ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal
www.orientjchem.org
ISSN: 0970-020 X
CODEN: OJCHEG
2026, Vol. 42, No.(5):
Pg. 2087-2097

# Molecular Mechanistic Insights into Selected Phytochemicals for the Management of Alzheimer's Disease

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http://dx.doi.org/10.13005/ojc/420526

(Received: March 02, 2026; Accepted: April 25, 2026)

**ABSTRACT**

Alzheimer's disease (AD) is a progressive neurodegenerative disease, which is marked by mental loss, impaired memory, and behavioural abnormalities, and is one of the causes of dementia in the world. Extracellular plaques of amyloid-beta, intracellular neurofibrillary tangles, cholinergic dysfunction, oxidative stress, neuroinflammation, and synaptic degeneration are all pathological characteristics of AD. Though, pharmacotherapy has improved, the currently used treatments are only symptomatic and fail to prevent the progression of the disease, which is why the development of safer and more effective therapeutic methods urgently requires attention. In the recent years, the phytochemicals as such, extracted using medicinal plants, have attracted a lot of attention because of multi-targeted actions, antioxidant activity, anti-inflammatory actions, and a relatively low level of toxicity. An array of natural products exhibits the potential of regulating amyloid deposition, mitigating the oxidative stress and impairing neuro-inflammatory processes and neuronal viability. Acetylcholinesterase (AChE) is one of the major therapeutic targets involved in the development of AD and, as well as being a part of cholinergic deficits, it speeds up the degradation of acetylcholine. AChE is an approved method of cognitive enhancing. Molecular docking has become an effective computational methodology in drug discovery, which allows determining the interaction of the ligand with the protein, binding specificities, and structural compatibility of phytochemicals with AChE. This review will be a synoptic summary of the molecular mechanisms of the chosen phytochemicals in AD and their docking interactions with AChE. Its results confirm that natural compounds have a therapeutic potential and require additional experimental proof and clinical translation.

**Keywords:** Alzheimer's disease; phytochemicals; acetylcholinesterase; molecular docking; neuroprotection; cholinergic hypothesis; oxidative stress; amyloid beta.

## INTRODUCTION

### Overview of Alzheimer's Disease

The most common cause of dementia in the world is the neurodegenerative disorder that is known as Alzheimer disease (AD). According to recent epidemiological estimates, over 55 million individuals worldwide have dementia, AD being almost 60-70

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percent of these cases, and it is expected that the number of cases will grow considerably by 2050 because of the aged population[1] AD has a global burden that is more than cognitive impairment that is accompanied by a big socioeconomic and healthcare burden. AD clinically manifests with progressive memory loss, executive dysfunction, language impairment, disorientation, and behavior disturbances, which eventually negatively affect the everyday functioning[2]. The pathophysiology of AD includes advancement of amyloid-beta (Aβ) plaques in the extracellular space and intracellular neurofibrillary tangles made of hyperphosphorylated tau protein, loss of synapses, and cell death[3].

**Existing Therapeutic Measures and Constrictions.**

The pharmacological interventions that are currently employed in the treatment of AD are mainly acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and NMDA receptor antagonist (memantine)[4]. These agents relieve symptoms by increasing or decreasing cholinergic transmission or the excitotoxicity without reversing or stopping disease progression. Anti-amyloid monoclonal antibodies against the pathology of the disease have recently been created, but the safety and their long-term effect are yet to be studied[5]. The shortcomings of current therapies are low clinical responses, side effects (gastrointestinal discomfort and bradycardia), high cost, and possible drug resistance[6]

**Reason behind Investigating Phytochemicals.**

The growing interest in the natural phytochemicals as therapeutic agents is based on their multi-target qualities and positive safety profiles, as used in neurodegenerative disorders. Several compounds that are plant derived have antioxidant, anti-inflammatory, anti-amyloidogenic, and cholinesterase inhibitory effects, which target several pathogenic pathways concomitantly[7]. In contrast to single-target synthetic drugs, phytochemicals tend to activate inter-molecular networks that engage in the pathogenesis of AD. In addition, the cognitive enhancement of traditional medicinal systems has traditionally been based on herbal preparations, which supports the exploration of ethnopharmacological views[8].

