Original Article

Challenges and Future Prospects: A Benefaction of Phytoconstituents on Molecular Targets Pertaining to Alzheimer's Disease

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ABSTRACT

Background: Many parts of the brain experience excruciating pain as a result of Alzheimer's disease, a form of dementia. Cognitive processes and neuropsychiatric regulation are disrupted by the numerous neuropathologies that exist. The everyday activities, social and professional lives, and overall health of the individual are all substantially impacted by this ongoing deterioration. In this, we comprehend the advantages and practicality of phytoconstituents on the molecular targets of Alzheimer's disease. **Materials and Methods:** In order to write this review study, we used internet databases of publications including PubMed, Science Direct, Google Scholar, and Scopus. **Results:** The use of pharmaceuticals has been a cornerstone in treating AD for a very long time. However, this strategy has numerous disadvantages. You must alter your treatment strategy now more than ever. Due to their advantages, which include decreased risk and negative effects from use, natural treatments made from plants are becoming increasingly widespread. The current situation study focuses on the anti-AD capabilities of phytoconstituents, sheds light on those currently engaged in clinical trials, and gathers data on their precise mechanisms of action in opposition to various neuropathologies associated with AD. **Conclusion:** The phytoconstituents will undoubtedly contribute to the development of novel, safer AD treatments that are superior to the currently existing pharmaceutical options, whether taken alone or in combination.

Keywords: Phytoconstituents, Alzheimer's disease, Acetylcholine esterase Tau, Drug development, Clinical trials.

INTRODUCTION

According to the observations of Auguste Deter, a 51 years old lady, German psychiatrist, and neuropathologist, Dr. Alois Alzheimer classified AD as a kind of dementia in Nov 1901. Alzheimer categorized the detected qualities as having "presenile dementia," using the same fundamental ideas for empathetic AD.[1]

Clinical signs of AD are characterized by advanced memory harm, disorientation, language difficulties, cognitive deficiencies for example, deterioration of verdict as well as choices, and deficits in thinking. Other neuropsychiatric symptoms associated with AD include hallucinations, delusions, anxiety, agitation, depression, and apathy. This continuous deterioration in cognitive functioning significantly impairs people's ability to perform basic everyday tasks, negatively affecting their capability to lead fulfilling personal and professional lives.[2]

Factors affecting the neuropathologies of Alzheimer's disease

The neuropathologies linked to AD are a result of the damaging deviations in the anatomical brain organization. Cerebral nerves linked with cognitive performance are wiped out as a result. It also contributes to impaired synaptic activation in brain circuits. There is a comprehensive description of the neuropathologies connected to AD, Amyloid plaques, cerebral amyloid angiopathy, neurofibrillary tangles, glial responses, and neuronal and synaptic loss are all symptoms of Alzheimer's disease.[3] Tangled deposits and plaques include examples of diseased disturbances that have been linked to the buildup of improperly produced proteins both inside and outside neurons. Amyloid β (Aβ) and phosphorylated tau protein are the two primary proteins that cause these degenerative lesions. The phosphorylated tau protein is found in venation cells, whereas Aβ is found in the extracellular matrix of nerve cells. The development of the neurite depends on Aβ,

