IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Natural Product As Solutions For Managing Neurodegenerative Disorders

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Abstract: Neurodegenerative disorders, particularly Alzheimer's disease (AD), pose a major health challenge with few effective treatments available. Projections show AD will affect 135 million people by 2050, placing a heavy burden on individuals and healthcare systems. Current treatments are often ineffective and can have significant side effects. Natural compounds from herbs, fruits, vegetables, and nuts have shown promise in preventing neurodegeneration and enhancing cognitive function in preclinical studies. The effectiveness of these compounds can be improved by incorporating them into nanocarriers like nanoparticles and nanogels, which enhance stability, targeting, and specificity. Additionally, alternative therapies such as acupuncture and dietary supplements may offer valuable approaches to managing and preventing AD.

Keywords:- **Natural products, Neurodegenerative diseases, Neuro inflammation, Oxidative stress, Nanotechnology, Acupuncture, alternative treatments**

INTRODUCTION

A broad category of medical illnesses known as neurodegenerative diseases occur when parts of the nervous system lose their structure and functionality. The clinical characteristics that characterize these diseases, such as dementia, tremor, stiffness, and bradykinesia, are the main basis for classification, but the anatomical distribution of the neurodegenerative lesion is also important (1). In both inherited and spontaneous neurodegenerative diseases, the primary cause of neuronal damage is the accumulation of misfolded brain proteins. (Figure1) (2). The most prevalent neurodegenerative disorders are Alzheimer's and Parkinson's, which are defined by an abnormal accumulation of protein inclusion inside the brain. While the gradual loss of neurons in Alzheimer's disease is triggered by an abnormal buildup of beta-amyloid and tau protein, Parkinson's disease exhibits inclusions known as Lewy bodies, which are mostly composed of α-synuclein. MS is the leading cause of disability among young adults following traumatic brain injury. MS's neurodegenerative state is caused by unfavorable immune-mediated mechanisms and persistent inflammation that induce demyelinating and neurodegenerative processes throughout the patient's life, rather than an excessive buildup of misfolded protein. Among the several molecular chains and risks. And some types of neurological disorders are listed in Figure 2. In this comprehensive review, I would be covering Alzheimer's disease and Parkinson's disease.

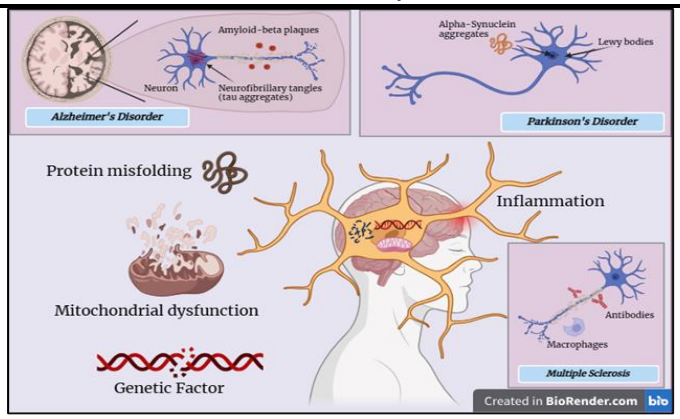

Figure 1. Causes And Risk Factors For Alzheimer's Disease, Parkinson's Disease, And Multiple Sclerosis

Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by the formation of neurofibrillary tangles, senile plaques, and the degeneration of synaptic connections, leading to cognitive and memory decline. It is the most common cause of dementia, accounting for 60-70% of cases.(3,4). Dementia itself refers to a set of symptoms that impair mental functions, behavior, memory, and emotions, caused by diseases like Alzheimer's, vascular dementia, and Lewy body dementia. In 1901, Alois Alzheimer first examined a 51-year-old patient, Auguste Deter, whose symptoms—such as memory loss, confusion, and delusions—led to the identification of what we now know as Alzheimer's disease. This disease disrupts communication between nerve cells in the brain, with symptoms varying based on the affected brain regions.(5-7).

