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Effects of antihypertensive agents on Alzheimer's disease biomarkers in hypertensive rats with experimentally induced Alzheimer's

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Abstract

Background and objective: The most common cause of dementia in the elderly is Alzheimer's disease (AD). Numerous research studies have demonstrated a connection between hypertension (HTN) and the risk of developing AD. An increasing amount of evidence indicates that cognitive function significantly declines in HTN patients due to pathogenic pathways such as atherosclerosis, arteriolosclerosis, stroke, and cerebral ischemia. This study aims to investigate the effects of antihypertensive drugs on AD onset and levels of AD biomarkers in a rat model of HTN–AD. Oral N-nitro-L-arginine methyl ester hydrochloride (L-NAME HCl) and intraperitoneal injections of scopolamine were used to induce HTN and AD, respectively.

Methods: Forty-two female Wistar albino rats were split into seven groups of six rats. Group I represented the negative control group. The six experimental groups received scopolamine (2 mg/kg) and L-NAME HCl (40 mg/kg), administered intraperitoneally. Group II represented the positive control. The rats in Groups III, IV, V, VI, and VII received a daily oral dose of donepezil (10mg/kg), telmisartan (10mg/kg), amlodipine (5mg/kg), bisoprolol (10mg/kg), or bumetanide (20mg/kg), respectively. Differences for all parameters were assessed using one-way analysis of variance, including for BP, between the control and drug-treated rats using the Statistical Package for Social Science (version 27). Statistical significance was assessed using the P-value<0.05

Results: Inducing HTN and AD in rats significantly elevated the levels of all serum parameters compared to the control group, alongside a noticeable rise in brain parameters. The largest statistically significant decreases—in serum tumor necrosis factor alpha, interleukin-6, and C-reactive protein—were noted in telmisartan-treated rats. The most statistically significant decrease in brain acetylcholinesterase was seen in bumetanide-treated rats. On the other hand, donepezil-treated rats showed the largest statistically significant decreases in brain amyloid-β 42, β-secretase, phosphorylated microtubule-associated protein tau, malondialdehyde, nitric oxide, serum total tau protein, and serum amyloid-β 42. Bumetanide-treated rats showed the greatest performance on the spontaneous alternation (73.66%) and total arm entry tests (57.66) compared those in the other treatment groups, while donepezil-treated rats spent more time (5.42 minutes) in the novel arms compared to those of the other groups.

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Conclusion: All the antihypertensive medications examined in this investigation effectively reduced the majority of plasma and brain biomarkers and therefore show great therapeutic potential, particularly bumetanide and telmisartan. According to this study, telmisartan and bumetanide, either alone or in combination with donepezil, may be effective medication options for neurodegeneration and risk mitigation in AD patients who also have HTN.

Keywords: Alzheimer's, Amlodipine, Bumetanide, Bisoprolol, Donepezil, Hypertension, Telmisartan.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that progresses over time and is characterized by a progressive loss of cognitive function that impairs the capacity for independent living (1). The steady decline in cognitive abilities due to AD typically begins with the loss of recent memories; over time, it impacts all cognitive capacities, leading to a total need for help with daily activities and eventually to premature death (2). Early evaluations uncovered more than 20 risk variables for AD, including age, aluminum exposure, family history, traumatic brain injury, and related comorbidities such as infection and vascular disease (3). One of the most significant risk factors for AD and cognitive deterioration is aging (4).

According to a study by Varkey and colleagues (5), the most prevalent concomitant ailment among dementia patients is HTN. Data on the prevalence of dementia and HTN, gathered from 186 nations, revealed that 15.8% of the world's population has HTN as a contributing factor for dementia (6). According to the findings of Varkey and colleagues, older persons with systolic BP readings above 160 mmHg have higher degrees of cognitive impairment, which could lead to AD (7).

It is important to consider what is known about the connections between high BP and HTN and their high risk for AD, vascular dementia, and HTN-associated stroke. Cognitive function significantly declines in HTN patients due to pathogenic pathways such as atherosclerosis, arteriolosclerosis, stroke, and cerebral ischemia (8). The vascular hypothesis pertaining to the onset of AD is rapidly gaining support. This theory holds that the early stages of AD are primarily microvascular and involve the narrowing of the brain artery (9).

