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CURCUMIN AN ANTICIPATED TREATMENT IN ALZHEIMER'S DISEASE: A REVIEW

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ABSTRACT

Individuals with mild cognitive declension are at a greater risk to evolve dementia with an annual development rate of up to 10-20%. Alzheimer disease is the most common a neurodegenerative disorder which consequently results in total intellectual disability. More than 30 million individuals are suffering from this disease. The cholinergic theory of dementia deterioration, where thinking, memory, and conduct problems are triggered, at least in part, by decreasing rates of acetylcholine (ACh) in the brain, first appeared more than 20 years ago. Presently, there is no remedy for this disease but in novel rejuvenations, it unveils a new horizon and researchers are examining new fields. When medical treatments become more complicated, the solution may be something easier. It proclaimed the effectiveness of a variety of generally benign types of therapeutics derived from plant origin as completion in Alzheimer's disease. The powdered turmeric rhizome has been widely used in India and other South Asian cuisines, and for a wide range of conditions is an integral part of ayurvedic medicine. Notwithstanding its well-documented medicinal efficacy, curcumin's restricted systemic bioavailability has impeded its production as a potential therapeutic agent for years. Curcumin is the best herb for prevention, treatment, and diagnosis of this disorder due to anti-Alzheimer characteristics with propitious feasibility. In sequitur, curcumin has the potential to be more competent than available treatments. However, its effectiveness as a therapeutic agent may be restrained by its low bioavailability.

KEYWORDS:– Alzheimer's disease, Acetylcholinesterase, Neurodegenerative, Curcumin, Neurogenesis, cognitive function.

1. INTRODUCTION

The Blood-brain barrier is known to hinder the treatment of neurodegenerative disorder such as Alzheimer‘s disease. The delivery of amyloid binding compounds into the brain is of greater significance to find out the amyloid accumulation for diagnostic purpose as well as to design treatments that reaches to the cerebral amyloid.[1] The brain is undoubtedly the trickiest body for the supply of active agents13. Driven by strong blood flow, the Blood-brain barrier (BBB) prevents brain penetration through the central nervous system (CNS).[2] Blood flow of several substances and molecules like medications shifts and impaired permeability of vessels are principal contributors of Brain injury pathophysiology.[3] Since life expectancy has risen with a high prevalence of chronic diseases that elucidate one of the significant Issues of upward pressure on the health services system, requesting long-term clinical management of the influenced individuals has been called for. Current estimation forecast that by 2050 dementia statistics sufferers will raise and threefold.[4] Across developed nations, Alzheimer's and other dementias are becoming a significant public health issue among the elderly. The dementias will also devastate developed countries where the population ages fastest; by 2020, about 70 percent of the world’s population aged 60 in the developing countries will live in India, with 14.2 percent of the world living in developing countries.[5] AD can be featured as developing, an unchangeable neurological disease that evolves slowly and leads to memory loss, unusual behaviour, personality changes and incapacity for thought[6] The AD pathology is also symbolized by chronic inflammation fuelled with the contribution of circulating cells in resident microglia and macrophages.[7] Beta -Amyloidal (bA) triggered recently neuronal cells were shown to have oxidative stress, the core element for AD illness. Therefore, BA modulation insult was speculated as an effective treatment approach to AD start-up power. Thanks to their engagement of oxidative stress caused by bA in the aetiology of AD, one of the most recent pharmacological methods preventive and neuroprotective AD interventions include therapy in antioxidants.[8] During cellular respiration and brain insults at rapid levels, partially reduced types of oxygen are released in the brain. This spike in free radicals production was reported to cause damage to the cell membranes, impairing the genes involved, RNA, lipids, and proteins (Gu et al., 1998). Oxidative stress is a disparity between free radical development levels and removal by endogenous antioxidant mechanisms such as enzymes

superoxide dismutase (SOD)glutathione peroxidase (GSHPx) and catalase, and even some low molecular weight restriction alpha-tocopherol, glutathione (GSH) and ascorbate (Wilson, 1997). This distortion is caused by various factors such as acidosis, metal transmission oxides, dopamines, glutamates, amyloid-beta peptides, and mitochondrial electron transport uncouplers. Lipid peroxidation is thought to be an essential and especially deleterious way of damaging neuronal oxidative injury that damages membranes and produces various secondary products, from fission as well as from endocyclic oxygenated neurotoxic fatty acids (Bassett and Montine, 2003). A reliable index of in vivo lipid peroxidation has proven to be an-degree of malondialdehyde (MDA) as one of the reactive oxidative (ROS).[9]The discovery of medications and the progress of Alzheimer's disease is a very significant and tedious process.[10] The number of synthetics is currently reduced. Medications required to treat the disorder. Indeed, numerous natural compounds have been investigated for their efficacy in the treatment of AD.

