RESEARCH PAPER

A Recent Update on Kojic Acid-Based Derivatives for the Treatment of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disease accompanied by cognitive decline, memory loss, oxidative stress, cholinergic dysfunction, amyloid-β (Aβ) plaque, tau hyperphosphorylation and metal ion dyshomeostasis. Although considerable progress has been made with existing therapeutic options, the drugs available primarily only address symptoms and do not stop the disease from worsening. Therefore, more efforts are being focused on the synthesis of multi-target-directed ligands based on natural products. Of these, Kojic acid and its derivatives have shown to be good pharmacophores based on their varied pharmacological properties including antioxidant, metal chelators, anti-inflammatory, neuroprotective, and enzyme inhibitory activities. Recently, it has been shown that kojic acid-based hybrids and dimers have potent inhibitory activity against acetylcholinesterase and butyrylcholinesterase, in addition to their ability to inhibit aggregation of Aβ and generation of reactive oxygen species. Moreover, the structural modification of the kojic acid scaffold has increased its BBB permeability and target selectivity, as well as its multifunctional therapeutic potential. This review outlines the latest advancement of design, synthesis, SAR and biological evaluation of the kojic acid derivatives for the management of Alzheimer's disease. In addition, molecular docking studies, multi-target approach and future prospects for optimization of kojic acid derivatives as anti-Alzheimer drugs have been emphasized in the review. These factors, together with the data already emerging, indicate that compounds derived from kojic acid could be useful lead compounds for the development of novel therapeutic agents for the treatment of Alzheimer's disease and related disorders that are more effective and safer.

Keywords: *Kojic acid derivatives, Alzheimer's disease, Acetylcholinesterase inhibition, Oxidative stress, multi-target-directed ligands.*

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1. INTRODUCTION

Alzheimer's disease (AD) is one of the most challenging and progressive neurodegenerative disorders of the brain (**Figure 1**) [1].It affects a person's cognitive and memory functions and is most often prevalent in an aging population, especially individuals aged 65 and older [2]. However, AD should not be considered a definitive or obligatory symptom of aging [3]. The clinical manifestation of AD is the inability to recall new information, and as the disease progresses, substantive changes in cognitive deficits lead to confusion and disarray, language and personality changes, and the inability to perform activities of daily living [4]. Neuropathologically, AD is characterised by marked degeneration of cholinergic neurons and synapses in the cerebral cortex and subcortical regions. The global burden of AD is rising at an alarming rate [5]. More than 55 million people currently live with the disease, a figure projected to increase to 152 million by 2050 as populations age [6]. In the United States alone, 6.7–6.9 million individuals aged 65 and older are affected [7]. Between 2000 and 2021, deaths related to AD increased by over 140%, despite declining mortality rates for heart disease, stroke, and HIV [8].

AD was first described in 1906 by German psychiatrist Alois Alzheimer, who identified characteristic changes in the brain of a middle-aged woman exhibiting dementia symptoms [9]. Pathologically, AD is associated by the aggregation of two toxic protein i.e. amyloid beta (Aβ), and tau outside and inside the neuron respectively [10]. The amyloid precursor protein (APP) is a vital transmembrane protein involved in key brain activities such as neuronal growth, synaptic plasticity, and cell adhesion [11]. It

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contributes to synapse formation, supports neuronal communication, and aids in various cellular processes such as signaling, adhesion, and mineral transport (**Figure 1**) [12]. APP also has neuroprotective properties and influences neural stem cell differentiation by promoting gliogenesis while inhibiting neurogenesis [13]. However, in AD, abnormal enzymatic cleavage of APP by β-secretase and γ-secretase triggers the generation of amyloid-beta (Aβ) peptides. Proteolytic processing of amyloid precursor protein (APP) generates amyloid-β (Aβ) peptides, primarily the Aβ40 and the more aggregation-prone Aβ42 isoform [14]. These peptides are very likely to change shape, which makes them misfold and then come together to form insoluble fibrillar aggregates that build up as extracellular amyloid plaques [15]. These plaques are a key sign of AD, highlighting the critical function of APP gene have been significantly associated with early-onset familial AD, highlighting the critical function of APP in maintaining neuronal homeostasis and its contribution to disease pathogenesis when improperly processed [16].

The pathophysiology of AD occurs due to the interaction between molecular mechanisms causing synapse dysfunction and subsequent neuron death [17]. One of such events includes the accumulation of soluble amyloid-β that are thought to be the most toxic agents because of their effect on disrupting synaptic plasticity and long-term potentiation [18]. At the same time, tau protein becomes abnormally phosphorylated, forming neurofibrillary tangles [19]. Microtubule destabilization and decreased axon transportation can occur as a consequence [20]. The development of mitochondrial dysfunction and production of a large amount of reactive oxygen species additionally worsen cellular conditions since they decrease energy metabolism and cause oxidation injuries [21]. Moreover, the prolonged activation of microglia keeps a high level of inflammation, increasing neural cell stress and degeneration [22]. Imbalance in glutamate neurotransmission leads to excitotoxicity because of constant influx of calcium ions into neurons and apoptosis induction (**Figure 1**) [23].

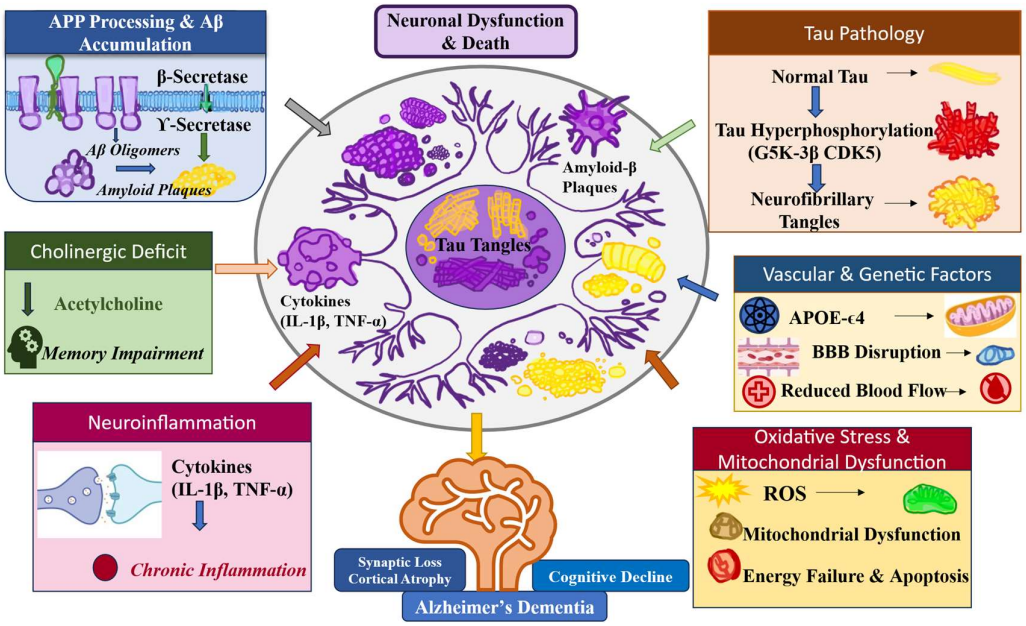

Figure 1. Pathophysiology of Alzheimer's disease.