The current review will examine in detail the molecular pathways of a few phytochemicals in relation to AD and will be able to assess the potential of the few phytochemicals as acetylcholinesterase inhibitors with the help of molecular docking. Consolidating the most recent discoveries made between 2020-2025, the research will aim to draw attention to potential promissory and promising natural compounds, explain their pattern of interaction with acetylcholinesterase, and provide comments on the prospective future of translational studies and drug development.

**Pathophysiology of Alzheimer's Disease**
**Amyloid Cascade Hypothesis**

Amyloid cascade hypothesis has continued to be a pivotal point in the pathogenesis of Alzheimer disease (AD). It hypothesizes that the overproduction and aggregation of amyloid-beta (Aβ) peptides, especially Aβ 42 to which extracellular plaques are formed, occur because of abnormal cleavage of amyloid precursor protein (APP) by b- and g-secretases[9]. It is believed that accumulated Aβ oligomers are very neurotoxic and interfere with synaptic plasticity, calcium homeostasis, and neuronal signaling.

**Tau Hyperphosphorylation and Neurofibrillary Tangles**

Tau protein is a microtubule-associated protein that is abnormally hyperphosphorylated in AD and is no longer bound to microtubules and is instead found in intracellular neurofibrillary tangles (NFTs). This process worsens the transport of axons and causes neuronal death[10]. Recent investigations clarify that the pathology of tau is more related to their cognitive loss than amyloid load[11].

**Hypothesis and Role of Acetylcholinesterase Cholinergic**

Cholinergic hypothesis explains that the degeneration of cholinergic neurons in the basal forebrain may have contributed to decrease in the levels of acetylcholine resulting in the impairment of memory. AChE increases the hydrolysis of acetylcholine and can also stabilize Aβaggregation by use of its peripheral anionic site[12].

**Oxidative Stress and Dysfunction of Mitochondria**

Excessive production of reactive oxygen species (ROS) and the inability to protect against oxidative stress are the causes of oxidative stress. The dysfunction of the mitochondria also worsens

neuronal injury by affecting the ATP production and enhancing apoptosis[13].

**Neuroinflammation and Microglial Activation.**

Persistent microglia and astrocyte activation is a cause of sustained neuroinflammation in AD. The presence of pro-inflammatory cytokines and chemokines increases neuronal injury and disease progression[14].

**Metal Ion Dyshomeostasis**

Metallic imbalance including copper, iron, and zinc encourages oxidative stress and Aggregation of Aβ, which also triggers neuronal toxicity[15].

This is caused by the activation of intrinsic apoptotic pathways which include caspases and mitochondrial signaling and results in progressive loss of neurons. Synaptic dysfunction, which is one of the earliest events in AD, has a close correlation with cognitive deterioration[16].

**Acetylcholinesterase as a Therapeutic Target**
**Structure and Active Site of AChE**

Acetylcholinesterase (AChE) is a serine hydrolase, which catalyses the superfast degradation process of the acetylcholine at cholinergic synapses. Structurally, AChE has a profound and slender groove which is lined with aromatic residues directing substrates to the catalytic active site (CAS)[17]. The CAS is made up of a catalytic triad, which is Ser203, His447, and Glu334, which catalyze the hydrolysis of the ester bonds. Moreover, the peripheral anionic site (PAS), which is close to the entrance to the gorge, is also regulating in terms of substrate binding and is also involved in facilitating amyloid-beta aggregation[18]. Both CAS and PAS are thought to interact with ligands in an advantageous way to inhibit them dually, as well as anti-amyloid.

**AChE mechanism of AD Progression**

In addition to having an enzymatic effect on the breakdown of acetylcholine, AChE also promotes the development of amyloid-beta fibrils by interacting with the PAS in the rogression of Alzheimer disease (AD)[19]. Heightened AChE activity is associated with cholinergic dysfunction, which causes a lack of synaptic transmission and cognitive impairment[20].

**Approved AChE Inhibitors by FDA**

Donepezil, rivastigmine, galantamine are commonly used AChE inhibitors in treating AD, symptomatically. Donepezil is an AChE selective inhibitor and cognitive enhancer[21]. Rivastigmine is a succinate inhibitor of AChE and butyrylcholinesterase, which selectively increases cholinergic transmission[22]. Galantamine is a reversible AChE inhibitor, as well as an allosteric modulator of nicotinic receptors.

