chronic ailments [148, 181, 182]. Diverse in vivo studies have also indicated its potential against pro-inflammatory diseases, cancers, neurodegenerative diseases, depression, diabetes, obesity, and atherosclerosis [183]. Besides its safety, low intrinsic toxicity [178], and tolerability, cost-effectiveness is an added advantage of this compound [164, 184-193]. Because of its amazing properties, CRM is being marketed in several countries of the world in various forms [160].

1.3.1. Metabolic pathway of CRM in rats

CRM undergoes successive reductions to hexahydrocurcuminol and hexahydrocurcumin **(Fig.2c),** probably through intermediates dihydrocurcumin **(Fig.2d)** and Tetrahydrocurcumin **(Fig.2e).** CRM also undergoes rapid molecular modification by conjugation, mostly in the liver, to the glucuronide, sulfate, and glucuronide–sulfate forms **(Fig.2).** It is reported in animal studies that phase I reduction reaction and phase II conjugation reaction were the major metabolic pathways of CRM. The metabolites of CRM were reported to exhibit various pharmacological responses like dihydrocurcumin diminished lipid accumulation, oxidative stress, and insulin resistance. This activity of dihydrocurcumin was observed in oleic acid-induced L02 and HepG2 cells [194, 195]. It is very interesting to note that Tetrahydrocurcumin is more hydrophilic, more stable, and has more potent responses than CRM when evaluated for an anti-inflammatory, antioxidant, neuroprotective agent, and anti-cancer properties [167]. CRM mostly degrades via oxidation pathway rather than through hydrolysis in quickly degrades in aqueous buffer [196].

1.3.2. Multiple molecular targets of CRM

It gives a diverse range of molecular targets and signaling pathways. It can interact with a huge number of different proteins such as nuclear factor E2-related factor 2 (Nrf2), β-catenin, NF-κB, p38 MAPK, DNA (cytosine-5)-methyltransferase-1, COX-2, 5-lipoxygenase, PGE_2, FOXO3, inducible NOS, ROS, cyclin D1, VEGF, glutathione, cytosolic PLA2, p-Tau (p-τ) and TNF-α. This ability of CRM facilitates selective modulation of multiple cell signaling

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pathways linked to different chronic diseases, which strongly suggest that it is a potent multi-targeted polyphenolic compound [138, 162-164, 166, 171, 180-183, 197].

CRM exhibited its activity in the treatment of AD when it binds to small Aβ species and is capable of sufficiently blocking Aβ aggregation and fibril formation [198] apart from this it also gives remarkable response due to a decrease in senile plaques and capability to reverse structure of atrophied dendrites [199]. It is known to destabilize the preformed fibrillar Aβ [200]. Reduction of glycogen synthase kinase-3 **(**GSK3) mRNA and protein levels by CRM causes decreased mitochondrial dysfunction, apoptosis, and synaptic toxicities in AD. CRM maintains the viability of cells and the functions of mitochondria [201, 202].

1.3.3. Roadbacks of CRM

Poor water solubility decreased oral bioavailability, and instability at intestinal pH is the major pharmaceutical challenges of oral bioavailability of CRM (**Table.2.)** [203]. Apart from that, CRM has a very short half-life and, and it is photodegradable [204, 205]. Such kind of road backs makes CRM one of the most challenging drugs in the pharmaceutical industry. After administration of CRM, its level was found low in serum, poorly absorbed from the gut. CRM shows its susceptibility to degradation, under alkaline conditions (pH > 7). It means CRM undergoes degradation with the pH changes. CRM degrades to Trans-6-(40-hydroxy-30-methoxyphenyl)-2, 4-dioxo-5-hexanal, ferulic acid, feruloylmethane, and vanillin within 30 min. In scientific reports, it was investigated that in acidic medium CRM exhibits slower degradation (less than 20%) at 60 min [206]. Oral administration of 400 mg of CRM to rats gives only traces of the unchanged drug in the liver and kidney. At 30 min, 90% of CRM was found in the stomach and Small intestine, but only 1% was present at 24 h [207], [140]. CRM is the most widely used molecule which is evinced by more than 9000 citations for research [149, 197].