2. Hypothesis of Alzheimer disease (AD)

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by a gradual decline in memory and cognitive functions (**Figure 2**) [24]. It is characterized by the degeneration and damage of neurons, especially in the cerebral cortex and some subcortical parts of the brain [25]. The specific pathogenesis of AD is not fully understood, but several related hypotheses have been suggested to clarify the onset and progression of this disorder [26]. The hypotheses concentrate on various molecular and cellular processes that play a role in neuronal damage and the breakdown of synaptic communication [27]. The most studied of them include the cholinergic, amyloid-beta (Aβ) hypothesis, oxidative stress hypothesis, tau hypothesis, and metal ion hypothesis [27].

2.1. Cholinergic Hypothesis

The cholinergic hypothesis is one of the earliest and most powerful theories of AD, which was first proposed by Davies and Maloney in 1976 (**Figure 2**) [28]. It indicated that the characteristic cognitive impairment in AD mainly results because of loss of cholinergic neurons and a deficiency of the neurotransmitter acetylcholine (ACh) in the brain [29]. ACh is very important in learning, memory and other higher cognitive functions. In the normal physiological conditions, choline acetyltransferase (ChAT) in presynaptic neurons catalyzes the synthesis of ACh by

reacting choline with acetyl-CoA [30]. The ACh synthesised is stored into vesicles and released into the synaptic cleft in the process of neurotransmission and binds to receptors on postsynaptic neurons to relay nerve impulses [31]. Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) hydrolyze ACh into choline and acetic acid terminating the signal, and provide synaptic balance [31]. In AD, the inactivity of ChAT, the disruption of ACh production and ACh by AChE contributes to the acceleration of cholinergic depletion that results in the impairment of neurotransmission in both cortical and hippocampal areas [32]. This deficiency plays a great role in the memory loss and cognitive impairments that are typical of AD [33]. It is on this basis that AChE and BChE inhibitors have been engineered as therapeutic agents to slow the breakdown of ACh, keep neurotransmitter levels appropriate in the synaptic cleft in some measure, to improve the cognitive abilities of AD patients [34]. These drugs are ineffective but are still a major component of the existing symptomatic treatment strategies [35].

2.2. Amyloid Beta and Tau Hypothesis

Amyloid-beta (Aβ) extracellular deposition and neurofibrillary tangles (NFTs) intracellular accumulation of hyperphosphorylated tau are the hallmarks of the amyloid cascade hypothesis, which states that these two abnormalities are the causes of neurodegeneration in AD (**Figure 2**) [36].Amyloid precursor protein (APP) is a synaptic membrane glycoprotein that is crucial to synaptic plasticity, cell adhesion, and iron regulation and may be processed through two different pathways: the non-amyloidogenic pathway, which involves α-secretase cleavage to produce neuroprotective soluble APPα, and the amyloidogenic pathway, in which soluble Aβ oligomers disrupt neuronal communication by binding receptors, including NMDAR, RAGE, p75NTR, which induces oxidative stress, calcium imbalance, mitochondrial dysfunction, kinase activation (JNK, p38MAPK, Cdk5, Dyrk1A), and release of inflammatory cytokines by microglia, worsening the condition [37] [38]. Concurrently, tau, which ordinally contributes to microtubules stability to aid axonal transport, hyper phosphorylates, dissociates from microtubules, and aggregates to NFTs disrupting intracellular trafficking and synaptic activity, ultimately resulting in neuronal death [39]. Oxidative stress and inflammation mediated by amyloid also amplify tau hyperphosphorylation, activating tau kinases and inhibiting phosphatases, and thereby linking Aβ and tau pathologies in a vicious circle that leads to the impairment of synapses, neuronal death, and eventual cognitive decline typical of Alzheimer disease (AD) [40].

2.3. Oxidative Stress Hypothesis

Oxidative stress plays a crucial role in ensuring cellular homeostasis, but the unbalance between the generation of reactive oxygen species (ROS) and the antioxidant capabilities of the brain results in the uncontrolled build-up of free radicals and dysfunction of the cell [41]. The main sources of ROS are mitochondria, as the key centers of cellular energy generation; when the mitochondrial redox system is disrupted, the escape of electrons and their subsequent interactions with oxygen to create superoxide anions (O_2) can further produce hydrogen peroxide (H_2O_2) and hydroxyl radicals (OH) [42]. These reactive species together with reactive nitrogen species (RNS), such as peroxynitrite, are capable of causing extensive damage to cellular components, such as lipids, proteins, DNA, and RNA, thus affecting neuronal function and survival [43]. This process is enhanced by metal ions, especially iron and copper, which catalyze reactions that generate highly reactive radicals [44]. Their destructive effect on transcription, replication, and important cellular pathways is especially damaging through the instability and short life of ROS [45]. This oxidative burden plays a large role in neurodegeneration and is thought to be an early pathogenic event in the development of AD, in the brain, which has a high energy and oxygen demand [46]. Therefore, there is a current interest in antioxidants as a possible treatment intervention, but the multifactorial nature of the disease has complicated successful intervention [47].

2.4. Inflammation and Metal ION Hypothesis

Neuronal activity requires bio metals like iron (Fe), copper (Cu) and zinc (Zn), which play a role in mitochondrial activity, synthesis of neurotransmitters, communication between synapses, and cellular plasticity (**Figure 2**)[48].However, in the case of AD, distortion of these metals is important in the development of the disease [49]. Abnormal deposition of Fe, Cu, and Zn in amyloid-β protein and neurofibrillary tangles (NFTs) disrupts protein balance, increases amyloidogenic processing of amyloid precursor protein, and stimulates the hyperphosphorylation of tau [50]. The augmentation of intracellular Fe augments β-secretase activity, whereas Fe^{2+} participation with Aβ causes a modification in its conformation, which leads to β-sheet aggregation; Cu^{2+} participation causes stabilization of fibrillar Aβ, and Zn^{2+} participation causes synaptic deposition of peptides, which stimulates the formation of plaques [51].

The imbalance of metals also disrupts the functions of kinases and phosphatases, increasing the aggregation of tau and the loss of synapses [52]. Along with promoting aggregation of proteins, iron and copper, through their redox properties, promote the formation of reactive oxygen species, which induces oxidative damage to DNA, proteins and lipids, and ferroptotic neuronal death occurs through iron-mediated lipid peroxidation [53]. At the same time, chronic metal disturbance triggers microglia and astrocyte activation, leading to prolonged secretion of pro-inflammatory cytokines and activation of the NLRP3 inflammasome, creating a vicious cycle of inflammatory environment that further accelerates Aβ and tau pathology [54]. Excess iron also downregulates furin expression, indirectly promoting β-secretase dependent amyloidogenic processing (**Figure 2**) [55].These mechanisms of oxidative stress, ferroptosis and neuroinflammation together comprise the inflammation-metal ion hypothesis, highlighting the importance of ensuring metal homeostasis

and indicating that metal-targeted modulation could be a promising therapeutic approach to slow neurodegeneration in AD [56].