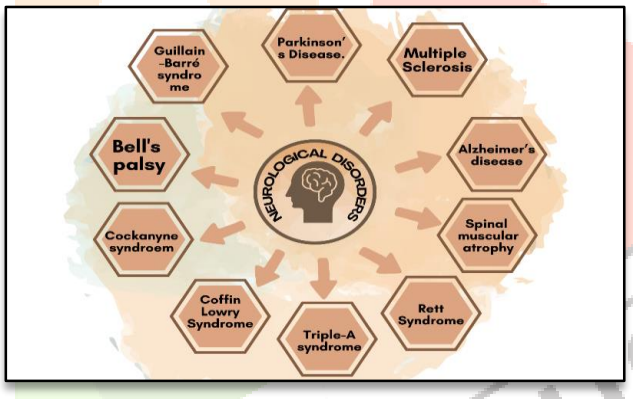

Figure 2: Neurodegenerative Diseases, Some Of The Types Of Neurodegenerative Disease

Over The Past Several Years

In 1972, the author began a neurology residency at Hospital das Clinicals, University of São Paulo, Brazil, where few residents were interested in higher nervous activities, including neuropsychology (8). At that time, Alzheimer's disease (AD) and Pick's disease were considered rare forms of presenile dementia, and most clinicians attributed dementia in the elderly to arteriosclerosis. However, vascular abnormalities remain common in AD cases, and small vessel disease is prevalent in elderly dementia, as noted by Kraepelin in 1910 (9-11). Over the next five decades, research on AD and dementia grew significantly. Publications using the term "Alzheimer's disease" increased from 615 in 1972–1981 to 100,028 in 2012–2021, a 162.6-fold rise. In contrast, publications with the term "dementia" grew 28.6 times during the same period. Notably, the 1985 edition of Marsel Mesulam's influential book on neuropsychology lacked a chapter on dementia or AD, but the 2000 edition included an 83-page chapter on aging (12-15).

Table 1: Papers On Alzheimer's Disease and On Dementia in General, Published by Registered Periodicals of The National Library of Medicine, Bethesda, Maryland, USA

Years (Period of 5 years)	Alzheimer's Disease	Dementia
1972 - 1976	131	1681
1977-1981	484	2642
1982-1986	2424	5364
1986-1991	6822	11865
1992-1996	9795	15016
1997-2001	14876	20720
2002-2006	20698	27664
2007-2011	28254	36097
2012-2016	41403	50537
2017-2021	58625	73315

IMPORTANT DISCOVERIES

In the early 1980s, researchers focused on identifying the components of senile plaques and neurofibrillary tangles in Alzheimer's disease (AD). In 1983, Allsop *et al*. (16). extracted a protein from the senile plaque core and determined its amino acid composition. In 1984, Glenner and Wong discovered β-amyloid, a protein found in senile plaques and in Down syndrome, suggesting a genetic link to AD. In 1987,(17). St. George-Hyslop *et al*. identified the amyloid precursor protein (APP) on chromosome 21. In 1986, Grundke-Iqbal *et al*. discovered tau protein in neurofibrillary tangles and its abnormal phosphorylation in AD. These findings led to the "tauists" and "β-aptists" debate, with genetics favoring the β-aptists and neuropathology supporting the tauists. In 1992, Hardy and Higgins proposed the Amyloid Cascade Hypothesis, suggesting that β-amyloid accumulation leads to tau hyperphosphorylation and neurodegeneration in AD.(18-20).

Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) are common neurodegenerative disorders that severely impact quality of life and lead to early mortality (21). PD is marked by the loss of dopaminergic neurons in the nigrostriatal pathway, causing motor issues like bradykinesia, tremors, and muscle stiffness, and is associated with α-synuclein protein aggregates (Lewy bodies) (22). ALS involves the degeneration of upper and lower motor neurons, resulting in paralysis and respiratory failure, with factors like oxidative stress, mitochondrial dysfunction, and excitotoxicity contributing to its progression. HD is caused by a CAG trinucleotide repeat expansion in the HTT gene on chromosome 4, leading to dopaminergic overactivity, GABA dysfunction in the basal ganglia, and symptoms such as cognitive decline, abnormal movements, and psychiatric disturbances (23-25).

MATERIAL AND METHODS:

In this study, a comprehensive review was conducted to explore the role of natural products in treating neurodegenerative diseases. Relevant literature was systematically searched using databases like Semantic Scholar, PubMed, and Scopus with keywords related to natural compounds and neurodegeneration. Data extraction and critical analysis were performed with transparency and adherence to ethical standards. The review highlights the potential of natural products as alternative therapeutic options for managing neurodegenerative disorders.

