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Investigating The Neuroprotective Role of Curcumin in Alzheimer's Disease Models

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ABSTRACT

Alzheimer disease (AD) is a pathological worsening process of neurodegenerative disease characterised by impaired thinking, memory and behavioural problems, which have a considerable health impact worldwide. There is no disease-altering treatment at the present day that can help limit the progression of the disease, which is why there is the strong necessity to develop a disease-modifying medication. Natural therapeutic explores in curcumin A polyphenolic compound, curcumin found in Curcuma longa (turmeric) has gained a lot of interests to potential natural therapeutic agent because of its powerful antioxidant, anti-inflammatory, anti-amyloid and chelation towards metals. This review provides a comprehensive study on the neuroprotective effects of curcumin in the case of Alzheimer disease, its biochemical and pharmacological profile in its application regarding unique chemical content, bioactive compounds of curcumin, and pharmacokinetic constraints, like poor bioavailability. In vitro studies at the preclinical level show that curcumin can limit neurotoxicity caused by amyloid beta, prevent the formation of aggregates, and limit oxidative and inflammatory injuries and in vivo-based rodent trials report both cognitive and behavioural enhancements as well as the decrease of amyloid plaque and hyperphosphorylation of tau proteins. However, several limitations like low bioavailability, absence of large-scale, clinical trials, and insufficiency of long range safety make clinical implementation poor. The future study is needed to create a nano formulation, which will improve its bioavailability and combination therapies, which will produce a synergistic neuroprotective effect. In general, curcumin has a large potential as effective safe multi-targeted therapy against Alzheimer disease and its relevance should be further investigated due to conducting well-conducted human trials that may determine its effectiveness.

Key Words:

Alzheimer's disease, Neurodegenerative disease, Curcumin, Polyphenols, Neuroprotection

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1. INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that typically progresses through three stages characterized by cognitive decline, memory disturbance, and behavioral issues and is a global public health crisis [1]. Although considerable research has been done into AD, disease-modifying medicines remain confined mostly to symptomatic therapies, including

no agents that have been shown to halt or reverse disease progression. In this regard, researchers have been highly focused on studying natural compounds with potential neuroprotective properties. Curcumin is a polyphenolic compound derived from the rhizome of Curcuma longa (turmeric) and has long been part of Asian medicine, employing anti-inflammatory, antioxidant, and healing properties. Recent preclinical studies have suggested curcumin is associated with AD models by targeting various disease-related mechanisms such as (i) Amyloid Beta aggregation (ii) Tau hyperphosphorylation (iii) oxidative stress and (iv) neuroinflammation. The disclaimer attempts to assess the neuroprotective role of curcumin in AD models, by systematically reviewing and appraising the mechanisms, experimental evidence and whether any translational opportunity exists for curcumin as a therapeutic option for its use in managing the symptoms of Alzheimer's disease.

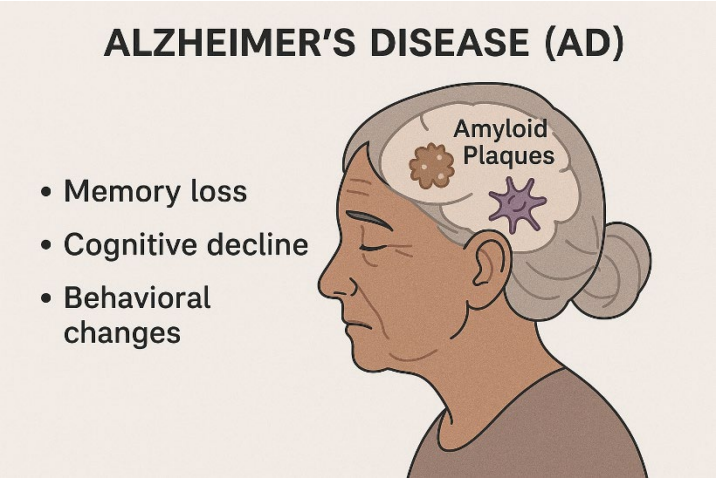

Figure 1: Alzheimer's disease [2]

The figure above in Figure 1 represents Alzheimer disease (AD) that is a neurodegenerative condition with progressive loss of memory, mental dysfunction and behavioural changes[3]. It describes the occurrence of amyloid plaques in the brain, these unusual protein deposits are regarded to be one of the main characteristics of the AD[4]. These plaques interfere with the transmission of neural communiques and cause death of the neurons, which results in loss of cognitive abilities as is commonly discovered when someone is affected[5].

1.1.Background Information and Context

Alzheimer disease (AD) is a slowly developing neurodegenerative pathology with the most significant manifestation of cognitive decline, memory loss, and disturbances of behaviour, which is predominantly conditioned by the pathologic hallmarks: amyloid beta aggregation, tau hyperphosphorylation, oxidative stress, and neuroinflammation [6-7]. As the number of individuals affected by AD is experiencing an upward trend globally, it is a major threat to public health and socioeconomic status[8]. The existing treatment methods are restricted to symptomatic and have little effect on the course of the disease, and are also accompanied by adverse effects, which confirms the urgent need to find more effective concepts that would avoid bringing significant harm to the patient. It is against this background that curcumin, a polyphenolic compound, a natural product, obtained through the rhizome of Curcuma longa (turmeric) has become an object of research due to its intense antioxidant, anti-inflammatory, and neuroprotective potential. The only limitations of using curcumin as a therapeutic

candidate are its ethno medicine value and untypical chemical structure which have been traditionally used in Ayurveda and Chinese medicine in treating various ailments and Alzheimer disease in particular is considered a promising therapeutic candidate.

