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Original Article

Nanomedicine based approach on mRNA delivery

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ABSTRACT

Messenger RNA (mRNA) has immense potential for developing a wide range of therapies, including immunotherapy and protein replacement. As mRNA presents no risk of integration into the host genome and does not require nuclear entry for transfection, which allows protein production even in non-dividing cells, mRNA-based approaches can be envisioned as safe and practical therapeutic strategies. Nevertheless, mRNA presents unfavorable characteristics, such as large size, immunogenicity, limited cellular uptake and sensitivity to enzymatic degradation, which hinder its use as therapeutic agent. While mRNA stability and immunogenicity have been ameliorated by direct modifications on the mRNAstructure, further improvements in mRNA delivery are still needed for promoting its activity in biological settings. In this regard, nanomedicine has shown the ability for spatiotemporally controlling the function of a myriad of bioactive agents in vivo. Direct engineering of nanomedicine structures for loading, protecting and releasing mRNA, and navigating in biological environments, can then be applied for promoting mRNA translation toward the development of effective treatments. Here, we review recent approaches aimed at enhancing mRNA function and its delivery through nanomedicines, with particular emphasis on their applications and eventual clinical translation.

Keywords: nanomedicinem RNA delivery, Alzheimer diseases.

INTRODUCTION

Nanomedicine is the application of nanotechnology to achieve innovation in healthcare. It uses the properties developed by a material at its nanometric scale 10-9 m which often differ in terms of physics, chemistry or biology from the same material at a bigger scale. Moreover, the nanometric size is also the scale of many biological mechanisms in the human body allowing nanoparticles and nanomaterials to potentially cross natural barriers to access new sites of delivery and to interact with DNA or small proteins at different levels, in blood or within organs, tissues or cells.At the nano-scale, the surface-to-volume ratio is such that the surface properties are becoming an intrinsic parameter of the potential actions of a particle or material. Coating of the particles and functionalization of their surfaces (even on multiple levels) are in this way extremely common to increase the biocompatibility of the particle and its circulation time in the blood, as well as to ensure a highly selective binding to the desired target.

Nanomedicine has the potential to enable early detection and prevention and to drastically improve diagnosis, treatment and follow-up of many diseases including cancer but not only. Overall, Nanomedicine has nowadays hundreds of products under clinical trials, covering all major diseases including cardiovascular, neurodegenerative, musculoskeletal and inflammatory. Enabling technologies in all healthcare areas, Nanomedicine is already accounting for approximatively 80 marketed products, ranging from nano-delivery and pharmaceutical to medical imaging, diagnostics and biomaterials.

Application of nanomedicine: Nanomedicine has numerous applications in the diagnosis, treatment, and prevention of various diseases.

Diagnostic Applications

- **Imaging:** Nanoparticles can be designed to target specific cells or tissues, allowing for enhanced imaging and diagnosis.
- **Biosensing:** Nanosensors can detect biomolecules, such as proteins, DNA, or RNA, enabling early disease detection.
- **Liquid Biopsy:** Nanoparticles can be used to detect circulating tumor cells or DNA in blood samples.

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Therapeutic Applications

- **Cancer Treatment:** Nanoparticles can deliver chemotherapy, targeted therapies, or immunotherapies directly to cancer cells.
- **Gene Therapy:** Nanoparticles can deliver genes to specific cells, enabling the treatment of genetic disorders.
- **Infectious Diseases:** Nanoparticles can deliver antibiotics, antivirals, or antifungals directly to infected cells.
- **Regenerative Medicine:** Nanoparticles can deliver growth factors, stem cells, or other therapeutic agents to promote tissue repair.

Preventive Applications

- **Vaccines:** Nanoparticles can deliver vaccines, enabling improved immune responses and protection against diseases.
- **Prophylactic Therapies:** Nanoparticles can deliver prophylactic therapies, such as antivirals or antibacterials, to prevent infections.