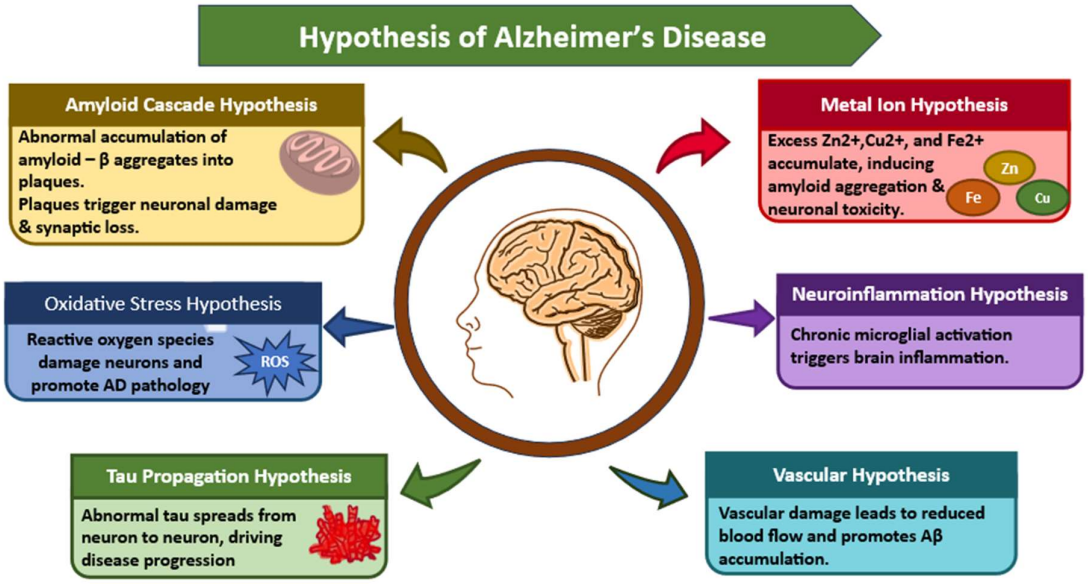

Figure 2: Hypothesis of Alzheimer's disease.

3. Current Treatment for Alzheimer's Disease

The current state of the art of treating AD is devoid of a specific curative therapy and the drugs approved by the United States Food and Drug Administration only provide symptomatic relief or slight disease progression or suppression, as opposed to turning the neuropathology back (**Figure 3**)[57].Current treatment modalities can be broadly categorized into acetylcholinesterase (AChE) inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonists, and new treatments, which focus on amyloid-beta (Aβ) pathology [58]. AChEIs are the primary treatment of mild to moderate AD and are believed to enhance cholinergic neurotransmission by blocking the breakdown of acetylcholine in the synaptic cleft [59].

This group includes donepezil, rivastigmine, and galantamine, but tacrine, which was the first agent to be approved by the United States Food and Drug Administration as an AChEI, was discontinued because of its intense hepatotoxicity associated with its chemical structure, despite its role in explaining important enzyme-binding interactions with the Trp84 residue of acetylcholinesterase [60]. Donepezil is extensively used because of its excellent safety profile and has been shown to be a reversible, non-competitive inhibitor which associates simultaneously with the catalytic anionic site and peripheral anionic site of acetylcholinesterase by aromatic π-π interactions with residues like Trp84 and Trp279, a property attributed to its benzyl piperidine scaffold (**Figure 4**) [61].Rivastigmine is a carbamate derivative, which exerts a pseudo-irreversible type of inhibition by covalent binding to enzymes and is the only known inhibitor of acetylcholinesterase and butyrylcholinesterase, but with a considerably higher selectivity toward central nervous system enzymes, thereby increasing therapeutic activity at reduced peripheral toxicity [62].

Amaryllidaceae plant derived galantamine is a reversible competitive acetylcholinesterase inhibitor and allosteric modulator of nicotinic acetylcholine receptors with a dual mode of action leading to increased acetylcholine release and increased cholinergic signaling with relatively low toxicity (**Figure 4**) [63]. Besides cholinergic dysfunction, glutamatergic excitotoxicity through overproduction of NMDA receptor activity plays a vital role in AD pathology, and the only FDA-approved NMDA receptor antagonist with clinical application is memantine, especially in moderate and severe disease stages [64]. Memantine is an uncompetitive, low-to-moderate affinity NMDA channel blocker that inhibits the pathological glutamate-induced calcium influx and does not alter physiological synaptic transmission needed to sustain learning and memory and can be used alone or with acetylcholinesterase inhibitors like donepezil [65]. In addition to synthetic scaffolds, natural product-based chemical scaffolds are still used to inform AD drug development, e.g. huperzine A, a compound of *Huperzia serrata*, which has strong reversible activity as an acetylcholinesterase inhibitor characterized by nicotinic receptor agonistic activity, highlighting the potential of hybrid molecular approaches in AD therapeutics although current treatments are more prone [66].

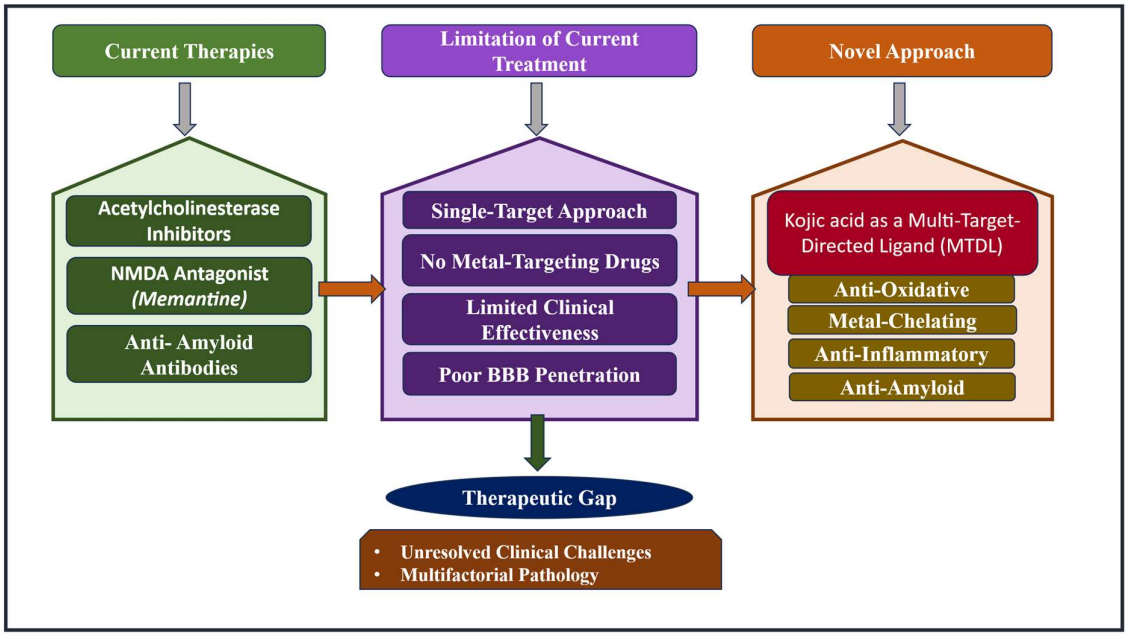

Figure 3. Current Alzheimer's disease treatment, limitation and novel approach of kojic acid.