2. Pathophysiology

While the aetiology of AD is unclear, it is apparent that path physiology is complicated and that there are multiple mechanisms for neuronal harm.[12] Over more than 100 years, the two neuropathic hallmarks of the condition, including amyloid plaques and neurofibrillary tangles, have been widely researched to explain the root mechanisms and to find new avenues of therapy.[13]AD's anatomical pathology involves senile plaques (SPs), that are quite microscopic foci of extracellular amyloid aggregation, and neurofibrillary tangles (NFTs), which are broad, non-membrane attached bundles of irregular fibers containing mostly of tau protein that comprise a significant portion of the perinuclear membrane.[14] While the role of AchE and its retardation in AD has been recognized, across the last decade, BuChE has played a vital role in the initiation, symptoms, development, and response to dementia alongside AChE. As AChE drops with time, BuChE increases as AD progresses. Consequently, BuChE may be considered more important than AChE as the disease progresses. The disruption of classical (enzymatic) functions in AChE and BuChE is an opportunity to enhance cholinergic neurotransmission and vascular responses.[15] The numbers of research explicitly demonstrate that the initiation of AD is usually accompanied by an intermediate period defined as mild cognitive impairment (MCI). This is an intermediate stage between natural aging and dementia, marked mainly by a memory loss without a clinically severe cognitive disability. While there is debate as to the transmission mechanism faces the most significant shifts with normal aging and how this trend varies from

normal aging in the brain and if it is accurate, clinically important improvements in the core cholinergic network have been reported in the aged brain tissue.[16] Alzheimer's disorder pathogenesis is not confined to the synaptic region but encompasses intense associations with immunological pathways in the brain. Miscellaneous and collated proteins bind to microglia and astroglia pattern-recognition receptors and activate an innate immune response marked by the release of mediators that lead to disease development and severity. Nascent research shows that inflammation plays a causal function in disease pathogenesis, and recognizing and regulating the connections between the immune system and the nervous system could be crucial to avoiding or slowing certain delayed-onset diseases of the CNS. The essential function of neuroinflammation is confirmed by the discovery that immune receptor genes, including TREM22 and CD33, 3, 4, are correlated with Alzheimer's disease.[17] Hippocampus–based memory and olfactory processing–is seriously impaired by the disorder. The overwhelming majority of AD reports are the late-type of the disorder. Although age is the greatest environmental risk factor for sporadic, the genotype of apolipoprotein E (apoE) is the greatest established genetic risk factor.[18] The progressive development of the depot of the amyloid plaque by brain amyloidogenesis over many years contributes to neuronal cell death, brain atrophy and deficiencies. The depletion of brain cortical and hippocampal neurons related to cognitive impairments and irregular behaviour. The amyloid b-protein (Ab) is neurotoxic and it build-ups in the brains of patients suffering from amyloid plaques and tau tangles; the disorder is considered responsible for AD, ab, and tau hyperphosphorylation. APP is an incorporated membrane protein present in neuronal structures and synapses. APP is a precursor protein. Ab, which contains amino acid traces 37e49, is generated by two enzymes, b- and g-secretase by APP through amyloidogenesis APP.[19]

The rigorous early learning approach of AD dementia could provide promising results, embrace diversity in MCI subjects with varying progression models and classify MCI subjects with a higher risk of developing AD. This means for prognosis and probably for the enrolment in clinical trials of people expected to thrive within certain timeframes.[20] The latest approaches tend to be based, at the pre-symptomatic level, on the potential neuroprotective activity of disease-modifying drugs, using biomarkers that predict the development of disease before developing an explicit disease.[21] There are several usable models of AD pathology, and each has its own advantages and drawbacks. This is particularly necessary to note that neither of the current models mimic all the characteristics

of person AD, and thus cannot be deemed descriptive models of AD as a total disorder.[22] Then the experimental models are in fact counterproductive and can be scrapped. This is possible that the use of simplistic animal models that represent a single feature of AD is not sufficient to replicate the disorder, and thereby to develop new therapies. A further hypothesis is that pathologies of Aβ and tau are endpoints for different pathways that cause the disease. A successful inhibition of Aβ and tau pathologies may therefore not lead in an effective anti-AD therapy.[23]

