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Transition Metals Based Anti-Alzheimer

[1] **Theresia O. Ambarita[1], Cinta Johanna Tessalonika Pasaribu[2],**
[1]Chemistry Department Faculty of Mathematics and Natural Science, Medan, Indonesia, Universitas Negeri Medan, 20221
[2]Chemistry Department Faculty of Mathematics and Natural Science, Medan, Indonesia, Universitas Negeri Medan, 20221
Email: theresoviaa@gmail.com[1]; cintajoannapasaribu1@gmail.com[2]

ABSTRACT

Alzheimer's disease (AD), a progressive neurodegenerative disease, is the most common cause of dementia. Amyloid-β protein's accumulation in amyloid plaques, oxidative stress, tau protein phosphorylation, poor energetics, mitochondrial dysfunction, membrane lipid dysregulation, inflammation, and neurotransmitter pathway disruption, play a part in the pathophysiology of Alzheimer's disease. AD is primarily characterized by the formation of amyloid-β (Aβ) aggregates. Transition metal complexes have recently been produced as chemical reagents for modifying Aβ aggregation. Transition metal complexes have tunable features such as the metal center's oxidation and spin states, as well as its coordination structure by altering the ligand bound to the metal center. These variable properties result in the reactivity of transition metal complexes with Aβ species and may lead to the regulation of the Aβ aggregation pathway. The purpose of this study is to describe the application of transition metals as active compounds in anti-Alzheimer's disease drugs. This study was compiled from online journals using secondary data searched by keyword. The results of the study show that some transition metals have potential therapeutic effects for AD. Ru can be an Aβ aggregation inhibition. Fe, Cu, and Zn transition metals are necessary for human survival and involved in AD triggering. Pt, Ni, Co, and V complexes play a role as multifunctional therapeutic agents against AD. This literature review includes a recently published (year>2000) report on the role of transition metals as anti-Alzheimer's.

Keywords: transition metal, Alzheimer's disease, Aβ aggregation, anti-Alzheimer.

INTRODUCTION

Alzheimer's disease (AD) is a neurological illness and the major cause of dementia (Christensen dan Pike 2015). Amyloid-β protein's accumulation in amyloid plaques in amyloid plaques, oxidative stress, tau protein phosphorylation, poor energetics, mitochondrial dysfunction, membrane lipid dysregulation, inflammation, and neurotransmitter pathway disruption, play a role in the pathophysiology of Alzheimer's disease (Kaddurah-Daouk, et al, 2013). Amyloid β-peptides (Aβ) polymerization into amyloid fibrils is critical, according to recent research (Hass & Selkoe, 2007). As a result, the design, manufacturing, and the identification of Aβ aggregation inhibitors for medicinal and preventative purposes of AD have gotten a lot of attention.

Chemical reagents based on transition metal complexes that can alter Aβ aggregation have been produced. Transition metal complexes, in general, have tunable features such as the metal center's oxidation and spin states, as well as its coordination structure by altering the ligand bound to the metal center. These variable properties result in transition metal complexes' reactivity with Aβ species and may lead to the regulation of the Aβ aggregation pathway (Suh, et al, 2019). Inhibiting the interactions between Aβ and metals that cause clinical symptoms like amyloid deposition and oxidative stress in Alzheimer's disease is one strategy to finding possible disease-modifying medicines for AD. In general, there are two types of molecules that may be capable of inhibiting such interactions. One of these entails preferentially occupying the metal binding site on Aβ to prevent metal coordination and thereby suppressing Aβ/metal interactions. (Kenche & Barnham, 2011).

Aβ deposition and oxidative stress, two pathognomonic aspects of AD, could be related to Aβ's interactions with metal ions. Synthetic Aβ will form aggregates with both Zn and Cu, while Aβ will produce reactive oxygen species when it reacts with Cu (ROS) (Bush, 2003; Smith et al., 2007). Barnham et al. (2008) compared the effects of a set of Pt complexes on the inhibition of the Aβ peptide to those of cisplatin in a pioneering study inspired by cisplatin. Mice were also subjected to in vivo experiments. Many additional Pt complexes have now been investigated as therapeutic treatments for Alzheimer's disease as a result of this research. Despite this, only a few of the investigations on the toxicity of new complexes have yielded promising results. However, because biologically significant metals like iron (Fe), zinc (Zn), and copper (Cu)

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appear to be dysregulated in Alzheimer's disease, most researchers are now focusing on them.

Metal ions play a role in both the structural structure of microorganisms and the biological activity of certain enzymes. Metal complexes were found to have great therapeutic efficacy, according to the literature (Gladish et al, 2020). Because many transition-metal complexes have strong photophysical and photochemical properties that can be used to predict how these complexes interact with biological molecules, these metal complexes have been widely studied for their potential applications in cellular uptake, tumor inhibition, and therapeutic activity via the simultaneous targeting and detection of a specific biomolecule using antibodies, peptides, and other molecules (Babu et al., 2021). The purpose of this study is to describe the application of transition metals as active compounds in anti-Alzheimer's disease treatment.