Mechanism And Therapeutic Targets of Neurodegenerative Disorders:

Neurodegenerative diseases (NDs) are marked by protein aggregation, oxidative stress, and inflammation in the central nervous system. Key pathological features include neurotransmitter depletion, abnormal ubiquitination, mitochondrial dysfunction, disrupted cellular transport, excitotoxicity, calcium imbalance, and excessive reactive oxygen species (ROS) production (26,27). These interconnected processes suggest common neurodegenerative pathways that can serve as potential therapeutic targets. Protein aggregates, such as amyloid plaques, are a hallmark of NDs, arising from the misfolding and accumulation of normally soluble proteins, highlighting shared mechanisms and treatment strategies across different neurodegenerative conditions (28-30).

ROLE OF NATURALLY DERIVED PRODUCTS AND THEIR METABOLITES AS AN ALTERNATIVE IN NEURODEGENERATIVE DISEASES:

Traditional medicines play a vital role in providing basic healthcare, especially in low-income countries, and are essential for maintaining overall health (31). Natural products remain a major source of bioactive compounds and potential drug candidates, with about one-third of current medicines derived from natural resources (32,33). Their therapeutic potential continues to be explored in modern medicine, leading to the discovery of new, effective, and biologically active drugs. For centuries, natural herbs have been used to treat various diseases and promote human health and well-being (34,35).

Emerging Treatment Needs

With the global rise in life expectancy and population, neurodegenerative disease (ND) cases are increasing rapidly, with dementia affecting around 50 million people worldwide and 10 million new cases annually (36,37). Current treatments offer limited effectiveness, cause side effects, and are costly, leading to a need for safer, more effective alternatives (38). Natural products and plant-based compounds, long used in traditional medicine, have shown promising neuroprotective potential. Many ND drugs, such as opioid alkaloids and anticholinesterase inhibitors, are plant-derived. However, despite their potential, clinical evidence on the safety and efficacy of these natural derivatives remains limited, highlighting the need for further research (39,40).

Table 2: Neurologically Protective Abilities of Naturally Occurring Substances and Their Derivatives in The Treatment of NDs (Preclinical Approaches)

Sr. No.	Plant origin	Principal components of plants	Neuroprotective activities	Model Used	References
1	Blueberries (*Vacciniumangustifolium*)	Polyphenols	Reduces ROS levels and activates stress pathways in the brain.	In vitro Neurodegenerative cell Model	(41)
2	*Capsicum annuum*	Capsicum	Prevents neurodegeneration in the significant nigra, cerebral cortex, and hippocampal regions by reducing the 5-lipoxygenase activity restores glutathione (GSH) levels, inhibits the rise of nitric oxide levels and brain malondialdehyde, and increases cholinesterase activity.	In vitro model /Retinone intoxication micemodel	(42)
3	*Curcuma longa*	Curcuminoids (Turmeric)	The treatment improves motor function and behavior, reduces iNOS and GFAP expression, and reduces nitrite production and proinflammatory cytokines in the striatum.	In vitro cell model/MPTP (1-methyl-4-phe- nyl-1,2,3,6-tetrahydropyridine) model	(43)
4	*Dioscorea nippoa*	Diosgenin	defends from neurological inflammation via inhibiting NF-κB, MAPK, ERK, JNK, and p38 pathways.	In vitro cell line studies on RAW 264 cells	(44)
5	*Sesamum indicum*	Sesame oil	It effectively repaired memory and intellectual	In vitro Rat model of AD	