3. Pharmacological intervention for alzheimer's disease

Drug development for diseases of the central nervous system (CNS) has forever been selectively challenging due to the encumbrance of the brain bioavailability of medicinal agents by the blood-brain barrier (BBB). The specified association of endothelial cells, astrocities, and pericytes limits the access of blood-borne molecules into the CNS.[24] Hardly any licensed therapy specifically targeted at AD pathology is presently available. Therapeutic options are symptomatic, with two distinct mechanisms of action designed to improve cognitive function: the cholinergic agonism and the N-methyl - D-aspartate receptor (NMDA)[25] Various technologies have been created to improve the disease cycle. In this respect, significant advances are directed at the Ab and tau therapy, which is a crucial element in the soon-to-be unveiling of this disease[26] Memantine is an antagonist of the NMDA; it reduces excitatory toxicity through the abolition of the ionotropic portal because glutamate is pathologically high in AD in the excitatory neurotransmitter. None of these verified drugs has been shown to have a true treatment effect; they are just a palliative care phase, with a decrease in effective power.[27]

Table no. 1: List of synthetic drugs.

Brand name	Dose	Generic name	MechaniSm of action	Route of administration	Reference
Aricept (Cipla, Intas, Solus, Eisai with Pfizer)	5mg-10mg	Donepezil	Cholinesterase inhibitors	Orally (Tablet), Orally disintegrating,oral solution	[28]
Namenda XR (Allergen) & Memantine (Forest Laboraties, Inc., H.Lundbeck,	5mg-28mg	Memantine	Miscellaneous central nervous system agent	Extended release capsule ,tablet, oral solution, extended release	[29]

Merza Pharma) Admentatab (Sun Pharma, Bondane Pharma)					
Exelon (Novartis Ltd., Torrent) Alzamine 18 (Zeemine 3)	1.5 mg-12mg	Rivastigmine	Cholinesterase inhibitors	Patch, capsule, oral solution, liposome, Transdermal patch, Tablet, film coated	[30]
Galantamine (Taj Pharmaceuticals Ltd.)	8 mg, 4 mg	Galantamine	Cholinesterase inhibitors	Extended release, oral solution,	[31]

3.1 Different product goals in AD are as follows

- Targeting amyloid binding protein
- Modulation of secretase enzyme
- Targeting tau protein
- Inhibition of tau phosphorylation
- Targeting microtubule stabilization
- Modulation of GABAergic neurons

3.2 Ayurvedic medicinal plants for alzheimer's disease

Naturopathic medicinal plants are becoming the sole most active source of drug discovery leads and more than a hundred innovative medicines are currently in clinical production. Several research reports have also identified the usage of different ayurvedic native plants and their tenants for the diagnosis of Alzheimer's disease.[32] The usage of herbal remedies is focused on the knowledge of several centuries of doctors and conventional medicines from diverse ethnic communities. In certain instances, the usage of herbal plants in conventional medicine benefits from the perception that hundreds of plants are often used globally to deter or treat illnesses without medical knowledge from conventional medicine.[33] Many of today's modern drugs were extracted from the plantation, and the great pharmacopeia was dominated by herbal medicines just two hundred years ago. As fundamental and clinical pharmacology became a leader in medicine, herbal medicine dropped drastically. Herbal treatment, however, is still of concern, especially in psychiatric and neurological disorders, in many diseases. There are some explanations for the problem: 1) patients are unsatisfied with

conventional therapy; 2) patients want strength over their health decision; 3) Medicine aligns with its moral values and beliefs. Numerous reports and documents are suggesting the particular role of drugs in the treatment of AD.[34] Throughout recent years, studies have concentrated on specific therapeutic strategies for the benefit of patients with AD. Foods rich in n-3 fatty acids, vitamins, and various classes of secondary polyphenolic plants were shown to be beneficial for many deleterious diseases (Stevenson et al, 2007; Willis et al., 2010).[35]

Table no. 2: List of herbal plants use as anti-Alzheimer therapy.

