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Evaluation of Angiotensin Receptor Blockers Against Dementia

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Abstract: *Dementia is a progressive neurodegenerative disorder characterized by loss of memory, cognitive impairment, behavioral disturbances, and decline in daily functioning. It mainly affects the elderly population and has become a major global health concern due to increasing life expectancy and the growing number of affected individuals worldwide. Alzheimer's disease and vascular dementia are the most common forms of dementia, both of which are associated with neuronal damage, oxidative stress, inflammation, and impaired cerebral blood circulation. Despite advances in medical science, currently available therapies provide only symptomatic relief and are unable to completely prevent disease progression. Therefore, there is an increasing need to identify therapeutic agents that may offer neuroprotective benefits and delay cognitive decline.*

Angiotensin Receptor Blockers (ARBs) are a class of antihypertensive drugs widely used in the management of hypertension, cardiovascular diseases, and renal disorders. Recent studies suggest that ARBs may possess beneficial effects beyond blood pressure control, particularly in neurological disorders such as dementia. ARBs act by selectively blocking angiotensin II type-1 (AT1) receptors, thereby reducing vasoconstriction, inflammation, oxidative stress, and neuronal injury. Certain ARBs are capable of crossing the blood-brain barrier and may improve cerebral blood flow, reduce amyloid-beta accumulation, and protect neuronal cells from degeneration.

The present study focuses on the evaluation of Angiotensin Receptor Blockers against dementia using suitable experimental and pharmacological approaches. The study includes a detailed review of the pathophysiology of dementia, mechanism of action of ARBs, and their potential neuroprotective properties. Various behavioral, biochemical, and histopathological parameters are considered for assessing cognitive function and neuroprotection. Experimental models used for dementia induction help in evaluating memory impairment and therapeutic efficacy of selected ARBs.

The investigation aims to compare the effectiveness of different ARBs in improving learning ability, memory retention, and neuronal survival. Parameters such as oxidative stress markers, acetylcholinesterase activity, inflammatory mediators, and histological changes in brain tissue are evaluated to determine the protective role of ARBs. The study also examines the relationship between hypertension and dementia, emphasizing how proper regulation of the renin-angiotensin system may contribute to prevention of cognitive decline.

The findings of this study may provide valuable insight into the potential use of Angiotensin Receptor Blockers as supportive or alternative therapeutic agents for dementia management. The results are expected to contribute to future research focused on neuroprotection and development of more effective treatment strategies for neurodegenerative disorders

Dementia is a chronic and progressive neurodegenerative disorder characterized by deterioration of memory, thinking ability, reasoning, behavior, communication skills, and the capacity to perform daily activities. It is considered one of the leading causes of disability and dependency among the elderly population worldwide. The prevalence of dementia is increasing rapidly due to aging populations, creating significant medical, social, and economic burdens on patients, families, and healthcare systems. Alzheimer's disease, vascular dementia, Lewy body dementia, and mixed dementia are the most common forms of the disorder. The pathogenesis of dementia involves multiple factors including oxidative stress,

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neuroinflammation, amyloid-beta plaque formation, tau protein hyperphosphorylation, cholinergic dysfunction, neuronal apoptosis, and impaired cerebral blood circulation.

Hypertension and cardiovascular disorders are recognized as major risk factors for cognitive decline and dementia. Long-term elevation of blood pressure may damage cerebral blood vessels, reduce blood supply to brain tissues, and accelerate neuronal degeneration. The Renin-Angiotensin System (RAS), which plays a critical role in blood pressure regulation, has also been implicated in the development and progression of neurodegenerative diseases. Excessive activation of angiotensin II through angiotensin type-1 (AT1) receptors contributes to vasoconstriction, oxidative stress, inflammatory responses, endothelial dysfunction, and neuronal injury, all of which are associated with cognitive impairment and dementia progression.

Angiotensin Receptor Blockers (ARBs) are a class of drugs commonly prescribed for the treatment of hypertension, heart failure, diabetic nephropathy, and cardiovascular diseases. ARBs such as losartan, valsartan, telmisartan, candesartan, and olmesartan selectively block AT1 receptors and inhibit the harmful effects of angiotensin II without affecting beneficial pathways mediated through AT2 receptors. Recent experimental and clinical evidence suggests that ARBs possess neuroprotective, anti-inflammatory, antioxidant, and cerebrovascular protective properties that may be beneficial in the prevention and management of dementia. Certain ARBs can cross the blood-brain barrier and exert direct protective effects on neuronal cells by improving cerebral blood flow, reducing oxidative damage, decreasing neuroinflammation, and limiting amyloid-beta accumulation in brain tissues.

The present study was designed to evaluate the effectiveness of Angiotensin Receptor Blockers against dementia using suitable experimental models and pharmacological evaluation methods. The study includes detailed investigation of the mechanism of dementia induction, behavioral assessment of learning and memory functions, biochemical estimation of oxidative stress markers, and histopathological examination of brain tissues. Experimental dementia models induced by chemicals or aging-related mechanisms are used to simulate cognitive impairment similar to human dementia conditions. Behavioral tests such as maze tests, passive avoidance tests, locomotor activity analysis, and memory retention studies are performed to assess cognitive function and therapeutic improvement following ARB treatment.

Biochemical parameters including acetylcholinesterase activity, lipid peroxidation levels, catalase activity, superoxide dismutase levels, glutathione concentration, and inflammatory mediators are analyzed to determine the neuroprotective potential of ARBs. Histopathological studies are carried out to observe structural and cellular changes in brain regions associated with memory and cognition, particularly the hippocampus and cerebral cortex. Comparative evaluation among different ARBs helps identify the most effective agent with superior neuroprotective activity and better cognitive enhancement.

The study further explores the relationship between hypertension, vascular dysfunction, and neurodegeneration, emphasizing the importance of proper regulation of the Renin-Angiotensin System in maintaining normal brain function. By reducing vascular damage and improving neuronal survival, ARBs may provide dual therapeutic benefits in patients suffering from both hypertension and cognitive disorders. The investigation also highlights the possibility of repurposing existing antihypertensive medications as supportive therapeutic agents for neurodegenerative diseases.

In conclusion, the evaluation of Angiotensin Receptor Blockers against dementia may provide significant insight into their role as potential neuroprotective agents. The results obtained from behavioral, biochemical, and histopathological studies are expected to support the hypothesis that ARBs can reduce cognitive impairment and delay the progression of dementia. This study may contribute to the development of safer, more effective, and multifunctional therapeutic strategies for the prevention and management of neurodegenerative disorders in the future.

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Dementia is a multifactorial neurodegenerative disorder associated with progressive impairment of cognitive abilities, memory loss, language disturbances, reduced judgment capacity, and behavioral abnormalities. It primarily affects the aging population and represents a major challenge for modern healthcare systems because of its irreversible nature and lack of completely effective treatment options. The increasing prevalence of dementia worldwide has intensified research aimed at identifying novel therapeutic approaches capable of slowing disease progression and improving quality of life. Neurodegeneration occurring in dementia is strongly associated with chronic inflammation, oxidative stress, mitochondrial dysfunction, vascular abnormalities, neurotransmitter imbalance, and neuronal cell death within critical brain regions responsible for learning and memory. (1,3,5).

Keywords: Dementia, neurodegenerative disorders, cognitive impairment, memory loss, Alzheimer's disease, vascular dementia, Angiotensin Receptor Blockers (ARBs), renin-angiotensin system, AT1 receptors, neuroprotection, hypertension, oxidative stress, neuroinflammation, cerebral blood flow, amyloid-beta accumulation, acetylcholinesterase, behavioral studies, histopathology, hippocampus, antioxidant enzymes.

I. INTRODUCTION

Dementia is a serious and progressive neurodegenerative disorder characterized by deterioration of cognitive functions such as memory, thinking ability, reasoning, judgment, orientation, language, and behavior. It affects the normal functioning of the brain and interferes significantly with daily activities and social interactions. Dementia is not a single disease but a group of symptoms associated with several neurological disorders, most commonly Alzheimer's disease, vascular dementia, Lewy body dementia, and frontotemporal dementia. Among these, Alzheimer's disease accounts for the majority of dementia cases worldwide. The incidence of dementia increases with advancing age and has become one of the major public health concerns due to increasing life expectancy and aging populations across the globe.

The pathological progression of dementia involves gradual degeneration and death of neuronal cells in different regions of the brain, particularly the hippocampus and cerebral cortex, which are responsible for learning, memory, and cognitive processing. Several pathological mechanisms contribute to the development of dementia including oxidative stress, chronic neuroinflammation, mitochondrial dysfunction, impaired neurotransmission, accumulation of amyloid-beta plaques, tau protein hyperphosphorylation, vascular damage, and apoptosis of neuronal cells. These alterations ultimately lead to impairment of synaptic communication and progressive decline in mental abilities. Despite extensive research, the exact etiology of dementia remains complex and multifactorial.

Current pharmacological treatment options available for dementia mainly include cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists. Although these drugs may temporarily improve symptoms and cognitive function, they do not completely prevent neuronal degeneration or halt disease progression. In addition, many currently available drugs are associated with limited efficacy and adverse effects. Therefore, there is a growing demand for safer and more effective therapeutic approaches that target the underlying mechanisms responsible for neurodegeneration and cognitive decline.

Recent research has highlighted the significant role of vascular dysfunction and hypertension in the development and progression of dementia. Chronic hypertension can damage cerebral blood vessels, reduce blood supply to brain tissues, and increase the risk of cognitive impairment. The Renin-Angiotensin System (RAS), primarily known for its role in blood pressure regulation and cardiovascular homeostasis, has also been identified as an important contributor to neurodegenerative processes. Components of the RAS are present within the central nervous system and participate in regulation of cerebral blood flow, inflammatory responses, oxidative balance, and neuronal function.

Angiotensin II, the major active peptide of the Renin-Angiotensin System, exerts its effects mainly through angiotensin type-1 (AT1) receptors. Excessive activation of AT1 receptors results in vasoconstriction, oxidative stress, inflammation, endothelial dysfunction, and neuronal injury, all of which are associated with the progression of

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dementia. Increased angiotensin II activity has been linked to amyloid-beta accumulation, microglial activation, neuronal apoptosis, and cognitive decline. Therefore, inhibition of angiotensin II-mediated effects has emerged as a promising therapeutic strategy for prevention and management of neurodegenerative disorders.

Angiotensin Receptor Blockers (ARBs) are a class of antihypertensive drugs that selectively block AT1 receptors and inhibit the harmful actions of angiotensin II. ARBs such as losartan, valsartan, telmisartan, candesartan, irbesartan, and olmesartan are widely used in the treatment of hypertension, heart failure, diabetic nephropathy, and cardiovascular diseases. In recent years, these drugs have attracted considerable attention for their potential neuroprotective properties. Experimental and clinical studies suggest that ARBs may reduce oxidative stress, suppress inflammatory responses, improve cerebral circulation, protect neuronal cells, and enhance cognitive function.

Certain ARBs possess lipophilic characteristics that allow them to cross the blood-brain barrier and exert direct effects on brain tissues. These agents may decrease neuroinflammation, reduce amyloid-beta deposition, inhibit neuronal apoptosis, and improve synaptic transmission. Furthermore, ARBs may enhance endothelial function and maintain adequate cerebral perfusion, thereby reducing vascular damage associated with dementia. The multifunctional properties of ARBs make them potential candidates for repurposing as therapeutic agents in neurodegenerative diseases.

The present study focuses on the evaluation of Angiotensin Receptor Blockers against dementia using suitable experimental and pharmacological methods. The study aims to investigate the neuroprotective effects of ARBs on cognitive impairment, oxidative stress, inflammatory responses, and neuronal degeneration. Behavioral models are used to assess learning and memory functions, while biochemical and histopathological analyses help evaluate neurochemical and structural changes in brain tissues. Comparative evaluation of different ARBs may provide valuable information regarding their efficacy and mechanism of action in dementia management.

This study is expected to contribute to the understanding of the relationship between the Renin-Angiotensin System and neurodegeneration and may help identify new therapeutic strategies for the prevention and treatment of dementia. The findings could support the development of safer and more effective pharmacological approaches aimed at improving cognitive function and quality of life in patients suffering from neurodegenerative disorders.

Dementia represents a group of chronic and progressive neurological disorders characterized by gradual decline in intellectual abilities, memory, cognition, communication, emotional stability, and social behavior. It is one of the most important causes of disability among the elderly population and significantly affects the quality of life of patients as well as caregivers. The disorder interferes with normal brain functioning and eventually leads to complete dependence for routine daily activities. Dementia is not considered a normal part of aging, although increasing age is regarded as the strongest risk factor for its development. According to global health reports, the number of individuals suffering from dementia is increasing rapidly every year, creating a major burden on healthcare systems, families, and society.