1.1.1. Overview of Alzheimer's Disease Pathology and Prevalence

Alzheimer disease (AD) represents the most prevalent type of the dementia that affects 60-70 percent of the dementia cases across the globe. It is a long-term neurodegenerative disease, mainly on an older population, which makes them lose memory, thinking, language, and the ability to solve problems. The amyloid deposit of extracellular amyloid beta plaques is the other hallmark of this disease and is accompanied by the intra-cellular formation of neurofibrillary tangles made up of hyper phosphorylated tau protein. Amyloid cascade hypothesis indicates that aggregation of A beta peptides are inhibitory to synaptic communication resulting to neurotoxicity and neurotoxicity. Broad synaptic aberration, loss of neurones, neuroinflammation, and oxidative stress are also in the disease. These changes are especially sensitive in the cognitive deficit of the AD patients as there is damage in the hippocampus and cortex. The prevalence of the disease is shocking and the numbers are expected to increase to 139 million by the year 2050 because of the ageing population.

1.1.2. Current treatment limitations.

1. **Symptomatic Relief Rather Than Disease Modification**

The management of Alzheimer s disease is presently based on typical treatment that aims at relieving the symptoms only but does not have any effect on the course of the disease itself[9]. The most popular drugs include cholinesterase inhibitors and memantine, which stimulate the action of neurotransmitters temporarily improving such cognitive symptoms as memory and attention. Nonetheless, such medications are not aimed at the pathological mechanisms, like the presence of amyloid beta or the presence of tau tangles, and, as such, even though patients may record short-term positives in their cognition and behavior, the progression of the disease simply takes over inside of the brain.

2. **Limited Efficacy**

Currently available drugs against Alzheimer are not very effective. A good example is the cholinesterase inhibitors that could have minor intellectual advantages during mild to moderate phases of the disease, although the gains are not always coherent to enhance daily operations or independence. On par, at moderate to severe stages, memantine is also associated with modestly beneficial effect, though the clinical course is not influenced significantly by its administration. This has led to dissatisfaction among many patients and care givers with the available treatment currently because of the insignificant and temporary effect it has on the patients.

3. **No Cure or Disease-Modifying Therapy**

Alzheimer has been studied intensively over decades and significant funding had been poured into the development of drugs to treat it, there is as yet no approved medicine available to cure it or modify it. Monoclonal antibodies against amyloid beta have been widely explored, but have not provided any clear overall clinical benefit in the clinical trial arena. This absence of a curative or outcome-stalling treatment remains one of its greatest challenges and therefore there

is increased need to develop innovative therapeutic strategies, which may effectively target the pathogenic neurodegenerative mechanisms in Alzheimer disease.

4. **Side Effects and Tolerability Issues**

The drugs that are presently considered in the pharmacological treatment of Alzheimer are also found to be accompanied by adverse effects that may influence compliance by patients as well as the quality of life. Cholinesterase inhibitors commonly produce gastrointestinal side effects like nausea, vomiting, diarrhoea and loss of appetite, as well as cramps and bradycardia in others. Instead, memantine may cause dizziness, headache, confusion, and constipation. The side effects may prevent the patient to remain in treatment or may necessitate dose changes which curtail efficacy of treatment in a therapeutic capacity.

5. **Limited Effect on Non-Cognitive Symptoms**

Cognitive impairment in Alzheimer is not the only feature but the presence of a series of non-cognitive symptoms also occurs, such as agitation, aggression, depression, anxiety, psychosis, and sleep disturbances. Available drugs are of little value in the treatment of these behavioral and psychological symptoms and they may severely affect the patients as well as overburden the care givers. There is thus an unfulfilled need of therapeutic agent that can simultaneously treat both cognitive deterioration and neuropsychiatric manifestation to enhance well-being of patients in general.

6. **Heterogeneity of Disease Pathology**

Multifactorial and heterogeneous pathology of Alzheimer is one of the main difficulties in treating it. There are various pathological mechanisms involved in the disease that are coupled together, they include amyloid beta aggregation, tau hyperphosphorylation, oxidative stress, neuroinflammation, mitochondrial dysfunction, and synaptic degeneration. The complexity of the disease pathways involved in neurodegeneration may thus make current treatments targeting one mechanism inadequate in terms of generating significant clinical outcomes e.g. amyloid beta deposition. This emphasizes the interest of investigating multi-targeted/combination therapy approaches.

1.1.3. Introduction to curcumin: source, chemistry, and traditional medicinal uses.

1. **Source of Curcumin**

The natural polyphenolic compound, Curcumin which is derived from rhizome of Curcuma longa, has spices, colouring agent, and traditional medicinal uses. It constitutes 2 5% of the entire dry weight of turmeric and is antioxidant, anti-inflammatory, antimicrobial and anticancerous[10]. The importance of curcumin has attracted a lot of scientific investigations on its therapeutic effects in the pathogenesis of different diseases, including neurodegenerative diseases such as Alzheimer disease.