Plant/herb	Mechanism of action	Reference
Hypericum perforatum	Inhibition of lipid peroxidation, anti-oxidant activity	[36]
Lepidium meyenii(Black Maca)	Reduced AChEactivity, reduced brain MDA level	[37]
Prunella vulgaris	Through the signaling of cholinergic transmitters and of methyl-D- aspartate receptors.	[38]
Cyprus rotundns	Decrease AChE level	[39]
Zizyphus jujube	AChE and cyclooxygenase-1&2 inhibitory action against histamine release and its activity	[40]
Lavendula officinalis (lavender)	Inhibitory effect of ach enzyme	[41]
Ginkgo biloba	Reduced level of peroxidation and amyloid-b- aggregation	[42]
Salvia officinalis(rosmarinic acid)	Improved cognitive function	[43]
Melissa officinalis	Anticholine receptor activity and modulate cognitive performance	[44]
Ginseng	Improved cognitive and psychomotor Function	[45]
Brahmi (bacopamonnieri)	Inhibit lipoxygenase activity	[46]
Shankhpushpi (convolvulus	Improve memory &cognitive function	[47]
Ashwagandha (withaniasomnifera)	Increase acetyl choline level	[48]
Oleuropein (olive oil)	Inhibit the formation of amyloid fibrils	[49]
Lypodiumserratum	Protection from neuronal apoptosis and amyloid induced oxidative injury.	[50]

Table no. 3: List of patents in alzheimer.

Title	Inventor	Patent Number	Assignee	Reference
The alz-50 monoclonal antibody and diagnostic assay for Alzheimer's disease	Hossein a. Ghanbari, lake forest, ill.	US-5811310	Albert Einstein college of Medicine. Of yeshiva univ. Bronx, n.y.	[51]
Methods and Compositions	Malcolm Ward, Cobham (GB);	US-8658133	Proteome Sciences plc, Cobham, Surrey	[52]

Relating To Alzhemers Disease	Vaksha Patel, Cobham (GB); Emma McGregor, London (GB); Nicola Leeds, Tonbridge (GB); Helen Byers, Cobham (GB); James Campbell, Cobham (GB); Kit-Yi Leung, Berkhamsted (GB); Jules Westbrook, Dublin (IE)		(GB)	
Purified antigen for alzheimer's disease, and methods of obtaining and using same	Raymond p. Zinkowski, northbrook, il (us); danielj. Kerkman, lake villa, il (us); russelle. Kohnken, skokie, il (us); john f. Debernardis, lindenhurst, il (us); peter davies, rye, ny (us	US-9334582	Molecular Geriatrics Corp	[53]
Methods for inhibiting and Reducing amyloid fibril formation Associated with alzhemer's Disease and other amylodoses	Gerardo Castillo, Seattle, WA (US); Alan D. Snow, Lynnwood, WA (US)	US-6607758	University of Washington, Seattle, WA (US)	[54]
Alzheimer's disease treatment with multiple therapeuticagents delivered to the olfactory region through a special idelivery catheter and on tophoress	Totada R Shantha, Stone Mountain, GA (US)	US-13473454		[55]
Delivery device containing venlafaxine and memantine and method of use thereof	Vergez JA, Faour J, Ricci MA, Pastini AC,	US-11870247	Osmotica Corp,	[56]
Transdermal delivery of systemically active central nervous	Carrara DN, Grenier A, Alberti I, Henry L, Decaudin C	US-11755923	Antares Pharma IPL AG,	[57]