which also enhances memory and shields the brain against harm, aging, and long-term potentiation.[4] Anomalies are frequently caused by mutations in the genes that create the APP, PS1, and PS2, the operational units of the penultimate endo-protease in the sequence of its biosynthesis.[5] Two main mechanisms by which APP is normally processed are the non-amyloidogenic and amyloidogenic pathways; one of these produces atypical Aβ, other one creates non-pathogenic, valuable amyloid products, like (sAPPα).[6] The proteolytic enzymes α, β, and γ-secretases are principally responsible for these two methods' digestion of APP.[7] When the mutant tau protein accumulates intracellularly, (NFTs) and other enclosure builds are produced.[8] Tau protein promotes tubulin assembly, which aids in the production of microtubules. The cytoskeletal elements known as microtubules are crucial for maintaining the shape and structure of the neuron.[9] Tau's ability to attach to tubulin is governed by its phosphorylation. Due to improper tau protein folding, AD develops when tau is unable to connect to microtubules.[10] As a result, fibrillary formations of tau begin to accumulate inside the neurons. NFTs have the potential to cause neuronal death by obstructing the transmission of the substances required for their survival and regular operation.[11] Another well-known factor in AD is oxidative stress. More oxidative stress markers and persistent glycation products are present in NFT and Aβ deposits. The pathogenesis of AD is made worse by elevated levels of substances that are chemically reacting in the body.[12] The study also suggests that a rise in Aβ-aggregation causes an increase in ROS, which causes mitochondrial damage-induced oxidative stress to follow.[11] References favor oxidative injury before Aβ-pathology.[13] Increased oxidative reactive substances in the brain exacerbate AD pathogenesis.[14] These cellular alterations could be visualized In the dual scattering of their various biological aggregates, they used the ToF-SIMS visualization technology, giving critical new data about the cellular microenvironment as AD develops.[15] The down-regulation of anti-apoptotic proteins and the active activation of particular apoptotic factors result in the usual neuronal loss associated with AD. Aberrant ABB processing, which results in abnormal calcium ions, is one of the factors that contribute to neuronal disorders and apoptosis.[16] Acetylcholine activity abnormalities have been observed in the early stages of AD, and these impairments have been linked to memory loss and negatively impact both cognitive and non-cognitive functioning.[17] IL-1β, IL-6, and TNF-α levels are elevated, pro-inflammatory genes are activated, and neuroinflammation results.[18] Moreover, it has been observed that AD patients have glial activation, increased nuclear factor kappa B (NF-κB) levels, and (TLR2 and TLR4).[19]

Brain regions impacted by AD

Several brain regions are impacted by AD, and one region may be significantly impaired while the surrounding region is unaffected.[20] The brain problems caused by AD have a distinctive pattern, which sets it apart after further neurodegenerative illnesses.[21] Explicit intellect regions affected in AD include the Hippocampus, Parahippocampus, Amygdala, Cingulate cortex, Medial Septal Nucleus, Subiculum, Nucleus Basalis Meynert, Locus Coeruleus, Nucleus Accumbens, Entorhinal cortex, Perirhinal cortex, Orbitofrontal Cortex, Prefrontal cortex, and Raphe Nuclei.[22] In 1991 and 1997, respectively, Heiko and Eva Braak provided a stage-by-stage explanation of the development of NFTs and senile plaques.[23] Although offering a different senile plaque progression staging in 2002.[24]

Drugs used to treat Alzheimer's disease at the moment

AChE, oxidative stress, inflammatory pathways, hormone therapy, and excess blood lipids are all aspects to think about, and other conditions are all targets for medication.[25] Some of the current pharmacological treatments for AD. Cholinesterase inhibitors like galantamine, rivastigmine, and donepezil are used as the preliminary stripe of resistance in contrast to AD. Memantine is also utilized for severe or moderate AD.[26] Sertraline, fluvoxamine, fluoxetine, paroxetine, citalopram, mirtazapine, venlafaxine, risperidone, ziprasidone, duloxetine and quetiapine, olanzapine, aripiprazole are just a few of the antidepressants that are used to treat depression in AD patients.[27] Many use benzodiazepines to lessen the agitation and anxiety caused by AD. There are several more drugs available to address the many symptoms of AD. Research into new AD treatments has been prompted by the existing ineffectiveness of available medications.[28] Recent studies have mostly therapy centered on A, ABB, and tau passing through different stages of a clinical study. These pharmaceutical treatments come with a variety of negative effects.[29] The development of therapeutic drugs with fewer side effects should therefore receive more attention.[30] The best alternative is composed of plant-based products, which also have fewer disadvantages and can be very helpful.[31] Numerous phytochemicals were studied and correlated to the characteristics of AD.[32]

Phytochemicals for the treatment of ALzheimer's Disease

Aβ targeted phytoconstituents

To target the Aβ peptides, the phytoconstituents addressed in this section frequently modify their APP and secretase activities. See in Table 1 for the list of the phytoconstituents.