2. **Chemistry of Curcumin**

Curcumin or differuloylmethane is a chemical product that has a molecular formula of C 21H 20O 6 and a molecular weight of 368.38g/mol. It has the chemical composition of a set of two aromatic rings with a seven-carbon chain with an unsaturated 9,10-unsaturated- 9,10-

unsaturated- 9,10-unsaturated-unsaturated unsaturated 9,10-SimusCaroontmoiety. The conjugation of curcumin makes it bright yellow with high absorbance that, in a way, contributes to antioxidant properties, anti-inflammatory, anti-cancer, and neuroprotective effects.

3. Traditional Medicinal Uses

Curcumin is a major component of turmeric which has been a component in different traditional medicine systems throughout Asia since centuries owing to its medicinal effects. Turmeric is hailed in Ayurveda because of its health giving properties where it is used in the treatment of respiratory diseases, liver disorders, digestive issues, skin diseases, inflammatory issues and arthritis. The Traditional Chinese Med use turmeric, under the name of Jiang Huang, to stimulate blood rolled, as well as to relieve pain. It also finds its use in the Indian cuisine, rituals and beauty. Traditional utilization of the bioactive compound curcumin and turmeric in variability of different types of medicine traditions encompasses its treatment effects, especially in chronic disorders, such as Alzheimer disease.

1.2. Objectives of the Review

- To evaluate existing research on curcumin's neuroprotective effects in AD models.
- To discuss underlying mechanisms of action.
- To identify gaps for future investigation.

1.3. Importance of the Topic

In the 21 st century, Alzheimer disease (AD) is a major public health problem because of an approximate 55 million people worldwide who have dementia. This figure is projected to almost triple to the 139 million by 2050 when it will place tremendous burden on economies and healthcare systems and families alike. The disease causes impairments in cognitive abilities, loss of independence, emotional and financial strains to the caregivers and the society. Nevertheless, AD has no cure, and its disease-modifying treatment is ineffective despite the progress in biomedical research. This underlines the necessity of innovative treatment interventions that are safe and which can prevent and/or retard the progression of the disease. The antioxidant, anti-inflammatory and anti-amyloid capabilities of natural compounds such as curcumin have attracted scientific attention since they represent the pathological processes of primary interest in AD. On such positive safety profile and long history of traditional use, curcumin is a candidate neuroprotector that is appealing. Testing the possibility of natural agents might become the path towards finding some affordable and easy-to-access remedies to reduce the devastating effects of AD in populations around the world.

2. ALZHEIMER'S DISEASE PATHOPHYSIOLOGY

Alzheimer s disease (AD) is a chronic brain degradable illness resulting in memory loss, cognitive impairment and behavioural abnormalities, and eventually causing loss of autonomy and death. Significantly, the pathophysiology of AD is much similar to other brain diseases which are multi-factorial in the sense that numerous biologic processes interact to involve the dysfunction and degeneration of the brain neurons[11]. It is primarily characterized by both the presence of extracellular aggregates of amyloid beta (concentration of amyloid beta plaques) and the development of intracellular neurofibrillary tangles that are made up of hyperphosphorylated tau protein[12]. These characteristic characteristics impair the

communication or synapses, breakdown of the transport system of the neurons and result in a cascade of many activities resulting in massive losses of neurons. Furthermore, neuroinflammation and oxidative stress are also important in accelerating the disease process through enhancing further injury and dying of neurons. The knowledge of the detailed processes of such changes is needed to provide the development of effective strategies in terms of the prevention or the slowing of the course of Alzheimer disease.

Table 1: Research study

Author(s) & Year	Objective / Focus	Methodology	Key Findings	Limitations / Remarks
Goozee et al. (2016)[12]	To examine the potential clinical value of curcumin in the prevention and diagnosis of Alzheimer's disease.	An analysis at preclinical and limited clinical studies on how curcumin might help prevent and diagnose Alzheimer's disease.	Curcumin has anti-inflammatory, antioxidant, and anti-amyloid characteristics, which make it a good candidate for diagnostic imaging because it binds to amyloid plaques.	Little clinical evidence; bioavailability is a considerable obstacle to its therapeutic translation.
Sadegh Malvajerd et al. (2019)[13]	To evaluate the neuroprotective potential of curcumin-loaded nanostructured lipid carriers in AD animal models.	Medical exploration of curcumin loaded nano-structured lipid carriers prepared and intravitally infused in AD induced rats; behavioural and biochemical examination carried out.	Formulated nano-curcumin ameliorated behaviour deficit, hippocampal antioxidant capacity, and amyloid betas, implying more potent therapeutic effects.	Inclined only in preclinical models; the evaluations of human pharmacokinetics and safety were required.
Abass et al. (2020)[14]	To analyse neuroprotective expression and properties of turmeric and curcumin.	Review on experimental assessments of turmeric and curcumin neuroprotection.	Verified that curcumin was neuroprotective through several mechanisms, namely antioxidant and anti-inflammatory mechanisms.	Mainly restricted to animal and laboratory studies; it was suggested to have additional clinical confirmation of

				its therapeutic utility.
Thakur et al. (2018)[15]	To provide an overview of the pathophysiology and management strategies for Alzheimer's disease.	Review regarding the pathology, development and treatment of the disease.	Outlined some pathological essentials e.g. amyloid beta aggregation, tau hyperphosphorylation, oxidative stress, and neuroinflammation; mentioned current available treatment e.g. cholinesterase inhibitors and NMDA receptor antagonist, and referred to other medicines e.g. herbal compounds.	Does not have critical appraisal of the other possible therapies; is mainly descriptive rather than quantitatively synthesized.