system drugs.				
Pharmaceutical formulations for parenteral use.	Bodor NS	US-5024998	University of Florida	[58]
Phenylamide and pyridylamide beta-secretase inhibitors for the treatment of alzhemers disease	James c. Barrow, harleysville, pa (us); craig a. Coburn, royersford, pa (us); harold g. Selnick, ambler, pa (us); shawn j. Stachel, perkasie pa (us); matthew g. Stanton, lansdale, pa (us); shaun r. Stauffer, schwenksville, pa (us); linghangzhuang, chalfont, pa (us); jennifer r. Davis, richboro, pa (us)	US-755.0481 b2	Merck & co., inc., rahway, nj (us)	[59]
Therapeutic curcumin derivatives	Inventors: reis yale, guerque (58) nm (us); steve f. Uspc .....ab couwer, hummelstown, pa (us);. Robert a. Orlando, placitas, nm (us); robert e. Royer, bosque farms, nm (56) ;ekaterina v. Bobrovnikova-marjon, philadelphia, solodar pa (us); lucy a. Hunsaker, . W oc ca. Albuquerque, nm (us)	Usoo884 1326b2	Stc.unm, alburquerque, nm (us)	[60]
Bioavailable curcuminoid Formulations for treating Alzhemiers disease and other Age-related dsorders	Sally A. Frautschy, Santa Monica, CA (US); Gregory M. Cole, Santa Monica, CA (US)	US-9192644	The Regents of the University of California, Oakland, CA (US); Department of Veterans Affairs, Washington, DC (US)	[61]
Amyloid binding nitrogen-linked compounds for the antemortem diagnosis of alzheimers disease in vivo imaging and	William e. Klunk; jay w. Pettegrew; pittsburgh, pa (us)	Us-6417178 b1	University of pittsburgh, pittsburgh,..... .... Pa (us)	[62]

prevention for amyloid diposits				
Assay method for Alzheimer's disease	Holtzman DM, DeMattos R, Bales KR, Cummins DJ, Paul SM,	US-7771722	Eli Lilly and Co	[63]
Treatment of amyloidosis assocated with alzhe mer disease usng modulators of proten phosphorylaton	Joseph D. Buxbaum, Flushing; Samuel E. Gandy; Paul Greengard, both of New York, all of N.Y.	US-5385915	The Rockefeller University, New York, N.Y.	[64]
Combination therapies for the treatment of Alzheimer's disease and related disorders	Elmaleh DR	US-9855276	General Hospital Corp,	[65]
Curcumin nanoparticles and methods of producing the same	Kar SK, Akhtar F, Ray G, Pandey AK	US-13056515		[66]
Combination comprising parthenolide for use in the treatment of alzheimer's disease and other neurodegenerative disorders	Bajic v, essack m,	US-	Bajic, Vladimir, Essack, Magbubah, King Abdullah University of Science, Technology (KAUST),	[67]
Intranasally administering curcumin prodrugs to the brain to treat alzheimer's disease	Di Mauro TM,	US-11736278	Di Mauro Thomas M,	[68]
Herbal formulation as memory enhancer in alzheimer condition	Palpu P, Rao CV, Kishore K, Gupta YK, Kartik R, Govindrajan R,	US-7429397	Council of Scientific, Industrial Research (CSIR),	[69]
Transdermal methods and systems for treating Alzheimer's disease.	Valia KH, Ramaraju VS	US-9248104	Core tech solutions inc,	[70]
Methods and Drug Products For Treating Alzhemers Disease	Allen D. Roses, Chapel Hill, NC (US); Rajneesh Taneja, Libertyville, IL (US)	US-9102666	Zinfandel pharmaceuticals,. inc. durham, nc (us); takeda	[71]

			pharmaceutical company limited, osaka (jp)	
Modified release formulations of Memantine oral dosage forms	Suneel K. Rastogi, Island Park, NY (US); Niranjan Rao, Belle Mead, NJ (US); Antonia Periclou, Jersey City, NJ (US); Wattanaporn Abramowitz, Hillsborough, NJ (US); Mahendra G. Dedhiya, Pomona, NY (US); Shashank Mahashabde, Kendall Park, NJ (US)	US-8039009	Forest Laboratories Holdings Limited (BM)	[72]
Composition to retard the onset of symptoms of alzheimer's disease.	Perry SC	US-8557310		[73]
Ethods of diagnosing alzheimer's disease	Jules Westbrook, Dublin (IE); Helen Byers, Cobham Surrey (GB); Malcolm Ward, Cobham Surrey (GB); Simon Lovestone, London (GB); Abdul Hye, London (GB); Stephen Lynham, London (GB); Richard Joubert, Niedernhausen (DE); Petra Prefot, Wiesbaden (DE); Karsten Kuhn, Hofheim (DE); Christian Baumann, Offenbad (DE); Juergen Schaefer, Lauterbach (DE); Thorsten Prinz, Hofheim (DE); Stefan Kienle, Frankfurt (DE)	US-7897361		[74]