**Limitations of AChE inhibitors in Current.**

These drugs have limited symptomatic effects and fail to stop neurodegeneration despite having clinical benefits. The major side effects are nausea, vomiting, bradycardia, and hepatotoxicity, which restrains long-term adherence[21].

**Novel Natural AChE Inhibitors Requirement.**

With these constraints, a growing interest has been placed on natural compounds, having the property of a multi-target, and with better safety profiles. Phytochemicals that can interact with CAS and PAS also have the potential to increase therapeutic efficacy through the combination of cholinesterase inhibition, anti-amyloid and antioxidant activity[23].

**Selected Phytochemicals and Their Molecular Mechanisms in AD**
**Alkaloids**

The biggest class of natural components is alkaloids that have neuroprotective capacities that have been distinguished. Galantamine which was first discovered in Galanthus species, is a reversible acetylcholinesterase and nicotinic receptor modulator that enhances cholinergic neurotransmission[24]. Berberine can reduce the production of Aβ and prevent the activity of b-secretase, suppress inflammatory and antioxidant functions[25]. Huperzina A, the active component of Huperzia serrata, has a high AChE inhibitory potential and prevents a neurotoxic and oxidative effect of Aβ[26].

**Flavonoids**

Neuroprotective properties of flavonoids include quercetin, kaempferol and luteolin which perform their protective functions in different ways. Meanwhile, quercetin suppresses the oxidative

stress levels and alters the PI3K/Akt and MAPK signaling pathways, which decreases the neuronal apoptosis[27]. Kaempferol is demonstrated to suppress the Aβaggregation and prevent neuroinflammatory mediators[27]. Luteolin inhibits microglial activation and prevents the synaptic dysfunction of Aβby antioxidant and anti-inflammatory mechanisms[28].

**Polyphenols**

The most common polyphenols that are studied on AD are curcumin, resveratrol and epigallocatechin gallate (EGCG)[29]. Curcumin suppresses the formation of amyloid plaques, chelates the metal ions, and mitigates neuroinflammation[30]. Resveratrol stimulates neuroprotective action via SIRT1 and reduces the oxidative effect[30]. EGCG disrupts Aβfibril, as well as enhancing inflammatory signaling cascades[31].

**Terpenoids**

Ginkgolides are terpenoids of Ginkgo biloba that promote synaptic plasticity and are antioxidants[32]. Bacopaside in Bacopa monnieri has AChE-inhibitory properties and ameliorates memory through cholinergic transmission[33].

**Phenolic Acids**

Caffeic acid and ferulic acid are good ROS scavengers and can control neuroprotective signaling[34]. Ferulic acid leads to a decreasing effect of Aβdeposition and inhibition of neuronal damage induced by oxidative stress[35], and caffeic acid has anti-inflammatory and anti-apoptotic properties in experimental AD models[34] .

**Table 1: Molecular Mechanisms of selected phytochemicals in AD**

| Chemical Class | Phytochemical | Molecular Mechanism in AD |
|---|---|---|
| Alkaloid | Galantamine | Reversible AChE inhibitor; nicotinic receptor modulation; enhances cholinergic neurotransmission. |
| Alkaloid | Berberine | Reduces Aβproduction; inhibits βsecretase; anti-inflammatory and antioxidant effects. |
| Alkaloid | Huperzine A | Potent AChE inhibition; protects against Aβ-induced neurotoxicity and oxidative stress. |
| Flavonoid | Quercetin | Reduces oxidative stress; modulates PI3K/Akt and MAPK pathways; decreases neuronal apoptosis. |
| Flavonoid | Kaempferol | Inhibits Aβ aggregation; suppresses neuroinflammatory mediators. |
| Flavonoid | Luteolin | Reduces microglial activation; prevents Aβ-induced synaptic dysfunction; antioxidant activity. |
| Polyphenol | Curcumin | Inhibits amyloid plaque formation; metal ion chelation; anti-inflammatory properties. |
| Polyphenol | Resveratrol | Activates SIRT1; reduces oxidative stress; neuroprotective signaling modulation. |
| Polyphenol | EGCG | Disrupts Aβ fibril formation; modulates inflammatory signaling pathways. |

**Molecular Docking Studies Targeting Acetylcholinesterase**

Molecular docking is a computer simulation which is employed to determine the desirable position in which a ligand fits into the active site of a target protein and to approximate the binding affinity. It is based on scoring functions to assess intermolecular interactions and conformational stability of ligand-protein complexes[36]. The strength and stability of the interaction is represented by the binding energy which is usually expressed in kcal/mol with a smaller binding energy implying a stronger bond. The hydrogen bond, p-p stacking, van der Waals force and hydrophobic interaction play a major role in the stabilization of ligands in the acetylcholinesterase (AChE)[37].