Table. 2. Challenges of CRM

Problems	References
• Lack of aqueous solubility, fast clearance from the systemic circulation, intestinal and hepatic metabolism	[170, 176]
• Extremely low serum levels.	[175, 207]
• Poorly absorbed from the gut	
• After Oral administration of 400 mg of CRM to rats only traces of unchanged drug were found in the liver and kidney. At 30 min, 90% of CRM was found in the stomach and small intestine, but only 1% was present at 24 h	
• Level of absorption and tissue distribution	[140]

It has been reported that from 12 g of CRM administered to human oral bioavailability was found 1% and the highest amount of plasma concentration was 0.051 μg/m while in rat and mouse it was recorded as 1.35 μg/mL (2 g/kg), and 0.22 μg/mL (1 g/kg) [208]. Hence, the major impediments towards the formulation development of CRM are poor absorption, extensive intestinal as well as hepatic metabolism, rapid elimination, and clearance [142, 152, 209, 210].

1.3.4. Approaches to overcome the challenges of CRM

In recent years, various strategies have been adopted to overcome the aforementioned challenges of both the drugs, CRM and DXH. These approaches are listed in table 3.

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Table. 3. Approaches to overcome challenges of CRM

Outcome of Problems	Approaches	References
	CRM	
Target in the MCF-7 breast cancer cells	• Transferrin-mediated solid lipid nanoparticles	[170, 211]
Increase the solubility of CRM in water	• γ -cyclodextrin liposomal nanoparticles • Human Serum Albumin Nanoparticles • PCL-PEG-PCL triblock copolymeric nanoparticles	[170, 212-214]
Increase in the oral bioavailability of CRM	• PLGA encapsulated nanoparticles • Apolipoprotein-E3 mediated poly(butyl)cyanoacrylate nanoparticles • PVP capped gold nanoparticles • Dextran sulphate chitosan nanoparticles • PCL-PEG-PCL triblock copolymeric nanoparticles	[170, 211, 214-219]
Cellular uptake of CRM	• Poly (lactide-co-glycolide) /polyethylene glycol encapsulated • Chitosan/ poly(caprolactone) nanoparticles	[170, 220-222]
Chronic myeloid leukemia cancer cells	• Transferrin-superparamagnetic iron oxide nanoparticles	[170, 222]
Targeting in cancer cells	• Biocompatible thermoresponsive polymeric nanoparticles	[170, 223]
Bioavailability and chemical stability	• Chitosan nanoparticles	[170, 224]

1.3.5. Pre-clinical and clinical impact of CRM

Results of clinical trials showed the clinical efficacy of CRM. However, it has not yet been approved for the use of humans. Ongoing clinical trials may provide evidence for its therapeutic potential in different pathological states and based on that it can provide novel therapeutics to the modern world [182, 197, 225]. Approximately 120 clinical trials have been successfully carried out so far. There are several systematic reviews /meta-analyses of CRM for human data are also available. CRM has been tested in an animal model of Alzheimer's disease. CRM at a concentration of 0–8 μM effectively disaggregates Abeta as well as prevents fibril and oligomer formation [198, 226]. Ethanolic extract of turmeric at 80 mg/kg orally administrated daily for three weeks effectively prevented cognitive deficits in AD [227]. CRM powder capsules cause a significant improvement of the behavioral symptoms in the AD when received a dose of 764 mg/day turmeric (100 mg/day CRM) orally for 12 weeks [228], Increase in PSD-95, synaptophysin, and camkIV expression levels was observed in the hippocampus of rat at 3–30 mg/kg of curcuminoid [226, 229]. In clinical studies with 36 Subjects Curcumin C3 Complex(®) an extract derived from the rhizomes (roots) of the plant *Curcuma longa* at 2, 4 g/day, orally for 24 weeks unable to demonstrate clinical or biochemical evidence of the efficacy of this formulation [230].