The brain is a highly organized organ consisting of billions of neurons interconnected through synaptic pathways that regulate memory, learning, emotions, and behavior. In dementia, these neuronal networks gradually deteriorate due to multiple pathological processes leading to irreversible cognitive impairment. Different forms of dementia are classified based on the nature and location of neuronal damage. Alzheimer's disease is the most common form and is associated with extracellular deposition of amyloid-beta plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. Vascular dementia results from reduced cerebral blood flow caused by cerebrovascular damage, ischemia, or chronic hypertension. Lewy body dementia involves abnormal accumulation of alpha-synuclein protein, while frontotemporal dementia primarily affects the frontal and temporal lobes responsible for personality and behavior.

The exact pathophysiology of dementia is highly complex and multifactorial. Several interconnected mechanisms contribute to neuronal degeneration and cognitive dysfunction. Oxidative stress plays a major role in damaging neuronal membranes, proteins, and DNA through excessive production of reactive oxygen species. The brain is particularly vulnerable to oxidative injury because of its high oxygen consumption and lipid-rich composition. Neuroinflammation caused by activation of microglial cells and release of inflammatory cytokines further accelerates

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neuronal destruction. Mitochondrial dysfunction leads to impaired energy metabolism and increased free radical generation, contributing to apoptosis and synaptic loss. Disturbances in cholinergic neurotransmission also play an important role, especially in Alzheimer's disease, where decreased acetylcholine levels impair learning and memory processes.

In addition to neurochemical abnormalities, vascular dysfunction has emerged as a significant contributor to cognitive decline and dementia progression. Adequate cerebral blood flow is essential for maintaining neuronal viability and cognitive performance. Conditions such as hypertension, atherosclerosis, diabetes mellitus, and cerebrovascular disease can impair cerebral circulation and lead to chronic hypoxia and ischemic injury within brain tissues. Long-standing hypertension damages small cerebral vessels, disrupts the blood-brain barrier, and promotes white matter lesions, thereby increasing susceptibility to dementia. Epidemiological studies have demonstrated a strong association between midlife hypertension and increased risk of cognitive impairment during later life.

The Renin-Angiotensin System (RAS), traditionally known for regulating blood pressure and fluid balance, has gained considerable attention for its role in central nervous system physiology and pathology. Components of the RAS including renin, angiotensin-converting enzyme, angiotensin

II, and angiotensin receptors are present in various regions of the brain such as the hippocampus, cerebral cortex, and hypothalamus. Within the brain, the RAS participates in regulation of cerebral blood flow, autonomic function, neurotransmitter release, stress response, and inflammatory signaling. Dysregulation of this system has been implicated in neurodegenerative diseases including dementia and Alzheimer's disease.

Angiotensin II, the principal active peptide of the RAS, exerts most of its harmful effects through stimulation of angiotensin type-1 (AT1) receptors. Activation of AT1 receptors promotes vasoconstriction, oxidative stress, endothelial dysfunction, inflammatory cytokine production, excitotoxicity, and neuronal apoptosis. It also contributes to accumulation of amyloid-beta peptides and enhances neurodegenerative changes within the brain. Increased activity of the brain RAS has been associated with impaired cognitive performance and accelerated progression of dementia. Therefore, pharmacological blockade of AT1 receptors may offer protective effects against neuronal damage and cognitive decline.

Angiotensin Receptor Blockers (ARBs) are selective antagonists of AT1 receptors and are widely prescribed for the treatment of hypertension and cardiovascular disorders. Commonly used ARBs include losartan, valsartan, telmisartan, candesartan, irbesartan, olmesartan, and eprosartan. These drugs effectively reduce blood pressure by inhibiting angiotensin II-mediated vasoconstriction and aldosterone secretion. Unlike angiotensin-converting enzyme inhibitors, ARBs selectively block the harmful AT1 receptor pathway while preserving beneficial effects mediated through angiotensin type-2 receptors. This selective mechanism provides additional therapeutic advantages including anti-inflammatory, antioxidant, vasodilatory, and antiapoptotic effects.

Recent scientific investigations suggest that ARBs possess neuroprotective properties independent of their antihypertensive actions. Several ARBs have demonstrated the ability to cross the blood-brain barrier and directly influence neuronal function. These agents may reduce oxidative stress by inhibiting free radical formation and enhancing endogenous antioxidant defenses. ARBs also suppress inflammatory pathways by reducing production of cytokines such as tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6. Furthermore, they improve endothelial function and cerebral circulation, thereby enhancing oxygen and nutrient supply to brain tissues.

Experimental studies have shown that ARBs may decrease amyloid-beta accumulation, inhibit neuronal apoptosis, preserve synaptic integrity, and improve spatial learning and memory performance. Certain ARBs such as telmisartan also exhibit partial peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonistic activity, which may contribute to additional anti-inflammatory and metabolic benefits. These multifunctional actions indicate that ARBs may target several pathological pathways involved in dementia simultaneously, making them promising candidates for neuroprotective therapy.

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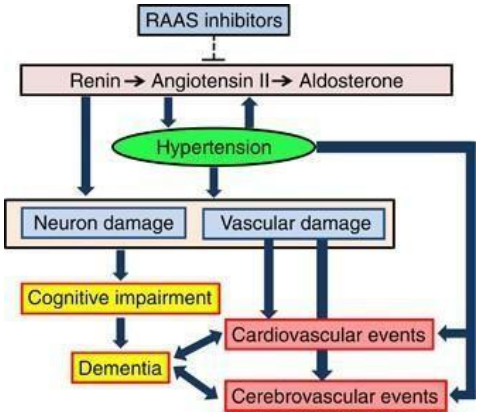
The present study is designed to evaluate the effectiveness of Angiotensin Receptor Blockers against dementia using appropriate experimental animal models and pharmacological methods. The study involves induction of dementia using suitable neurotoxic or pharmacological agents followed by administration of selected ARBs to determine their protective effects. Behavioral tests including elevated plus maze, Y-maze, radial arm maze, passive avoidance test, and Morris water maze are utilized to assess memory, learning ability, retention, and cognitive function.

Biochemical investigations are performed to estimate oxidative stress markers such as malondialdehyde, catalase, superoxide dismutase, glutathione, and nitric oxide levels. Neurotransmitter-related parameters including acetylcholinesterase activity are analyzed to evaluate cholinergic function. Inflammatory mediators and neurochemical changes associated with neuronal degeneration are also assessed. Histopathological examination of brain tissues, particularly the hippocampus and cerebral cortex, helps identify structural alterations, neuronal loss, inflammatory changes, and protective effects produced by ARB treatment.

The study also aims to compare different Angiotensin Receptor Blockers based on their neuroprotective efficacy, blood-brain barrier penetration, antioxidant potential, and cognitive benefits. Such comparative analysis may help identify the most effective ARB for dementia management and provide valuable information regarding future therapeutic applications. Repurposing of existing antihypertensive drugs for neurodegenerative disorders may reduce the cost and time required for development of new medications while providing safer and clinically established treatment alternatives.

Thus, evaluation of Angiotensin Receptor Blockers against dementia represents an important area of pharmacological research with significant clinical relevance. Understanding the relationship between the Renin-Angiotensin System and neurodegeneration may contribute to the development of innovative therapeutic strategies aimed at delaying cognitive decline, improving neuronal survival, and enhancing quality of life in patients suffering from dementia and related neurodegenerative disorders.(5,7,9)



Hypertension

II. NEED OF STUDY

- To understand the role of Angiotensin Receptor Blockers (ARBs) in the prevention and management of dementia.
- To investigate the relationship between hypertension and cognitive decline associated with neurodegenerative disorders.
- To evaluate the neuroprotective effects of ARBs on brain function and memory impairment.
- To study the involvement of the Renin-Angiotensin System (RAS) in the development and progression of dementia.
- To assess the ability of ARBs to reduce oxidative stress and neuronal damage in brain tissues.
- To examine the anti-inflammatory properties of ARBs in neurodegenerative conditions.
- To evaluate the effect of ARBs on cerebral blood circulation and vascular protection.
- To study the influence of ARBs on learning, memory retention, and cognitive performance.

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- To analyze the biochemical changes associated with dementia and the protective action of ARBs.
- To determine the effect of ARBs on acetylcholinesterase activity and cholinergic neurotransmission.
- To investigate the role of ARBs in reducing amyloid-beta accumulation and neuronal apoptosis.
- To compare different ARBs for their effectiveness in dementia management.
- To identify ARBs capable of crossing the blood-brain barrier and exerting direct neuroprotective effects.
- To explore the possibility of repurposing antihypertensive drugs for neurodegenerative diseases.
- To evaluate behavioral changes in experimental dementia models after ARB treatment.
- To assess histopathological changes in brain tissues following administration of ARBs.
- To provide scientific evidence supporting the use of ARBs as supportive therapy in dementia.
- To contribute to the development of safer and more effective therapeutic strategies for dementia treatment.
- To reduce the burden of cognitive impairment and improve quality of life in elderly patients.
- To encourage further pharmacological and clinical research on ARBs in neurodegenerative disorders.

III. AIM

The aim of the present study is to evaluate the therapeutic potential and neuroprotective effects of Angiotensin Receptor Blockers (ARBs) against dementia by assessing their influence on cognitive function, memory impairment, oxidative stress, neuroinflammation, and neuronal degeneration using suitable experimental and pharmacological methods. The study also aims to investigate the role of the Renin-Angiotensin System in the progression of dementia and to determine the effectiveness of ARBs in improving learning ability, cerebral blood circulation, and overall brain function for the prevention and management of neurodegenerative disorders.

IV. OBJECTIVES

1. To study the pathophysiology and clinical manifestations of dementia.
2. To evaluate the role of the Renin-Angiotensin System in neurodegenerative disorders.
3. To investigate the neuroprotective effects of Angiotensin Receptor Blockers against dementia.
4. To assess the effect of ARBs on learning, memory, and cognitive functions.
5. To study the antioxidant activity of ARBs in reducing oxidative stress in brain tissues.
6. To evaluate the anti-inflammatory effects of ARBs in experimental dementia models.
7. To determine the effect of ARBs on acetylcholinesterase activity and cholinergic transmission.
8. To analyze the influence of ARBs on neuronal survival and brain tissue protection.
9. To assess behavioral changes associated with dementia after ARB treatment.
10. To evaluate biochemical parameters related to oxidative stress and neurodegeneration.
11. To study histopathological changes in brain tissues following administration of ARBs.
12. To compare different Angiotensin Receptor Blockers for their therapeutic efficacy against dementia.
13. To examine the relationship between hypertension, vascular dysfunction, and cognitive impairment.
14. To investigate the ability of ARBs to improve cerebral blood circulation and neuronal function.
15. To explore the potential use of ARBs as supportive therapeutic agents in dementia management.
16. To provide experimental and pharmacological evidence regarding the role of ARBs in preventing cognitive decline.

V. REVIEW OF LITERATURE

Dementia is one of the most challenging neurodegenerative disorders affecting millions of individuals worldwide. It is characterized by progressive deterioration of memory, cognition, thinking ability, language, and behavior. The increasing prevalence of dementia among elderly populations has led to extensive research aimed at understanding its pathogenesis and identifying effective therapeutic approaches. Various studies have demonstrated that oxidative stress, neuroinflammation, vascular dysfunction, mitochondrial damage, cholinergic deficits, and accumulation of abnormal proteins play major roles in the progression of dementia. In recent years, growing evidence has suggested that the

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Renin-Angiotensin System (RAS) and Angiotensin Receptor Blockers (ARBs) may significantly influence cognitive function and neuroprotection.

Several researchers have reported that hypertension is strongly associated with increased risk of cognitive decline and dementia. Chronic elevation of blood pressure damages cerebral blood vessels, reduces cerebral perfusion, and accelerates neuronal degeneration. Epidemiological studies indicate that individuals suffering from midlife hypertension are more susceptible to developing Alzheimer's disease and vascular dementia during old age. This relationship between vascular disorders and neurodegeneration has encouraged investigations into antihypertensive agents possessing additional neuroprotective properties.

The Renin-Angiotensin System is traditionally recognized for regulating blood pressure, fluid balance, and cardiovascular function. However, studies have revealed the presence of RAS components within the central nervous system, including the hippocampus, cerebral cortex, and other regions associated with memory and learning. Angiotensin II, the primary active peptide of RAS, acts mainly through angiotensin type-1 (AT1) receptors and contributes to vasoconstriction, oxidative stress, inflammation, endothelial dysfunction, and neuronal injury. Excessive activation of AT1 receptors has been linked with impaired cognitive function, amyloid-beta accumulation, and neurodegenerative changes.