2.1. Amyloid beta aggregation.

Pathological aggregate Formation of amyloid beta (A beta) peptides is one of the key pathological features of Alzheimer disease (AD). The amyloid precursor protein (APP) generates the A peptides sequentially by cleavage of protease beta and gamma secretase enzymes. A42 is one of these peptides, and it is more inclined to aggregation because of being hydrophonic. First, soluble oligomers are created by A beta monomers and they are easily neurotoxic and interfere with synaptic functioning. With time, these oligomers proceed to aggregate to form insoluble fibrils, which can later deposit as extracellular amyloid plaques in the brain parenchyma, especially in the hippocampus and cortex. Amyloid plaques interrupt the inner communication processes of neurons, cause dysfunction in synapses, stimulate microglia, and trigger a wave of neuroinflammatory processes that eventually result in the death of neurons and subsequent reduction in cognitive abilities typical of Alzheimer disease.

2.1.1. Tau hyperphosphorylation.

Irregular tau protein modification is another important pathology characteristic of Alzheimer an illness. In healthy physiological states, tau is a microtubule binding protein that maintains microtubule intactness and facilitates axonal transport of an axon. Tau in Alzheimer disease is hyperphosphorylated, thus having a lower affinity towards microtubules to the point of detachment and formation into paired helical filaments. These threads collect to make intracellular neurofibrillary tangles (NFTs) inside neurons. NFTs formation destabilizes the neuron structure by impairing the axonal transport and the cytoskeleton. This leads to loss of synapses, functional impairment of neurons and loss of neurons associated with the magnitude of cognitive impairment in victims of Alzheimer disease.

2.1.2. Neuroinflammation and oxidative stress

Neuroinflammation and oxidative stress are key features in the development of Alzheimer's disease. The accumulation of amyloid beta plaques, and neurofibrillary tangles sequentially activates resident immune cells in the central nervous system, microglia, and astrocytes. Upon activation, microglia secrete proinflammatory cytokines and chemokines, including TNF-α, IL-1β, and IL-6, creating a continued inflamed environment which follows with neuronal damage and loss. Along with this, there is an increase in reactive oxygen species (ROS), and a decrease in endogenous antioxidant capacity, which leads to oxidative stress. As ROS influences lipids, proteins, and DNA, this can hinder normal cellular function and promote neurodegeneration. Additionally, the presence of neuroinflammation not only promotes neurodegeneration along the trajectory of amyloid beta and tau pathology, but it could also magnify the toxic effects of these amyloid beta and tau pathologies, leading to an ongoing cycle of neurodegeneration in Alzheimer's dry.

2.2. Curcumin: Biochemical and Pharmacological Profile

Curcumin, the main bioactive agent of the rhizome of the Curcuma longa (turmeric), has a specific biochemical and pharmacological characteristic, which supports its diverse therapeutic functions. Being a natural polyphenol, curcumin has a unique chemical structure in the form of two aromatic ring systems where the o-methoxy phenolic groups are linked by a seven-carbon scaffold inside of which an alpha,beta-unsaturated 2,4-dicarbonyl so-called 2,4-diketone group presents. This structure bestows upon curcumin the bright yellow colour, as well as making it a strong antioxidant, anti-inflammatory and metal-chelating substance[16]. In addition to curcumin, turmeric possesses other similar curcuminoids: be it demethoxycurcumin or bisdemethoxycurcumin, they are also a part of the source of biological effects provided by turmeric. Pharmacologically, curcumin has been highly explored in pharmacological properties that regulate various inflammatory molecular targets, oxidative stress, apoptosis, amyloid aggregation, and several other therapeutic irregularities by enhancing the possibility of treating chronic illnesses such as Alzheimer disease. Nonetheless, in spite of this amazing bioactivity, the limitations of its clinical translation are in its dreadful pharmacokinetics; low aqueous solubility, poor absorption, rapid metabolism, and systemic elimination, which lead to extraordinarily poor bioavailability. This has led to invention of new formulation approaches in order to improve its stability, absorption and efficacy. On the whole, these peculiarities of the biochemical structure of curcumin and its diverse pharmacological effects become the basis of its investigation as the prospective neuroprotective in the aspect of Alzheimer disease model [17].

2.2.1. Chemical structure and bioactive components

Curcumin is the primary curcuminoid compound found in turmeric with a distinguished polyphenolic structure, which contributes to antioxidant, anti-inflammatory and neuroprotective effects[18]. It has bioactive ingredients, such as demethoxycurcumin and bisdemethoxycurcumin, which improves its therapeutic effects. Learning about the chemical structure and active compounds of curcumin is of great significance in enhancing the utilization of it in disease prevention and treatment such as Alzheimer.