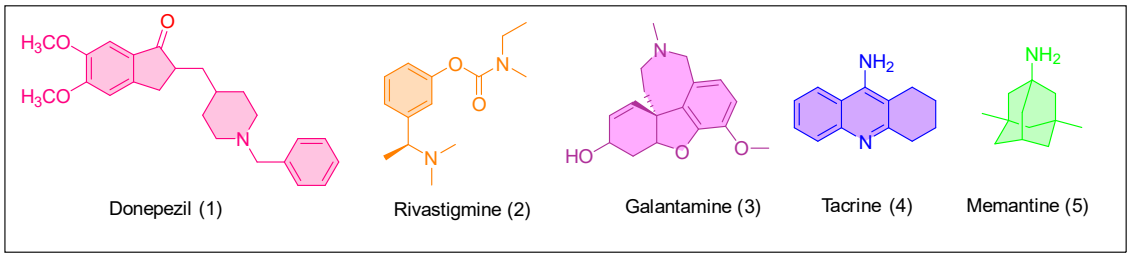

Figure 4. Pharmaco-therapies approved by US-FDA for the treatment of Alzheimer's disease.

Figure 1. US-FDA Approved Drugs used in treatment of Alzheimer's Disease

4. Advances in Kojic acid inspired medicinal chemistry

Kojic acid (5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one) is a naturally occurring fungal secondary metabolite arising in carbohydrate fermentation by organisms like *Aspergillus* and *Penicillium*, and is a structurally and pharmacologically versatile small molecule with increasing application across medicinal chemistry (**Figure 5**) [67]. Although it has been known for a while that this molecule strongly inhibits tyrosinase, we clarify that its hydroxypyranone framework, in some cases, can have a rare combination of metal-chelation and redox-modulation properties [68]. These can lead to a simultaneous decrease of oxidative stress and capture of redox-active metals such as iron, copper, and zinc which are key players in amyloid pathologies [69]. Taking all that into consideration, we argue that the mechanistically linked axial components of metal-amyloid control in the multifactorial cascades of AD, metal homeostasis control can inhibit the aggregation of amyloid-b, thereby reduce the Fenton-like oxidative cycles and relieve the associated neurotoxic deterioration in the memory areas of the hippocampus [70]. In addition to these effects, kojic acid modulates the amyloidogenic processing by inhibiting β-secretase-induced amyloid- β synthesis and discouraging aggregation of peptides, thus decreasing the toxicity associated with plaques (**Figure 5**) [71].Its antioxidant activity is also supported by its ability to activate the Nrf2 signaling pathway, which results in an increase in cytoprotective enzymes, inhibition of reactive oxygen species, decreased lipid peroxidation, and inhibited neuronal apoptosis [72]. At the same time, kojic acid reduces chronic neuroinflammation by regulating the TLR4/NF- κB signaling pathway, leading to a decrease in microglial and astrocytic activation, a decrease in pro-inflammatory cytokine release, and the maintenance of neuronal architecture and synapsis [73]. Such synchronized actions result in enhanced synaptic plasticity and cognitive functions in preclinical models [74]. Notably, kojic acid is an example of a multi-target-directed ligand, (MTDL) that combines antioxidant, anti-amyloid, metal- regulatory, and anti-inflammatory capabilities into a small molecular scaffold, thus fitting the current network-based therapeutic approach to complex neurodegenerative diseases [75]. Recent progress in medicinal chemistry has further increased its potential with a combination of rational structural changes, such as dimerization, heteroaryl substitution, and hybridization with neuroactive pharmacophores, which improve lipophilicity, target

engagement, blood- brain barrier permeability, and overall pharmacokinetic profiles and some also have acetylcholinesterase inhibitory activity, further expanding their therapeutic spectrum [76].

Notwithstanding these promising properties, there are still important translational issues, especially regarding how to maximize brain bioavailability and in vivo efficacy, which requires further efforts to improve scaffold engineering and superior drug delivery approaches (**Figure 5**) [77]. Kojic acid, together, is an example of a chemically accessible and mechanically integrated scaffold, and we suggest that its capacity to combine redox regulation with metal-mediated amyloid regulation makes it a metal-regulatory neuroprotective pharmacophore, providing a rational and innovative model of next-generation multi-target therapeutics in AD [78].

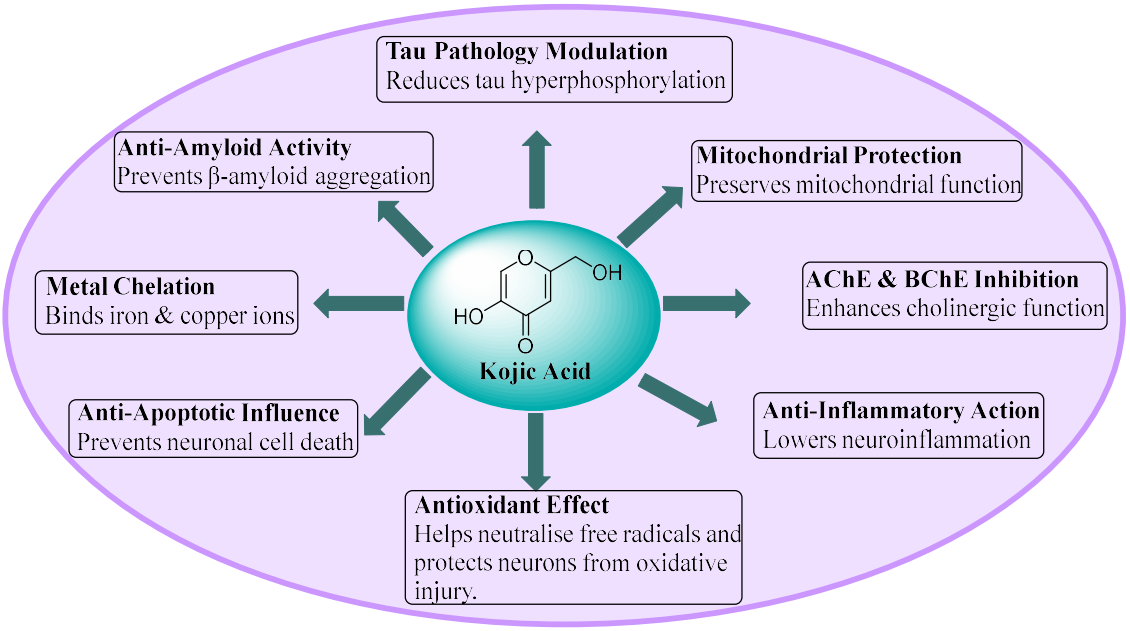

Figure 5. Structure of Kojic acid and its biological activity.