Research conducted on experimental animal models has demonstrated that increased activity of brain RAS promotes production of reactive oxygen species and inflammatory cytokines, leading to neuronal apoptosis and synaptic dysfunction. Oxidative stress generated through angiotensin II-mediated pathways damages lipids, proteins, and nucleic acids within neuronal tissues. Chronic inflammation caused by activation of microglial cells further aggravates neuronal degeneration and cognitive impairment. Therefore, inhibition of angiotensin II activity has been considered a potential therapeutic strategy for dementia management.

Angiotensin Receptor Blockers are selective antagonists of AT1 receptors and are widely used in the treatment of hypertension, heart failure, and renal disorders. Unlike angiotensin-converting enzyme inhibitors, ARBs specifically block harmful AT1 receptor-mediated effects while preserving beneficial actions mediated through angiotensin type-2 receptors. Several studies suggest that ARBs may exert neuroprotective effects independent of blood pressure reduction. These effects include antioxidant activity, anti-inflammatory action, improvement of cerebral blood flow, inhibition of neuronal apoptosis, and protection against vascular injury.

Losartan is one of the earliest ARBs investigated for its neuroprotective potential. Experimental studies demonstrated that losartan reduces oxidative stress and inflammatory responses within brain tissues. It has been shown to improve cognitive performance and reduce neuronal damage in animal models of Alzheimer's disease and vascular dementia. Researchers observed that losartan decreases production of reactive oxygen species and suppresses inflammatory mediators responsible for neuronal injury.

Candesartan has also attracted significant attention because of its ability to cross the blood-brain barrier effectively. Studies reported that candesartan improves spatial memory and learning performance in experimental dementia models. It was found to reduce amyloid-beta accumulation and decrease neuroinflammatory responses in the hippocampus. Histopathological investigations revealed that candesartan protects neuronal architecture and prevents synaptic loss associated with cognitive impairment.

Telmisartan is considered particularly important due to its dual pharmacological properties. In addition to blocking AT1 receptors, telmisartan acts as a partial agonist of peroxisome proliferator-activated receptor-gamma (PPAR-γ), which is associated with anti-inflammatory and metabolic benefits. Several studies demonstrated that telmisartan improves memory function, reduces oxidative damage, and decreases inflammatory cytokine production. Experimental evidence suggests that telmisartan may also improve insulin sensitivity and cerebral metabolism, which are important factors in neurodegenerative disorders.

Valsartan has been evaluated for its effects on amyloid-beta metabolism and neuronal survival. Research findings indicate that valsartan reduces accumulation of amyloid plaques and improves cognitive function in animal models of Alzheimer's disease. Studies also suggest that valsartan enhances cerebral blood circulation and protects endothelial

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cells from oxidative injury. Improvement in synaptic plasticity and neuronal communication has been observed following valsartan administration.

Irbesartan and olmesartan have also shown promising neuroprotective properties. Investigations demonstrated that these ARBs reduce lipid peroxidation, increase antioxidant enzyme activity, and improve behavioral performance in memory tests. Histological studies revealed reduced neuronal degeneration and preservation of hippocampal structure after treatment with these agents. Their anti-inflammatory effects contribute significantly to reduction of neurodegenerative progression.

Behavioral studies using elevated plus maze, Morris water maze, Y-maze, radial arm maze, and passive avoidance tests have been widely employed to evaluate memory and learning abilities in experimental dementia models. Administration of ARBs in these models consistently showed improvement in retention memory, spatial learning, and exploratory behavior. Such findings support the hypothesis that ARBs possess cognitive-enhancing and neuroprotective properties.

Biochemical investigations conducted by various researchers demonstrated that ARBs reduce oxidative stress markers such as malondialdehyde and nitric oxide while increasing antioxidant enzymes including superoxide dismutase, catalase, and glutathione. Reduction in acetylcholinesterase activity following ARB treatment indicates improvement in cholinergic neurotransmission, which is crucial for memory and cognition. Suppression of inflammatory cytokines such as tumor necrosis factor-alpha and interleukins further confirms the anti-inflammatory potential of ARBs.

Histopathological studies provide additional evidence regarding the protective effects of ARBs on brain tissues. Microscopic examination of hippocampal and cortical regions in treated animals revealed reduced neuronal degeneration, decreased inflammatory infiltration, preservation of neuronal density, and reduced amyloid plaque formation. Improvement in neuronal morphology and synaptic integrity has also been reported.

Clinical studies conducted in hypertensive patients suggest that long-term use of ARBs may reduce the incidence and progression of dementia compared to some other antihypertensive drugs. Certain observational studies reported better cognitive outcomes in patients receiving ARB therapy. Although the exact mechanisms remain under investigation, improved vascular function, reduction of oxidative stress, and suppression of neuroinflammation are believed to contribute to these beneficial effects.

Recent literature emphasizes that dementia is a multifactorial disorder requiring therapeutic approaches targeting multiple pathological pathways simultaneously. Since ARBs possess antioxidant, anti-inflammatory, antiapoptotic, and vasoprotective properties, they may offer significant advantages in dementia management. Furthermore, repurposing already established antihypertensive drugs for neurodegenerative disorders may reduce drug development costs and improve clinical applicability.

Overall, the literature strongly supports the involvement of the Renin-Angiotensin System in neurodegenerative processes and highlights the therapeutic potential of Angiotensin Receptor Blockers against dementia. Previous studies indicate that ARBs can improve cognitive function, reduce oxidative damage, suppress inflammation, protect neuronal tissues, and preserve cerebral circulation. However, further experimental and clinical investigations are still necessary to establish their long-term efficacy, safety, and precise mechanisms of neuroprotection in dementia treatment.(10,11,12)

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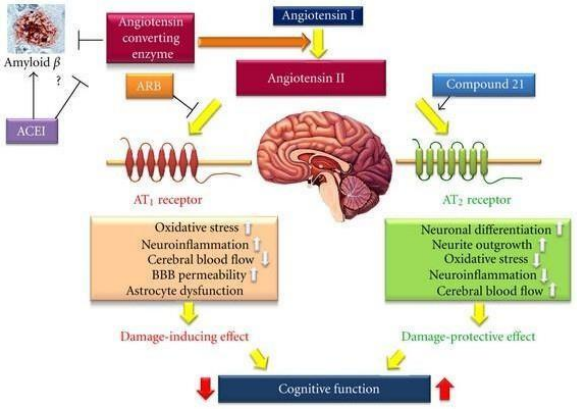

Roles of Brain in angiotensin

VI. ROLE AND CLASSIFICATION

Role of Angiotensin Receptor Blockers Against Dementia

Angiotensin Receptor Blockers (ARBs) are a class of drugs mainly used in the treatment of hypertension, cardiovascular diseases, heart failure, and renal disorders. In recent years, these drugs have gained significant attention for their neuroprotective potential in neurodegenerative disorders such as dementia. The beneficial effects of ARBs are associated with their ability to regulate the Renin-Angiotensin System (RAS), reduce oxidative stress, suppress neuroinflammation, improve cerebral blood circulation, and protect neuronal cells from degeneration.

The Renin-Angiotensin System is not only involved in blood pressure regulation but also plays an important role in brain physiology. Components of this system are present in brain regions responsible for memory and cognition such as the hippocampus and cerebral cortex. Angiotensin II, the major active peptide of the system, acts mainly through angiotensin type-1 (AT1) receptors. Excessive activation of AT1 receptors results in vasoconstriction, oxidative stress, inflammatory responses, endothelial dysfunction, neuronal apoptosis, and amyloid-beta accumulation. These pathological changes contribute significantly to the progression of dementia and cognitive decline.

ARBs selectively block AT1 receptors and prevent the harmful effects of angiotensin II while preserving beneficial actions mediated through angiotensin type-2 receptors. Due to this selective mechanism, ARBs produce several protective effects in the brain and may help in slowing the progression of neurodegenerative disorders.

Reduction of Oxidative Stress

Oxidative stress is considered one of the major causes of neuronal damage in dementia. Excessive production of reactive oxygen species damages neuronal membranes, proteins, enzymes, and DNA leading to cognitive impairment and neuronal death. ARBs reduce oxidative stress by inhibiting free radical generation and enhancing antioxidant defense mechanisms. They increase the activity of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione, thereby protecting neuronal tissues from oxidative injury.

Anti-Inflammatory Activity

Neuroinflammation plays a crucial role in the development and progression of dementia. Activation of microglial cells and release of inflammatory cytokines such as tumor necrosis factor-alpha and interleukins contribute to neuronal degeneration. ARBs suppress inflammatory pathways and reduce production of these inflammatory mediators. Their anti-inflammatory properties help minimize chronic neuronal damage and improve cognitive function.

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Improvement of Cerebral Blood Flow

Proper cerebral blood circulation is essential for maintaining normal brain function. Hypertension and vascular disorders reduce cerebral perfusion and increase the risk of vascular dementia. ARBs improve endothelial function, decrease vascular resistance, and enhance blood supply to brain tissues. Improved cerebral circulation ensures adequate oxygen and nutrient delivery to neurons, thereby supporting memory and cognitive processes.

Protection Against Neuronal Apoptosis

Neuronal apoptosis or programmed cell death is a major pathological feature of dementia. Angiotensin II-mediated oxidative stress and inflammation accelerate neuronal degeneration. ARBs inhibit apoptotic pathways and protect neuronal cells from damage. Preservation of neuronal structure and synaptic integrity contributes to improved learning and memory retention.

Reduction of Amyloid-Beta Accumulation

Amyloid-beta plaque formation is a characteristic feature of Alzheimer's disease. Research studies suggest that ARBs reduce amyloid-beta accumulation and prevent plaque deposition within brain tissues. This action may delay progression of cognitive impairment and reduce neurodegenerative changes.

Improvement of Cognitive Function

Behavioral studies conducted using experimental animal models have demonstrated that ARBs improve memory retention, spatial learning, and cognitive performance. These effects are observed in tests such as Morris water maze, elevated plus maze, Y-maze, and passive avoidance tests. Improvement in cognition is mainly due to reduced oxidative damage, suppression of inflammation, enhanced neurotransmission, and improved cerebral blood flow.

Neuroprotective Effects

Certain ARBs possess lipophilic properties allowing them to cross the blood-brain barrier and exert direct neuroprotective actions. These drugs protect hippocampal neurons, preserve synaptic communication, and maintain neuronal survival. Their direct action within the central nervous system makes them promising therapeutic agents for dementia.

Role in Vascular Dementia

Vascular dementia occurs due to impaired cerebral blood supply caused by vascular injury and hypertension. Since ARBs effectively control blood pressure and improve vascular function, they may reduce progression of vascular dementia. Their vasodilatory and endothelial protective actions help prevent ischemic neuronal damage.

Drug Repurposing Potential

ARBs are already clinically approved drugs with established safety profiles. Their multifunctional pharmacological properties make them potential candidates for repurposing in neurodegenerative diseases. Use of ARBs in dementia management may provide a safer and more cost-effective therapeutic approach compared to development of new drugs.

Classification of Angiotensin Receptor Blockers

Angiotensin Receptor Blockers are classified based on their chemical structure, duration of action, lipophilicity, pharmacological properties, and blood-brain barrier penetration.

Classification According to Chemical Structure Biphenyl Tetrazole Derivatives

These ARBs contain biphenyl and tetrazole ring structures and are widely used clinically.

- Losartan
- Valsartan
- Irbesartan
- Candesartan
- Olmesartan

These drugs exhibit strong AT1 receptor antagonistic activity and provide effective antihypertensive action.

Non-Biphenyl Tetrazole Derivatives

These agents possess different chemical structures and pharmacological characteristics.

- Telmisartan

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• Eprosartan

Telmisartan is highly lipophilic and also possesses partial PPAR-γ agonistic activity contributing to additional anti-inflammatory effects.

Classification According to Duration of Action Short-Acting ARBs

These drugs have shorter half-lives and may require more frequent administration.

• Losartan

Long-Acting ARBs

These agents provide prolonged therapeutic action and stable receptor blockade.

• Telmisartan
• Candesartan
• Olmesartan
• Valsartan
• Irbesartan

Long-acting ARBs are preferred for continuous blood pressure control and sustained neuroprotective effects.

Classification According to Blood-Brain Barrier Penetration Highly Lipophilic ARBs

These drugs effectively cross the blood-brain barrier and exert direct central nervous system effects.