Composition to enhance the bioavailability of curcumin	Antony B	US-9861677	Arjuna Natural Extracts Ltd,	[75]
Use of preparations of curcuma Pants	H. P.T. Ammon; Hasan Safayhi, both of Tibingen; Samuel N. Okpanyi, Wiesbaden, all of Germany	US-5401777	SteigerwaldArzneimittelwerk GmbH, Darmstadt, Germany	[76]
Method of inhibiting alzhemer's Disease	Patrick C. May, Carmel, Ind.	US-5552415	Eli Lilly and Company, Indianapolis, End.	[77]
Water soluble composition comprising curcumin having enhanced bioavailability and process thereof	Deshpande JV, Kulkarni SK,	US-9259401	Omniactive health technologies ltd.	[78]
Formulation of curcumin with enhanced bioavailability of curcumin and method of preparation and treatment thereof	Antony B, Kuriakose MA	US-10543277	Arjuna Natural Private Ltd,	[79]

4. Curcumin in alzheimer's disease and its ability

Curcumin (diferuloylmethane), a yellow filament extracted from the turmeric root ball, has been documented to have a broad variety of therapeutic actions.[80] Curcumin is a known polyphenol derived via long curcuma (a colony of Zingiberaceae). It has demonstrated anti-inflammatory, anti-oxidant, wound healing, hepatoprotective, neuroprotective, cardioprotective, anticarcinogenic, and anti-AIDS potentials.[81] The key component in the rhizome contains (1.7-bis(4-hydroxy-3-methoxyphenyl), hepadien-3.5-dione, and curcumin-difeloylmethane. The medicinal effects are apparently due to curcuminoids.[82] This is a part of the family of curcuminoids and was used in conventional medicines for decades. It offers curry, as a seasoning, with its unique color and taste.[83] Curcumin is one of the substances that readily produce successful strikes owing to its chemical composition in product screening assay rather than specific pharmacological behaviour (Baell, 2015; Baell and Walters, 2014). Most of the explanations why curcumin is considered an extremely acute agent and in certain assays

behaves like medication are that it changes membrane properties.[84] Curcumin already has a high binding association for beta-amyloid. Considering the importance of beta aggregation in AD pathogenesis, curcumin's capacity to interfere with beta-amyloid makes it worthwhile as a potential prevention agent and as a potential preventive agent and an imaging agent for AD.[85] Curcumin is usually hydrophobic and sometimes soluble in dimethylsulphoxide, acetone, ethanol, and oils. This has a great absorption of around 420 nm.[86] Latest research suggests that curcumin can play a vital role in AD management and is extremely useful as a responsive diagnostic weapon, health-promoting life-long neutraceutical, and mega-target medication (Belkacemi et al., 2011; Goozee et al., 2016).[87] Research on curcumin showed that curcumin activates human cognitive functions in humans. Multiple groups developed and synthesized curcumin and its variants and empirically validated using AD cell and mouse models and documented good anti-amyloid binding interaction properties on curcumin.[88]

Nevertheless, much of the known curcumin behaviours are focused on experiments performed in vitro and in vivo primarily. In context, one study found that curcumin in the BV2 microglial cell line mitigates LPS mediated neuroinflammation and cytokine development (Cheng et al. 2001).[89]Curcumin was fairly low in the in vitro assay and the ex- vivo AChE model lacking benefit, whereas it was incredibly successful in the memory-boosting test, indicating additional mechanisms. While the combination of curcuminoids can have stronger therapeutic characteristics over curcumin with its medicinal usage in AD.[90] That curcuminoid mixture reveals a variety of behaviours that can be beneficial in enhancing AD signs which impact different targeting sites (Dohare et al., 2008; Lin et al., 2008; Sreejayan and Rao,

4.1 The method used for the enhancement of solubility of curcuma longa linn

Curcumin is a hydrophobic medication of poor aqueous solubility that requires effective strategies. In addition to the hydrophilic additives, CUR solubility, the formation of solid dispersion was promoted.[91] Curcumin's poor oral bioavailability has restricted its clinical development when traditional medicine is implemented; new policies are required to boost the systemic bioavailability of Curcumin; three strategies have already been implemented either alone or in combination: (1) transmission formulations, (2) cell metabolism co-administration or efflux therapy; and (3) synthetic analogs to hinder in vivo extraction and metabolism.[92]