Other Applications

- **Wound Healing:** Nanoparticles can deliver growth factors, antibiotics, or other therapeutic agents to promote wound healing.
- **Tissue Engineering:** Nanoparticles can deliver cells, growth factors, or other therapeutic agents to promote tissue regeneration.
- **Neurological Disorders:** Nanoparticles can deliver therapeutic agents across the blood-brain barrier, enabling the treatment of neurological disorders.

Emerging Applications

- **Personalized Medicine:** Nanoparticles can be designed to deliver personalized therapies based on an individual's genetic profile.
- **Synthetic Biology:** Nanoparticles can deliver genetic materials, enabling the creation of new biological pathways or circuits.
- **Nanorobotics:** Nanoparticles can be designed to perform specific tasks, such as targeting cancer cells or repairing damaged tissues.

Advantages:

1. **Enhanced Stability and Protection:**
   Nanoparticles provide a protective shield for mRNA molecules, preventing degradation by nucleases and enzymatic activities. This Enhanced stability ensures the preservation of the therapeutic payload during transport to the target cells.
2. **Improved Cellular Uptake**
   Nanoparticles facilitate efficient cellular uptake of mRNA by promoting endocytosis or direct fusion with cell membranes. Surface Modifications can enhance the interaction with cell receptors, promoting internalization and improving overall delivery efficiency.
3. **Targeted Delivery**
   Functionalization of nanoparticles allows for targeted delivery to specific tissues or cells. Ligands or antibodies can be conjugated to the nanoparticle surface, enabling site-specific delivery and minimizing off-target effects.
4. **Controlled Release**
   Nanoparticles can be engineered to enable controlled release of mRNA, providing sustained therapeutic effects. This feature allows for The modulation of gene expression over time, enhancing the overall efficacy of mRNA-based therapies.

Disadvantages:

1. **Immunogenicity**
   Nanoparticles themselves may trigger immune responses, leading to potential adverse effects. Surface modifications and proper selection of materials are critical to minimize immunogenic reactions and ensure the safety of the delivery system.
2. **Off-Target Effects**
   Despite efforts to achieve targeted delivery, nanoparticles may still interact with unintended cells or tissues, leading to off-target effects. This can result in undesired side effects and impact the overall safety profile of the mRNA delivery system.
3. **Toxicity Concerns**
   Certain nanoparticle materials may exhibit inherent toxicity, raising concerns about their long-term safety. Understanding the Biocompatibility of nanoparticles and conducting thorough toxicity assessments are essential for clinical translation.
4. **Regulatory Challenges**
   The regulatory approval process for nanoparticle-based mRNA delivery systems involves addressing unique challenges, such as Characterizing the complex interactions between nanoparticles and biological systems. This can

result in delays in the translation of These technologies to clinical applications.

mRNA (messenger RNA) delivery has several advantages, including:

1. **Therapeutic Advantages**

- **Transient Expression:** mRNA is degraded by the cell after translation, reducing the risk of long-term toxicity.
- **No Risk of Genome Integration:** mRNA does not integrate into the host genome, minimizing the risk of insertional mutagenesis.
- **Flexibility in Protein Expression:** mRNA can be designed to express a wide range of proteins, including antibodies, enzymes, and growth factors.

2. **Delivery Advantages**

- **Non-Viral Delivery:** mRNA can be delivered using non-viral vectors, such as liposomes or nanoparticles, which are generally safer and more tolerable than viral vectors.
- **Easy to Manufacture:** mRNA is relatively easy to manufacture and can be produced in large quantities using in vitro transcription.
- **Rapid Development:** mRNA-based therapies can be rapidly developed and tested, as the production process is relatively fast and flexible.

3. **Immunological Advantages**

- **Activation of Immune Response:** mRNA can activate the immune system to produce a specific response, making it a promising tool for vaccine development.
- **Antigen Presentation:** mRNA can be used to express antigens, which can be presented to the immune system to stimulate a specific response.
- **Cancer Immunotherapy:** mRNA-based cancer immunotherapies can be designed to express tumor antigens, stimulating an immune response against cancer cells.