1. **Chemical Structure of Curcumin**

Chemically, the curcumin is challengingly named as diferuloylmethane and its molecular formula is as well given by C 21 H 20 O 6 and has a molecular weight of 368.38 g/mol. Its structure is composed of two aromatic rings having a o-methoxy and phenolic hydroxyl group which is essential in its antioxidant activity. The aromatic rings are separated by a seven-carbon linker that has the function of 1,2-unsaturated 2-diketone that is capable of keto-enol tautomerism. Curcumin exists mainly in the enol form under a physiological condition and this increases the capacity of curcumin to interact with several biological targets. It is the conjugated structure, consisting of contrasting double bonds in the rings between aromatic domains and the central part of beta-diketone, that is the determinant factor behind the bright yellow colour and the light absorption process by curcumin at the accessible wavelengths of the visible spectrum which also makes it to help with photoprotection.

2. Bioactive Components in Turmeric

Properties of turmeric are mainly due to bioactive compounds, which are diverse in nature and they perform the therapeutic role. The most common active compounds among these are the curcuminoids, out of which the most abundant and therefore the strongest in pharmacologic effect, used, curcumin being 2-5 percent of the total dry weight of turmeric. Curcumin is famous with powerful antioxidant, anti-inflammatory and neuroprotection effects. The two other curcuminoids are demethoxycurcumin (with one less methoxy group than curcumin and with the same antioxidant and anti-inflammatory activities) and bisdemethoxycurcumin (with both meth oxies lost but with overall similar biological activities but with slightly reduced potency). These three curcuminoids compound each other to create maximum medicinal power of turmeric. Furthermore, turmeric has volatile oils which include turmerone, atlantone and zingiberene that give it the flavor that it has and also act as anti-inflammatory and antimicrobial. There are other constituents (such as polysaccharides, which have immunomodulatory effect, proteins and resins which further improve its medicinal profile). This extract of curcuminoids and other bioactive compounds is the basis to core turmeric application in tradition medicine and its new-found role in contemporary pharmacological research.

2.2.2. Pharmacokinetics and bioavailability challenges.

Although curcumin has pharmacological potential, the challenges that threaten its use as therapy are its pharmacokinetics and bioavailability[19]. Its oral bioavailability is low, eliminated fast through pathways that result in poor therapeutic levels at target sites and a need to enhance its effectiveness in clinical use requires such interventions.

1. **Poor Water Solubility**: Curcumin has a high hydrophobicity, and is virtually insoluble in water, so that the gastrointestinal tract is not effectively dissolved, and that poor absorption is achieved following oral administration.
2. **Low Absorption Efficiency**: Curcumin is poorly soluble thus its permeability across the intestinal mucosa is low leading to its low absorption into systemic circulation.
3. **Rapid Metabolism**: Upon absorption, curcumin is subjected to massive first pass hepatic and intestinal wall metabolism into inactive metabolites including curcumin glucuronide and curcumin sulfate via the processes involved with the formation of glucuronide and sulphate.

4. **Short Half-Life**: Curcumin has a low biological half-life and thus will be removed rapidly through the system and will have low plasma levels to perform prolonged therapeutic effect.

5. **Poor Tissue Distribution**: Curcumin lacks bioavailability, so its delivery to target tissues, especially the brain, is limited, reflecting poor bioavailability and the incapacity of this compound to cross the blood-brain barrier in meaningful amounts.

6. **Low Systemic Bioavailability**: The net effect of low solubility, low absorption, extensive metabolism leading to poor bioavailability and a high rate of excretion is very low systemic bioavailability (<1 per cent) representing a significant challenge in achieving the pharmacological advantages in clinical practice.

3. PRECLINICAL STUDIES OF CURCUMIN IN AD MODELS

Curcumin has also demonstrated the potential of protecting the nerves through preclinical researches in models of Alzheimer[20]. In tests and experiments to discover new medicines and treatments, the in vitro and in vivo studies were able to demonstrate that curcumin could affect main pathological features associated with AD, including the aggregation of amyloid beta, the hyperphosphorylation of tau, oxidative stress, and neuroinflammation. The comprehension of these outcomes is essential at the assessment of the therapeutic potential of curcumin.

3.1. In vitro Studies

Cell based studies have exploited the field of neuroprotection by using cultured neuronal cells and inhibiting the neurotoxic action of amyloid beta (A amalgam (A beta) peptides, one of the most significant elements of the pathology of Alzheimer disease by curcumin. Studies that have been done on the protection mechanisms of curcumin usually use human neuroblastoma cells line (e.g. SH-SY5Y) or isolated primary cortical/hippocampal neurons [18]. The results indicate that curcumin is able to diminish A-b induced cytotoxicity, inhibit apoptosis in neurones and preserve cell vitality. Mechanically, curcumin prevents A aggregation and disaggregation of pre-formed A fibrils meaning the reduction in its neurotoxicity. Furthermore, curcumin powerfully stimulates antioxidant effects, neutralizes reactive oxygen species (ROS) induced by A beta exposures and inhibits the oxidative stress against neuronal proteins, lipids and DNA. It also inhibits A beta induced inflammatory responses by down regulation of pro-inflammatory cytokines and inhibition of inflammatory signalling pathways like NF- kB and thus preventing neuro inflammation. The totality of these in vitro findings is consistent with the idea that curcumin helps the neuron withstand neurotoxicity induced by A perform its anti-amyloid, antioxidant and anti-inflammatory properties[21].