5. Kojic acid-based derivatives for the management of Alzheimer disease

5.1. Kojo Tacrine based hybrids:

In the year 2018, ***Youssef Dgachi et al.*** reported the rational design of KojoTacrines (KTs), A novel class of hybrid molecules that integrate the key pharmacophoric features of tacrine and kojic acid as multitarget – directed ligands for AD, exhibiting modest yet selective acetylcholinesterase (AChE) inhibition together with pronounced antioxidant and neuroprotective effects against amyloid-β-induced toxicity (**Figure 6**)[79]. Among this series, the 3-methoxy-substituted derivative **3c** emerged as the most potent lead compound, effectively inhibiting Electrophorus electricus AChE (IC_{50} = 0.64 ± 0.06 μM) and selectively inhibiting human AChE in the low-micromolar range (IC_{50} =4.52 ± 0.24 μM), while displaying markedly reduced hepatotoxicity compared with tacrine. In addition, **3c** showed the highest antioxidant capacity within the series (ORAC = 4.79 ± 0.39), surpassing both kojic acid and ferulic acid, surpassing both kojic acid and ferulic acid, and demonstrated significant neuroprotective activity against $Aβ_{-40}$ in neuronal models, collectively highlighting the KojoTacrine scaffold and **3c** as promising multimodal lead candidates for future AD drug discovery (**Figure 6**).

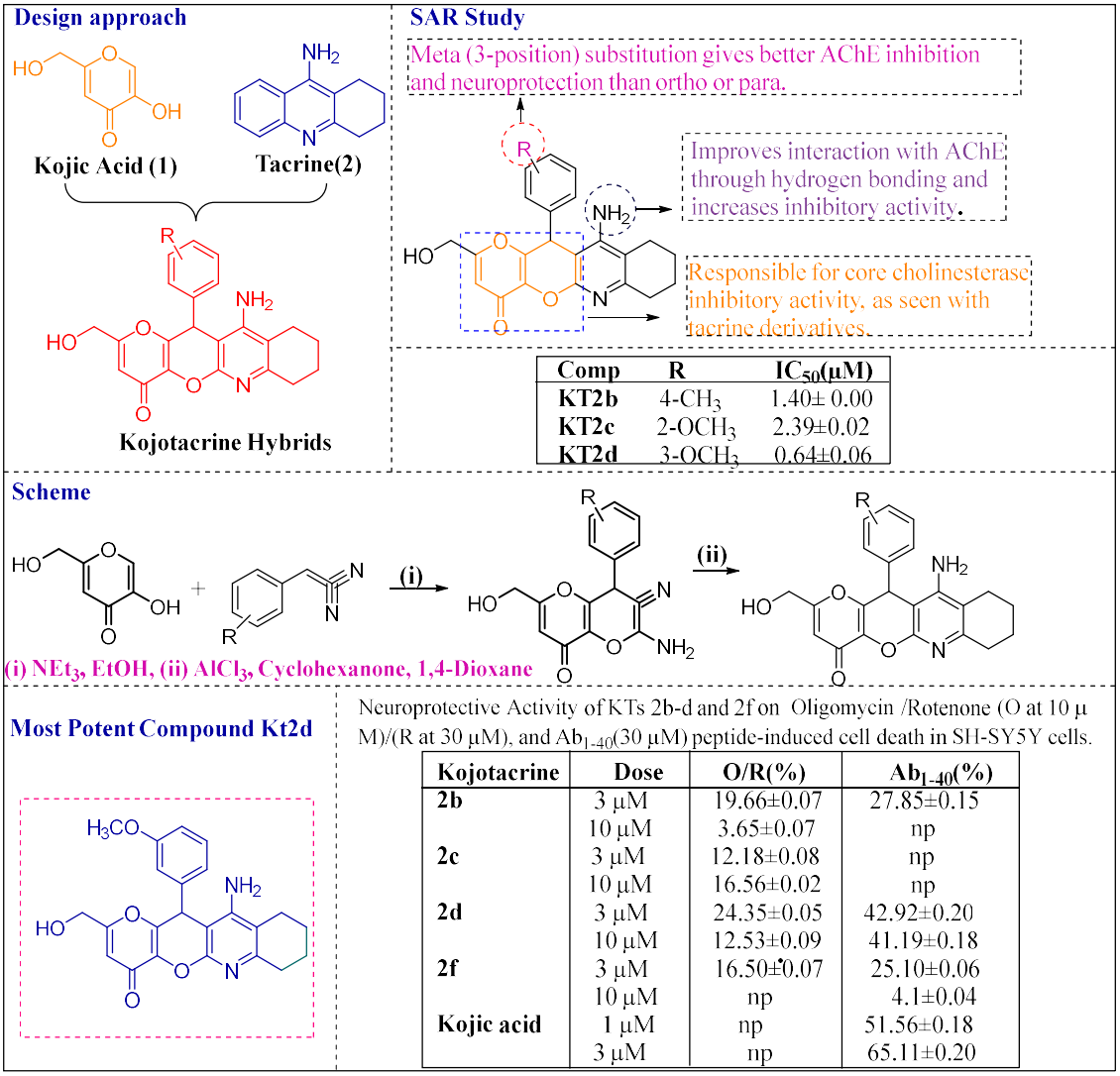

Figure 6. Design, Synthesis and SAR of Kojo Tacrine based Hybrids, Reagents and Conditions. (i) Net_3 (Triethylamine) EtOH (Ethanol), (ii) Cyclohexanone, $AlCl_3$, 100°C, 1,4-Dioxane.

5.2. Tacrine based Cyclopentapyranopyridine- Kojic Acid Hybrids

In the year 2021, *Babaee et al.* reported the design and synthesis of a novel series of tacrine-based cyclopentapyranopyridine- and tetrahydropyranoquinoline-kojic acid hybrids as potential AD agents (**Figure 7**). [80].The study was based on the multitarget drug design approach, combining the antioxidant and neuroprotective qualities of kojic acid with the powerful acetylcholinesterase (AChE) inhibitory scaffold of tacrine. The synthetic hybrids preference for central cholinergic modulation was highlighted by biological evaluation, which showed that they selectively inhibited AChE over butyrylcholinesterase with IC values in the low-to-moderate micromolar range. Cyclopentapyranopyridine-kojic acid derivatives outperformed tetrahydropyranoquinoline analogues in terms of AChE inhibition among the tested compounds. Molecular docking studies confirmed that compound **9f** was the most active candidate with strong AChE inhibition (IC = 4.18 μM), mixed type inhibition kinetics, and dual interaction with both catalytic and peripheral anionic sites of AChE (**Figure 7**). Furthermore, compound 6f showed favourable in silico ADME properties and moderate neuroprotective effects against oxidative stress-induced neuronal damage. All these results highlight the therapeutic potential of tacrine-kojic acid hybridisation and confirm compound **9f** as a versatile lead for additional AD medication development.