			deficits, repaired AChE and Aβ excessive expression, and reduced oxidative damage in the brain.		(45)
6	*Vitis vinifera*	Reserverat rol	Reduces proinflammatory mediators, including iNOS, NF-κB, COX-II, and AP-1, while increasing IL-10 levels.	In vitro cell line studies/ 3-(4,5-dimethyl-thi- azol-2-yl)-2,5-diphenyl tetrasodium bromide (MTT) assay in BV2 microglia cells	(46)
7	*Nicotiana tabacum*	Osmotin	Lowering of Aβ accretion and BACE-1 expression improves memory loss, stops Aβ from causing neuronal-HT22 cells to become neurotoxic, and cures synaptic impairments.	In vitro Y Maze test	(46)
8	*Coptis chinensis*	Berberine	initiates the AKT/GSK-3β/Nrf2 regulation, induces the release of NGF and BDNF, and inhibits COX-II, iNOS, TNF-α, NF-κB, and IL-1β.	In vitro cell line studies/MTT assay in BV2microglia cells	(47,48)
9	*Morus alba*	Quercetin	suppresses the stimulation of NF-κB, COX-II, GSK-3β, and 5-LOX enzymes, and participates in the scavenging of radicals that are free.	In vitro animal model/MTTP (1,2,3,6-tetrahy- dropyridine) induced neurodegeneration	(49)
10	*Vitis vinifera*	Polyphen ols	suppresses the expression of Bcl-2 and caspase-3 and reduces the expression of iNOS, PARP, and TNF-α as well as the amount of nitrotyrosine.	Mice model of autoimmune encephalomy-elitis	(50)

One Of the Example: Curcuma longa (Turmeric)- Spice of Life: (3rd main)

Turmeric, known as "Indian Saffron," is a perennial rhizome from the Zingiberaceae family, rich in active compounds like turmerone oil and curcuminoids, particularly curcumin (51). Widely used as a spice, turmeric also possesses antioxidant, anti-inflammatory, anti-cancer, and anti-amyloid properties, with its medicinal use dating back to ancient Ayurvedic, Siddha, and Unani systems (52,53). Recent studies, such as those using Cur-loaded PBCA nanoparticles (CUR-PBCN), have enhanced curcumin's brain delivery and sustained drug release, highlighting its potential as a multitarget therapeutic agent for various diseases (54).

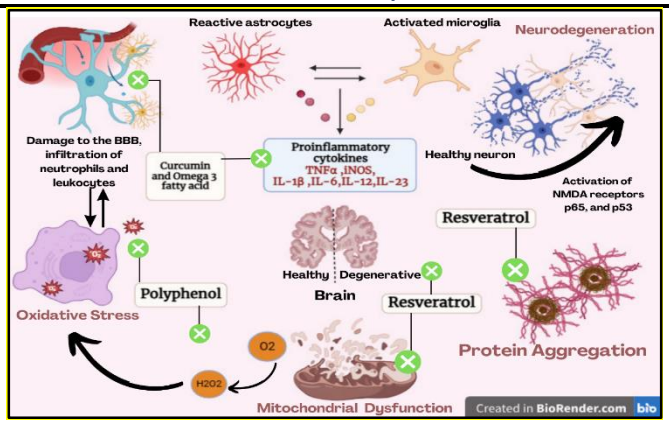

Figure.3 Neurodegenerative Pathways And Role Of Bio Actives In The Prevention Of Neurodegenerative

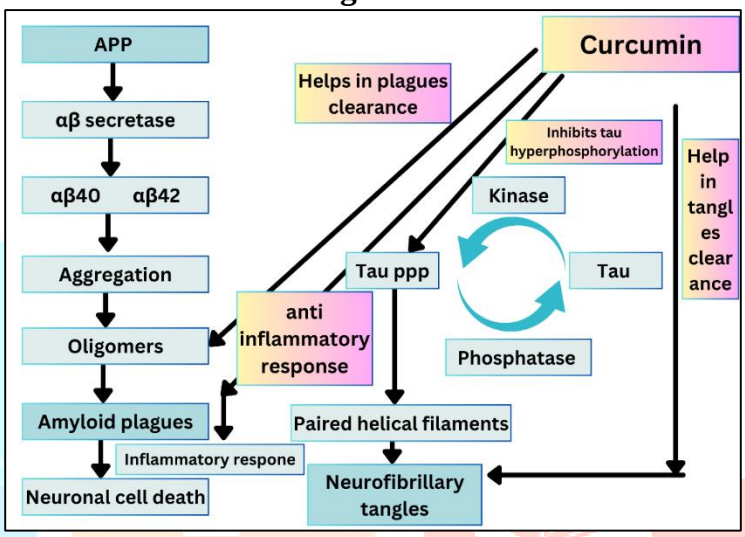

Figure.4: The following flow chart depicts the several methods via how curcumin provides neuroprotection against Alzheimer's disease. The active drugs prevent the formation and neurotoxicity of Aβ and hyperphosphorylated tau, both histological markers of Alzheimer's disease.