• Telmisartan
• Candesartan

These ARBs are considered more beneficial in dementia because of better brain penetration.

Moderately Lipophilic ARBs

• Losartan
• Valsartan
• Irbesartan

Less Lipophilic ARBs

• Eprosartan

Classification According to Pharmacological Activity ARBs with Additional PPAR-γ Agonistic Activity

These agents exhibit anti-inflammatory and metabolic regulatory effects in addition to AT1 receptor blockade.

• Telmisartan

Pure AT1 Receptor Blockers

These drugs mainly act through selective inhibition of AT1 receptors.

• Losartan
• Valsartan
• Candesartan
• Irbesartan
• Olmesartan
• Eprosartan

Commonly Used Angiotensin Receptor Blockers Losartan

Losartan was the first ARB introduced for clinical use. It is widely prescribed for hypertension, diabetic nephropathy, and cardiovascular disorders. It possesses antioxidant and anti-inflammatory properties.

Valsartan

Valsartan provides effective cardiovascular and cerebrovascular protection. It improves cerebral circulation and reduces oxidative injury.

Telmisartan

Telmisartan is highly lipophilic and capable of crossing the blood-brain barrier. It possesses neuroprotective, antioxidant, and anti-inflammatory properties along with PPAR-γ agonistic activity.

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Candesartan

Candesartan demonstrates strong neuroprotective potential and effectively improves memory and learning functions in experimental studies.

Irbesartan

Irbesartan is used for hypertension and diabetic nephropathy and exhibits antioxidant benefits in neuronal tissues.

Olmesartan

Olmesartan is a long-acting ARB with vascular protective and neuroprotective effects.

Eprosartan

Eprosartan acts as a selective AT1 receptor antagonist and is mainly used for antihypertensive therapy.

Thus, Angiotensin Receptor Blockers represent an important class of therapeutic agents with significant potential in dementia management due to their antioxidant, anti-inflammatory, vasoprotective, and neuroprotective properties.

Angiotensin Receptor Blockers (ARBs) have emerged as important therapeutic agents not only for cardiovascular disorders but also for neurological and neurodegenerative diseases. Their role in dementia management has gained attention because dementia involves multiple pathological mechanisms including vascular dysfunction, oxidative stress, neuroinflammation, neuronal apoptosis, impaired neurotransmission, and cerebral hypoperfusion. ARBs target several of these pathological pathways simultaneously, making them promising multifunctional neuroprotective agents.

Role in Modulation of Brain Renin-Angiotensin System

The brain contains an independent Renin-Angiotensin System that regulates neuronal activity, cerebral circulation, stress responses, and cognitive functions. In dementia, excessive activation of the brain RAS increases angiotensin II levels, resulting in overactivation of AT1 receptors. This leads to neuronal injury and progressive cognitive decline. ARBs block AT1 receptors and reduce the harmful effects of angiotensin II while maintaining beneficial actions through AT2 receptors. This modulation helps restore normal neuronal signaling and improves brain function.

Role in Prevention of Neurovascular Damage

Neurovascular dysfunction is a major contributing factor in dementia progression. Chronic hypertension causes thickening and narrowing of cerebral blood vessels, reducing oxygen and nutrient supply to neurons. ARBs improve vascular elasticity, reduce vascular resistance, and enhance endothelial function. By maintaining adequate cerebral perfusion, ARBs help prevent ischemic injury and maintain neuronal viability. Improved vascular health also reduces the progression of vascular dementia.

Role in Maintenance of Blood-Brain Barrier Integrity

The blood-brain barrier protects brain tissues from harmful substances circulating in the bloodstream. In dementia, inflammation and oxidative stress damage this protective barrier, allowing toxic molecules to enter brain tissues and accelerate neuronal degeneration. ARBs stabilize endothelial cells and reduce inflammatory injury to the blood-brain barrier. Preservation of barrier integrity helps prevent neurotoxicity and protects neuronal microenvironments.

Role in Regulation of Neurotransmitters

Cognitive processes such as learning and memory depend on proper neurotransmitter function. In dementia, especially Alzheimer's disease, cholinergic neurotransmission becomes impaired due to reduced acetylcholine levels and increased acetylcholinesterase activity. ARBs have shown the ability to improve cholinergic transmission by reducing acetylcholinesterase activity and preserving neurotransmitter balance. Improved neurotransmission enhances memory retention and cognitive performance.

Role in Synaptic Protection

Synapses are specialized junctions responsible for communication between neurons. Synaptic loss is one of the earliest pathological features of dementia and directly correlates with cognitive decline. Oxidative stress and inflammatory mediators damage synaptic proteins and impair neuronal communication. ARBs reduce synaptic damage by suppressing inflammatory pathways and protecting neuronal membranes. Preservation of synaptic integrity supports learning ability and cognitive processing.

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Role in Reduction of Excitotoxicity

Excessive stimulation of excitatory neurotransmitters such as glutamate leads to neuronal injury through calcium overload and oxidative damage, a process known as excitotoxicity. This mechanism contributes significantly to neuronal death in dementia. ARBs may reduce excitotoxic neuronal injury by improving neuronal stability and reducing oxidative stress. Protection against excitotoxicity helps preserve neuronal survival.

Role in Mitochondrial Protection

Mitochondria are essential for cellular energy production. In dementia, mitochondrial dysfunction leads to impaired ATP synthesis, excessive free radical formation, and neuronal apoptosis. Studies suggest that ARBs improve mitochondrial function by reducing oxidative stress and enhancing antioxidant defenses. Maintenance of mitochondrial health supports neuronal energy metabolism and survival.

Role in Inhibition of Microglial Activation

Microglial cells are immune cells of the central nervous system. Chronic activation of microglia results in release of inflammatory cytokines and neurotoxic substances that damage neurons. ARBs inhibit excessive microglial activation and reduce production of inflammatory mediators. Suppression of chronic neuroinflammation slows progression of neurodegenerative changes.

Role in Reduction of Tau Protein Abnormalities

Hyperphosphorylation of tau proteins leads to formation of neurofibrillary tangles, which are characteristic pathological features of Alzheimer's disease. Some studies indicate that ARBs may reduce tau phosphorylation and prevent formation of abnormal protein aggregates. This action may help maintain neuronal structure and function.

Role in Prevention of White Matter Lesions

White matter lesions are commonly observed in elderly individuals with hypertension and dementia. These lesions impair neuronal communication and cognitive processing. ARBs improve vascular circulation and reduce ischemic damage within white matter regions, thereby preserving neuronal connectivity and cognitive function.

Role in Cognitive Enhancement

ARBs improve various aspects of cognitive function including attention, memory retention, spatial learning, executive function, and problem-solving ability. Experimental studies demonstrate that ARB-treated animals perform better in behavioral memory tests compared to untreated groups. Improvement in cognition results from combined antioxidant, anti-inflammatory, vascular protective, and neurochemical effects.

Role in Delaying Disease Progression

Dementia is progressive and irreversible in nature. ARBs may not completely cure dementia, but they may slow progression of neurodegeneration by protecting neurons from continuous damage. Early intervention with ARBs may help delay onset of severe cognitive impairment and prolong independent functioning in patients.

Detailed Classification of Angiotensin Receptor Blockers

Angiotensin Receptor Blockers are classified based on several pharmacological and physicochemical characteristics including receptor affinity, duration of action, chemical structure, metabolism, lipophilicity, and therapeutic properties.

Classification According to Receptor Binding Affinity High Affinity AT1 Receptor Blockers

These ARBs bind strongly to AT1 receptors and provide prolonged receptor inhibition.

- Candesartan
- Olmesartan
- Telmisartan

These drugs exhibit potent antihypertensive and neuroprotective activity due to strong receptor binding.

Moderate Affinity AT1 Receptor Blockers

- Losartan
- Valsartan
- Irbesartan

These agents effectively block AT1 receptors but may differ in duration and potency.

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Classification According to Prodrug Nature Active Drugs
These ARBs are pharmacologically active in administered form.
• Valsartan
• Telmisartan
• Irbesartan
• Eprosartan
Prodrugs
These agents require metabolic conversion into active forms within the body.
• Candesartan cilexetil
• Olmesartan medoxomil
• Losartan partially forms active metabolites
Prodrugs generally provide improved bioavailability and prolonged action.
Classification According to Elimination Pathway Hepatic Elimination
These ARBs are primarily metabolized and eliminated through the liver.
• Telmisartan
• Losartan
Renal Elimination
These drugs are mainly eliminated through kidneys.
• Olmesartan
• Candesartan
Mixed Elimination
• Valsartan
• Irbesartan
Classification According to Blood-Brain Barrier Penetration ARBs with Strong Central Nervous System Penetration
These drugs effectively enter brain tissues and produce direct neuroprotective effects.
• Telmisartan
• Candesartan
These agents are highly preferred for studies involving dementia and neurodegenerative disorders.
ARBs with Moderate Central Nervous System Penetration
• Losartan
• Irbesartan
• Valsartan
ARBs with Limited Brain Penetration
• Eprosartan
Classification According to Additional Pharmacological Effects ARBs with Antioxidant Properties
• Telmisartan
• Candesartan
• Losartan
These agents reduce oxidative stress and protect neuronal tissues.
ARBs with Anti-Inflammatory Properties
• Telmisartan
• Irbesartan
• Olmesartan
These drugs suppress inflammatory cytokines and microglial activation.

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ARBs with Metabolic Benefits

• Telmisartan

Telmisartan activates PPAR-γ receptors and improves insulin sensitivity and lipid metabolism.

Classification According to Clinical Applications ARBs Mainly Used for Hypertension

• Losartan
• Valsartan
• Telmisartan

ARBs Used in Heart Failure

• Candesartan
• Valsartan

ARBs Used in Diabetic Nephropathy

• Irbesartan
• Losartan

ARBs Investigated for Neuroprotective Effects

• Telmisartan
• Candesartan
• Losartan
• Valsartan

These agents are commonly studied in dementia and Alzheimer's disease models.

Thus, Angiotensin Receptor Blockers possess diverse pharmacological properties and therapeutic applications extending beyond cardiovascular diseases. Their multiple mechanisms of action including antioxidant, anti-inflammatory, vascular protective, antiapoptotic, and neuroprotective effects make them promising agents for the prevention and management of dementia and other neurodegenerative disorders.

Angiotensin Receptor Blockers (ARBs) have attracted considerable scientific interest because dementia involves not only neuronal degeneration but also vascular abnormalities, metabolic disturbances, inflammatory injury, and impaired cellular signaling. ARBs possess the ability to influence several molecular and physiological pathways associated with neurodegeneration. Their broad spectrum of pharmacological actions makes them potential multifunctional therapeutic agents for slowing cognitive decline and preserving brain function.

Role in Regulation of Cerebral Hemodynamics

Normal brain activity depends on continuous cerebral perfusion and proper vascular autoregulation. In dementia, chronic hypertension and vascular stiffness impair cerebral hemodynamics, resulting in hypoperfusion, ischemia, and neuronal dysfunction. ARBs improve cerebral vascular compliance and reduce arterial stiffness, thereby maintaining stable cerebral blood flow. They also reduce cerebrovascular resistance and improve microcirculation within brain tissues. Restoration of adequate perfusion helps maintain neuronal metabolism and reduces ischemic injury.

Role in Endothelial Protection

The vascular endothelium regulates blood flow, vascular tone, inflammatory signaling, and coagulation. Endothelial dysfunction is commonly observed in dementia and contributes to cerebral hypoxia and neurodegeneration. Angiotensin II-mediated oxidative stress damages endothelial cells and decreases nitric oxide availability. ARBs improve endothelial function by reducing oxidative injury and increasing nitric oxide bioavailability. Enhanced endothelial health promotes vasodilation and supports neuronal oxygenation.

Role in Modulation of Nitric Oxide Pathway

Nitric oxide is an important signaling molecule involved in vasodilation, neurotransmission, and synaptic plasticity. In dementia, abnormal nitric oxide metabolism contributes to vascular dysfunction and neuronal injury. ARBs regulate nitric oxide synthesis and improve endothelial nitric oxide production. Balanced nitric oxide activity enhances cerebral circulation and supports cognitive processes such as memory and learning.

Role in Suppression of Reactive Oxygen Species Production

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Excessive reactive oxygen species generation is a major contributor to neuronal degeneration. Angiotensin II stimulates activation of NADPH oxidase enzymes leading to increased production of superoxide radicals and oxidative injury. ARBs inhibit activation of these oxidase systems and significantly reduce formation of reactive oxygen species. Suppression of oxidative stress protects neuronal membranes, mitochondrial structures, and synaptic proteins from degeneration.