4. **Other Advantages**

- **Personalized Medicine:** mRNA-based therapies can be tailored to individual patients, allowing for personalized medicine approaches.
- **Combination Therapies:** mRNA can be combined with other therapies, such as chemotherapy or radiation therapy, to enhance treatment efficacy.
- **Regenerative Medicine:** mRNA can be used to deliver genes that promote tissue repair and regeneration, making it a promising tool for regenerative medicine applications.

❖ **mRNA delivery :**

Messenger RNA (mRNA) mediates the translation of genetic information from genes into proteins. Delivering exogenous mRNA into cells allows to transiently produce proteins in a precise manner. Such mRNA-mediated transfection offers an attractive alternative to plasmid DNA (pDNA)- based gene therapy by expressing proteins even in non-dividing and hard to transfect cells without the risks of genomic integration. Moreover, while pDNA needs to be delivered inside the nucleus of targeted cells, the access of mRNA to the cytosol and the subsequent engagement with the translation machinery of the cells are sufficient to obtain the proteins of interest. The mRNA delivered inside the cells can also last for several days, which is convenient for developing efficient therapeutic strategies, as well as commercially viable approaches.On the other hand, mRNA presents inherent limitations for being used as a stand-alone drug, including fast degradation by nucleases, limited cellular uptake, and immunogenicity. While the immunogenic signals triggered by mRNA could be exploited for vaccination or immunotherapy applications, Major efforts have been dedicated to reduce mRNA immunogenicity and improve the stability of the molecule by either chemical modification or by RNA architectonics, aiming at increasing the significance of mRNA as a therapeutic agent. Nevertheless, mRNA is still susceptible to degradation and the cellular uptake of naked mRNA should be improve for eliciting adequate amounts of proteins. Thus, the development of safe carrier systems capable of intracellular delivery of intact mRNA molecules is fundamental for progressing into effective treatments.

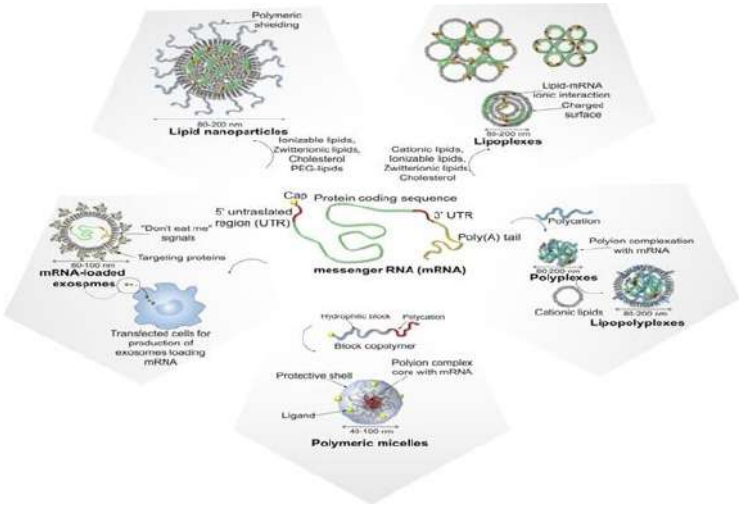

Figure 1.Nanomedicine approaches for mRNA delivery

Various platforms are under intense research and development for the delivery of mRNA based on their unique ability to promote navigation in biological environments, intracellular delivery and engagement with the translation machinery of cells. A wide range of nano-scaled carriers are under intense investigation for developing mRNA delivery systems. Viral vectors, which have been extremely useful for delivering other nucleic acids, have been among the first carriers to be considered for developing mRNA delivery systems .Nevertheless, viral carriers present intrinsic limitations, such as small packing size, immunogenicity, cytotoxicity and complex production processes,5 which have spurred the development of safe and effective non-viral vehicles. These non-viral vehicles can benefit from a myriad of biocompatible synthetic and natural materials for attaining specific physicochemical and functional features directed to develop mRNA-loaded nanomedicines with improved mRNA bioavailability, targeting to specific tissues and cells, and enhanced cellular uptake and intracellular release of mRNA molecules (Figure 1).Thus, various non-viral strategies have achieved major breakthroughs in the in vivo delivery of mRNA, 27as well as in the clinical translation of mRNA-based therapies.Here, we present the recent progress in mRNA-loaded nanomedicine toward innovating vaccination, immunotherapy, treatment of genetic disorders and protein replacement approaches. We have focused on the different non-viral strategies with emphasis on the employed materials and the advantages offered by each approach. Moreover, the mRNA modification methods are also reviewed, highlighting opportunities for synergistically enhancing nanomedicine efficiency. Finally, the trends in the application of mRNA-loaded nanomedicines and their future perspectives are discussed.