METHOD

The method used is a literature review, in which theoretical references relevant to the case or topic are sought by tracing the sources of writings that have been previously written. The literature review includes a summary of the theory of findings as well as other research materials gathered from reference sources to serve as the foundation for study. The documentation technique was employed for data collection, which includes tracking textual sources covering numerous themes and issues mentioned. These sources include books, online journals, research results, as well as data related to research materials. In searching for data using the keywords of Alzheimer's disease and transition metals. This study was compiled from the online literature of local and international journals using secondary data that had been screened based on keywords. The data analysis technique used is descriptive quantitative which in the form of data. This technique focuses on some relevant literature. This literature study covers recently published (year > 2000) reports on transition metals' role in Alzheimer's disease. The data is then processed, analyzed, and abstracted into a narrative that explains the results and conclusions focusing on transition metals based anti-Alzheimer.

RESULT AND DISCUSSION

Metal ions as chelating agents

1. Copper

Copper is thought to be the most redox reactive metal ion. Copper ion interaction with Aβ can be defined as a three-step process. Endogenous reductants bind to copper first, followed by the reduction of Cu(II) to Cu (I). Copper interacts with Aβ directly, enhancing Aβ aggregation and the toxicity of amyloid oligomers and plaques (Cheignon et al, 2018). The amino acid residues histidine His6His13His14 and tyrosine (Tyr10) influence copper binding to Aβ. After chemically attaching to Aβ (greater affinity to Aβ1-42 compared to Aβ1-40), Cu(II) is reduced to Cu(I), creating hydrogen peroxide as a byproduct that has a high potential to be reduced to hydroxyl radical. As a result, the complexation of copper in Aβ increases neurotoxicity, now has increased reduction potential (Jomova, et al, 2011).

2. Iron

Iron, as a redox active metal, has also been related to Alzheimer's disease pathogenesis. Iron ions, unlike copper ions, do not immediately interact with and bind to Aβ. (Budimir, 2011). Within the brain, iron exists in both redox-inactive Fe3+ and redox-active Fe2+ forms. They can also be found in zero-oxidation-state Fe0 or as ionic compounds like magnetite Fe3O4. All forms are potential inducers of Aβ aggregation, triggering the iron redox cycle and the formation of ROS (Telling, et al, 2017; Everett, et al, 2020). Iron concentrations and enhanced free radical generation were seen in the cerebellum and glia cells of Alzheimer's disease patients (Wang, et al, 2020).

3. Zinc

Metal ions can affect the physiological functions of the Aβ/tau processing in AD and are both directly and indirectly involved. Zinc-(α-secretases) and copper-dependent enzymes (-β-secretases) in particular control the production of A; these enzymes cannot function normally when metal ions are out of balance. Accordingly, excessively high zinc concentrations boost the Aβ peptides' resistance to α-secretase cleavage and so encourage a rise in Aβ content. Additionally, it has been discovered that zinc can prevent the APP's α-secretase from cleaving activity, which elevates APP's processing by β- and γ-secretases and increases the production of extracellular Aβ plaques (Di Natale et al., 2022). Some research reveals that unusually high concentrations of Zn2+ have been explored in the brains of AD patients, implying a relationship between Zn2+ homeostasis imbalance and AD pathogenesis (Miller, et al, 2010). According to one study, Zn2+ enhances both Aβ40 and Aβ42 aggregation, but only at an early stage (Lee, et al, 2018). In another investigation, high Zn2+

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concentrations were found to increase NADPH-oxidase reaction and ROS formation (particularly mitochondrial ROS production) in AD patients. As a result, excessive zinc triggered Aβ cascade reaction (Wang, et al, 2020). Other studies, on the other hand, demonstrate a considerable drop in Zn2+ in Alzheimer's patients (Ventriglia, et al, 2015).

Metal chelation therapy, a potential treatment for Alzheimer's disease

Treatments for Alzheimer's disease have been proposed based on the hypothesis that AD pathology is related to the interaction of metal ions with Aβ. Many studies have suggested that metal chelation therapy could be used to stimulate metal-Aβ interactions and so treat Alzheimer's disease (Budimir, 2011). Metal chelation therapy begins with the injecttion of chelators (chelating agents) into the bloodstream, which bind to and eliminate the targeted metals (Flora & Pachauri, 2010). According to research, metal chelating compounds must meet the following characteristics in order to be used as potential treatments for Alzheimer's disease.

1. Small molecular weight
2. Target specific: must be able to selectively bind to specific metal ions linked to Aβ.
3. No charge or low charge: must be able to penetrate the blood-brain barrier (BBB)
4. Lack of toxicity
5. There is a low probability of negative effects.