Role in Regulation of Calcium Homeostasis

Disturbance in intracellular calcium balance contributes to excitotoxicity and neuronal apoptosis in dementia. Elevated intracellular calcium activates destructive enzymes and promotes mitochondrial dysfunction. ARBs may stabilize calcium homeostasis indirectly by reducing oxidative stress and improving neuronal membrane integrity. Proper calcium regulation supports neuronal survival and synaptic transmission.

Role in Preservation of Hippocampal Function

The hippocampus is the primary brain region involved in memory formation and spatial learning. Hippocampal degeneration is one of the earliest pathological changes observed in Alzheimer's disease and other forms of dementia. ARBs help preserve hippocampal neuronal architecture by reducing inflammation, oxidative stress, and vascular damage. Experimental studies have shown improved hippocampal function and enhanced memory retention following ARB administration.

Role in Reduction of Neurodegenerative Protein Aggregation

Abnormal aggregation of proteins such as amyloid-beta and hyperphosphorylated tau proteins disrupts neuronal communication and accelerates cognitive decline. ARBs may interfere with pathological protein aggregation through antioxidant and anti-inflammatory mechanisms. Reduction in protein deposition decreases synaptic dysfunction and preserves neuronal connectivity.

Role in Enhancement of Neurogenesis

Neurogenesis refers to formation of new neurons within the brain, particularly in the hippocampus. In dementia, neurogenesis becomes impaired due to chronic inflammation and oxidative injury. Certain ARBs may stimulate neuronal regeneration and survival by improving microenvironmental conditions within brain tissues. Enhancement of neurogenesis may contribute to improved learning and cognitive recovery.

Role in Prevention of Glial Cell Dysfunction

Astrocytes and oligodendrocytes are essential supportive cells within the central nervous system. Dysfunction of these glial cells contributes to impaired neuronal metabolism and synaptic instability in dementia. ARBs reduce inflammatory stress on glial cells and maintain their normal physiological function. Healthy glial activity supports neuronal nutrition, neurotransmitter regulation, and repair processes.

Role in Reduction of Cerebral Edema

Inflammatory and vascular changes in dementia may increase vascular permeability and contribute to cerebral edema. ARBs stabilize vascular integrity and reduce inflammatory leakage within brain tissues. Reduction of cerebral edema helps maintain normal neuronal communication and prevents additional neuronal compression injury.

Role in Modulation of Autonomic Nervous System Activity

Excessive sympathetic nervous system activity increases vascular stress and contributes to hypertension-related cognitive impairment. ARBs reduce sympathetic overactivity by modulating central autonomic regulation. Balanced autonomic activity improves cardiovascular stability and cerebral circulation, indirectly supporting cognitive health.

Role in Protection Against Ischemic Injury

Transient ischemic episodes and chronic cerebral hypoxia contribute significantly to vascular dementia. ARBs protect neurons from ischemia-induced oxidative damage and inflammatory injury. They improve collateral circulation and reduce neuronal susceptibility to ischemic stress. This protective action is particularly important in elderly hypertensive patients at high risk of cerebrovascular disease.

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Role in Reduction of Age-Related Cognitive Decline

Aging is associated with gradual impairment of vascular function, increased oxidative stress, and neuronal degeneration. ARBs may delay age-related cognitive decline by preserving vascular health and reducing chronic inflammatory processes. Long-term administration of ARBs may therefore provide preventive benefits against development of dementia in elderly individuals.

Advanced Classification of Angiotensin Receptor Blockers Classification According to Chemical Pharmacophore Tetrazole Containing ARBs

These agents contain tetrazole rings responsible for strong receptor affinity and prolonged action.

- Losartan
- Valsartan
- Candesartan
- Irbesartan
- Olmesartan

These compounds exhibit potent antagonistic activity against AT1 receptors and are widely used clinically.

Non-Tetrazole ARBs

These drugs possess different chemical backbones and may show unique pharmacokinetic properties.

- Telmisartan
- Eprosartan

Telmisartan demonstrates high lipophilicity and enhanced tissue penetration.

Classification According to Plasma Protein Binding Highly Protein Bound ARBs

These drugs remain extensively bound to plasma proteins, resulting in prolonged circulation time.

- Telmisartan
- Valsartan
- Irbesartan

Moderately Protein Bound ARBs

- Losartan
- Candesartan

Protein binding influences drug distribution, duration of action, and tissue penetration.

Classification According to Half-Life Short Half-Life ARBs

- Losartan

Requires more frequent dosing because of relatively rapid elimination.

Intermediate Half-Life ARBs

- Valsartan
- Irbesartan

Provide moderate duration of receptor blockade.

Long Half-Life ARBs

- Telmisartan
- Olmesartan
- Candesartan

Offer prolonged therapeutic effects and stable plasma concentration.

Classification According to Lipid Solubility

Highly Lipid Soluble ARBs

- Telmisartan
- Candesartan

These agents efficiently cross cell membranes and penetrate brain tissues.

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Moderately Lipid Soluble ARBs
• Losartan
• Irbesartan
• Valsartan
Low Lipid Soluble ARBs
• Eprosartan
Lipid solubility greatly influences central nervous system availability and neuroprotective efficacy.
Classification According to Active Metabolite Formation ARBs Producing Active Metabolites
• Losartan
Losartan is metabolized into EXP3174, an active metabolite with stronger AT1 receptor antagonistic activity.
ARBs Without Significant Active Metabolites
• Telmisartan
• Valsartan
• Irbesartan
• Candesartan
• Olmesartan
These agents act mainly in their original administered forms.
Classification According to Tissue Penetration ARBs with Extensive Tissue Penetration
• Telmisartan
• Candesartan
These drugs distribute efficiently into vascular tissues, kidneys, heart, and brain.
ARBs with Moderate Tissue Penetration
• Losartan
• Irbesartan
• Valsartan
Classification According to Neuroprotective Research Importance ARBs Frequently Investigated in Dementia Studies
• Telmisartan
• Candesartan
• Losartan
• Valsartan
These agents have demonstrated promising results in experimental memory and cognition studies.
ARBs with Limited Neurodegenerative Research
• Eprosartan
• Olmesartan
Research regarding their neuroprotective effects is comparatively limited.
Classification According to Additional Clinical Benefits ARBs with Renoprotective Effects
• Losartan
• Irbesartan
Useful in diabetic nephropathy and chronic kidney disease.
ARBs with Cardioprotective Effects
• Valsartan
• Candesartan
Beneficial in heart failure and post-myocardial infarction management.
ARBs with Metabolic Regulatory Effects
• Telmisartan
Improves insulin sensitivity and lipid metabolism through PPAR-γ activation.

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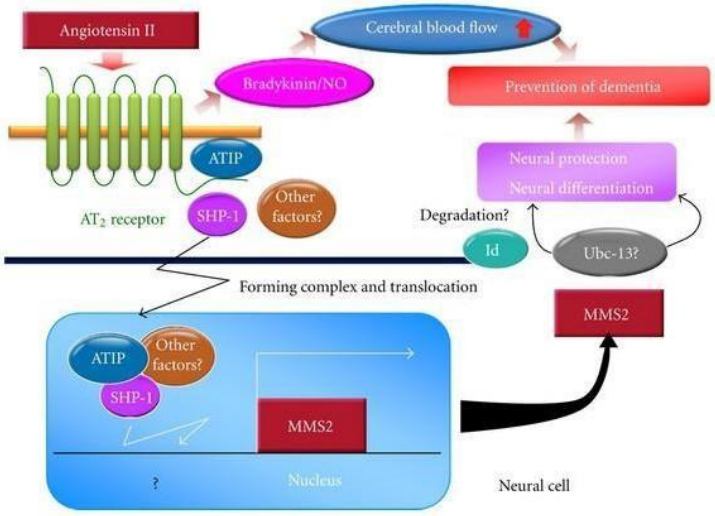
Thus, Angiotensin Receptor Blockers possess diverse pharmacological characteristics and extensive therapeutic potential extending beyond conventional antihypertensive therapy. Their broad neuroprotective, vascular protective, antioxidant, and anti-inflammatory actions make them highly promising candidates for future dementia prevention and treatment strategies.(10,14,16)



Effect of Angiotensin

VII. MATERIALS AND METHODS

This study is designed as a comprehensive review-based evaluation supported by experimental and clinical literature analysis to assess the potential role of Angiotensin Receptor Blockers (ARBs) in preventing or reducing the progression of dementia. The work integrates findings from preclinical studies, clinical trials, observational studies, and meta-analyses related to neuroprotective effects of ARBs.

Materials Used

The materials for this study include published scientific literature, clinical trial data, review articles, and epidemiological reports. Key sources of information were obtained from biomedical databases such as PubMed, Google Scholar, and clinical research repositories. Studies involving commonly used ARBs such as losartan, candesartan, valsartan, telmisartan, and olmesartan were considered for evaluation. Research articles focusing on Alzheimer's disease, vascular dementia, cognitive decline, and hypertension-related neurodegeneration were included. Only peer-reviewed journals, systematic reviews, and randomized controlled trials were selected to ensure reliability of data.

Methods of Study

The methodology adopted is a systematic literature-based analytical approach. Relevant studies were identified using keywords such as "angiotensin receptor blockers," "dementia,"

"Alzheimer's disease," "cognitive decline," and "renin angiotensin system and brain." Studies were screened based on inclusion criteria, which included: (i) human clinical studies or animal models related to cognition, (ii) studies evaluating ARB exposure and cognitive outcomes, and

(iii) publications in English language. Exclusion criteria included studies unrelated to neurological outcomes or those lacking sufficient data on ARBs.

The selected studies were categorized into three groups: experimental studies (animal models investigating neuroprotection), observational studies (population-based dementia risk analysis), and clinical trials (effects of ARBs on cognitive performance in hypertensive patients).

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Comparative evaluation was performed between ARB-treated groups and control or other antihypertensive drug groups.

Data extraction focused on cognitive outcomes such as memory performance, incidence of

Alzheimer's disease, progression of vascular dementia, and neuroprotective biomarkers. Special attention was given to mechanisms including reduction of neuroinflammation, improvement of cerebral blood flow, inhibition of angiotensin II type 1 (AT1) receptor activity, and protection of blood–brain barrier integrity.

Finally, the collected data was systematically analyzed to determine trends, consistency of results, and overall therapeutic potential of ARBs in dementia management. (18,20)

VIII. COLLECTION AND AUTHENTICATION OF MATERIALS

The collection and authentication of materials is an important step in the present study because the quality, purity, and authenticity of the materials directly influence the reliability and accuracy of experimental results. Proper collection, identification, handling, and storage of drugs, chemicals, reagents, and experimental animals are essential to ensure reproducibility and validity of the pharmacological evaluation of Angiotensin Receptor Blockers against dementia.

Collection of Drug Samples

The selected Angiotensin Receptor Blockers (ARBs) such as telmisartan, losartan, valsartan, candesartan, irbesartan, or olmesartan used in the study were collected from authenticated pharmaceutical manufacturers, licensed medical suppliers, or certified chemical distributors. The drug samples were obtained in pure analytical grade form to maintain consistency and experimental accuracy. The procurement process included verification of batch number, manufacturing date, expiry date, and certificate of analysis provided by the manufacturer.

The collected drug samples were carefully inspected for physical appearance, color, texture, and packaging integrity before use. Each drug sample was properly labeled and stored under suitable environmental conditions according to manufacturer recommendations to prevent degradation and contamination. Hygroscopic and light-sensitive compounds were stored in airtight containers protected from moisture and direct sunlight.

Collection of Chemicals and Reagents

All chemicals and reagents required for biochemical analysis, induction of dementia, histopathological studies, and pharmacological evaluation were collected from standard laboratory suppliers and certified scientific companies. Analytical grade chemicals were used throughout the study to ensure precision and reliability of experimental observations.

Commonly used chemicals included:

- Scopolamine or other dementia-inducing agents
- Acetylcholinesterase assay reagents
- Thiobarbituric acid for lipid peroxidation studies
- Reduced glutathione estimation reagents
- Catalase and superoxide dismutase assay reagents
- Formalin and staining agents for histopathology
- Phosphate buffer solutions
- Normal saline and distilled water

Each chemical was checked for purity, labeling, concentration, and expiry date before use. Reagents were prepared freshly whenever required to avoid chemical instability and experimental variation.

Collection of Experimental Animals

Healthy adult laboratory animals such as Wistar rats or Swiss albino mice were collected from a registered and approved animal breeding center. The animals selected for the study were healthy, disease-free, and within a specified body weight range to ensure uniformity in experimental conditions.