1.3.6. Assurance of safety evaluation

Toxicity study of CRM can be covered on the basis of doses i.e., at therapeutic doses and higher doses. At its therapeutic doses it reacts with number of enzymes for instance, glutathione S-transferase (GST) inhibition can lead to impaired detoxification and potential toxic drug−drug contraindications or cardiotoxicity due to the human ether-a-go-go-related gene (hERG) channel inhibition [231-233]. Secondly, high doses of CRM have been reported to be toxic for cells inducing

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apoptosis. It has been shown as cytotoxic responses against cancer cell lines, normal human lymphocytes, and noncancerous cell lines [232, 234]. It was found from the study that CRM at the dose of 8 mg/kg up to 3.6 g daily is found to be safe [235]. It was observed from the study conducted by Sharma RE et al (2004) that CRM at a dose of 3.6 g daily was found to be safe. A study was conducted on 15 patients suffering from advanced adenocarcinoma of the colon or rectum. Different doses of 450 mg to 3.6 g daily were given to patients up to 4 months and data was collected. It was found that CRM showed no toxicity and was well tolerated. Only minor cases of mild g.i.t adverse effects were observed in some patients. The reduction in the level of inflammatory mediators i.e. PEG_2 was observed with the daily consumption of 3.6 g of CRM [235]. Chen et al in 2014 published an iron impairment study on thirty 12 months old mice. The effect of 0.2% CRM along with dietary supplements in iron, copper, and zinc status of mice was evaluated. A significant reduction in iron level was observed whereas no effect was seen on the levels of copper and zinc. It was concluded from the study that long-term CRM supplementation may cause iron deficiency [236].

Phase I human trial showed safety profile of CRM when tested on 25 subjects with 8000 mg of CRM/day for three months and none of the toxicity was reported. Another five clinical trials using 1125–2500 mg of CRM/day have also been found safe. CRM was also investigated at 6 g/day orally for 4–7 weeks in other trials and again observed extremely safe [237, 238]. In various diseased states also CRM found safe. A good safety profile has been reported for CRM (500 to 8000 mg/day, three months) in patients with cardiovascular diseases with their risks, in a patient with pre-malignant lesions of internal organs [239, 240]. It was concluded safely in patients with different types of cancers like colorectal cancer at doses ranging from 36-180 mg/day for up to 4 months, breast cancer up to 6000 mg/day, and pancreatic cancer at 8000 mg/day for 2 months [241-243]. To overcome its pharmaceutical challenges various formulations are now available and investigated. Evaluating its routes of administration, in short-term intravenous dosing of liposomal formulation, CRM is safe up to a dose of 120 mg/m^2 in a clinical trial, while in a dose-escalation study in patients with metastatic cancer a dose of 300 mg/m^2 over 6 h reported being the maximum tolerated dosage. Besides, one case of hemolysis and one death associated with intravenous CRM preparations were reported [244-246].

1.3.7. Need of nanoformulations of CRM

Nano medicine is the way to manage AD in a well-defined manner. Nanomedicines provide state-of-the-art alternative approaches to overcome the challenges in drug transport across the BBB. The main reason to introduce nano formulations is the presence of a fully functional semipermeable BBB, which provides an obstacle for the transmigration of drugs, peptides, vectors, and molecules across it and to the CNS. The BBB and its selective transport of molecules into the brain oppose the efficacious delivery of various therapeutic agents. In addition, the BBB also negatively affects drug efficacy and tolerance, because large doses of drugs are needed to reach levels above the minimum effective concentration in the brain. Nanotechnology inclusive of nanoparticulate systems offers an opportunity to overcome such problems [247-249] associated with the drugs. There are various pieces of evidence in which nano formulation of CRM showed a beneficial effect in the treatment of AD. Inhibition of Nrf2, NF-*k*B, and Akt phosphorylation Tau/decreased expression of APOJ/increased expression of GLRX and TRX was observed in a cellular model of Neuroblastoma cell line (SK-N-SH cells) when CRM -loaded PLAG NPs was investigated [250]. g7-NPs-CRM investigated in primary hippocampal cell cultures/Aß $_{(1–42)}$ showed the therapeutic benefits in AD by the decrease in Oxidative stress, Inflammation, NF-kB, and increase of IkB with the promotion of Aß disaggregation [251, 252]. CRM-loaded PLGA-PEG nanoparticles conjugated with B6 peptide when investigated for AD in HT22 cells showed a narrowing of the diameter of CRM with the increase in Cellular uptake **(Fig.3.)** [253].