Metal chelators with the aforementioned qualities will successfully bind to targeted metal ions associated with Aβ, causing their dissociation and elimination (Budimir, 2011).

Aβ and amyloid plaques are deciding signs of Alzheimer's disease. Metal ions, particularly copper and iron, interact with Aβ in the brains of Alzheimer's disease patients, producing ROS such as superoxide anion, hydrogen peroxide, and hydroxyl radical. This method enhances Aβ aggregation and raises Aβ plaque toxicity. ROS causes damage to both Aβ and the molecules around it, resulting in protein, lipid, DNA, and RNA impairment. Metal chelation therapy has been proposed as a strategy for agitating metal-Aβ interactions in the treatment of Alzheimer's disease. Metal chelators injected into the bloodstream will target and remove metals associated with Aβ, effectively stopping the activity of causative chemicals. Common chelator medications used for AD therapy that have yielded positive results includes tetrathiomolybdate (TTM), bathophenanthroline, desferrioxamine (DFO), bathocuproine (BC), penincillamine, trientine, bis (thiosemicarbazone),.

Table 1. Analysis of transition metals as anti-Alzheimer

Name, Year of Research	Research Methods	Research Result
Spinello, et al, 2016	Chelating ligands' anti-Aβ aggregation function, the use of metal complexes as diagnostic probes, and possible medications, are the subjects of this review.	Curcumin or flavonoid derivatives, the chelating agents, are used to catch metal ions conscientious for Aβ aggregation currently. The use of platinum, ruthenium, and cobalt complexes of a variety of heterocyclic ligands, among other things, could be a promising new way to battle Alzheimer's disease.
Gladis, et al, 2020	The metal content was determined using a gravimetric method, cobalt, copper, zinc, and nickel as cobalt pyridine thiocyanate, cuprous thiocyanate, zinc ammonium phosphate, and nickel dimethylglyoximate, respectively.	The current study demonstrates how to make metal complexes with Schiff base ligands (1,10-phenanthroline-2,9-dicarboxaldehyde condensation with 2-aminophenol). The Cu(II) complex, when compared to the usual inhibitor (DNJ), demonstrated effective inhibitory activity of a-glucosidase, which could be important for anti-alzheimer and other associated illnesses.
Lakey-Beitia, et al, 2021	The chelating characteristics of polyphenols, which are natural sources of possible MPACs, are discussed in this review, as well as	Polyphenols' chelation activity prevents metal imbalance, reduces ROS production, and disrupts Aβ fibril patterns. Polyphenols' chelation potential could be

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	their potential therapeutic effects in preventing metal ion dyshomeostasis in a moderate chelation treatment for Alzheimer's disease. Because these d-block transition metals are necessary to humans, are very plentiful in the CNS, and are involved in AD triggering, the authors have concentrated on Cu, Zn, and Fe.	linked to their anti-amyloidogenic capabilities, which allow ternary complexes to form between Aβ, metal ions, and the polyphenol. Polyphenols' chelation potential and antioxidant characteristics, according to the authors, make them strong pleiotropic candidates for chelation treatment chemicals. Polyphenols, they believe, have therapeutic promise for Alzheimer's disease. Polyphenols are a naturally occurring compound that interacts with the Aβ-metal complex and transition metal ions.
Boulguemh, et al, 2020	To determine the antioxidant properties of Copper (II) complexes of respective formula [Cu(L)2] and [Cu2(μ-Cl)2(HL)2Cl2], the ABTS radical scavenging and the reduction of copper (II)-neocuproine [Cu(II)-Nc] (CUPRAC) methods were used.	Due to the presence of sulfur and -NH groups in the structure of compound 1 and 2 in this research, these chemicals have a significant inhibitory impact on the reduction of copper(II)-neocuproine [Cu(II)-Nc] CUPRAC or the free radical ABTS, compound 1 was more active than 2 for the two methods. However, compound 2 with diμ-chloro bridged Cu(II) was superior to the reference chemical, Galentamine. in terms of efficacy for AChE inhibition; this remarkable discovery necessitates additional research into in vivo evaluation in order to reinforce the new result and place this product on the list of the most potent anti-Alzheimer standards.
Gao, et al, 2014	To exhibit an increased Aβ inhibition compared to the Wells-Dawson-type POM by using a high-throughput screening method, the designed and synthesized transition metal-functionalized POMds are used based on quantitative thermodynamics studies, the fluorescence of an Aβ-ECFP fusion expression system, PC12 cell toxicity , and a ThT fluorescence assay.	A Ni-metallated POM derivative can boost performance sixfold. Quantitative thermodynamic studies demonstrate that transition metal-functionalized POMds with specified histidine-chelated binding sites have enhanced cytotoxicity and stronger inhibitory effects due to higher Aβ binding affinity. Furthermore, the POMds-Dawson-Ni and POMds-DawsonCo had superior effects for inhibiting Aβ-mediated peroxidase-like activity, implying that our developed and manufactured POMds could be dual-functional therapeutic agents for Alzheimer's disease. In this way, the research contributes to our knowledge of inorganic metal complexes as multifunctional medicinal agents: design and synthesis for Alzheimer's disease.