Tau antagonistic phytoconstituents

Various antagonistic phytoconstituents can be current AD treatments. The following Table 2 lists a few phytoconstituents that target tau.

Table 1: List of bioactive constituents used against Aβ plaques.

Plant	Component/extract	Activity
Curcuma longa	Curcumin	Predicaments to tiny Aβ species and successfully prevents Accretion, fibril production, and self-assembly of Aβ.[33] Diminishes the amount of the senile plaques and undoes the structural alterations in the atrophied dendrites.[34] Weakens the preformed fibrillar Aβ structure.[35] Diminishes Aβ via lowering the amounts of the GSK3 protein and mRNA, which lowers apoptosis and malfunction in the mitochondria.[36] Reduces synaptic toxicity and mitochondrial dysfunction in AD while preserving cell viability, mitochondrial dynamics, and biogenesis.[37]
	Isoxazoles and Pyrazoles. (Curcumin derivatives)	Blocks APP metabolism. Rises macrophage cellular absorption of Aβ.[38]
Ginkgo biloba	Extract	Enhances the soluble form of APP (sAPPα) by shifting the manner of APP metabolism more in the direction of the Aβ-secretase pathway.[39] Reduces circulating free cholesterol levels, which improves APP processing and amyloidogenesis in turn, lowering the stages of Aβ.[40]
Panax ginseng	Ginsenoside Rg1	Prevents the production of Aβ through the GSK3β beta/tau signaling pathway.[41]
	Ginsenoside Rb1, Rb2, CK, F1, Rh1, Rh2 and Re.	The β-Secretase activity must be suppressed.[41]
	Ginsenoside Rh2	Inhibits APP endocytosis by lowering the levels of lipid rafts and cholesterol.[42]
	Gintonin	Decreases Aβ production and lessens the neurotoxicity caused by Aβ.35 Changes the signaling pathways of the lysophosphatidic acid (LPA) receptor, which activates the non-amyloidogenic Aβ pathways.[41]
Bacopa monniera	Bacoside A	The developed aggregates of Aβ are effectively dissolved.[43]
	Extract	The extract's impact on oligomeric Aβ led to a considerable reduction in the levels of Aβ40 and Aβ42.[44]
Centella siatica	Asiaticoside	Inhibits (PLA2) enzymes, particularly cPLA2, and sPLA2, which are responsible for the neurotoxicity caused by Aβ.[45]
	Aqueous extract	enhances cognitive performance. Decreases the Aβ-associated aberrant behavior in mouse models. decreases the MC65 cells' production of Aβ aggregates.[46]
Rosmarinus officinalis	Carnosic acid	Aβ-42 secretion is decreased.[47] Inhibits the non-amyloidogenic pathway's processing of APP.[47] Decreases AB-40 and sAPPβ, while sAPPα is increased (a product of the non-amyloidogenic pathway).[48] increases the activity of α-site APP-cleavage, which in turn causes an inhibition of the formation of Aβ-42 and Aβ-43, by enhancing the mRNA expression of the α-secretase TACE.[48]