AutoDock and AutoDock Vina are some of the most popular docking programs that use Lamarckian genetic algorithms and empirical scoring functions to estimate binding shapes[37]. Glide works with grid-based algorithms and provides a great amount of accuracy in virtual screening[37]. PyRx is an integrated virtual screening platform that has AutoDock Vina to perform effective ligand screening[38].The basic docking protocol includes choosing a suitable protein structure in the Protein Data Bank (PDB), removing the water molecules, adding hydrogen atoms, and geometry optimization[39]. Energy minimization and charge assignment is part of the ligand preparation. The search can be limited to a grid box defined around the active site. To measure the reliability of the protocol, validation is usually done by re-docking of co-crystallized ligands[40].

The effective AChE inhibitors react with the catalytic triad residues (Ser203, His447, and Glu334) and peripheral anionic site residues (Trp286 and Tyr341)[41]. Dual-site binding increases the inhibitory capacity and have the potential to decrease amyloid aggregation. Comparative studies usually compare phytochemicals with standard drugs such as donepezil[42].The new docking data and reports of positive binding affinities of the compounds berberine, curcumin, and quercetin; those being interacted with in a hydrogen bond and some p-p stacking up and down the AChE gorge[43]. The role of hydroxyl residues and aromatic rings in binding stability and anti-binding activity is demonstrated by studies on structure-activity relationship (SAR)[42].

**Structure-Activity Relationship (SAR) Insights**

The structure-activity relationship (SAR) analysis offers important insight into the molecular characteristics which increase acetylcholinesterase (AChE) inhibitory capacity.

**AChE inhibitory functional groups**

Having tertiary amines, carbonyl groups, and heterocyclic rings is also a significant feature of binding in the catalytic active site (CAS) of AChE. The groups containing nitrogen undergo electrostatic interaction with anionic residues in the active gorge, increasing the inhibitory potential[44]. Methoxy and hydroxyl replacements also increase the hydrogen bonding capacity and ligand stabilization of the CAS and peripheral anionic site (PAS)[45].

**Relevance of hydroxyl groups.**

The presence of hydroxyl groups is important in establishing hydrogen bonds with the important residues like Ser203, His447 and Tyr341. Polyhydroxy compounds especially flavonoids and polyphenols have greater binding affinity of reduced hydrogen bonding and radical scavenging capacity[42]. Nevertheless, this can lead to too much hydroxylation that can decrease the membrane permeability, which will influence pharmacokinetic characteristics[38].

**Role of aromatic rings**

The aromatic rings are involved in the p-p stacking interactions with the tryptophan and phenylalanine residues that line the AChE gorge (especially at Trp286 at the PAS). Such hydrophobic interactions increase the anchoring of ligands and dual-site binding behavior, which relates to enhanced effects as an inhibitor and anti-amyloid[46].

**Lipophilicity and permeability through the blood-brain barrier.**

The best lipophilicity is needed to cross blood-brain barrier (BBB). Balanced hydrophobic compounds with a specific molecular weight have higher bioavailability to the CNS. Unfavourable polarity, or high molecular size, can restrict the penetration of BBB despite of good binding affinity attempts in silico[47].

**ADMET and Drug-Likeness Evaluation**

The properties of absorption, distribution, metabolism, excretion, as well as toxicity (ADMET) should be assessed to decide on the translational potential of phytochemicals when used as acetylcholinesterase inhibitors in Alzheimer disease.