Metal complexes are a promising class of anti-drugs Alzheimer's in the lab, having the potential to stop β-amyloid 1-42 aggregation and scavenge its poisonousness. Three typical Ruthenium(III) complexes on Fig. 1 (NAMI A, KP1019, and PMRU20) were tested in an in vitro model of Alzheimer's disease. In comparison to the other two ruthenium complexes, PMRU20 proved to be extremely effective in shielding cortical neurons from Aβ 1-42 poisoning. The author also discovered that at the concentrations used, PMRU20 is nearly toxicity-free in vitro. Furthermore, in vitro tests

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revealed that the complex has a low toxicity, indicating that it could be a promising neuroprotective agent (Messori, et al, 2013).

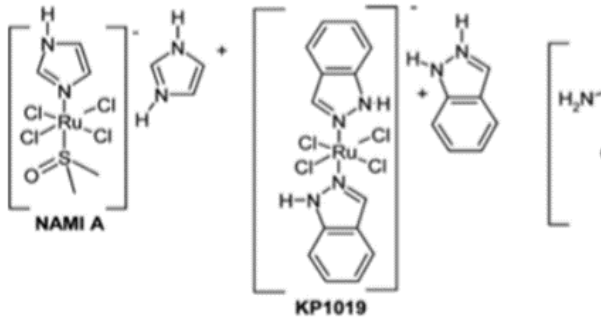

Figure 1. Ruthenium Compounds as Anti-Alzheimer

Copper is a redox-active metal with numerous biological applications. As a result, its distribution and oxidation state are strictly controlled. A significant body of clinicopathological, circumstantial, and epidemiological evidence implies that copper dysregulation plays a key role in Alzheimer's disease development. Therapeutic approaches aimed at regulating copper are promising, but there are still significant gaps in our knowledge of copper biochemistry, amyloidogenesis, and the nature of oxidative stress in the brain. Diμ-chloro bridged Cu(II) is found to be an effective anti-Alzheimer (Boulguemh,et al, 2020). Dong Y (2018) also proposed that vanadyl complexes have a lot of promise as a therapy for Alzheimer's disease. Ruthenium(II) polypyridyl complex Aβ with MTDL potential, in which one of the parent complex's phenanthroline ligands has been changed to give improved AChE inhibition as well as Aβ aggregation inhibition. Ruthenium(II) polypyridyl complexes have been studied for their AChE inhibition kinetics and anti-Aβ aggregation potential. (Vyas, et al, 2014).

A novel family of chiral inhibitors to improve the selectivity of Aβ while minimizing negative effects is developed (Li, et al, 2014). The research is based on the fact that the α-helix in the Aβ enzyme's 13-23 region plays an important role in fibril production. To create chiral Fe supramolecular complexes, the authors used the chirality of l-amino acids and the 3D peptide structure of α-helix. The metallocomplexes can suppress Aβ fibrillation enantioselectively. Furthermore, laboratory studies revealed that the compounds have superoxide dismutase activity. This study paved the way for specific medications to be used in Alzheimer's disease.

Overall, significant efforts have been made to discover and create procedures for the construction of novel physiologically relevant transition metal complexes as potential therapies for degenerative disorders (especially Alzheimer's disease). Biomolecules, such as lipid membranes, may alter amyloidogenic peptide aggregation mechanisms, including Aβ and islet amyloid polypeptide; consequently, such interactions would be crucial to address when building new transition metal complexes for management of amyloidogenic peptide aggregation (Suh, et al, 2019).

CONCLUSION

Many studies have suggested that metal chelation therapy could be used to stimulate metal-A interactions and so treat Alzheimer's disease. Metal chelation therapy begins with the injection of chelators (chelating agents) into the bloodstream, which bind to and eliminate the targeted metals. Chemical reagents based on transition metal complexes that can alter Aβ aggregation also have been produced. Transition metal complexes, in general, have tunable features such as the metal center's oxidation and spin states, as well as its coordination structure by altering the ligand bound to the metal center. Some transition metals have potential therapeutic effects for AD. Ru can be an Aβ aggregation inhibition. Fe, Cu, and Zn transition metals are necessary for human survival and involved in AD triggering. Pt, Ni, Co, and V complexes play a role as multifunctional therapeutic agents against AD. Valuable efforts have been made and are constantly being made to find and create methodologies for the construction of novel physiologically relevant transition metal complexes as chemical tools and possible therapies for Alzheimer's disease.

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