Plant	Component/extract	Activity
Withania somnifera	Withanamides A and C.	Inhibits fibril formation by specifically binding to the Aβ active motif (25-35).[49]
		LRP levels in plasma are increased.[50]
		increases the liver's expression of the Aβ-degrading enzymes neprilysin (NEP) and LRP, which raises plasma levels of Aβ-42/40 and lowers brain levels of Aβ-monomers.
		(LRP is a key receptor on the cell surface that plays a role in removing Aβ from the fluid surrounding brain cells. Furthermore, it facilitates the endocytosis of APP, influencing the synthesis of Aβ).[50]
	Extract	decreases the amounts of the cluster in chaperones and RAGE receptors on receptors linked with Aβ aggregation neuropathologies.[51]
	Withanolides and withanoside	Removes Aβ peptides out from the brain and encourages its accumulation in plasma to degrade it.[52]
Magnolia officinalis	Extract	Cleaves Aβ from APP, reducing the activity of β-secretase.
		Reduces the expression of APP, its product, C99, and the enzyme that breaks down APP, β site APP cleaving enzyme 1 (BACE1).
		Decreases β-secretase activity to prevent memory loss.[53]

AChE targeted phytoconstituents

To increase acetylcholine levels in AD brains, the majority of phytotherapy strategies focus on lowering increased AChE activity. The phytoconstituents that work to lessen AChE activity include those that are listed in Table 3.

Phyto-constituents in the clinical trials

A new strategy for treating AD involves using phytoconstituents with anti-AD effects. To assess their efficacy as a treatment and latent negative effects, human trials consume stood conducted in recent years.[74] The first natural phytoproduct to be examined in a clinical trial for this was nicotine, which debuted in 1992.[75] Galantamine, an alkaloid derived then plants in the Amaryllis family, was recently created.[76] Galantamine is still being tested in clinical trials today. Nonetheless, it has FDA approval and is currently used to treat moderate to serious complaints of AD.[77] Similar to Physostigmine, the Calabar bean is a naturally occurring source of para-sympathomimetic alkaloids. The FDA developed and approved its semi-synthetic derivative, rivastigmine, which is specified for the behavior of AD dementia.[78] Figure 1 depicts numerous phytochemicals that are being evaluated versus AD and are currently in phase two clinical studies for the establishment of AD therapies.

Challenges in phytoconstituents-Based Pharmacotherapy

Currently, since it proves various facts, such as the inefficiency of traditional medications and the offensive routine of synthetic pharmaceuticals, certifying its negative belongings, alternative therapies using plant-derived natural chemicals are becoming popular nowadays.[79] Nonetheless, because of their extremely concentrated doses or mode of use, numerous plants are widely used to treat a variety of anomalies and illnesses without suffering from their poisonous effects, which can cause serious toxicity.[80] Several enigmatic issues about the effectiveness and protection of different usual items persist unresolved, along with unexplained hazardous properties.[81] Without screening, these uncharacterized compounds may cover up the action of latent compounds that produce inaccurate results.[82] Despite being aware of their potential, the majority of chemicals produced from natural products that cause neurodegeneration have only been used conventionally. Their lack of clinical effectiveness that is statistically significant is the main issue.[83] Nearly all published studies on Natural substances can safeguard the brain. Compounds are based on *in vitro* cell-based research, which should be supported by well-conventional *in vivo* substantiations confirming their anti-AD effects bioavailable and should penetrate BBB. The mechanism of action of phytochemicals that target a wider variety of AD pathophysiology is complex. Although AChE inhibitors can improve cognitive abilities, they are unable to stop or slow the progression of AD. Hence, developing a single treatment that may be effective in contradiction of all important AD targets, such as Aβ formation, fibrillation, Aβ-mediated oxidative stress, and soreness, may be the most fruitful method of classifying AD therapies.[82]

Future perspective for drug development for AD

Monoclonal antibodies as anti-AD agents

Several ideas have proposed the use of monoclonal antibodies (mAbs) in immunotherapy-related anti-Aβ treatment strategies to precisely eliminate amyloid plaques formed in AD.[84] To perform this effect, the appropriate antibody must initially traverse the BBB and enter the brain.[85] Later then, it must exhibit a significantly lower affinity for monomers while exhibiting a high affinity for aggregated amyloid, demonstrating its Phagocytosis

Table 2: List of plant ingredients that prevent tau aggregation.