CLINICAL INVESTIGATIONS ON THE POTENTIAL OF NATURAL DERIVATIVES TO CURE NEURODEGENERATIVE DISEASES.

Clinical studies are being conducted to explore and evaluate various treatment approaches for neurodegenerative diseases (NDs), focusing on cognitive enhancement, anti-amyloid and anti-tau therapies, anti-inflammatory effects, neuroprotection, and neurotransmitter regulation to manage behavioural and mental symptoms. Several natural compounds have shown neuroprotective potential in clinical trials, with ongoing research aiming to clarify their mechanisms and therapeutic value. Table 3 and 4 summarize key clinical studies and dosage assessments of these phytonutrients (21).

Table 3: Clinical Trials Regarding Phytoconstituents And Phytochemicals Used To Treatment/Cure Of NDs (21)

Sr.no	Phytoconstituents	Mechanism of action	NCT number	Sponsor	Status
1	Ginkgo biloba	Antioxidant function and anti-aggregation of amyloid	NCT03090516	Nanjing Medical University	Recruiting
2	Guanfacine	Alpha-2A-adrenergic receptor agonist, an effective 5-HT2B receptor agonist.	NCT03116126	Imperial College London	Recruiting
3	Coconut oil	Diminished expression of the	NCT01883648	University of South Florida	Terminated

		protein ADP-ribosylation factor-1			
4	Caffeine	Affects the serum concentrations of levodopa and enhances the motor system by antagonistically binding to adenosine receptors.	NCT01738178	Research Institute of the McGill University Health Centre	Recruitment Completed
5	Huperzine-A	In Alzheimer's disease, cholinesterase inhibitors reduce both soluble and insoluble beta-amylase levels.	NCT00083590	-	Recruitment-Completed

Table 4: Clinical Trials and Individuals Assessment Doses of Different Phytochemicals as A Protective of Neurons.

Sr.no	Mechanism of action	Mechanism of action	Dose	Clinical Trial Data References	References
1	**Edaravone (Trade Name: Radicava)**	Anti-free radical	3 mg/kg, (two times a day for 14 days)	In Japan, the chemical was approved in 2001 for the treatment of ischemic stroke due to its promising potential.	(55)
2	**Dl-3-n-butylphthalide**	A multi-target medication protects mitochondria while also acting as an antioxidant, anti-apoptotic, and anti-inflammatory.	40 mg/kg-200 mg/kg	The chemical was proven to be useful in the management of ischemic stroke and was sanctioned for the same therapy in China in 2002.	(56)
3	**Baicailein from *Scutellaria baicalensis***	A multi-target medication promotes antioxidants, anti-apoptosis and anti-inflammatory, and mitochondrial protection. It also inhibits the LOX/p38/cPLA2 pathway and suppresses NF-κB activation. Additionally, it inhibits the LOX/p38/cPLA2 pathway and suppresses NF-κB activation.	24 mg/kg (i.v) dose	Healthy male and female volunteers participated in phase I trials that were one-center, randomly assigned, placebo-controlled, double-blind, with a single dose-escalation.	(57)

4	**Scutellarin (scutellarein-7-O-glucu- ronide) from *Erigeron breviscapus***	works by reducing inflammation and microglial activation.	30–40 ml/day for 8–12 days was found to be safe and effective along with Dengzhanxixin	It has a lot of clinical usage potential. Dengzhanxixin injections have just received permission in China for the treatment of ischemia shock (approval number Z53021569). The primary ingredient in this injection is scutellarin.	(58)
5	**Naringenin**	It reduces inflammation, lessens BBB dysfunction, suppresses NF-κB, and increases Nrf2-mediated antioxidants.	120 (mg/kg) i.v for 15 min	Clinical studies in phase1 (NCT0358255), recruiting	(59)