3.1.1. In vivo Animal Studies

Animal approaches are important in determining the therapeutic value of curcumin in Alzheimer,s disease i.e. they help in giving an ideas about the impact of curcumin in a whole organism or whole animal. The studies employ different rodent models, which closely resemble most of the pathological known aspects of human AD including the presence of amyloid plaques, hyperphosphorylation of tau, neuroinflammation, and in cognitive impairments. The evaluation of the effectiveness of curcumin in these models contributes to the insight into the pharmacological effects, maximum dosages, and routes of its administration, and ways to

enhance the effects on behavioural and cognitive outcomes, which can contribute to the eventual formulation of curcumin as an intervention in Alzheimer disease prevention in terms of neuroprotection[22].

- **Rodent Models of AD**

Alzheimer disease Therapeutic potential of curcumin has been evaluated using different rodent models in vivo. Commonly utilized mouse models are transgenic mice that express human amyloid precursor protein (APP) and presenilin mutations (e.g., APP/PS1, Tg 2576 mice), and develop amyloid plaques comparable to those found in human AD, and direct brain injection of A 8 peptides by intracerebroventricular (ICV) injections which are used to induce an AD-like pathology in the mouse brain. Such models make it easier to study the actions of curcumin regarding amyloid deposition, tau pathology, oxidative stress, neuroinflammation, and cognitive deficits.

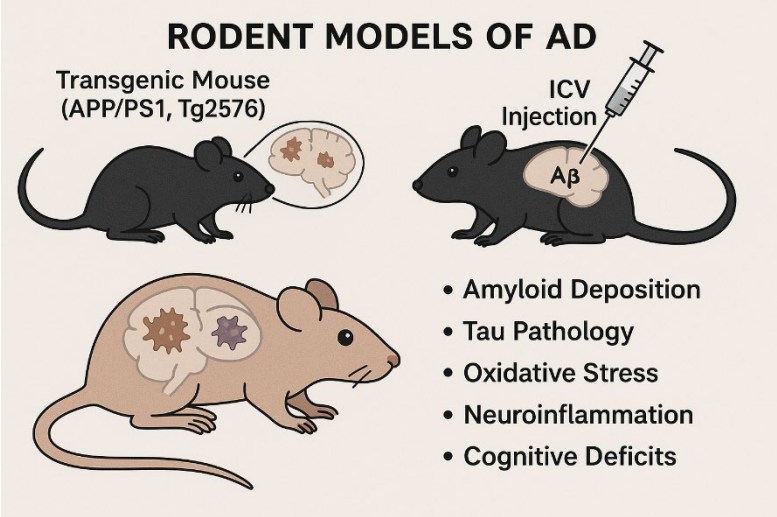

Figure 2: Rodent Models of AD[23]

The rodent models used in studying Alzheimer disease (AD) are demonstrated in figure 1. Transgenic mice like APP/PS1 and Tg2576 contain human genes linked to familial AD which causes the development of amyloid relate plaques similar to humans. The second strategy is the use of intracerebroventricular (ICV) administration of amyloid-beta (A0) peptides in order to induce an AD-like neurodegeneration. Researchers can hence use these models to determine the efficacy of therapeutic agents such as curcumin based on their effects on amyloid accumulation and tau pathology, oxidative stress, neuroinflammation and cognitive impairment.

- **Dosage, Administration Routes, and Behavioral/Cognitive Outcomes**

In the present animal studies, curcumin has also been used in different pre conduction methods oral gavage, dietary supplementation and even through intraperitoneal administration, but in quantities varying between 20 mg/kg body weight per day up to 500 mg/kg of body weight per day or depending on the type of study conducted and the formulation considered. Its results have been always consistent with the outcomes indicating that the curcumin treatment yields:

- **Reduced amyloid plaque burden** and soluble Aβ levels in the brain.

- **Decreased tau hyperphosphorylation** and neurofibrillary tangle formation.
- **Attenuation of oxidative stress and neuroinflammation** by reducing ROS levels and pro-inflammatory cytokines.
- **Improved synaptic plasticity and neuronal integrity.**

Curcumin-treated rodents improve on behavioral measure of learning and memory, including Morris water maze, Y-maze, and novel object recognition, which is a significant indicator of improved cognitive behavior and improved AD-like impairment. These in vivo data suggest the promise of curcumin as a multifunctional anti-inflammatory/anti-oxidant, and may promote its future development and translation to clinical efficacy as an AD disease modifying agent, despite issues of both bioavailability and feasibility.

3.2.Mechanisms of Neuroprotection

Neuroprotection in Alzheimer s disease (AD) is now an important issue since it influences the structure and functions of the neurons, and prevents or delays possible injuries that occur during pathological conditions such as oxidative stress levels, inflammatory reactions, glutamate excitotoxicity, and amyloid proteins aggregation[24].

1. **Anti-Amyloid Activity**

Curcumin has direct effect on Abeta proteins blocking the aggregation of toxic oligomers and fibrils. It has also been known to destabilize pre-existing amyloid plaques thus decreasing the load of plaques in the brain. It prevents neuronal damage and central synapses through this anti-amyloid effect.

2. **Inhibition of Tau Hyperphosphorylation**

Curcumin alters enzyme that mediate tau phosphorylation like glycogen synthase kinase-3beta (GSK-3beta) and protein phosphatase 2A. Curcumin normalizes the aberrant hyperphosphorylation of tau protein by regulating these enzymes and thereby preventing the formation of neurofibrillary tangles and the stability of cytoskeleton of the neurons.