Plant	Component/ extract	Activity
Curcuma longa	Curcumin	Interacting with the 4R0N tau inhibits the aggregation of pure tau by liquifying the polymers, and speeds up the disaggregation of tau.[54]
Panax ginseng	Ginsenoside	By manipulation of GSK-3β, Tau K18 fragment dissociation, and aggregation were considerably reduced.[55]
	Ginsenoside Rg1 and Rd	Modulates the GSK-3β/Tau signaling pathway to reduce the toxicity of tau.[55]
	Ginsenoside Rd	Enhance the activity of PKB/Akt, a crucial kinase in charge of inhibiting GSK-3β activity and raising PP-2 A.[55]
Bacopa monniera	Extract	It Lessens tau's hyperphosphorylation and the toxicity that tau causes.[43]
Rosmarinus officinalis	Carnosic Acid, Carnosol, Epiisorosmanol, Rosmanol, and Rosmarinic acid.	Action that prevents tau from accumulating.[56] Reduces tau aggregation by interacting via salt bridges with 306 VQIVYK 311 fibers.[56]
Uncaria rhynchophylla	Rhynchophylline and isorhynchophylline.	Minimizes tau hyperphosphorylation and high calcium ions.[57]
Vitis vinifera	Meganatural-Az	Reduces the production and synaptic plasticity consistency that isn't folded correctly.[58]
Grapeseed (Vitis)	Proanthocyanidins-enriched grape seed Extract.	decreases aggregation of tau proteins by interacting non-covalently with their polyphenols.[59]
Salvia miltiorrhiza	Tanshinone IIA	via altering the calcium and p35/cdk5 pathways, protects against tau hyperphosphorylation and numerous other pathologies caused by Aβ. Reduces Cdk5 activation, which reduces tau hyperphosphorylation in primary cortical neurons.[60]
	Salvianolic acid B	Suppresses tau hyperphosphorylation and inhibits GSK-3β activity *in vitro*.[61]
Ganoderma lucidum	Triterpenoids (GLTs)	Lowers the quantity of NFT in the cytoplasm clearly (of AD mice).[62]
Allium sativum	Aged Garlic extract	Decreases the activity of GSK-3β to lower tau phosphorylation.[63]
Camellia sinensis	(−)-Epigallocatechin-3-gallate	Phosphorylated tau epitopes are removed by controlling the amplification of Huntingtin, Aβ, and α-synuclein in primary neurons.[64]
Azadirachta indica	Limonoids	Prevents tau aggregation that is overwhelming, producing pieces of tau that are thin, short, and fragile.[65]
	Nimbin and Salannin	Decreases the cytotoxicity caused by tau.[65]
Rhodiola rosea	Salidroside.	Reduces the phosphorylation of tau by modifying the GSK-3β pathway.[66]
Cornus officinalis	Cornel iridoid glycoside (CIG)	Lowers the risk of tau hyperphosphorylation. Increases PI3K/AKT pathway activity and reduces GSK-3β-mediated tau hyperphosphorylation. Increases PP2A by preventing PP2Ac's demethylation at Leu309, which is thought to be a contributing reason to the preeminent equal of tau hyperphosphorylation. This increases PP2A, which in chance decreases tau hyperphosphorylation by maintaining the balance between GSK-3β and PP2A.[67]
Myrica cerifera	Myricanol	Encourages tau autophagic clearance.[68]
Cinnamomum zeylanicum	Cinnamaldehyde	Avoids tau filament production and the process of nucleation.[69] Stop the oxidation caused by H_2O_2 from forming high-molecular-weight tau species.[69]

Table 3: Phytoconstituents with anti-AChE action.