**Lipinski's Rule of Five**

The Rule of Five by Lipinski is still a popular method of oral drug-likeness assessment. Compounds are said to be good when they have a molecular weight 500 Da, hydrogen bond donor 5, hydrogen bond acceptors 10, and logP 5. Even though a large number of phytochemicals meet these requirements, there are polyphenols with numerous hydroxyl groups, which can oversee hydrogen bonding limits, and thus can influence permeability. However, the moderate deviations can still be tolerated under central nervous system (CNS) drugs in case other pharmacokinetic parameters are optimised[48].

**Blood Brain Barrier (BBB) Permeability.**

To ensure the successful management of neurodegenerative disorders, it is important that BBB penetration occurs. Balanced lipophilic compounds with low polar surface area (<90 A 2) and medium molecular flexibility have a higher chance of crossing the BB. Commonly used in silico tools predicting CNS permeability of phytochemicals include Swiss ADME and pkCSM[49].

**Toxicity Prediction**

Premature toxicity screening lowers the failure of drugs in late stage. Risks that are assessed by computational models include hepatotoxicity, cardiotoxicity (hERG inhibition), mutagenicity, and cytotoxicity. A variety of natural compounds have a relatively lowest predicted toxicity profile in comparison with synthetic inhibitors[50].

**Pharmacokinetic Considerations**

Therapeutic efficacy depends greatly on metabolic stability, cytochrome P450 interactions, plasma protein binding and half-life. Phytochemicals can readily be metabolized; thus, nano-structural-engineering or biological modification can be used to increase health conditions[51].

**Multi-Target Potential of Phytochemicals**

Alzheimer disease (AD) is a complex and multifactorial condition that requires therapeutic agents that would have the ability to regulate multiple pathological pathways at the same time. Phytochemicals are also being considered as multi-target agents; this may have the benefit of complimenting single target synthetic medications.

**Dual inhibition (AChE + BACE1)**

Multiple natural products are dual acetylcholinesterase (AChE)- and b-secretase (BACE1)-inhibitors and thus resolve cholinergic dysfunction and amyloid-beta synthesis. Dual targeting capable of minimising Ab formation and at the same time enhancing synaptic transmission. It has also been shown that molecular docking and in vitro research indicate that some flavonoids and alkaloids can be effective on active sites of both enzymes and have greater therapeutic potential[41].

**Anti-inflammatory pathways**

Activated microglia mediate chronic neuroinflammation that is a contributor to the development of AD. Phytochemicals polyphenols and terpenoids mediate inflammatory pathways, including NF-kB, MAPK, and NLRP3 inflammasome activation and decrease the release of pro-inflammatory cytokines. This immunomodulatory effect facilitates the survival of the neurons and retards the neurodegeneration[52].

**Antioxidant effects and anti-apoptotic effects.**

AD pathology is characterized by oxidative stress. The natural antioxidants eliminate reactive oxygen species and support endogenous antioxidant activity, including the presence of SOD and catalase. Moreover, phytochemicals mediate the regulation of apoptotic mechanisms by regulating the activities of Bcl-2, Bax, and caspase, which protects neurons against programmed cell death[53].

**Network pharmacology perspective.**

Network pharmacology is a systems biology combined with bioinformatics initiative aimed at mapping multi-target interactions of phytochemicals through interconnecting molecular pathways. This method focuses on the synergies and determines the important regulatory nodes in AD development[8].

***In vitro* and *in vivo* discrepancies.**

Numerous experiments of good acetylcholinesterase inhibition and anti-amyloid effect are carried out *in vitro* either by means of enzyme assays or by using cell lines of neurons. Nevertheless, these microsystems are not considered the paramount replication of human brain microenvironment, such as blood-brain barrier permeability, metabolism, and immune interactions. The compounds with high docking scores or enzymatic activity can be less effective in an animal model because of pharmacokinetic limitations[54].

**Lack of clinical trials**

Even though there is preclinical evidence in favor of the neuroprotective properties of a few phytochemicals, randomized controlled trials are still scarce. There must be clinical validation to ensure the safety, ideal dosing, and long-term effects of AD on patients. The inconsistency in the study design, small sample sizes, and the short follow-up periods also restrict the generalizability of the results[55].

**Bioavailability issues**

Most natural compounds, especially polyphenols, also have poor oral bioavailability because of low solubility, prompt metabolism, and low blood-brain barrier penetration. Nano formulations are some of the strategies being considered to address these obstacles together with structural modifications[56].