3. **Antioxidant Properties**

Curcumin behaves also like a potent free radical scavenger owing to its phenolic hydroxyl groups and conjugated double bonds. It scavenge the reactive oxygen species (ROS) and up regulate the endogenous antioxidant enzymes, such like the superoxide dismutase (SOD), catalase and glutathione peroxidase. (neuronal) oxidative stress responses:::/Degradation of proteins, Lipids and DNA from Oxidative Damage by (neuronal) antioxidant defense.

4. **Anti-Inflammatory Effects**

AD progression is a major issue dependent on chronic neuroinflammation, which is a drive of activated microglia and astrocytes. Curcumin also down-regulates the synthesis of pro-inflammatory cytokines (e.g. TNF- 2, IL- 1b, IL- 6) and signal transduction mechanisms such as nuclear factor-kappa B (NF- xb) and cyclooxygenase- 2 (COX- 2). Curcumin relieves neuroinflammatory processes, decreasing nervous cell damage and promoting more favorable microclimate in the brain.

5. Metal Chelation

Unusual childhod concentrations of metal ions (iron, copper, zinc) may stimulate aggregation of A and oxidative stress. It has been shown that, the 1,3-diketone structure of curcumin permits a chelation of metal ions which lessens metal-stimulated A aggregation and constrains the metal catalyzed oxidative responses in the brain.

6. Modulation of Cell Signaling and Apoptosis

Curcumin affects several cellular signaling pathways that involve survival and apoptosis, these include the PI3K/Akt and MAPK pathways. With the help of control over these pathways, curcumin is promoting neuronal survival, preventing apoptotic cascades, increasing synaptic plasticity.

3.3.Methodologies Used in Existing Studies

The methodologies utilized in previous literatures that have established the neuroprotective property of curcumin on the Alzheimer disease (AD) model are broad and varied in terms of protocols, models, and assays used[25]. Familiarity with these approaches is cornerstone in assessing the validity of results and antecedent of research gaps and future preclinical and clinical studies in development of curcumin as a therapeutic agent in AD.

3.3.1. Experimental Designs

Research on curcumin neuroprotective characteristics has employed a wide array of experiment designs to determine its performance and the mechanisms. In vitro studies mostly follow a controlled experiment format in which neuronal or glial cell cultures are treated with a concentration of amyloid beta (A B) peptides in order to achieve a AD-like toxicity then a range of concentration of curcumin is added to determine dose-dependent effects. Randomised controlled studies prevail in the area of in vivo experiments using animal models, mostly using rodents, which are separated into three groups as control, as a diseased model, and a curcumin treated model to assess the effect of curcumin on the behaviour, biochemical and histological changes. There are also studies that utilize dose-escalation and time-course designs in efforts to establish optimal dose, duration of treatment as well as safety profile. Altogether, these designs promote rational procedures to conduct a systematic assessment of neuroprotective effects of curcumin.

3.3.2. Models and assays employed.

Neuroprotective mechanisms of Curcumin in the study of Alzheimer disease are carried out through numerous models and tests. Human neuroblastomas cell lines and rodent neurons are used to recreate AD pathology in vitro. In vivo experiments involve transgenic rodent model or the ICV injection model. Measures of the curcumin activity entail cell viability, amyloid agglomeration, Western blotting, ELISA, immunohistochemistry, and behavioral evaluation. These models give in-depth information on the neuroprotective action of curcumin and its promise as a medicine in the research of Alzheimer disease.

3.3.3. Strengths and weaknesses of methods used.

- **Strengths**

Alzheimer triumphed over curcumin research by using transgenic rodent models, in vitro assays, animal behavior experiments and biochemical assays. These approaches offer a pathophysiologic importance, quick screening of the processes of curcumin, and quantitative functions of its antioxidant and anti-inflammatory action. Such techniques allow assessment of therapeutic effects of curcumin in the disease representative environment that supports sophisticated in vivo experiments.

- **Weaknesses**

The currently available research relating to the neuroprotective effect of curcumin in Alzheimer disease has a number of limitations. The poor conversion of the in vitro data into in vivo data and inability of rodent model to completely reflect human pathology of AD. The inconsistencies in dosage forms and routes of administration of curcumin make the comparison of data and meta-analyses difficult. The low bioavailability of in vivo curcumin limits high concentration and the short lifespan of animal studies does not reflect the progression of human Alzheimer disease.

3.4.Limitations in Current Research

1. **Poor Bioavailability of Curcumin**: Curcumin possesses very low oral bioavailability because it does not bind with water well, metabolizes fast, and eliminates quickly in the body. This restricts its capacity to achieve concentrations necessary in effective therapy in the brain, and this becomes a very serious obstacle to its applicability in Alzheimer clinical treatment.
2. **Limited Translation from Animal Models to Humans**: Despite successful results indicating neuroprotective action in preclinical studies of cell and animal models, in many cases the results do not offer realistic measures of transfer to human clinical studies due to differences in metabolism, physiology, and pathology of the animal models, and thus limit proven efficacy in humans.
3. **Inadequate Long-Term Safety and Dosing Data**: Long term safety of high dose administration of curcumin is not well documented in humans. There is uncertainty regarding the ideal dosing schemes that could yield long-term curative benefits without the unwanted effects thereby limiting the adoption of this drug as a neuroprotective compound at the clinical use level.
4. **Variability in Formulations and Study Designs**: No consistency of data exists because various formulations, doses, routes of administration and duration of treatment are applied in existing studies. Such variance makes it difficult to compare and do meta analysis and implement standardised use protocols of curcumin as therapy in Alzheimer disease.
5. **Lack of Large-Scale Human Clinical Trials**: Majority of the current study is based on pilot studies or preclinical studies. Further need is to have well-designed and large, randomised controlled trials in humans to confirm efficacy, safety and mechanism of action of curcumin to recommend its use in the management of Alzheimer s disease.