Plant	Component/ extract	Activity
Ginkgo biloba	Extract	The brains of aged animals have an activity that normalizes acetylcholine receptors.[70]
Bacopa monniera	Extract	Lowers AChE action.[35]
Centella asiatica	Asiaticoside and Madecassoside	AChE blockers.[71]
Melissa officinalis	Phenolic compounds	Muscarinic and nicotinic acetylcholine receptors are bound, and their activity is inhibited.[72]
	Rosmarinic acid	Increases choline availability and binds to and inhibits AchE.[73]
Lavandula angustifolia	Lavender	Increases choline availability and binds to and inhibits AchE.[73]
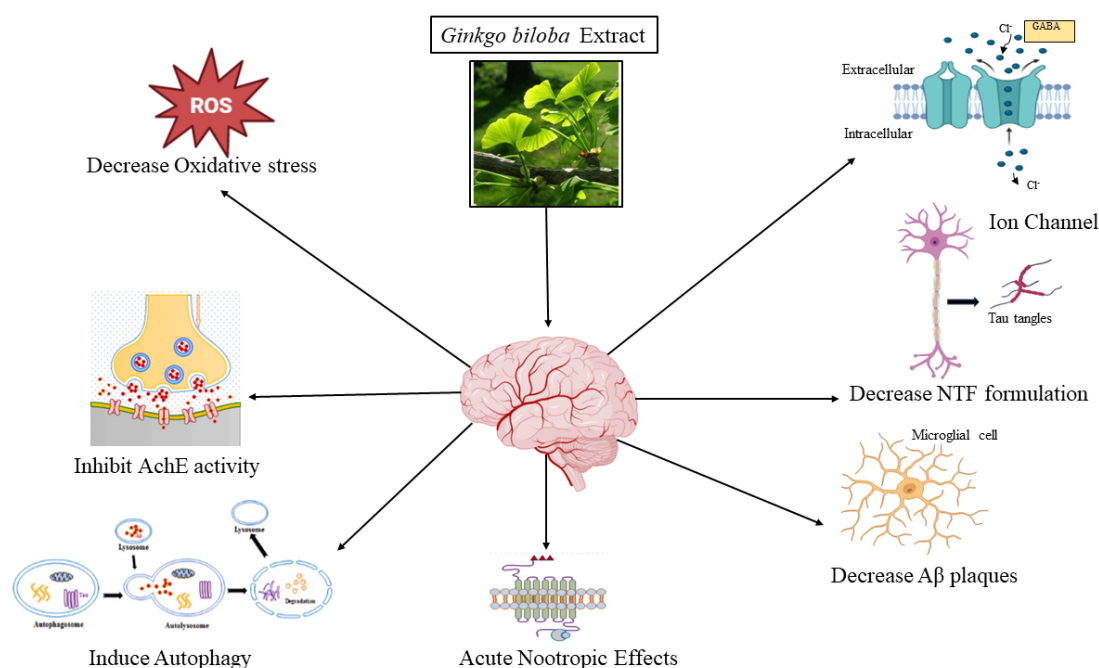
Figure 1: Effect of *Ginkgo biloba* phytoconstituents on neuroprotective characteristics.

action mediated by Fc receptors within invading microglia or macrophage/monocytes.[86]

Due to their poor efficacy, bapineuzumab and further medications that particularly target amyloid plaques and fibrils were not successful.[87] Phase 3 trials for medicines that target amyloid monomers, such as solanezumab, have failed to show improvement in cognitive function.[88] The anti-amyloid antibodies described in Table 4 exhibited significant outcomes in their phase 2 and 3 studies.

The selective anti-oligomer drug ALZ-801/tramiprosate is regarded as the next generation because it does not bind amyloid plaque and is not connected to ARIA-E events.[91] As a result, oral ALZ-801 provides senior patients with the right at-home dosage and may also be used to potentially treat individuals who are presymptomatic and have a high possibility of getting

AD.[91] A human monoclonal antibody called aducanumab (BIIB037) is being tested as an Alzheimer's disease treatment. Since 2017, Biogen and Eisai Co., Ltd. have worked together on the international development and commercialization of aducanumab. To estimate the efficiency and attention of aducanumab, two multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase 3 trial studies were steered: EMERGE and ENGAGE. Aducanumab might be the first medication to implicitly alter the course of AD if it is authorized. Acunumab was submitted by Biogen to the FDA in July 2020.[92]

Artificial Intelligence in AD Management

The understanding of organelle interactions from a pathophysiological and prognosis perspective has advanced thanks to AI and ML technologies in the design and simulation of healthcare for AD.[93] deploying ML approaches and ab initio

Table 4: Anti-amyloid activity research using humanized monoclonal anti-bodies.