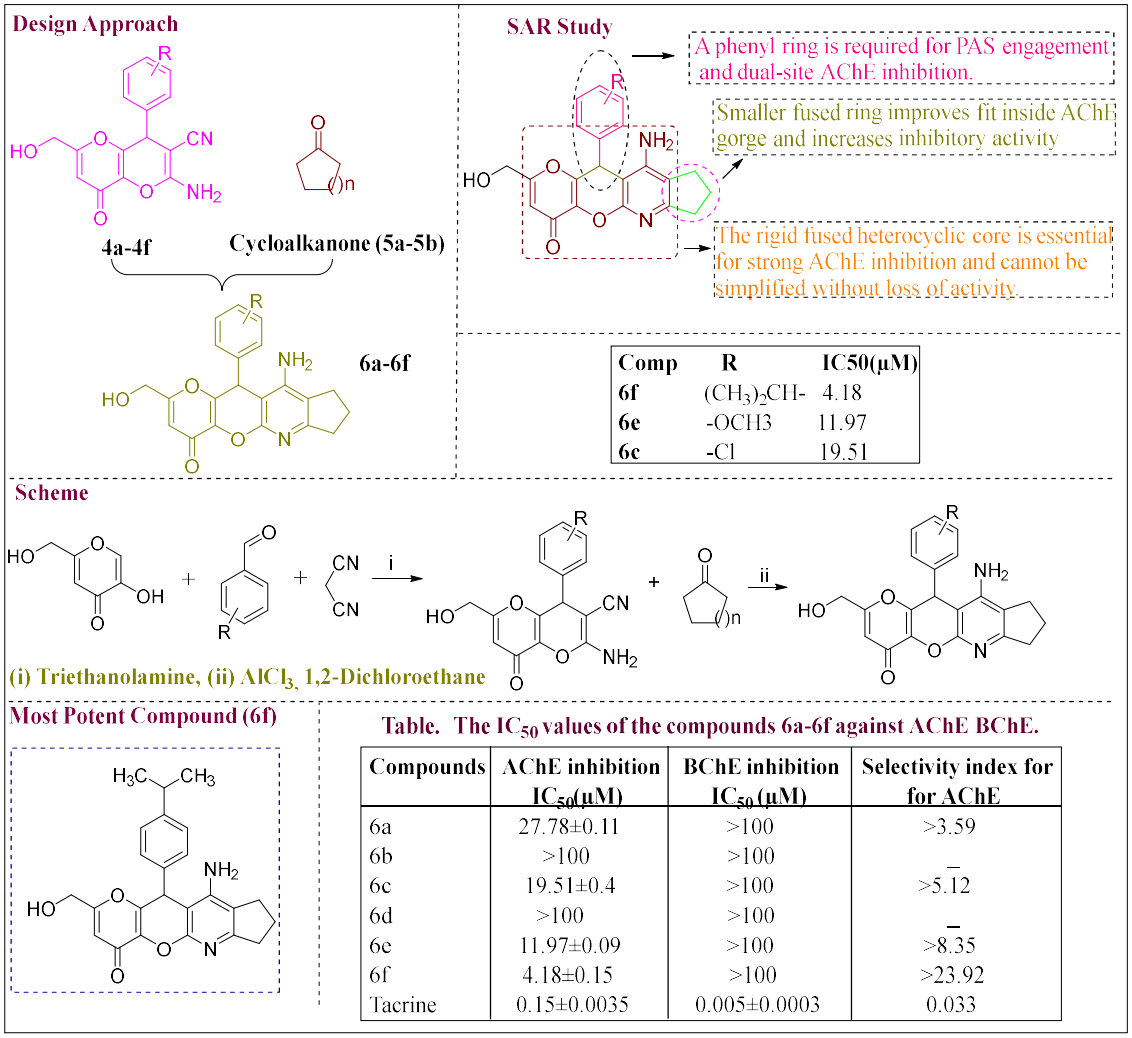

Figure 7. Design, Synthesis and SAR of Tacrine based cyclopentapyranopyridine- kojic acid hybrids (**9f**), Reagents and conditions. (i) Triethanolamine, reflux ethanol, (ii) $AlCl_3$, 1,2-Dichloromethane reflux.

5.3. Kojic Acid Dimer

In the year 2025, ***Talbatov et al.*** performed an extensive computational analysis to examine the anti-Alzheimer's efficacy of the kojic acid dimer (KAD) by analysing its interaction, in both unbound and metal-coordinated states, with the amyloid-β (Aβ) peptide (**Figure 8**) [81]. The authors used density functional theory and docking-based methods to show that KAD binds to Aβ in a way that depends on the metal, with zinc ions playing a key role. Their results showed that Zn^{2+} helps make ternary KAD-metal-Aβ complexes, but Cu^{2+} does not. Among the investigated complexes, the KAD2-Zn complex emerged as the most potent and thermodynamically stable complex. The complexes tend to target the histidine-rich $Aβ_{13-20}$ segment (**Figure 8**). This interaction was shown to be thermodynamically feasible and minimally disruptive to peptide conformation, suggesting inhibition of early amyloid aggregation events. In contrast, although KAD forms stable binary complexes with Cu^{2+}, copper does not assist Aβ binding, indicating mechanistic divergence between metal chelation and amyloid inhibition. The author proposed that kojic acid-based dimers could be effective scaffolds for the creation of metallodrug, potentially influencing metal-induced amyloid aggregation pathways associated with AD. This perspective highlights a novel strategy for the growth of multifunctional agents designed to target metal-induced neurotoxicity and amyloid plaque accumulation.