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- **Regenerative Medicine:** mRNA can be used to deliver genes that promote tissue repair and regeneration, making it a promising tool for regenerative medicine applications.

mRNA delivery disadvantages:

1. **Technical Challenges**

- **Instability:** mRNA is prone to degradation by nucleases, which can reduce its effectiveness.
- **delivery Efficiency:** mRNA delivery can be inefficient, with only a small percentage of cells taking up the mRNA.
- **Cell-Specific Delivery:** Targeting specific cell types with mRNA can be challenging.
- **immunological Challenge**
- **Immune Activation:** mRNA can activate the immune system, leading to inflammation and other adverse effects.
- **Antibody Response:** mRNA can stimulate an antibody response, which can reduce its effectiveness.
- **Immune Suppression:** mRNA can also suppress the immune system, which can increase the risk of infections.

2. **Safety Concerns**

- **Toxicity:** mRNA can be toxic to cells, particularly at high doses.
- **Off-Target Effects:** mRNA can have off-target effects, where unintended genes are expressed.
- **Genetic Mutations:** mRNA can also introduce genetic mutations, which can be passed on to future generations.

3. **Regulatory Challenges**

- **Regulatory Framework:** The regulatory framework for mRNA delivery is still evolving and can be unclear.
- **Manufacturing Standards:** Manufacturing standards for mRNA delivery products can be variable.
- **Quality Control:** Ensuring quality control and consistency in mRNA delivery products can be challenging.

4. **Other Disadvantages**

- **Cost:** mRNA delivery can be expensive, particularly for complex diseases.
- **Scalability:** Scaling up mRNA delivery for large patient populations can be challenging.
- **Storage and Handling:** mRNA delivery products require specialized storage and handling, which can be inconvenient.

mRNA delivery system :

mRNA—or messenger RNA—is a molecule that contains the instructions or recipe that directs the cells to make a protein using its natural machinery. To enter cells smoothly, mRNA travels within a protective bubble called a Lipid Nanoparticle. Once inside, our cells read the mRNA as a set of instructions, building proteins that match up with parts of the pathogen called antigens. The immune system sees these foreign antigens as invaders—dispatching defenders called antibodies and T-cells—and training the immune system for potential future attacks. So, if and when the real virus comes along, the body might recognize it sounding the alarm to help defend against infection and illness.

Nanomedicine has used to treat diseases:

- **Infectious Diseases :**

1. Antibacterial nanoparticles
2. Antiviral nanoparticles
3. Antifungal nanoparticles
4. Vaccine delivery

- **Neurological Disorders:**

1. Alzheimer's disease
2. Parkinson's disease
3. Stroke
4. Brain cancer

- **Cardiovascular Diseases:**

1. Atherosclerosis
2. Heart failure
3. Myocardial infarction
4. Hypertension

- **Autoimmune Diseases:**

1. Rheumatoid arthritis
2. Lupus
3. Multiple sclerosis
4. Type 1 diabetes

- **Ophthalmic Diseases:**

1. Age-related macular degeneration
2. Diabetic retinopathy
3. Glaucoma
4. Cataracts

- **Dermatological Diseases:**

1. Psoriasis
2. Atopic dermatitis
3. Acne
4. Skin cancer

- **Respiratory Diseases:**

1. Asthma
2. Chronic obstructive pulmonary disease (COPD)
3. Cystic fibrosis
4. Lung cancer

- **Orthopedic Diseases:**

1. Osteoarthritis
2. Osteoporosis
3. Bone cancer
4. Tissue engineering

➢ **Alzheimer diseases:**

Alzheimer's disease (pronounced "alz-HAI-mirs") is a brain condition that causes a progressive decline in memory, thinking, learning and organizing skills. It eventually affects a person's ability to carry out basic daily activities. Alzheimer's disease (AD) is the most common cause of dementia.Alzheimer's disease mainly affects people over age 65. The higher your age over 65, the more likely you'll develop Alzheimer's.Some people develop Alzheimer's disease before age 65 — typically in their 40s or 50s. This is called early-onset Alzheimer's disease. It's rare. Less than 10% of ADcases are early-onset.Alzheimer's disease is common. It affects approximately 24 million people across the world.

Alois Alzheimer, a German physician, reported the first case of Alzheimer's disease in 1907 .He first saw Auguste Deter, a 51-year-old woman, in 1901. Auguste's husband Karl brought her to a mental hospital after she began exhibiting unusual behavior, including hiding items, threatening neighbors, and accusing her husband of adultery. She also lost the ability to do daily activities such as cooking and housework. Auguste came under Alzheimer's care at a mental hospital in Frankfurt. There he observed and recorded her behavioral patterns: she could speak but not write her own name, she could name objects such as a pencil but not the food she was eating, she was polite sometimes but loud and offensive at other times. He diagnosed Auguste with "presenile dementia" .Upon her death in 1906, Alzheimer's biopsy of her brain revealed diffuse cortical atrophy and "particular changes in cortical cell clusters" . Alzheimer described plaques and tangles of nerve fibers which researchers would identify in the 1980's as beta amyloid plaques and neurofibrillary tangles of tau . That year, Alzheimer gave a presentation on Auguste at a German psychiatry conference, asserting these cortical lesions to be the cause of her symptoms. He published a research paper the next year, and a psychiatry textbook in 1910 named the disorder 'Alzheimer's disease.'The clinical diagnostic criteria for AD were standardized in the U.S. in 1984. They were revised in 2011 and 2018 to create separate diagnoses for the preclinical, mild cognitive impairment (MCI) and dementia stages of AD and to recognize the role of biomarkers in AD diagnosis

➢ **Pathophysiology of Alzheimer Disease :**

Neuronal loss and/or pathology may be seen particularly in the hippocampus, amygdala, entorhinal cortex and the cortical association areas of the frontal, temporal and parietal cortices, but also with subcortical nuclei such as the serotonergic dorsal raphe, noradrenergic locus coeruleus, and the cholinergic basal nucleus. The deposition of tangles follows a defined pattern, starting from the trans-entorhinal cortex; consequently the entorhinal cortex, the CA1 region of the hippocampus and then the cortical association areas, where frontal, parietal and temporal lobes are particularly affected. The extent and placement of tangle formation correlates well with the severity of dementia, much more so than numbers of amyloid plaques.The accretion of tau proteins correlates very closely with cognitive decline and brain atrophy, including hippocampal atrophy. In the neuropathology of Alzheimer's disease there is a loss of neurons and atrophy in temporofrontal cortex, which causes inflammation and deposit the amyloid plaques and an abnormal cluster of protein fragments and tangled bundles of fibers due to this there is an increase in the presence of monocytes and macrophages in cerebral cortex and it also activates the microglial cells in the parenchyma.7 Summary of pathophysiology of AD are shown in fig