Name of drug	Selectivity for soluble amyloid oligomers	% Clearance of CSF p-tau (% versus placebo)	Clearance of Amyloid plaque	ARIA-E	Clinical trial	Reference
Aducanumab	L	15	H	>30%	Phase 3	89
gantenerumab	P	31	H	>30%	Phase 3	85
BAN2401	H	13	H	10%	Phase 2	89
ALZ-801/tramiprosate	High (Blocks oligomers creation)	Not assessed	No interface	There were no happenings (due to the lack of contact with the amyloid plaque and vascular amyloid).	Phase 3	90

ARIA-E: Amyloid-related imaging abnormalities with effusion or edema CSF: Cerebrospinal fluid High-H Low-L P-Partial.
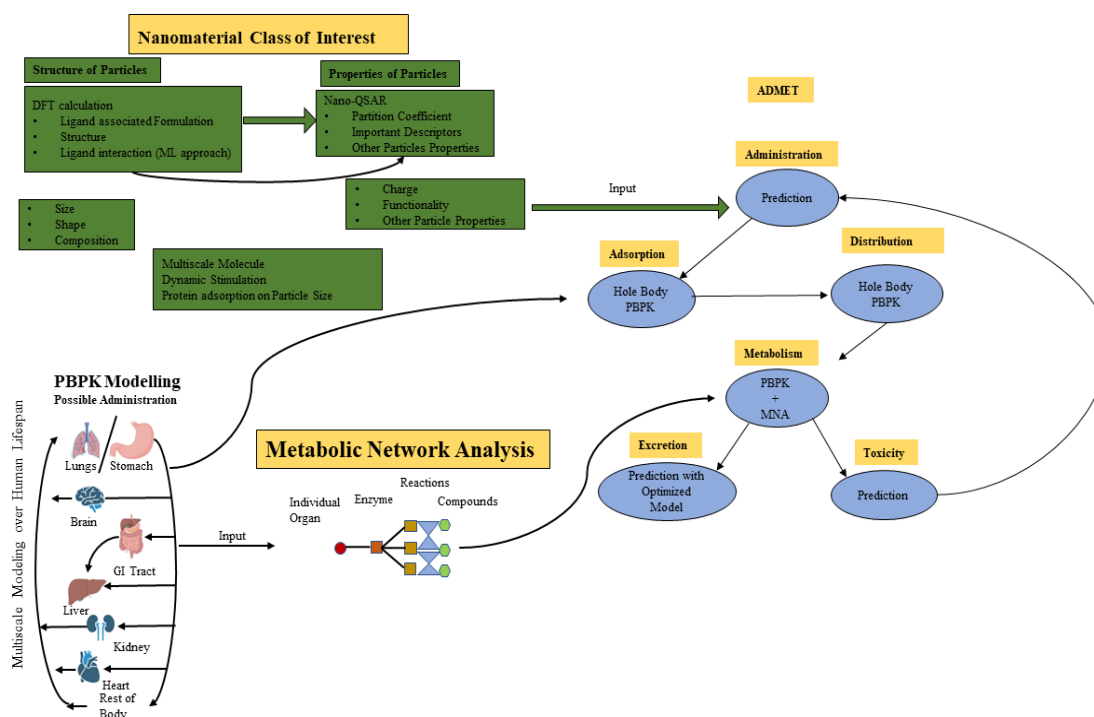