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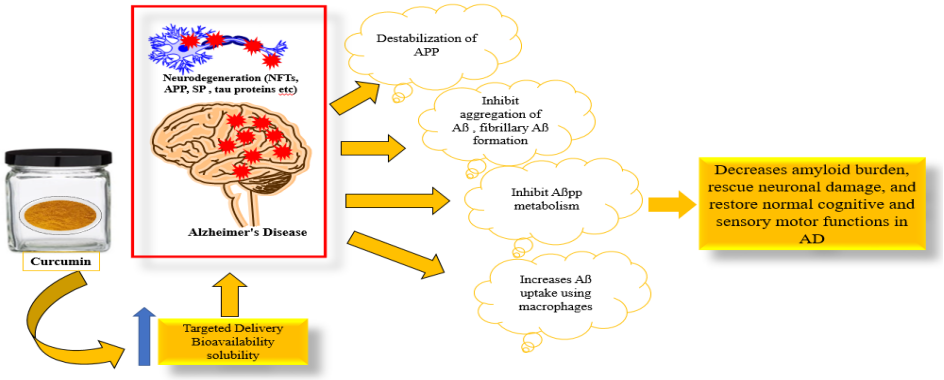

Fig.3. Therapeutic impact of nano-CRM in AD

The principle of neuropathology of AD involves aggregation of amyloid plaques and NFTs extracellularly and intracellularly respectively and hyper phosphorylated tau protein. Various hypothesis of AD suggests a theory of β-amyloid deposit, tauopathy, oxidative stress, excessive load of calcium with alterations of cholinergic, and glutamatergic neurotransmission. Among these theories the most accepted one is β-amyloid cascade and for accelerating the AD pathogenesis [50, 118, 121, 122, 252]. Nano Formulation of CRM have now emerged as a novel strategy for treatment of AD [247, 254] as well as various neurological disorders like neuropathic pain. This neuropathic pain is disease or defect of somatosensory nervous system. CRM along with duloxetine can be helpful in the treatment of neuropathic pain with respect to the naïve form or raw form was illustrated well in our recent publication [142, 152, 210]. Neuroprotective efficacy of CRM-encapsulated biodegradable poly (lacticco-glycolic acid) (PLGA) nanoparticles (NPs) on neural stem cells (NSCs) proliferation and differentiation was investigated [252, 254]. It has been first time reported that reelin, nestin, and Pax6, a panel of genes concerned with neuronal proliferation and self-renewal, were up-regulated by Cur-PLGA-NPs [254]. Wnt/β-catenin signaling is involved in self-renewal of NSC/progenitor cells. Cur-PLGA-NPs also reversed learning and memory deficit in an amyloid beta-induced rat model of AD-like phenotypes [254]. Investigating the effect of selenium and CRM drug delivery system in transgenic mice demonstrated the inhibitory effect of nano spheres on Aβ aggregation and decreasing inflammation in AD pathogenesis [255]. The effects of CRM-loaded nanoparticles on Nrf2, NF-*k*B and Akt/pTau were in accordance with its anti-inflammatory and antioxidant properties. The above-mentioned pathways are involved in the regulation of oxidative stress, inflammation, neuronal survival, and phosphorylation of tau protein. Hence, cur-NPs prevented Akt activity and Tau phosphorylation, as well as suppressed activation of Nrf2 and NF-κB signaling pathways [250]. The other in vivo studies mentioned in **table. 5.**

Table.5. Nano formulation of CRM in AD

Formulations of CRM	Dose (mg/Kg)	Name of model	Animal Used	Investigational remarks	References
Cur-PLGA-NPs	5,10, and 20	Aβ-induced	Rat	• Increased Pax6 and reelin expression • Increased NSCs proliferation, Self-renewal, Neuronal differentiation • Decreased Expression of Axin12, APC, GSK-3ß/Increased Cyclin-D1 and TCF/LEF Promoter activity expression of Wnt3, LRPP-5, LEF	[252, 254]