4. DISCUSSION

The click mechanism of Curcumin in Alzheimer is discussed, and it includes neuroprotective effects like antioxidant activity, anti-inflammatory activity, anti-amyloid activity, tau activity, and metal chelation activity[26]. Nonetheless, there are still some major research gaps such as lack of large-scale clinical trial and low bioavailability. Formulations such as nano formulations are much needed to enhance sorbability and stability of curcumin[27]. Combination therapy with other neuroprotective drugs should also be studied in the future so that an effective therapy of AD is found. On the whole, the potential of curcumin is not utilized to the maximum, and translational research is required.

4.1.Interpretation of Findings

The overall conclusion of available preclinical experiments is the knowledge of multi-targeted neuroprotective actions of curcumin in Alzheimer disease models. Curcumin was also found to prevent the aggregation of amyloid beta, tau hyperphosphorylation, have a strong antioxidant effect and inhibit neuroinflammatory process, sparing the neuronal organization and functioning[28]. The unification of these processes emphasizes that curcumin can regulate important pathological processes of AD progression. Notwithstanding these encouraging results, it is important to interpret them in the light of methodological issues like limitation of bio-availability and difference in the model system[29]. Altogether, the combined analysis indicates that curcumin targets the neuroprotective effects via the operation of various molecular pathways and validates its role as a multi-functional therapeutic agent.

4.2.Implications and Significance

Findings of such studies are of great importance to the application of curcumin based therapies in managing Alzheimer disease. Curcumin is a promising candidate as a disease-modifying drug as it has multiple disease targets as opposed to symptomatic treatment. The fact that it has a natural origin, and has safe application since long periods in traditional medicine also adds to its therapeutic value. Provided that the challenge of its bioavailability is addressed, curcumin-based therapy has potential as a safer, affordable and improvised neuroprotective approach, particularly in low-resource areas. Therefore, it is important because of what it may lead to in terms of preventive and therapeutic measures towards Alzheimer disease as well as other neurodegenerative conditions[30].

4.3.Research Gaps

Despite there is plenty of evidence on curcumin through preclinical studies, there exist some critical research gaps that curtail the clinical translation of curcumin. To start with, it has no large-scale human clinical studies that assess its effectiveness, optimal dose and long-term safety in patients with Alzheimer disease. Sample size and duration of most of the existing clinical trials results in low generalisability. Second, more effective drug delivery is required to circumvent the low bioavailability of curcumin as well as to achieve adequate therapeutic levels in the brain. These gaps find solutions absolutely crucial to the confirmation of the curcumin therapeutic value and consent of the same as a neuroprotective agent in the clinical practice.

4.4.Future Directions

Future research should be directed to the creation of nano formulations or the development of a more accurate delivery system (nanoparticles and liposomes, solid lipid carriers) to make curcumin more soluble, stable and bioavailable to increase its effectiveness in its therapeutic effects in the brain. Moreover, studies on the combination therapies of curcumin with other neuroprotective compounds or current anti-Alzheimer agent can also help produce synergistic effects by hitting two or more birds with a single stone. These combinatorial therapies had the potential of producing optimal therapeutic responses, cut the dose required, and minimise its side effects, resulting to more effective and complete therapeutics of Alzheimer disease.

5.CONCLUSION

In conclusion, curcumin holds great promise as a neuroprotective agent in Alzheimer's disease due to its multifunctional mechanisms of action, including suppression of amyloid beta aggregation, reduction of tau hyperphosphorylation, strong antioxidant and anti-inflammatory properties, and chelation of toxic metals, which together maintain neuronal integrity and enhance cognitive performance in preclinical models, suggesting its potential as a disease-modifying rather than purely symptomatic treatment. The review highlights these key insights, reiterating its importance in light of the rising global burden of Alzheimer's disease, where existing treatments only alleviate symptoms without halting disease progression. Curcumin, with its multi-targeted neuroprotective effects, established safety, and long history of traditional medicinal use, emerges as a promising therapeutic candidate. However, challenges remain regarding its low bioavailability, limited correlation between animal and human effects, and lack of long-term safety data. Therefore, to translate these preclinical findings into clinical use, it is recommended to conduct large-scale, high-quality randomized human clinical trials to validate effective formulations, determine optimal dosage, and assess long-term safety; to explore advanced drug delivery systems such as nanoformulations to improve bioavailability and brain targeting; and to investigate combination therapies with other neuroprotective or approved Alzheimer's treatments to achieve synergistic effects and address the multifactorial nature of the disease. Overall, curcumin remains an attractive and promising option for future drug development to address the growing global caseload of Alzheimer's disease, warranting further rigorous investigation to establish its clinical effectiveness.

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