- Micronization
- Synthetic analogs and conjugates

- Complexation
- Quercetin

Nanoformulation- Nevertheless low water solubility and sub-optimal systemic absorption from the gastrointestinal tract may reflect circumstances that lead to its failure in clinical trials. Polymeric nanoparticular curcumin encapsulated (NanoCurcTM) is designed to improve the bioavailability of curcumin. It is water-soluble. Treatment of NanoCurcTM protects human SK-N-SH cells from insults mediated in neuronal differentiation by ROS (H2O2). NanoCurcTM also protects human SK-N-SH cells that had previously suffered H2O2 insults.[93]

In work on phytoformulation, the production of nanodosage types (polymeric nanoparticles and nanocapsules, liposomes, strong lipid nanoparticles, phytosomes, and nano-emulsion, etc.) has a range of advantages for herbal medicines, including enhancing solubility and bioavailability, toxicity safety, enhancing pharmacological efficiency, enhancing stability and improve the distribution of tissue macrophages, continuous transmission, physical and chemical degradation safety.[94]

Micronization- Current size reduction methods involve mechanical micronizationstrategies that are straightforward ways to reduce the substance's particle size and increase the surface region, consequently increasing the solubility through the deterioration of poorly soluble substances.[95] Previously, electrospraying was successfully like to manufacture micro-or nano-sized particles with medicinal usage. In this study, polyvinylpyrrolidone (PVP) curcumin-containing microspheres were designed to improve the bioavailability of minimal-water soluble curcumin by electrospraying.[96]

Solid dispersion- A variety of methods for the production of CUR soluble formulations have been produced such as the packing of CUR ontoliposomesor nanoparticles, SEDDS, and CUR cyclodextrin complexations. Given the lengthy process of complication, cyclodextrin's elevated molecular weight and the processing medium's pHrestrict their usability.[97]

Complexation- The in situ research on intestinal absorption has shown that α-CD and DM-β-CD have enhanced the low oral absorption of CUR. The ideal absorption enhancer was 50mM α-CD, especially, and the intestinal membrane induced no significant toxicities. Cellular transportation Study and review of Western blotting showed 50mM α-CD was

present. A significant improvement effect on low paracellular permeation absorbed the product by opening the near intersection by controllingClaudine-4 voice. The increased membrane is also used fluidity suggested that α-CD could have in the presence of 50mM α-CDMedicine via a transcellular pathway was advocated for permeation.[98] Cyclodextrin-glycosyltransferase (CGT) enzymatic degradation of starch generates cyclic oligomers, cyclodextrins (CDs).[99] Nanosponges focused on cyclodextrin have been used as drug delivery mechanisms in recent years to improve the therapeutic efficacy and bioavailability of the badly water-soluble drugs. These are primarily used to improve the efficiency of solubilisation and to extend the release of molecules in hydrophobic products.[100]

Quercetin- Quercetin is a flavonoid with highly marked antioxidant and anti-inflammatory function. Quercetin provided little transdermal distribution in various forms of formulations except for the usage of penetration stimulants.[101]

4.3 Various types of formulation of curcumin

Currently, many antioxidant and anti-inflammatory dietary supplements of curcumin are available on the market: BCM-951, TheracurminTM, CurcuVIVATM, CurcuMIND, Long-Vida RD CAVACURMIN1, BiocurcumaxTM, and many more products. The in vivo burn wound-healing efficacy of BiocurcumaxTM on rats was systematically studied by Durgaprasad et al. and the result demonstrated treatment groups showed better-wound healing with complete wound restoration compared with control groups. Over the years, various topical formulations of curcumin including nano-architectures have been developed and evaluated for augmenting the wound-healing activity of curcumin. The main reason for preferring the topical nanoformulation of curcumin is to offer solubility, better bioavailability, and sustained release of curcumin in an active form, which is certainly of great benefit for providing a constant dose of the drug for prolonged periods to improve wound healing. Understanding the perfect dose of curcumin is essential for multiple targets, and above all its complex role in the inflammatory response is needed to be addressed before further clinical development.[102]

Table no. 4: List of curcumin formulation use for alzheimer's treatment.