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				• Decreased Expression of Wif-1,Dkk-1 • Increased p-GSK-3β cells • Decreased p-β-catenin cells • IncreasedGSK-3β phosphorylation • Decreased phosphorylation of β-catenin	
Low density lipoprotein mimic nanostructured lipid carrier modified with lactoferrin-loaded CRM	6	Administrating Aβ1-42 and D-gal in rats	Rats	• Decreased MDA level • Decreased Damage associated with oxidative stress • Decreased Lipid peroxidation	[256]
Selenium/ CRM-PLGA nanosphere		5XFAD Transgenic mice	Mice	• Decreased Aß aggregation and toxicity	[252, 255]
CRT-conjugated PLGA	2	AD transgenic mic	Mice	• Decreased Activated glial cell • Increased Number of synapses • Decreased IL-6, TNF-α • Restoration of antioxidant activity (Decreased ROS) • Increased SOD, Increased Spatial memory • Improvement in behavioral deficit and suppression of astrogliosis and microgliosis	[257]
CRM with PLGA	2	APP/PS1dE9 mice	Mice	• Decreased Aß42 • Decreased Aß 40 • Increased SOD • Decreased TNF-α • Decreased IL6 • Decreased ROS • Increased Synapse number • Inhibit APP cleavage • Suppress microgliosis and astrogliosis	[258]
CRM-loaded PEG-PLA NPs	23	Tg2576 mice	Mice	• Increased memory	[259]
PLGA-PEG-B6/CRM		APP/PS1 mice	Mice	• Enhance the spatial learning and memory capability • Inhibit the generation of BACE1, APP, and PS1	[253]

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				• Decreased tau phosphorylation and Aß aggregation	
CRM nanoparticle polymeric nanoparticle encapsulated curcumin	25	-	-	• ameliorated ROS-mediated damage in both cell culture and in animal models	[260]

Abbreviations: PLGA, Poly (lactic-co-glycolic acid); NPs, Nanoparticles; APP, Amyloid precursor protein; AD, Alzheimer's disease; SOD, Superoxide dismutase; ROS, Reactive oxygen species; NSCs, Neural stem cells; PEG-PLA, Polyethylene glycol- polylactic acid; SDH, Succinate dehydrogenase; MDA, Malondialdehyde; GSH, Reduced glutathione; iNOS, Inducible nitric oxide synthase; MBP, Myelin basic protein; PDGFR, Platelet-derived growth factor receptor; BDNF, Brain-derived neurotrophic factor; NGF, Nerve growth factor.

1.3.8. Limitations and future directions

Regarding safety studies, it is very important to understand that extensive studies were conducted for the safety concern of CRM at its different doses, diseased conditions, and preclinical studies. In all the cases it has been observed that it is safe. But reporting of CRM safety has been performed for a very short period so far and, there is a lack of evidence regarding the consequences of its chronic administration. Apart from that, now a days various studies are going on CRM to overcome its challenges. Consequently, trials and more studies are essentially required to be conducted especially on novel formulations and in the long term of its use. CRM nanoformulations showed remarkable improvement in efficacy as well as bioavailability which is evident from its in-vitro as well as in-vivo studies. However, dose calibration is required with the frequency of dosing and this can be achieved by extensive investigations. Moreover, more studies are required to investigate the toxicity (if any) and efficacy of CRM-loaded NPs in large groups of individuals. Furthermore, combination therapy can be a milestone to crack decrease the dose of the main therapeutic agent loaded with CRM-NPs. Hence, further studies are required to investigate the biocompatibility and biodegradability of nano drugs and, preparation of CRM-loaded NPs to treat neuroinflammation, excitotoxicity, and DNA damage.

Conclusion

CRM is known as Indian golden spice which is now spread from kitchen to clinic due to its outstanding safety profile with several pleiotropic activities. Its pharmacological significance ranges from anti-inflammatory, antioxidant, neuroprotective, anti-cancer, anti-diabetic, and its complications and anti-protein aggregate effects. Its, low aqueous solubility, rapid clearance, and poor stability in the body fluids limit its clinical application. Currently, nano-based delivery systems are opening a new horizon to tackle the aforementioned problems. In the present study, we have documented many factors affecting AD, its biological signatures, and the importance of CRM in vitro, in vivo, and clinical trials. Its product is available in the market as GNCHerbal Plus®Turmeric Curcumin capsules, Vitamin Shoppe Curcumin C3 Complex capsules [261]. The potential impact of CRM-NPs in the prevention and treatment of AD also explained. Different treatment strategies with nano-CRM efficiently tackled various signaling pathways to treat AD and neurological disorders. We can also predict and acknowledge that drug delivery of CRM using nanotechnology which can bring revolution in the area of traditional drug delivery systems and ayurvedic approach modified drugs will be extremely efficient compared to the current standard.

Disclosure

The authors report no conflicts of interest in this work.

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