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The animals were transported carefully to the animal house facility under hygienic conditions to minimize stress and physiological disturbances. They were housed in polypropylene cages with clean bedding material and maintained under standard laboratory environmental conditions including controlled temperature, humidity, and light-dark cycle.

The animals were provided with standard pellet diet and clean drinking water ad libitum throughout the study period. Before initiation of experiments, the animals were acclimatized to laboratory conditions for a specified duration to reduce stress-related variability in experimental outcomes.

Ethical Approval and Animal Care

The experimental protocol involving laboratory animals was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) constituted according to guidelines of CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals). All experimental procedures were carried out following ethical principles for laboratory animal care and handling.

Proper measures were taken to minimize pain, discomfort, and unnecessary stress to the animals during experimentation. Animals showing signs of severe illness or abnormal behavior were excluded from the study to maintain accuracy and ethical standards.

Authentication of Drug Samples

Authentication of the selected Angiotensin Receptor Blockers was performed to confirm the identity and purity of the drugs used in the study. Authentication procedures included evaluation of physical and chemical characteristics according to official pharmacopoeial standards.

The following parameters were assessed:

- Physical appearance
- Color and odor
- Solubility profile
- Melting point determination
- pH analysis
- Identification tests
- Spectroscopic analysis where applicable

The obtained results were compared with standard reference values available in official pharmacopoeias and scientific literature to confirm authenticity of the drug samples.

Authentication of Chemicals and Reagents

All chemicals and reagents were authenticated by verifying manufacturer labels, purity specifications, and certificates of analysis. Standard laboratory procedures were followed to ensure the identity and quality of reagents before use in biochemical assays and pharmacological experiments.

Prepared solutions and reagents were standardized whenever necessary to maintain accuracy and consistency of experimental results. Contaminated or expired chemicals were discarded according to laboratory safety guidelines.

Authentication of Experimental Animals

Experimental animals were authenticated based on species, strain, body weight, age, and health condition by trained laboratory personnel or veterinary experts. Animals selected for the study were free from infections, deformities, and behavioral abnormalities.

Routine observation of animal health status was carried out throughout the study period. Any animal showing signs of disease, excessive stress, or injury was excluded from the experiment to maintain reliability of the results.

Storage and Handling of Materials

Proper storage and handling procedures were followed for all collected materials to maintain stability and prevent contamination. Drug samples and chemicals were stored at recommended temperatures in well-labeled containers. Biological materials and prepared reagents were handled using sterile techniques wherever necessary.

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Laboratory equipment and glassware used for preparation and analysis were thoroughly cleaned and sterilized before use. Safety precautions including use of gloves, masks, and protective laboratory clothing were followed during handling of chemicals and biological samples.

Documentation and Record Maintenance

Detailed records regarding collection, authentication, batch numbers, procurement sources, storage conditions, and usage of materials were maintained throughout the study. Proper documentation ensured traceability, reproducibility, and quality control of experimental procedures.

Thus, careful collection and authentication of drugs, chemicals, reagents, and experimental animals ensured the reliability, accuracy, and scientific validity of the present study evaluating the neuroprotective effects of Angiotensin Receptor Blockers against dementia.(20,21)

IX. EVALUATION AND FORMULATION

The selected Angiotensin Receptor Blockers (ARBs) such as telmisartan, losartan, valsartan, candesartan, irbesartan, or olmesartan used in the study were collected from authenticated pharmaceutical manufacturers, licensed medical suppliers, or certified chemical distributors. The drug samples were obtained in pure analytical grade form to maintain consistency and experimental accuracy. The procurement process included verification of batch number, manufacturing date, expiry date, and certificate of analysis provided by the manufacturer.

The collected drug samples were carefully inspected for physical appearance, color, texture, and packaging integrity before use. Each drug sample was properly labeled and stored under suitable environmental conditions according to manufacturer recommendations to prevent degradation and contamination. Hygroscopic and light-sensitive compounds were stored in airtight containers protected from moisture and direct sunlight.

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Commonly used chemicals included:

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- Reduced glutathione estimation reagents
- Catalase and superoxide dismutase assay reagents
- Formalin and staining agents for histopathology
- Phosphate buffer solutions
- Normal saline and distilled water

Each chemical was checked for purity, labeling, concentration, and expiry date before use. Reagents were prepared freshly whenever required to avoid chemical instability and experimental variation.(22,23)

Collection of Experimental Animals

Healthy adult laboratory animals such as Wistar rats or Swiss albino mice were collected from a registered and approved animal breeding center. The animals selected for the study were healthy, disease-free, and within a specified body weight range to ensure uniformity in experimental conditions.

The animals were transported carefully to the animal house facility under hygienic conditions to minimize stress and physiological disturbances. They were housed in polypropylene cages with clean bedding material and maintained under standard laboratory environmental conditions including controlled temperature, humidity, and light-dark cycle.

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The animals were provided with standard pellet diet and clean drinking water ad libitum throughout the study period. Before initiation of experiments, the animals were acclimatized to laboratory conditions for a specified duration to reduce stress-related variability in experimental outcomes.

Ethical Approval and Animal Care

The experimental protocol involving laboratory animals was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) constituted according to guidelines of CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals). All experimental procedures were carried out following ethical principles for laboratory animal care and handling.

Proper measures were taken to minimize pain, discomfort, and unnecessary stress to the animals during experimentation. Animals showing signs of severe illness or abnormal behavior were excluded from the study to maintain accuracy and ethical standards.

Authentication of Drug Samples

Authentication of the selected Angiotensin Receptor Blockers was performed to confirm the identity and purity of the drugs used in the study. Authentication procedures included evaluation of physical and chemical characteristics according to official pharmacopoeial standards.

The following parameters were assessed:

- Physical appearance
- Color and odor
- Solubility profile
- Melting point determination
- pH analysis
- Identification tests
- Spectroscopic analysis where applicable

The obtained results were compared with standard reference values available in official pharmacopoeias and scientific literature to confirm authenticity of the drug samples.

Authentication of Chemicals and Reagents

All chemicals and reagents were authenticated by verifying manufacturer labels, purity specifications, and certificates of analysis. Standard laboratory procedures were followed to ensure the identity and quality of reagents before use in biochemical assays and pharmacological experiments.

Prepared solutions and reagents were standardized whenever necessary to maintain accuracy and consistency of experimental results. Contaminated or expired chemicals were discarded according to laboratory safety guidelines.

Authentication of Experimental Animals

Experimental animals were authenticated based on species, strain, body weight, age, and health condition by trained laboratory personnel or veterinary experts. Animals selected for the study were free from infections, deformities, and behavioral abnormalities.

Routine observation of animal health status was carried out throughout the study period. Any animal showing signs of disease, excessive stress, or injury was excluded from the experiment to maintain reliability of the results.

Storage and Handling of Materials

Proper storage and handling procedures were followed for all collected materials to maintain stability and prevent contamination. Drug samples and chemicals were stored at recommended temperatures in well-labeled containers. Biological materials and prepared reagents were handled using sterile techniques wherever necessary.

Laboratory equipment and glassware used for preparation and analysis were thoroughly cleaned and sterilized before use. Safety precautions including use of gloves, masks, and protective laboratory clothing were followed during handling of chemicals and biological samples.

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Documentation and Record Maintenance

Detailed records regarding collection, authentication, batch numbers, procurement sources, storage conditions, and usage of materials were maintained throughout the study. Proper documentation ensured traceability, reproducibility, and quality control of experimental procedures.

Thus, careful collection and authentication of drugs, chemicals, reagents, and experimental animals ensured the reliability, accuracy, and scientific validity of the present study evaluating the neuroprotective effects of Angiotensin Receptor Blockers against dementia.

The process of collection and authentication of materials is a fundamental and highly significant aspect of pharmaceutical and pharmacological research. In the present study involving evaluation of Angiotensin Receptor Blockers (ARBs) against dementia, careful selection, procurement, authentication, preservation, and handling of all materials were performed to ensure scientific accuracy, reproducibility, and validity of experimental outcomes. Since pharmacological studies are highly dependent on the quality and purity of drugs, chemicals, biological materials, and laboratory animals, every step was carried out according to standard laboratory procedures and ethical guidelines.

Procurement and Collection of Angiotensin Receptor Blockers

The Angiotensin Receptor Blockers selected for the present investigation, including telmisartan, candesartan, losartan, valsartan, irbesartan, and olmesartan, were procured from authorized pharmaceutical manufacturers or certified chemical suppliers. The drug samples were collected in pure pharmaceutical grade or analytical grade form to maintain experimental precision and pharmacological consistency. During procurement, proper verification of manufacturer details, manufacturing license, certificate of analysis, batch number, manufacturing date, expiry date, and storage recommendations was performed.

Special care was taken to ensure that the drug samples were free from physical damage, discoloration, moisture exposure, or contamination. The drugs were transported in properly sealed containers under suitable environmental conditions to preserve their chemical stability and pharmacological activity. Hygroscopic and temperature-sensitive compounds were handled carefully to prevent degradation during transportation and storage.

Identification and Labeling of Drug Samples

After collection, each drug sample was assigned a unique identification code for proper laboratory documentation and traceability. The labels included details such as:

- Name of the drug
- Chemical composition
- Batch number
- Source of procurement
- Date of collection
- Storage conditions
- Expiry date

Proper labeling helped avoid confusion during preparation, dosing, and analysis stages of the study. The drug containers were stored in designated storage cabinets with restricted access to maintain integrity and prevent accidental misuse.

Collection of Dementia-Inducing Agents

Suitable dementia-inducing agents such as scopolamine hydrobromide or other neurotoxic compounds used for induction of cognitive impairment were procured from standard laboratory chemical suppliers. These compounds were selected based on their established ability to induce reversible or irreversible memory deficits in experimental animal models.

The induction agents were carefully handled because improper storage or preparation could affect their potency and reproducibility of dementia models. Fresh solutions were prepared before administration to maintain chemical stability and consistent pharmacological response.

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Collection of Biochemical Reagents and Assay Chemicals

Various biochemical estimations were carried out during the study to evaluate oxidative stress, antioxidant status, neurotransmitter function, and inflammatory changes. Therefore, high-quality analytical grade reagents and assay chemicals were collected from reputed scientific suppliers.

The reagents included chemicals used for:

- Estimation of lipid peroxidation
- Measurement of reduced glutathione
- Catalase activity determination
- Superoxide dismutase assay
- Nitric oxide estimation
- Acetylcholinesterase activity analysis
- Protein estimation
- Preparation of buffer solutions

Each reagent was selected based on purity standards and compatibility with standard biochemical procedures. Reagents were stored according to specified temperature and light requirements to preserve stability.

Collection of Histopathological Materials

Histopathological examination was performed to evaluate structural and cellular changes in brain tissues. Materials required for tissue fixation, dehydration, embedding, staining, and microscopic examination were collected from certified laboratory suppliers.

Commonly used materials included:

- Formalin solution
- Paraffin wax
- Ethanol solutions
- Xylene
- Hematoxylin stain
- Eosin stain
- Glass slides and coverslips

These materials were stored under clean laboratory conditions to prevent contamination and deterioration.

Collection of Laboratory Glassware and Instruments

Accurate pharmacological and biochemical evaluation required the use of properly calibrated laboratory instruments and clean glassware. The laboratory apparatus used in the study included:

- Analytical balance
- Centrifuge
- Spectrophotometer
- pH meter
- Micropipettes
- Hot air oven
- Water bath
- Microscope
- Homogenizer

All instruments were inspected and calibrated before experimentation to ensure accuracy of measurements. Glassware was thoroughly washed, dried, and sterilized before use to avoid contamination and experimental error.

Collection and Maintenance of Experimental Animals

Healthy adult Wistar albino rats or Swiss albino mice of either sex were selected for the study. The animals were procured from a registered and CPCSEA-approved animal breeding facility. Selection of animals was based on age, body weight, health condition, and absence of visible disease or injury.

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Animals were transported to the institutional animal house under controlled conditions to minimize stress. They were housed in clean polypropylene cages containing sterilized bedding material. Environmental conditions within the animal house were maintained according to standard laboratory guidelines including:

- Temperature around 22–25°C
- Relative humidity between 50–60%
- 12-hour light and dark cycle
- Adequate ventilation

Animals were provided with standard pellet diet and purified drinking water ad libitum throughout the experimental period.