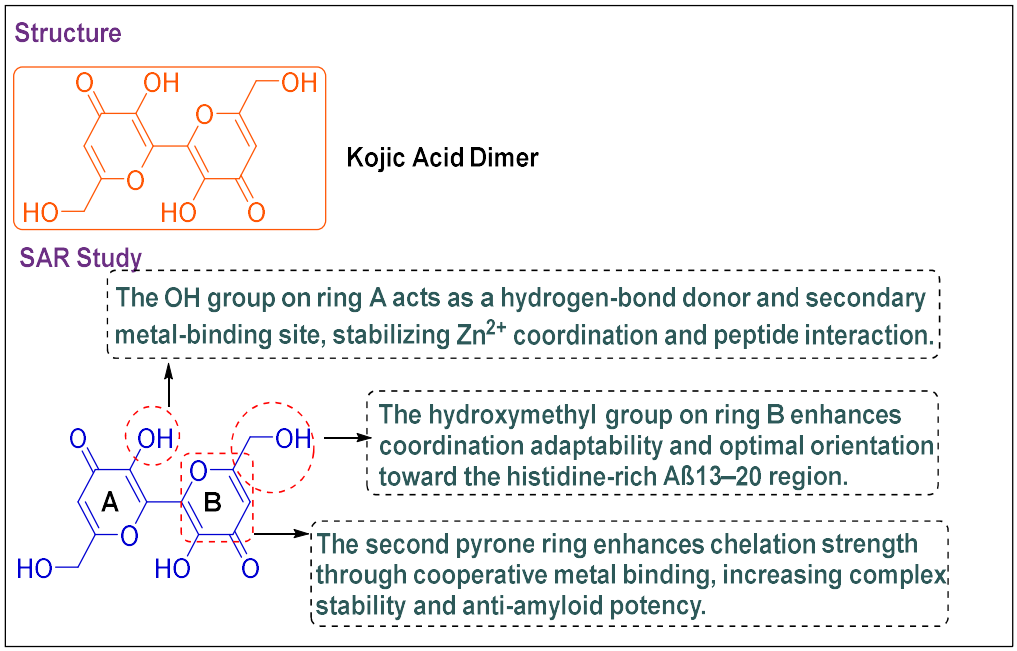

Figure 8. Structure and SAR of Kojic acid dimer.

5.4. Miscellaneous

In the year 2015, *Birendra Kumar Singh et al.* introduced a novel method for improving the therapeutic profile of kojic acid by developing kojic acid-peptide conjugates with enhanced stability, reduced toxicity, and better potency as tyrosinase inhibitors (**Figure 9**) [82]. The method innovatively targeted the kojic acid with carbonyldiimidazole to construct the tyrosinase inhibitors, followed by the Fmoc method of solid-phase peptide synthesis to append the peptide chains. Singh et al. achieved high-resolution and high-fidelity constructs using this method. Of the synthesized tyrosinase inhibitors, **KA-PS** and **KA-CR9** provided the most suppression of tyrosinase with 82-84%, and **KA-PS** was the most effective of the two in the biological screening (**Figure 9**). The addition of the peptide segments reduced the cytotoxicity **KA-PS** and **KA-CR9** would have shown as the parent kojic acid and increased the stability of the inhibitors. **KA-PS** was reported to be effective in suppression of tyrosinase and a reduction of melanoma with no to little impact on the viability of the cells.

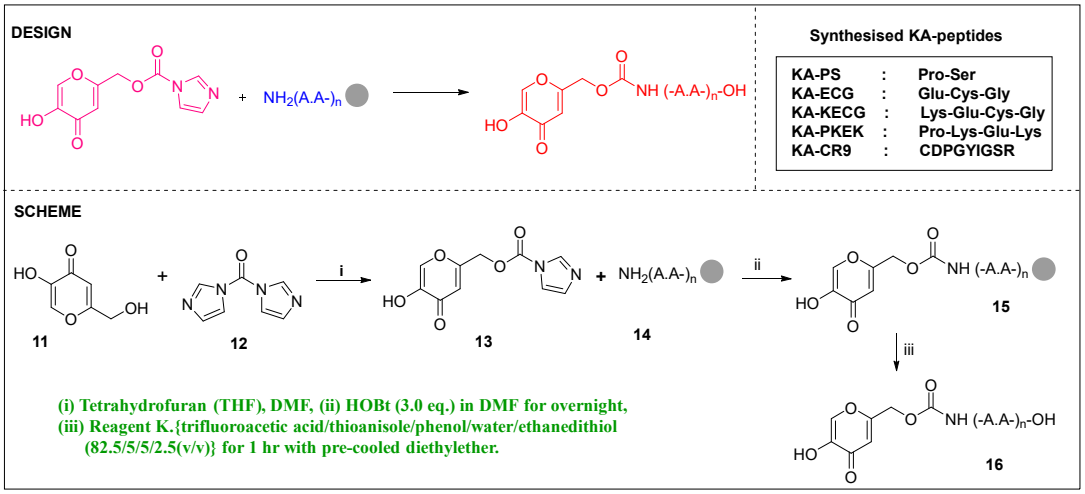

Figure 9. Design and Synthesis of Kojic acid peptides (KA-peptides) **16** in the presence of (i) Tetrahydrofuran (THF), DMF, (ii) HOBt (3.0 eq.) in DMF for overnight, (iii) Reagent K.{trifluoroacetic acid/thioanisole/phenol/water/ethanedithiol (82.5/5/5/2.5(v/v)} for 1 hr with pre-cooled diethylether.

In the year 2025, ***Meiqun Ye et al.*** reported design and synthesis of several kojic acid-piperazine hybrid derivatives with potent tyrosinase inhibitory action as part of the scaffold hybridization approach to increase the

efficacy and safety of the derivatives (**Figure 10**) [83]. The compounds were synthesized via coupling of substituted benzoic acids with N-Boc- piperazine using HBTU followed by the removal of the protecting group and conjugation with kojic acid. Among all the derivatives, **compound 23o** displayed the most significant inhibitory effect as a result of the systematic assessment of the entire library **(23a-23r). Compound 23o** exhibited a tyrosinase inhibitory action with an **IC_{50}** value of **0.21** mM, which was about three-fold lower as compared to the parent compound (**Figure 10**). Kinetic analysis of the enzyme revealed a competitive mode of inhibition which was substantiated by the fluorescence and the molecular docking studies portraying that the compound had a strong fit to the active site of the enzyme. Mechanistically, the kojic acid moiety was involved in interaction with the catalytic copper ions of tyrosinase enzyme, whereas the piperazine moiety contributed additional stabilizing interactions, collectively resulting in enhanced inhibitory effect. Additionally, the lead molecule exhibited high antioxidant and anti- browning activity, alongside reduced cytotoxicity, thus offering a superior pharmacological profile. Structure-activity relationship studies revealed the critical role of substituent effects, specifically the para-bromo substituent, in achieving optimal activity. Overall, this study underscores the potential of molecular hybridization in improving kojic acid-based scaffold molecules and point to their derivatives, notably **compound 23o**, as attractive leads for the design of highly efficacious and nontoxic tyrosinase inhibitors.