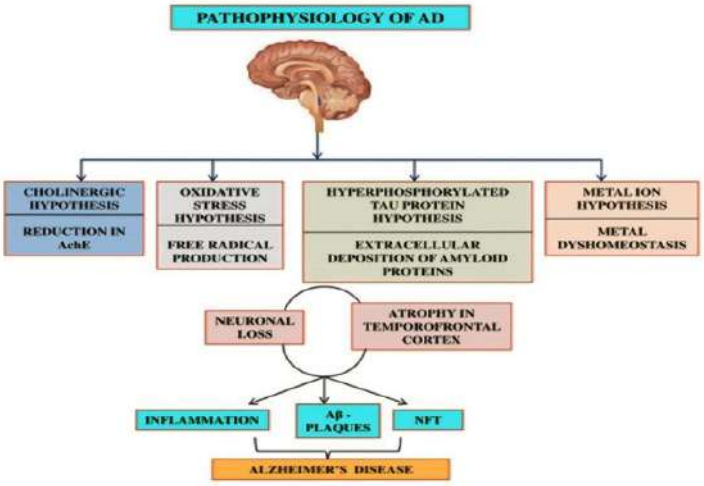

Figure no: 2

- **Stages of alzheimer diseases:**
- Mild(early)
- Moderate(middle)
- Severe(late)
- **Symptoms Of ADs :**
- Depression
- Loss of interest in activities
- Social withdrawal
- Mood swings
- Not trusting others
- Anger or aggression
- Changes in sleeping habits
- Wandering
- **Diagnosis:**
- Blood test
- Magnetic resonance imaging (MRI)
- Computerized tomography (CT)scan
- **Treatment Of AlzheimersDisease :**

Turmeric :

Fig 3 : Turmeric

Synonyms:-Curcuma

Biological source:-

Turmeric is prepared rhizome of Curcuma longa Linn. (Zingiberaceae). It is perennial herb of ginger family, having thick rhizome; origins in Southern Asia; widely grown in China and India Indonesia and other tropical countries.

Chemical Constituents:-

Turmeric contains 3-7% orange-yellow colored volatile oil which is mainly composed of turmerone (60%), a, ß-atlantone and zingiberene (25%) with minor amounts of 1,8 cineole, aphellandrene, d sabinene and borneol. Others than above it contains yellow coloring matter including 0.3-5.4%.

Curcumin: Curcumin is the main polyphenol derived from Curcuma longa L' rhizome, a plant used as a spice, preservative, yellowish dye and as a medicine in Ayurvedic and Chinese medicine. This polyphenol has several medicinal properties as antioxidant, anti-inflammatory, anti-HIV, antibacterial and antitumor effect. In addition, curcumin is also used as a therapeutic agent in inflammatory bowel disease, pancreatitis, arthritis, some types of cancer , head trauma , anxiety, Parkinson's , depression, Alzheimer's disease], as well as acting as BDNF restorer. Most of curcumin' benefits can be attributed to its anti-inflammatory action, obtained by the modulation of the expression and production of enzymes such as cyclooxygenase-2 (COX-2), lipoxygenase and inducible nitric oxide synthase (iNOS), and by the inhibition of inflammatory cytokines, including interleukin (IL) -1, -2, -6, -8 and -12, tumor necrosis factor alpha (TNF-α), monocyte chemotactic protein (MCP), among others . In neurodegenerative and neuropsychological diseases, its role in restoring BDNF levels and, consequently, promoting neurogenesis, it's extremely important and may contribute to the reversal of cognitive and mood

disorders . Polyphenols metabolites can activate cellular stress response pathways, leading to upregulation of neuroprotective genes, such as BDNF