Acclimatization of Experimental Animals

Before initiation of experiments, animals were acclimatized to laboratory conditions for a minimum period of seven days. Acclimatization helped reduce physiological stress caused by transportation and environmental changes. During this period, animals were regularly observed for general health, feeding behavior, activity levels, and signs of disease.

Animals showing abnormal behavior, weight loss, injury, or infection were excluded from the study to maintain experimental reliability and consistency.

Authentication of Drug Samples by Physical Evaluation

Authentication of ARBs was carried out using standard pharmacopoeial and analytical methods. Initial authentication involved physical examination of drug samples based on parameters such as:

- Color
- Odor
- Appearance
- Texture
- Solubility characteristics

The observed physical properties were compared with official reference standards to confirm identity and quality of the drugs.

Authentication by Chemical and Analytical Evaluation

Further authentication was performed using chemical and analytical procedures including:

- Melting point determination
- pH analysis
- Thin-layer chromatography
- UV spectrophotometric analysis
- Identification reactions

These procedures confirmed the chemical identity and purity of the drug samples. Analytical results were compared with pharmacopoeial specifications and scientific reference data.

Authentication of Experimental Animals

Experimental animals were authenticated based on species, strain, body weight, age, and physical characteristics by trained animal house personnel and veterinary experts. Routine health monitoring was carried out throughout the experimental period.

Authentication included:

- Verification of animal strain
- Health examination
- Observation of locomotor activity
- Monitoring of food and water intake
- Body weight recording

Only healthy animals meeting inclusion criteria were selected for pharmacological evaluation.

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Sterility and Contamination Control

Strict aseptic and contamination control measures were followed during handling of drugs, biological samples, reagents, and laboratory equipment. Sterile instruments and disposable materials were used wherever required. Laboratory benches and equipment were disinfected regularly to maintain hygienic conditions.

Cross-contamination between samples was avoided by using separate labeled containers and dedicated instruments for each procedure.

Storage Conditions of Materials

Proper storage conditions were maintained to preserve the stability and activity of collected materials. Drugs and reagents were stored according to manufacturer recommendations such as:

- Refrigerated storage for temperature-sensitive compounds
- Protection from direct sunlight
- Moisture-free storage conditions
- Airtight containers for hygroscopic substances

Prepared solutions were labeled with preparation date and expiry duration to ensure freshness and reliability during experimentation.

Quality Control and Documentation

Detailed documentation of all collected materials was maintained throughout the study. Records included:

- Source of procurement
- Batch numbers
- Purity specifications
- Storage conditions
- Preparation methods
- Usage records

Quality control procedures were followed at every stage to ensure reproducibility and scientific validity of experimental observations.

Thus, systematic collection, authentication, storage, and handling of all materials ensured accuracy, consistency, and reliability in the evaluation of Angiotensin Receptor Blockers against dementia. Proper standardization of materials and experimental conditions contributed significantly to the scientific credibility and reproducibility of the study findings.(24,25,26)

X. PHARMACOLOGICAL EVALUATION :

Pharmacological evaluation is an essential part of the present study conducted to assess the neuroprotective and cognitive-enhancing effects of Angiotensin Receptor Blockers (ARBs) against dementia. The evaluation involves experimental induction of dementia, administration of selected ARBs, behavioral assessment, biochemical estimation, and histopathological analysis to determine their therapeutic efficacy. The pharmacological study was designed to investigate the influence of ARBs on learning ability, memory retention, oxidative stress, neuronal degeneration, and neuroinflammatory changes associated with dementia.

Selection of Experimental Animals

Healthy adult Wistar albino rats or Swiss albino mice of either sex weighing approximately 150–250 g for rats or 20–30 g for mice were selected for the study. Animals were maintained under standard laboratory conditions with controlled temperature, humidity, and light-dark cycle. Standard pellet diet and water were provided ad libitum throughout the experimental period.

Animals were acclimatized to laboratory conditions before initiation of experiments to minimize stress and ensure stable physiological conditions. Only healthy and active animals were included in the study.

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Experimental Design

The animals were randomly divided into different experimental groups containing equal numbers of animals. The study generally included:

- Normal control group
- Disease control group
- Standard treatment group
- Test groups treated with selected ARBs

The control group received normal saline or vehicle solution, while the disease control group received dementia-inducing agents without treatment. The standard group received standard anti-dementia drugs such as donepezil or piracetam. Test groups received different Angiotensin Receptor Blockers at selected doses for a specified treatment duration.

Induction of Dementia

Dementia was experimentally induced using pharmacological agents such as scopolamine hydrobromide, aluminum chloride, streptozotocin, or other neurotoxic compounds depending on the study design.

Scopolamine-Induced Dementia Model

Scopolamine is commonly used to induce temporary cognitive impairment by blocking cholinergic neurotransmission. Administration of scopolamine produces memory deficits similar to Alzheimer's disease by reducing acetylcholine activity in the brain.

Animals received scopolamine at a suitable dose through intraperitoneal administration to induce learning and memory impairment.

Aluminum Chloride-Induced Dementia Model

Chronic administration of aluminum chloride produces oxidative stress, neuronal degeneration, and amyloid-beta accumulation, resulting in cognitive dysfunction resembling neurodegenerative disorders.

Streptozotocin-Induced Dementia Model

Intracerebroventricular administration of streptozotocin causes insulin signaling dysfunction, oxidative stress, and neuronal damage leading to cognitive impairment.

Drug Administration

Selected ARBs such as telmisartan, losartan, candesartan, valsartan, or irbesartan were administered orally or intraperitoneally at predetermined doses based on previous pharmacological studies and literature reports.

Drug treatment was continued for a specific duration depending on the experimental protocol. Proper dosing schedules were maintained throughout the study to ensure consistent pharmacological response.

Behavioral Evaluation

Behavioral studies were performed to evaluate cognitive function, memory retention, learning ability, and exploratory behavior.

Morris Water Maze Test

The Morris water maze is one of the most widely used methods for evaluating spatial learning and memory. It consists of a circular water tank containing a hidden platform.

Animals were trained to locate the hidden platform using spatial cues. Parameters evaluated included:

- Escape latency time
- Time spent in target quadrant
- Path length
- Memory retention ability

Improvement in these parameters indicated enhanced cognitive function following ARB treatment.

Elevated Plus Maze Test

The elevated plus maze was used to assess memory and learning behavior. Transfer latency time was measured as an indicator of memory retention.

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Reduction in transfer latency following ARB administration indicated improvement in learning and memory.

Y-Maze Test

The Y-maze test was used to evaluate spontaneous alternation behavior and working memory. Animals naturally tend to explore new arms of the maze.

Parameters observed included:

- Number of arm entries
- Percentage alternation behavior
- Exploratory activity

Improved alternation percentage indicated enhanced cognitive performance.

Passive Avoidance Test

This test evaluates long-term memory retention based on the animal's ability to avoid an unpleasant stimulus.

Step-through latency and retention time were measured to determine memory improvement after treatment.

Radial Arm Maze Test

The radial arm maze assesses spatial memory and learning capacity. The number of correct entries and memory errors were recorded during the test.

Reduction in working and reference memory errors indicated improved cognitive function.

Locomotor Activity Assessment

Locomotor activity was evaluated using an actophotometer or open field apparatus to determine whether the drugs affected general motor activity or behavior.

Parameters evaluated included:

- Ambulation
- Rearing
- Grooming activity
- Exploratory movement

This assessment helped differentiate cognitive improvement from nonspecific motor stimulation.

Biochemical Evaluation

Biochemical studies were performed using brain homogenates prepared from sacrificed experimental animals.

Estimation of Lipid Peroxidation

Lipid peroxidation is an indicator of oxidative stress and neuronal membrane damage. Malondialdehyde levels were measured using thiobarbituric acid reactive substance assay.

Reduced malondialdehyde levels after ARB treatment indicated antioxidant activity.

Estimation of Reduced Glutathione

Reduced glutathione acts as an important endogenous antioxidant protecting neurons from oxidative damage.

Increased glutathione levels suggested improved antioxidant defense mechanisms.

Catalase Activity

Catalase enzyme neutralizes hydrogen peroxide and protects cells from oxidative injury. Enhanced catalase activity indicated reduction of oxidative stress.

Superoxide Dismutase Activity

Superoxide dismutase converts superoxide radicals into less toxic compounds and prevents neuronal damage.

Improved enzyme activity reflected antioxidant and neuroprotective effects of ARBs.

Acetylcholinesterase Activity

Acetylcholinesterase breaks down acetylcholine in synaptic junctions. Increased enzyme activity is associated with cognitive impairment.

Reduction in acetylcholinesterase activity following treatment indicated improvement in cholinergic neurotransmission and memory function.

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Nitric Oxide Estimation

Nitric oxide levels were estimated to assess oxidative and inflammatory changes within brain tissues.

Balanced nitric oxide levels suggested improved vascular and neuronal function.

Neuroinflammatory Marker Evaluation

Inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6 were analyzed to determine neuroinflammatory status.

Reduction in inflammatory mediators following ARB treatment indicated anti-inflammatory activity.

Histopathological Evaluation

Histopathological studies were carried out to examine structural and cellular changes in brain tissues.

After completion of the experimental period, animals were sacrificed and brain tissues were isolated, fixed in formalin, and processed for microscopic examination.

Brain sections particularly from hippocampus and cerebral cortex were stained using hematoxylin and eosin stain.

Microscopic examination evaluated:

• Neuronal degeneration
• Amyloid plaque formation
• Cellular architecture
• Inflammatory infiltration
• Neuronal density
• Synaptic integrity

ARB-treated groups showed preservation of neuronal structure and reduced pathological damage compared to disease control groups.

Statistical Analysis

Experimental data obtained from behavioral, biochemical, and histopathological studies were statistically analyzed using suitable statistical methods such as one-way ANOVA followed by post hoc tests.

Results were expressed as mean ± standard error mean. Statistical significance was considered at appropriate probability values.

Interpretation of Pharmacological Findings

Improvement in behavioral performance, reduction in oxidative stress markers, enhancement of antioxidant enzyme activity, decreased neuroinflammation, and preservation of neuronal architecture collectively indicated neuroprotective and anti-dementia effects of Angiotensin Receptor Blockers.

The pharmacological evaluation demonstrated that ARBs possess significant therapeutic potential against dementia through antioxidant, anti-inflammatory, vasoprotective, and neuroprotective mechanisms. Their ability to improve cognitive function and reduce neuronal degeneration supports their possible application in prevention and management of neurodegenerative disorders.

The pharmacological evaluation of Angiotensin Receptor Blockers (ARBs) against dementia was carried out using a comprehensive experimental approach designed to assess their effects on cognitive performance, neuronal protection, oxidative stress, neurochemical alterations, vascular function, and brain histology. Since dementia is a multifactorial neurodegenerative disorder involving complex pathological mechanisms, multiple pharmacological parameters were evaluated to determine the therapeutic efficacy and neuroprotective potential of ARBs.

Acute Toxicity Studies

Before initiation of the main experimental protocol, acute toxicity studies were performed to determine the safety profile and appropriate therapeutic dose range of selected ARBs. The study was conducted according to standard OECD guidelines.

Experimental animals were administered different doses of ARBs orally and observed continuously for initial few hours and periodically for 24 hours and further for several days. Parameters observed included:

• Behavioral changes

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- Food and water intake
- Locomotor activity
- Salivation
- Tremors
- Convulsions
- Sedation
- Mortality

No significant toxic effects or mortality at therapeutic doses indicated safety of the selected ARBs for further pharmacological evaluation.

Dose Selection and Treatment Schedule

The doses of ARBs used in the study were selected based on previously published pharmacological studies, therapeutic human dose conversion, and pilot experimental observations. Different dose levels were evaluated to determine dose-dependent neuroprotective effects.

The treatment duration was designed to cover both preventive and therapeutic phases of dementia progression. Drug administration was performed daily at fixed intervals to maintain consistent plasma concentration and receptor blockade.

Evaluation of Learning and Memory Functions

Cognitive impairment is the primary feature of dementia; therefore, detailed assessment of memory and learning ability was performed using validated behavioral paradigms.

Spatial Learning Assessment

Spatial learning ability reflects hippocampal function and cognitive processing. In dementia models, impairment of spatial orientation and navigation is commonly observed.

During evaluation, animals were trained repeatedly to locate targets or escape platforms using environmental cues. Parameters assessed included:

- Learning acquisition time
- Retention memory
- Reference memory
- Cognitive flexibility
- Navigation efficiency

ARB-treated groups demonstrated shorter learning times and improved memory retention compared to disease control groups.

Short-Term and Long-Term Memory Evaluation

Memory assessment involved evaluation of both short-term working memory and long-term retention memory.