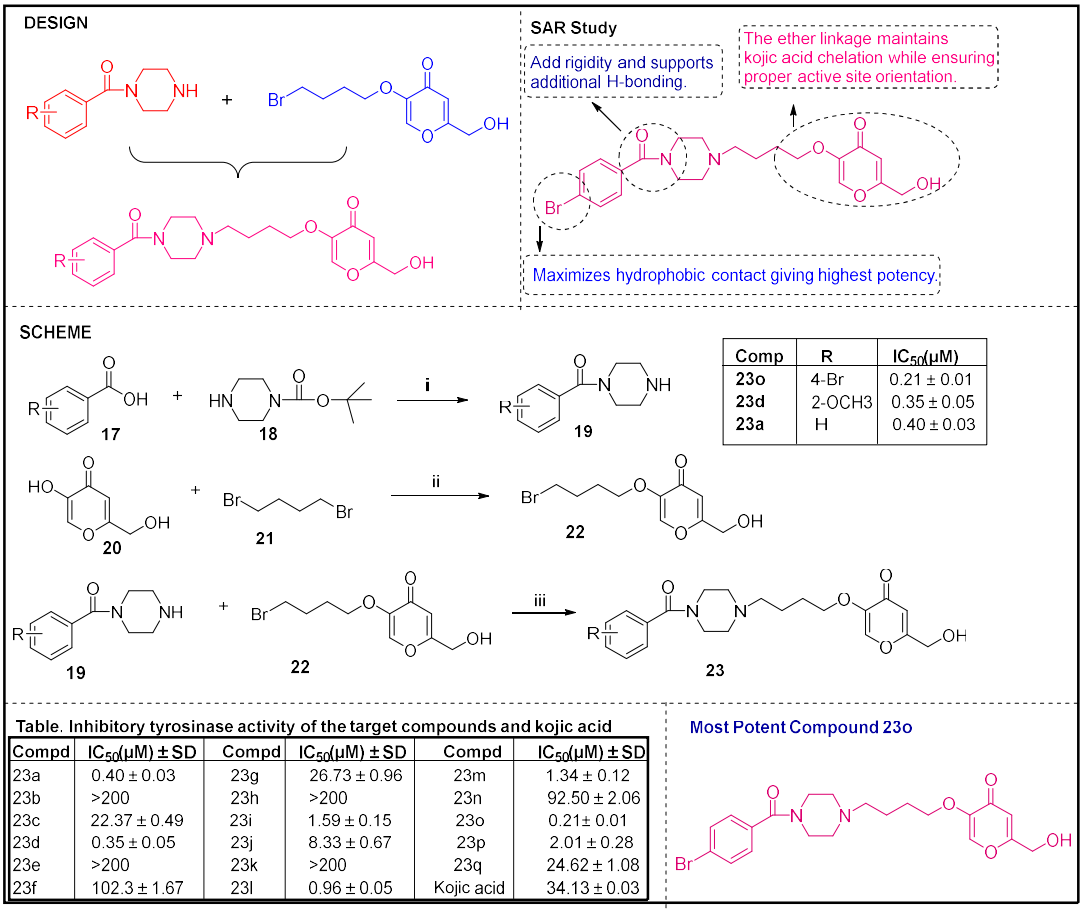

Figure 10. Design, Synthesis and SAR of Kojic acid-piperazine hybrids **23o**, Reagents and Conditions. (i) HBTU/DIEA, DMF, RT, (ii) K_2CO_3/DMF at 65°C, (iii) K_2CO_3/KI, Acetone at 60°C.

In the year 2021, ***Khan et al.*** revealed a substantial advancement in Alzheimer's disease research by reframing kojic acid, a 4-pyrone-based heterocyclic compound, as a multifunctional neuroprotective drug rather than solely a conventional tyrosinase inhibitor [84]. In the present study, we investigated a compound that showed a unique multi-target-directed ligand (MTDL) profile acting on multiple pathological cascades in an **$A\beta_{1-42}$** induced neurotoxicity model. The finding of kojic acid normalization of **BACE-1** expression and Aβ generation represents the mitigation of a core pathogenic process underlying the development of amyloid burden in AD. Apart from amyloid modulation, it also potentiated endogenous antioxidant defensive systems through the activation of Nrf2/HO-1 axis to effectively reestablish redox homeostasis and attenuate oxidative neuronal damage. Furthermore, the compound

suppressed neuroinflammatory responses by inhibition of TLR4/NF-κB signaling and reduction of associated pro-inflammatory mediators such as TNF-α and IL-1β. Synaptic protein expression is reconstituted aiding its ability to maintain functional integrity and neuronal connectivity. This complementary mechanism of anti-amyloidogenic, antioxidant, and anti-inflammation highlights a potential new therapeutic avenue for the treatment of AD and shows that kojic acid is an excellent lead compound for therapeutic interventions.

6. CONCLUSION AND FUTURE PERSPECTIVE

Alzheimer Disease (AD) is a global crisis with complex and diverse symptoms that include dyshomeostasis of metals, abnormal tau aggregation, oxidation, chronic neuroinflammation, and amyloid-β peptide accumulation. Currently available treatments are unable to alter pathology and focus solely on symptom relief. Understanding the complexity of the pathology of AD reinforces the need for new therapeutic strategies. Designing anti-AD drugs that simultaneously affect multiple pathways is crucial due to the multifactorial nature of AD. Kojic acid is a valuable scaffold in AD drug development because of its cytoprotective, antioxidant, and metal- binding properties. Structural modifications for kaempferol derivatives, including hybridization with other approved drugs, addition of linkers, or expansion of the structure, are expected to yield products with increased potency. Designing polyfunctional anti-AD agents with a focus on amyloid deposits, inhibitors of cholinesterase, and neuroprotective agents is possible. The ability of these compounds to alter the structure of the hydroxypyranone and binding metals allows for simultaneous design of multiple AD drugs to target the various pathways.

These discoveries recast kojic acid as a multifunctional scaffolding system with promise in the neurodegeneration drug discovery field, as opposed to a simple tyrosinase inhibitor. In summation, the data presented in this review reinforce the idea that multifaceted-directed drugs can be deserving candidates for derivatives of kojic acid. Combining a myriad of therapeutic functions within one molecular construct is a significant advancement towards the development of more effective and comprehensive approaches to the treatment of AD.

Although there has been a stable development in the production of drugs derived out of kojic acid, the application of these drugs in actual medical practice continues to be limited by a few major challenges. A significant part of the existing evidences is based on laboratory research and initial tests on animals, which points to the strong necessity of conducting more convincing research that could help to bridge the gap between animals and humans. Development of these compounds will involve extensive in vivo testing, which will be followed by well-planned clinical trials to ensure that they are effective, safe and can be used long-term in individuals. One of the priorities regarding the future research is the thorough explanation of structure-activity relationships, in particular, of multi-target engagement and pathway specificity. Knowledge of how exquisite structural alterations can change the biological reactions at the molecular level is important to maximize target selectivity, which in consequence would minimize the potential occurrence of adverse reactions due to off-target binding. To that end, the combination of advanced computational technologies, including artificial intelligence-based drug design, high-resolution molecular modeling and dynamic simulations strategies offers an effective and future-oriented solution to speed up the rational drug development process and achieve a substantial improvement in predictive accuracy. Another significant obstacle is the efficient brain delivery. Considering the limiting characteristics of the blood-brain barrier, novel formulation strategies, including nanocarrier-based systems, prodrugs, and targeted delivery platforms should be considered to enhance central nervous system penetration and therapeutic activity. At the same time, the broadening of research to new areas of interest, i.e., ferroptosis, mitochondrial dysfunction, and neuroimmune interactions, can potentially present new therapeutic opportunities and increase the range of the functional attributes of kojic acid derivatives. Such advancements highlight the potential of these compounds in defining future disease-modifying therapies to AD.

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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Research data is not shared.

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