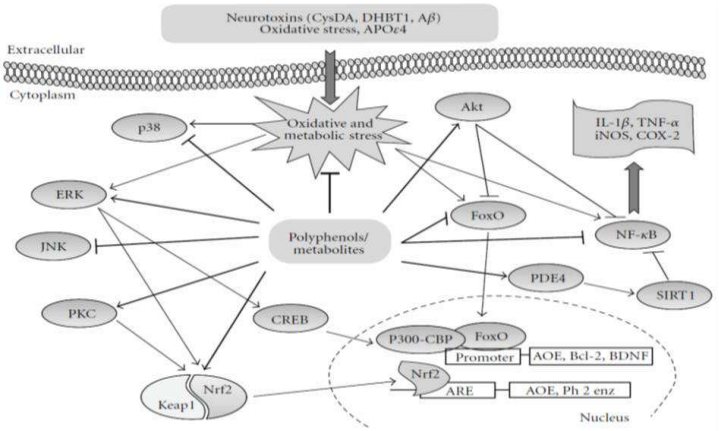

Figure: 4

Metabolic routes involved in the biological effects of polyphenols, such as curcumin, mainly in neurological and neuropsychological disorders. They can act in vivo by activating cellular stress response mechanisms leading to upregulation of neuroprotective genes Curcumin's low absorption, rapid metabolism and rapid excretion makes its bioavailability very low. When administered orally at a dose of 1 g/kg, its fecal excretion is around 75%, achieving very low plasma concentrations, in both rat and human studies. However, the association with piperine, an alkaloid derived from black pepper (Pipernigrum L) and long pepper (Piperlongum L), is capable of increasing the bioavailability of some drugs by inhibiting intestinal and hepatic glucuronidation. The administration of 20mg/kg of piperine with 2g/kg of curcumin in rats increases its bioavailability by 154% compared to administration of 2g/kg of curcumin alone. In humans, administration of 20mg of piperine with 2g of curcumin increased its bioavailability by 2000% compared to administration of 2g of curcumin alone. Piperine is capable of increasing absorption, plasma concentration, and bioavailability of curcumin in both rats and humans without significant side effects. Piperine is a non-specific drug metabolism inhibitor, with low discrimination between different forms of cytochrome P-450. In rats, orally administered piperine strongly inhibits the hepatic activity of aryl hydrocarbon hydroxylase (AHH) and UDP-glucuronyltransferase, with a potent inhibitory effect on pharmacological metabolism . Moreover, another way to overcome its low bioavailability is through the use of curcumin-loaded lipid-core nanocapsules. Considering the fact that curcumin is a liposoluble compound, this formulation is able to stabilize it and improve its absorption and biological activities.

- **Mechanism Of Action Of Curcumin In Alzheimers Disease:** Curcumin's mechanisms of action are pleiotropic. It targets the two histological markers of AD, A_ and tau. Additionally, curcumin modulates other aspects of the disease process. It also binds copper, lowers cholesterol, modifies microglial activity, inhibits acetylcholinesterase, enhances the insulinsignaling pathway, and is an antioxidant.

Aβ inhibition

Since the deposition of A_ plaques is the characteristic feature of AD, curcumin has been studied for its ability to prevent the formation and accumulation of A_. Intragastriccurcumin administration to a mice model of AD reduced A_ formation by downregulating BACE1 expression, the enzyme that cleaves A_PP to A. The curcumin-administered rats were alleviated from synaptic degradation and had improved spatial learning and memory outcomes. Similarly, Di Martino et al. identified curcumin as inhibitor of BACE1 in vitro. Another enzymatic target for the production of A_ is presenilin-1 (PS-1), a protein in the _-secretase complex and a substrate for glycogen synthase kinase-3_ (GSK-3_). _-secretase and GSK-3_ are both implicated in the generation of A_. When human neuroblastoma SHSY5Y cells were treated with curcumin, there was a marked reduction in the production of A_. There was also a decrease in PS-1

and GSK-3_ protein levels in a dose- and time-dependent manner, suggesting that curcumin decreased A_ production through inhibition of GSK-3_-dependent PS1 activation. In a rat model of AD, oral administration of curcumin was shown to reduce hippocampal A_ accumulation, along with improvement of cognitive impairment in a passive avoidance task and the Morris water maze, a test of spatial learning and memory . Promisingly, curcumin has shown to inhibit the formation and accumulation of A_ in vitro and in vivo, suggesting the possibility of comparable results in a clinical context.In addition to inhibiting A_ production, curcumin has been demonstrated to inhibit aggregation and promote disaggregation of fibrillar A_ in vivo and invitro. This mechanism may be due to the structure of curcumin: an in vitro study postulated that the hydrophobicity of curcumin or the interactions between the keto or enol rings of curcumin and aromatic rings of A_ dimers destabilized the attractions requisite for the formation of beta-sheets in A_ plaques. In addition, curcumin's polar hydroxyl groups on the two aromatic rings of the molecule interact with polar pockets of the A_ peptide, rendering it suitable to destabilize beta-sheets. The inflexible linker between the two aromatic rings is conducive to this binding property. The neuroprotective effects of curcumin are not limited to its prevention of A_ fibril formation, but may also be implicated in its prevention of A_-mediated neurotoxicity. A study of human neuroblastoma SHSY5Y cells showed that curcumin protected against A_ membrane-mediated neurotoxicity by reducing the rate of A_ insertion into the plasma membrane. Curcumin attenuated A_-membrane interactions and reduced A_-induced membrane disruption in artificial lipid bilayers, thereby potentially circumventing high calcium influx and cell death. Curcumin may also prevent intracellular calcium elevation by mediating the A induced phosphorylation of the NMDAreceptor. Moreover, curcumin may shift the A_ aggregation pathway to the formation of nontoxic conformers. Thapa et al.demonstrated that curcumin promoted
the formation of nontoxic, "off-pathway" soluble oligomers and prefibrillar aggregates. The same study demonstrated that curcumin also reduced the toxicity induced by a variety of A_ conformers, including monomeric, oligomeric, prefibrillar, and fibrillar A_. However, these studies were conducted in vitro, and do not necessary have in vivo translation.