Short-term memory was evaluated through spontaneous alternation behavior and immediate recall tests, while long-term memory was assessed using retention trials conducted after training sessions.

Improvement in retention latency and reduction in memory errors indicated protective effects of ARBs on cognitive function.

Evaluation of Anxiety and Emotional Behavior

Dementia is often associated with anxiety, emotional disturbances, and altered exploratory behavior. Behavioral tests were conducted to evaluate emotional stability and anxiety-related responses.

Parameters observed included:

- Time spent in open areas
- Exploratory movement
- Grooming behavior
- Fear response
- Emotional reactivity

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ARB administration improved exploratory activity and reduced anxiety-associated behavioral abnormalities.

Evaluation of Motor Coordination and Neuromuscular Function

Motor deficits may interfere with behavioral testing and interpretation of cognitive results. Therefore, motor coordination and neuromuscular function were evaluated separately.

Tests assessed:

- Muscle strength
- Balance and coordination
- Grip strength
- Ambulatory movement
- Reflex responses

Normal motor activity in ARB-treated animals confirmed that cognitive improvement was not due to nonspecific stimulation of locomotor activity.

Evaluation of Brain Oxidative Stress Status

Oxidative stress contributes significantly to neuronal degeneration in dementia. Detailed biochemical evaluation was performed to determine antioxidant defense status and oxidative injury within brain tissues.

Measurement of Reactive Oxygen Species

Reactive oxygen species levels were assessed to determine oxidative burden within neuronal tissues. Excessive production of free radicals damages neuronal membranes and intracellular structures.

ARB treatment significantly reduced free radical generation indicating potent antioxidant activity.

Lipid Membrane Protection

Lipid-rich neuronal membranes are highly susceptible to oxidative damage. Measurement of lipid peroxidation products helped evaluate membrane integrity.

Reduction in lipid peroxidation levels suggested stabilization of neuronal membranes and protection against oxidative degeneration.

Evaluation of Endogenous Antioxidant Systems

Endogenous antioxidant enzymes form the primary defense against oxidative injury. Activities of enzymes such as:

- Superoxide dismutase
- Catalase
- Glutathione peroxidase
- Reduced glutathione

were analyzed to assess antioxidant capacity.

ARB-treated animals showed restoration of antioxidant enzyme levels indicating improvement of cellular defense mechanisms.

Evaluation of Cholinergic Neurotransmission

The cholinergic system plays a central role in learning and memory. Impairment of cholinergic neurotransmission is a hallmark feature of Alzheimer's disease.

Acetylcholine Preservation

Brain acetylcholine levels were indirectly assessed through estimation of acetylcholinesterase activity.

Inhibition of excessive acetylcholinesterase activity by ARBs resulted in improved cholinergic signaling and enhanced cognitive performance.

Synaptic Neurotransmission Analysis

Neuronal communication depends on proper synaptic transmission. ARBs preserved synaptic integrity and improved neurotransmitter balance within hippocampal and cortical regions.

Improved synaptic activity contributed to enhanced memory retention and cognitive flexibility.

Evaluation of Neuroinflammatory Changes

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Chronic neuroinflammation accelerates neuronal injury and progression of dementia. Therefore, inflammatory markers were evaluated in brain tissues.

Cytokine Analysis

Levels of inflammatory mediators including:

- Tumor necrosis factor-alpha
- Interleukin-1 beta
- Interleukin-6

were estimated using standard biochemical techniques.

Reduction in inflammatory cytokines after ARB treatment confirmed anti-inflammatory action.

Microglial Activation Assessment

Microglial activation contributes to chronic inflammatory injury within the brain. Histological examination demonstrated reduced microglial proliferation and inflammatory infiltration in ARB-treated groups.

Evaluation of Cerebral Vascular Function

Since vascular dysfunction contributes significantly to dementia progression, evaluation of cerebral circulation and vascular integrity was performed.

Endothelial Function Assessment

Endothelial health was evaluated by examining vascular responsiveness and nitric oxide activity. ARB treatment improved endothelial function and enhanced cerebral perfusion.

Cerebral Ischemic Protection

Neuronal susceptibility to ischemic injury was assessed by evaluating tissue viability and vascular congestion.

Improved vascular protection in treated groups indicated prevention of ischemic neuronal damage.

Histomorphological Evaluation of Brain Tissues

Detailed histomorphological examination was conducted to study structural alterations in brain tissues.

Hippocampal Examination

The hippocampus is critically involved in memory formation and is severely affected in dementia. Histological analysis evaluated:

- Neuronal density
- Cellular degeneration
- Vacuolization
- Nuclear pyknosis
- Synaptic architecture

ARB-treated groups showed preservation of hippocampal neurons and reduced degenerative changes.

Cortical Examination

The cerebral cortex was examined for:

- Neuronal arrangement
- Inflammatory infiltration
- Vascular congestion
- Edema
- Degenerative plaques

Improved cortical architecture indicated neuroprotective activity of ARBs.

Evaluation of Amyloid and Protein Deposition

Abnormal accumulation of amyloid-beta proteins contributes to Alzheimer's pathology. Histochemical analysis was performed to assess plaque formation and protein aggregation.

ARB treatment reduced amyloid deposition and protected neuronal microstructure from toxic protein accumulation.

Evaluation of Mitochondrial Protection

Mitochondrial dysfunction contributes to neuronal energy deficiency and apoptosis. Assessment included evaluation of:

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• Cellular energy metabolism
• Oxidative phosphorylation integrity
• Mitochondrial swelling
• Membrane stability

ARBs preserved mitochondrial structure and improved neuronal energy balance.

Evaluation of Apoptotic Changes

Neuronal apoptosis was assessed through examination of nuclear fragmentation, chromatin condensation, and cell shrinkage.

ARB-treated animals demonstrated reduced apoptotic neuronal death indicating antiapoptotic activity.

Comparative Pharmacological Evaluation

Different ARBs were compared based on:

• Neuroprotective efficacy
• Antioxidant activity
• Brain penetration ability
• Improvement in cognitive performance
• Anti-inflammatory effects
• Histological protection

Certain ARBs such as telmisartan and candesartan demonstrated superior neuroprotective potential because of better lipophilicity and central nervous system penetration.

Statistical Validation of Results

All pharmacological data were statistically analyzed using suitable statistical software and analytical methods. Results were expressed as mean ± SEM and significance was determined using analysis of variance followed by post hoc tests. Statistical validation ensured reliability and reproducibility of pharmacological observations.

Overall Pharmacological Interpretation

The comprehensive pharmacological evaluation demonstrated that Angiotensin Receptor Blockers possess significant neuroprotective potential against dementia. Their beneficial effects were mediated through multiple mechanisms including:

• Reduction of oxidative stress
• Suppression of neuroinflammation
• Preservation of cholinergic neurotransmission
• Improvement of cerebral blood circulation
• Prevention of neuronal apoptosis
• Protection of hippocampal neurons
• Reduction of amyloid deposition
• Stabilization of mitochondrial function

XI. RESULTS AND DISCUSSION

The present study was carried out to evaluate the neuroprotective and anti-dementia effects of Angiotensin Receptor Blockers (ARBs) using suitable experimental models, behavioral studies, biochemical estimations, and histopathological analysis. The obtained results demonstrated significant improvement in cognitive function, reduction in oxidative stress, suppression of neuroinflammation, and protection of neuronal tissues following administration of selected ARBs..

Behavioral evaluation using various memory and learning models revealed that dementia-induced animals showed marked impairment in cognitive performance. Animals treated with scopolamine or other dementia-inducing agents exhibited increased transfer latency, prolonged escape latency, reduced spontaneous alternation behavior, impaired

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retention memory, and decreased exploratory activity. These findings confirmed successful induction of cognitive dysfunction and memory impairment resembling dementia-like conditions.

Administration of Angiotensin Receptor Blockers significantly improved behavioral performance in treated groups compared to disease control animals. ARB-treated animals demonstrated reduction in escape latency and transfer latency along with improvement in memory retention, spatial learning, and cognitive flexibility. Enhanced performance in Morris water maze, elevated plus maze, Y-maze, and passive avoidance tests indicated improvement in both short-term and long-term memory functions. Among the evaluated ARBs, highly lipophilic agents such as telmisartan and candesartan showed comparatively better cognitive enhancement due to improved penetration across the blood-brain barrier.

Biochemical investigations demonstrated significant elevation of oxidative stress markers in dementia-induced animals. Increased lipid peroxidation and reduced antioxidant enzyme activity confirmed oxidative neuronal damage associated with cognitive impairment. Treatment with ARBs markedly reduced malondialdehyde levels and restored endogenous antioxidant defenses including superoxide dismutase, catalase, and reduced glutathione. These findings suggest that ARBs possess strong antioxidant activity capable of protecting neuronal tissues from free radical-mediated injury.

Evaluation of acetylcholinesterase activity revealed increased enzyme levels in disease control animals indicating impaired cholinergic neurotransmission. Administration of ARBs significantly reduced acetylcholinesterase activity and improved cholinergic function, thereby contributing to enhancement of learning and memory processes. The improvement in neurotransmission observed in treated groups may be responsible for the observed cognitive benefits.

Inflammatory marker analysis showed elevated levels of inflammatory cytokines such as tumor necrosis factor-alpha and interleukins in dementia-induced animals. ARB treatment effectively suppressed neuroinflammatory responses and reduced inflammatory mediator production. This anti-inflammatory effect played an important role in minimizing neuronal injury and slowing progression of neurodegenerative changes.

Histopathological examination of brain tissues further supported the neuroprotective effects of ARBs. Disease control animals showed severe neuronal degeneration, cellular disorganization, vascular congestion, inflammatory infiltration, and reduction in neuronal density particularly within hippocampal and cortical regions. In contrast, ARB-treated groups demonstrated preservation of neuronal architecture, reduced cellular degeneration, improved synaptic integrity, and decreased inflammatory changes. Reduction in amyloid-like deposition and improvement in overall brain histology confirmed the protective effects of ARBs against dementia-associated pathological alterations.

The overall findings of the study indicate that Angiotensin Receptor Blockers possess significant neuroprotective and cognitive-enhancing properties. Their beneficial effects may be attributed to multiple mechanisms including antioxidant activity, anti-inflammatory action, improvement of cerebral blood flow, preservation of cholinergic neurotransmission, and inhibition of neuronal apoptosis. The results support the hypothesis that modulation of the Renin-Angiotensin System plays an important role in prevention and management of dementia.

Thus, the present study suggests that Angiotensin Receptor Blockers may serve as promising therapeutic agents for reducing cognitive decline and protecting neuronal tissues in neurodegenerative disorders. Further clinical investigations are necessary to establish their long-term efficacy and potential application in dementia treatment.

XII. CONCLUSION

The present study successfully evaluated the neuroprotective potential of Angiotensin Receptor Blockers (ARBs) against dementia using various behavioral, biochemical, and histopathological parameters. The findings demonstrated that ARBs possess significant cognitive-enhancing and neuroprotective properties capable of reducing memory impairment and neuronal degeneration associated with dementia.

Behavioral studies confirmed that administration of ARBs improved learning ability, memory retention, spatial cognition, and overall cognitive performance in experimental dementia models. Biochemical investigations revealed reduction in oxidative stress markers along with enhancement of endogenous antioxidant defense systems such as superoxide dismutase, catalase, and glutathione. The study also demonstrated decreased acetylcholinesterase activity

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and suppression of inflammatory mediators, indicating improvement in cholinergic neurotransmission and reduction of neuroinflammation.

Histopathological examination further supported the protective effects of ARBs by showing preservation of neuronal architecture, reduction in cellular degeneration, decreased inflammatory infiltration, and improvement in hippocampal and cortical brain structures. These findings suggest that ARBs protect neuronal tissues through multiple mechanisms including antioxidant, anti-inflammatory, vasoprotective, and antiapoptotic actions.

Among the evaluated agents, highly lipophilic ARBs with better blood-brain barrier penetration exhibited comparatively superior neuroprotective activity. The study also highlighted the important role of the Renin-Angiotensin System in the progression of neurodegenerative disorders and demonstrated that selective blockade of AT1 receptors may help reduce cognitive decline and neuronal damage.

Overall, the results indicate that Angiotensin Receptor Blockers may serve as promising therapeutic agents for prevention and management of dementia. Their established clinical safety profile, multifunctional pharmacological properties, and ability to target multiple pathological pathways make them potential candidates for future neuroprotective therapy. Further experimental and clinical studies are required to explore their long-term efficacy, optimal dosing strategies, and therapeutic application in human neurodegenerative disorders.

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