THE APPLICATION OF NANOTECHNOLOGY IN THE CREATION OF PHYTOCHEMICALS AND MEDICATION FORMULATION

Phytoconstituents possess valuable anticancer, antioxidant, and neuroprotective properties, but their clinical effectiveness is often limited by poor solubility and low bioavailability (60). These challenges have hindered the pharmaceutical industry's ability to scale natural substances from lab research to commercial use. Nanotechnology offers a promising solution by enhancing the solubility, stability, and targeted delivery of these compounds through advanced systems like nano spreads, nano emulsions, nanogels, and nanoparticles. Such nano formulations improve drug bioavailability, protect against premature degradation, and ensure efficient delivery to specific sites (61). Additionally, lipid-based carriers and hydrogels further enhance stability and targeted distribution, offering potential for more effective therapies. Tables and figures summarize these nanotechnology-based delivery strategies for phytoconstituents (62-64).

Table 6: Nanotechnology-based phytochemicals utilized for treating NDs.

Sr. no	Phytoconstituents	Drug Delivery System	Combating disease	References
1	Resveratrol	Nanostructured lipid carriers, and solid lipid nanoparticles (SLNPs)	Treatment of ADs	(Fonseca-Santos *et al.* 2015) (27)
2	Curcumin	PLGA based nanoparticles	Treatment of ADs	(Yavarpour-Bali *et al.* 2019) (65)
3	Naringenin	Nanoemulsions	To combat PDs and treatment of ADs	(Nouri *et al.* 2019) (59)

4	Quercetin	PLGA nanoparticles, nanoencapsulation	To combat PDs and treatment of ADs	(Enteshari Najafabadi *et al.* 2018) (66)
5	Epigallocatechin -3 gallate	Selenium nanoparticles coated with Tet-1 peptide	peptide Increase neuronal alpha-secretase, Increased oral bioavailability.	(Singh *et al.* 2015) (67)
6	Ferulic acid	SLPNs	Antioxidant action	(68)
7	Huperzine-A	Lactoferrin-conjugated N-trimethylated chitosan nanoparticles	Increased cohesion	(Wen *et al.* 2017) (69)

ACUPUNCTURE

Acupuncture is an ancient Chinese technique that dates back over 3,000 years. It is gaining international recognition as a supplemental medicine system for a wide range of diseases. Heat, pressure, or sharp, thin needles are used to trigger nerve receptors in particular areas on the body through the connective tissue. It is assisted by mechanical, electrical, or other physical operations. Ding et al. discovered that manual acupuncture may considerably enhance spatial learning, relearning, and memory. skills in SAMP8 mouse models of Alzheimer's. Acupuncture therapy may enhance cerebral blood flow (CBF) in the prefrontal lobe and hippocampal regions, which is a sensitive biomarker for early perfusion deficits in Alzheimer's disease (70,71).

VISION FOR THE FUTURE

The Prevalence of hypertension, depression, and neurodegenerative illnesses is rising at an alarming rate, despite the fact that these conditions are typically incurable, poorly tolerated, and have negative side effects. To create effective anti-disease medications, research into our traditional herbs is necessary. Since several of the phytochemicals discussed in this study have demonstrated clinically beneficial effects in the suppression of AD, they may be employed as a possible medication against AD. A significant change from a single target drug development approach to a multi-target drug development approach would yield a more effective drug development strategy because AD is caused by a variety of factors, and herbal compounds are best suited for such situations. Given that they have been used since ancient times, are the least likely to have negative side effects, and are also reasonably priced, herbal plants will surely yield encouraging results in such a situation. Future benefits may result from the new functional identification for AD.

CONCLUSION:

There is strong evidence from preclinical research that phytoconstituents have therapeutic promise as neuroprotectors. Compounds from nature have widely recognized biological activities, including the ability to scavenge reactive oxygen species, antioxidant action, antiproliferative activity, antibacterial and anticancer capabilities, and neuroprotective benefits. Numerous natural compounds have shown promise in preventing neurodegenerations, such as luteolin, hesperidin, resveratrol, and genistein. Yet, problems with solubility, stability, and effectiveness that prevent their clinical translation restrict their medicinal potential. According to recent research, adding natural materials to nanocarriers such as nanogels, nanoparticles, and nanostructured lipid carriers can increase their therapeutic efficacy. This approach may be able to get beyond the drawbacks of natural chemicals and greatly increase the stability, solubility, and specificity of bioactive molecules, which would increase their therapeutic efficacy.

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