Tau inhibition:

Hyperphosphorylated tau and its aggregation into neurofibrillary tangles are crucial to the pathogenesis of AD, and numerous studies have shown that curcumin to prevent tau hyperphosphorylation and neurotoxicity. GSK-3_ is an enzyme that adds phosphate groups onto serine and threonine amino acid residues and regulates the phosphorylation of tau. Accordingly, inhibition of GSK-3_may protect cells from tau-induced neurotoxicity and curcumin has been identified as such an inhibitor .Huang et al.demonstrated that curcumin inhibited hyperphosphorylation of tau through another mechanism. In human neuroblastoma SHSY5Y cells, curcumin inhibited tau hyperphosphorylationthrough the phosphatase and tensin homologue (PTEN)/protein kinase B (Akt)/GSK-3_ pathway, a cellular signaling pathway induced by a.

Curcumin may also have a role in tau tangle clearance and alleviating tau-induced neurotoxicity. BCL2 associated athanogene 2 (BAG2) is a molecular chaperone that delivers tau to the proteasome for
degradation. When rat primary cortical neurons were treated with curcumin, BAG2 was significantly upregulated and hyperphosphorylated tau levels decreased. Importantly, curcumin doubled BAG2 levels at low concentrations that were clinically relevant. However, this study did not use neurons in a pathological state, so curcumin's clinical applicability in the context of BAG2 and AD may be limited. In a nematode model of tauopathycurcumin was effective in alleviating tau-induced neuronal dysfunction. In the curcumin-treated nematodes, the amount of acetylated _-tubulin, an indicator of microtubule stabilization, was significantly greater than the noncurcumin treatment group. This result suggests that curcumin may have mitigated the neurotoxicity of tau by improving microtubule stabilization. This result indicates that curcumin has the potential to modulate tau-induced toxicity even in the absence.

CONCLUSION :

Curcumin has been speculated to be able to prevent and treat AD, but research elucidating its specific mechanisms of action has only been performed in the past several decades. Foremost, curcumin inhibits the two key histological features of AD, A_ plaques and

tau tangles. Its other mechanisms of action relate to other risk factors, physiological activities, or biomarkers associated with AD. Curcumin binds copper, lowers cholesterol, prevents inflammatory microglial activity while enhancing A_ microglial phagocytic activity, inhibits AChE, mediates the insulin signaling pathway, and restores redox balance. The diverse array of the effects of curcumin and its disease modifying properties may have a notable impact on the future of drug treatment for AD. AChEinhibitors and NMDA antagonists are the current mainstay treatments, but these drugs only target a singledisease pathology and do not delay the onset of the disease or alter its progression. Moreover, their efficacy declines as neurons degenerate. In contrast, the effects of curcumin are multi-targeted and it has theability to modify the disease process. More researchneeds to be done to improve the bioavailability ofcurcumin so that the success of pre-clinical studiescan be translated to clinical outcomes. If curcuminis confirmed to show the same efficacy in humans asin in vitro and in vivo studies, the disease-modifyingtreatment of AD is a worthwhile possibility

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