**Standardization challenges**

Differences in the sources of plants, the extraction technique and phytochemical concentration can influence the internal consistency and reproducibility of the findings. The absence of standardized formulations makes it harder to optimize the dose and approve it by the authorities[57].

**Future Perspectives**

The development of phytochemical-based therapeutics with the aim of treating the Alzheimer disease (AD) should incorporate novel technologies and stringent translational approaches. Poor bioavailability and low penetration to the blood-brain barrier (BBB) are one of the significant drawbacks of natural compounds. Nanocarrier delivery systems that have demonstrated promise encompass liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nano emulsions. These systems enhance pharmacokinetic features and minimize the systemic toxicity to rise the therapeutic effectiveness of neurodegenerative disorders. Since AD is a multifactorial pathology, combination therapy with simultaneous targeting of multiple pathways can have better clinical results. When used together with traditional acetylcholinesterase inhibitors or the anti-amyloid agents, phytochemicals have the potential to be synergetic, causing minimal adverse reactions. The multi-target approaches match the complicated molecular architecture of AD development. Machine learning and artificial intelligence technologies are changing the approach to drug discovery, increasing the pace of virtual screening, modeling up to ADMET, and optimizing lead compounds. Docking AI-based platforms increase the accuracy and find new phytochemical derivatives that have higher binding affinity and selectivity.

**Simulations of molecular dynamics.**

MD simulations will help complement the existing docking tests, as they evaluate stability, conformational mobility, and some long-term interaction of the proteins with the ligand under physiological conditions. This is a methodology that enhances binding predictions and complementary finds of computations.

**Clinical validation**

Finally, to determine safety, efficacy, and standard dose of phytochemical-based interventions in AD patients, large-scale randomized clinical trials are required.

## CONCLUSION

Alzheimer disease (AD) is a multifactorial and disease neurodegenerative disorder with accumulation of amyloid-beta, hyperphosphorylation of tau, cholinergic dysfunction, oxidative stress, neuroinflammation and progressive loss of the synapses. The existing therapeutic agents especially the acetylcholinesterase (AChE) inhibitors are merely symptomatic and lack the ability to prevent the disease progression. There is growing evidence on why it is necessary to simultaneously focus on several pathological pathways to produce appropriate clinical responses.

Phytochemicals which are medicinal plants have become potential candidates in the management of AD because of their multi-target action such as AChE inhibition, anti-amyloidogenic, antioxidant, anti-inflammatory modulation, and apoptotic signaling regulation. Their structural diversity, which is comparatively favorable safety profiles and their capacity to react with the catalytic active site and peripheral anionic site of AChE maximizes their therapeutic relevance. Besides, multiple natural compounds exhibit dual-site binding capabilities, which imply supplemental advantage of decreasing amyloid aggregation in addition to cholinergic modification.

Molecular docking has achieved a great deal in terms of predicting binding affinities, interaction pattern and structure-activity relationships, thereby enhancing the identification and optimization of natural AChE inhibitors. Computational methods when used together with ADMET tests and molecular dynamics simulations give useful information about drug-likeness and stability prior to experimental testing.

Altogether, natural AChE inhibitors are a promising direction of the creation of safer multi-target therapy of AD. To change phytochemical-based strategies into a working therapeutic intervention translating one will require future research to incorporate computational modeling, advanced delivery systems, and clinical validation.

**ACKNOWLEDGEMENTS**

The authors sincerely acknowledge the support and encouragement provided by their respective institutions. We also thank colleagues and mentors for their valuable discussions and guidance during the preparation of this review article.

**Conflict of Interest**

The authors declare that there is no conflict of interest regarding the publication of this review article.

**Funding Source Statement**

This review article did not receive any specific fund from funding agencies.

**Author's Contributions**

Deepa P: Conceptualization, literature search, manuscript drafting and editing. Nimmy Varghese: supervision and final approval. All authors have read and approved the final manuscript.

**Data Availability Statement**

This article is a review based on previously published studies. No new data were generated or analyzed during this study. Therefore, data sharing is not applicable.

**Ethical Approval Statement**

Ethical approval was not required for this review article as it does not involve any human participants or experimental animals.

**Informed Consent Statement**

Informed consent is not applicable since this study is a review of published literature and does not involve human subjects.

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