Figure 2: A futuristic hybrid multimodal system for relating *in vitro* models.[52]

simulated to enhance physiological stability for robust qualitative analyses and to aid *in silico* simulations and contextual contributes significantly to relatively secure advancements in neurotoxicology/neuro medicine.[94] Also, investigators consume shown the probable, actuality, difficulties, and upcoming advancements that AI and ML bring in enhanced AD treatment strategy and noxiousness forecasts exploiting phytochemical and enhancements in plant nano bionics.[95] The NEM-based nano-sensors used in this project are also important instruments for monitoring plant signaling pathways and physiology, permitting us to execute non-invasive, intrusive, and actual time studies of both biological and chemical issues for enhanced crop viability.[96] As a result, we believe there is a chance that incorporating information from NEM-based nano-sensors into present precision medicine, urban farming, and seedlings nano bionics is evolving innovations that may serve as an agroecological strategy Figure 2.[97]

Increasing evidence indicates that AD neuropathology is complex and therefore includes a variety of biological processes. The same diverse strategies are required for its treatment because AD is a complicated and multifaceted illness. The successful eradication of AD pathology is likely facilitated by early disease detection, combination therapy, and lifestyle choices.[98] Unhealthy eating can increase the likelihood of developing AD disease, according to several studies.[99] In addition, antioxidant-supplemented meals have been demonstrated to enhance the antioxidant status, reinstate rehabilitated AChE and BChE activity, and highlight AD pathophysiology.[100] Several research has focused primarily on the suppression and eradication of Aβ also senile plaques, as

stated previously in this appraisal, as the amyloid cascade concept has been marginalized for the past two decades. The major goal of current investigation techniques is to measure the amounts of Aβ (1-42), total Tau and phosphorylated Tau in the brain and CSF fluid utilizing MRI imaging processes.[101]

Dendritic spine deficits clearly show the cognitive deterioration seen in AD, and regrettably, amyloid-centric therapies have failed to improve patients' cognizance.[102] Such flaws should be thought about for potential future innovative drug development as they could be seen as an early sign of memory circuit destabilization.[103] The amyloid cascade theory should not be the only criterion for novel pharmacological therapy; rather, synaptic events should be the primary focus to understand the etiology of this disease.[104] The upcoming treatment for AD would therefore be created on a chemotherapy-like multidrug and multi-target strategy. Even however, it is unclear how these potential medication therapies will be communicated with the appropriate subgroups or even in what order they would be chosen. Such trends would effectively change the therapeutic landscape, such as non-amyloid methods.[82]

CONCLUSION

The phytoconstituents will undoubtedly contribute to the development of novel, safer AD treatments that are superior to the currently existing pharmaceutical options, whether taken alone or in combination.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ABB: Amyloid β-protein; **AchE:** Acetylcholinesterase; **AD:** Alzheimer's Disease; **AI:** Artificial Intelligence; **APP:** Amyloid precursor protein; **Aβ:** Amyloid-beta; **BACE1:** Beta-site APP-cleaving enzyme 1; **BBB:** Blood-brain barrier; **BChE:** Butyrylcholinesterase; **FDA:** Food and Drug Administration; **GSK3:** Glycogen synthase kinase 3; **IL-6:** Interleukin 6; **LPA:** Lysophosphatidic acid; **LRP-1:** Low-density lipoprotein receptor-related protein-1; **MABS:** Monoclonal antibodies; **ML:** Machine learning; **MRI:** Magnetic resonance imaging; **NEM:** Nano-engineered material; **NEP:** Neprilysin; **NETs:** Neurofibrillary tangles; **PLA:** Phospholipase A2; **PS1:** Presenilin-1; **PS2:** Presenilin-2; **RAGE:** Receptor for advanced glycation end products; **ROS:** Reactive oxidative species; **TLR2:** Toll-like receptor 2; **TNF-α:** Tumor necrosis factor α.

SUMMARY

The phytoconstituents will undoubtedly contribute to the development of novel, safer AD treatments that are superior to the currently existing pharmaceutical options, whether taken alone or in combination.

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