Implementation	Blending	Fabricator	Reference
Meriva	Phytosome methodology (curcumin, soy lecithin, microcrystalline cellulose as well as 18-20% curcuminoids)	Indonesia , Italy	[103]
LongVida	SLCP^{TM} Patented combination of (solid lipid curcumin particle lipids, phosphotidyl choline and 20% curcumin)	Verdure Science , USA	[104]
CurQfen^{TM}	Fenugreek soluble combination of fibre and 40% curcumin	Spiceuticals , India (Akay Group)	[105]
Micro Active curcumin	25% curcuminoids, a authorized blending of polyglycerol esters of fatty acids, medium linked by triglycerides, hydroxypropylmethylcellulose, sodium alginate and microcrystalline cellulose	BioactivesLLC , USA	[106]
Micronized curcumin	Micronized powder: 58.3% triacetin, 16.7% panodan and 25% curcumin pulver	Raps GmbH & Co., KG , Germany	[107]
Novasol	Liquid micelles: 93%Tween-80 and 7% curcumin dust	Frutarom , Israel	[108]
CurcuWin	63%-75% polyvinyl pyrrolidine, 10%-40% celluloisic by-product ,1-3% natural antioxidants and 20-80% wrench out turmeric	OmniActiveHealthTechnologies , India	[109]
Biocurcumax^{TM} (BCM-95)	Curcuminoid, essential oil of turmeric (45%ar-turmerone) and curcuminoids	Arjuna Natural Extracts Ltd. India (Dolcas Biotech)	[110]
Curcumin C3 complex+ Bioperine	Combination Bioperine and curcuminoids	Sabina, USA	[111]
Cavacurcumin	Gamma-cyclodextrin as well as 15%(w/w) aggregate of curcuminoids	WackerChemie AG, Germany	[112]

Theracurcumin™	Colloidal-nanoparticals (12%curcuminoids, 46% glycerine, 4% gum ghatti, 38% water, and 10% curcumin	Theravalues Corp., Japan	[113]

5. Limitation and Future research

This polyphenol was shown to hit manysignaling molecules and demonstrated cellular activityand the entire organism level providing a basis for its use in multifactorial human disease. Although most of the present - monotargated therapies available are attributed to several side effects. curcumin was found to be safe for human use even in Doses of grams. However, most of the documented curcumin activities are based on in vitro and in vivo studies only. Curcumin was still not enacted for use with any human disease. Thus, more enormous and more thoroughly controlled human studies are carried out. Future work will concentrate on putting this fascinating molecule at the core of treatment therapeutics for human diseases. This molecule is needed to demonstrate the protection and effectiveness of polyphenol.[114] While some synthetic medication has been progressively introduced to treat learning and memory disability, their therapeutic effects are observed, most of them are discarded. Worldwide the tendency of humans towards natural medicine is growing. Although one or more of the medicinal plants and their constituents mentioned in the article do still not completely comprehend the mechanism of anti-dementia action of the highest rates of herbal extracts and their compounds, work through the inhibition of AChE and activation of acetylcholine. Even if cholinesterase inhibitors opened up such as tacrine and donepezil limited the number of AD patients and soothed their symptoms, most patients with Alzheimer's disease have not yet benefited significantly from significant financial investment in research and development projects.[115]

CONCLUSION

There seems to be no cure for halting AD or preventing it. Five medications that gradually enhance symptoms have been licensed by the U.S. food and drug administration. The efficacy of such medicines differs across the population. Hardly any of the therapies accessible currently changes the fundamental path of this fatal condition. Revolutionary healthcare approaches need to be introduced in the group environment and statistically validated based on interventions identified by respondents and clinically meaningful results recognized both by respondents and their carriers. Despite massive success over the years in AD science and emerging paradigms, basic problems have not yet been overcome in both the clinical

definition and the diagnostic criteria. For wind-up, recovery approaches may provide a range of measures that meet various targets. As mentioned for many of these herbs, a putative pharmacological target such as receptor or transmitter is in fact; none of the herbs can be said to cure "the whole condition".

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CONFLICT OF INTEREST

Author declare no conflict of interest.

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