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Improvements in experimental methods for assessing HTN as a risk factor for AD have resulted in several modifications to the original AD vascular theory. First, HTN speeds up the microvascular damage brought on by HTN for numerous AD clinical symptoms, such as blood–brain barrier disruption and subsequent neuroinflammation, as well as cerebral microhemorrhages. Neuroinflammation has been observed to be crucial to the occurrence of both AD and HTN (10). The amyloid cascade hypothesis of AD claims that increased levels of amyloid β (Aβ) cause multifarious and progressive Cerebro microvascular damage, which eventually leads to AD onset and the early-stage cognitive dysfunctions associated with plaque (11). Summarizing the clinical evidence of AD in humans from the amyloid hypothesis as well as the vascular theory, elevated blood pressure appears to worsen Aβ-induced Cerebro microvascular damage, worsening AD and accelerating its progression (12).

The purpose of this study is to examine the effects of antihypertensive medications on AD progression and AD biomarker levels in an induced AD–HTN rat model in order to better understand the relationship between the two conditions. Changes in Aβ 42, phosphorylated microtubule-associated protein tau (pMAPT/ptau), and tau, which are crucial neuropathological indicators of AD, were investigated in the serum and brain. Additionally, we examined the impacts of HTN and AD on the levels of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-a), C-reactive protein (CRP), malondialdehyde (MDA), nitric oxide (NO), acetylcholinesterase (AChE), and β-secretase.

Materials and methods

Animals

In this study, 42 female Wistar albino rats, weighing 180–220 g and aged 4–5 months, were assessed. Six rats were kept in each cage with a 12-hour light–dark cycle (light on at 7:00 am and light off at 7:00 pm) at 24°C and 55±5% humidity for one week before the experiment's start. The rats had unrestricted access to water and were fed standard rat pellet diets. The Hawler Medical University College of Pharmacy provided the animals (Iraq-Erbil). The Hawler Medical University College of Pharmacy's ethics committee approved this work under permission number HMUECPH-04112024-83. During the research project, we ensured compliance with the Guide for the Care and Use of Laboratory Animals, established by the National Academy of Sciences and published by the National Institutes of Health.

Drugs and chemicals

Enzyme-linked assay (ELISA) kits for rat TNF-a, CRP, inducible NO, IL-6, AChE, Aβ 42, β-secretase, pMAPT/ptau, MDA, and tau protein were purchased from

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Sunlong Biotech Co., Ltd (China). N-nitro-L-arginine methyl ester hydrochloride (L-NAME HCl) was purchased from Shanghai Macklin Biochemical Co., Ltd (China). Scopolamine hydrobromide was purchased from USP (Rockville, MD, United States). The following medications were purchased from a pharmacy: donepezil hydrochloride 10mg tablets (Al-Taqaddom Pharmaceutical Industries, Amman, Jordan), telmisartan 80mg tablets (Boehringer Ingelheim, Ingelheim, Germany),amlodipine besylate 5mg capsules (Pfizer, Paris, France), bisoprolol hemifumarate 5mg tablets (Merck, Darmstadt, Germany), and bumetanide 1mg tablets (AllphamedPharbilArzneimittel, Göttingen, Germany).

Experimental design

In the study, 42 Wistar albino rats were divided into seven groups, each consisting of six rats. Group I was the negative control group, with the rats being given saline water. In all other groups, HTN and AD were induced. HTN was induced by orally administering L-NAME HCl 40 mg/kg per day by gastric gavage from Day 1 until the end of the study (Day 29) (18,19). AD was induced by administering scopolamine intraperitoneally at a dose of 2 mg/kg per day (20,21) from Day 8 until the end of the study. Group II was the positive control group. Rats in Groups III, IV, V, VI, and VII were given experimental medications from Days 15 to 29, as follows:

Group III received a daily oral dosage of 10 mg/kg donepezil (17).

Group IV received a daily oral dosage of 10 mg/kg telmisartan (23).

Group V received a daily oral dosage of 5 mg/kg amlodipine (19).

Group VI received a daily oral dosage of 10 mg/kg bisoprolol (20).

Group VI received a daily oral dosage of 20 mg/kg bumetanide (21).

The correct dosages were obtained by dissolving the oral medicines in regular saline. The animals received the medications through oral gavage. On Day 28, the rats completed the spontaneous alternation test in the Y-maze, and their BPs were measured. On Day 29, all rats were fasted for six to eight hours in the morning. The rats were then anesthetized using xylazine (10 mg/kg) and ketamine (125 mg/kg) (17). Their brains were removed and processed for brain biomarkers, and blood samples were taken. All measures were taken to minimize the rats' suffering and guarantee their welfare, including proper handling, environmental enrichment, and the use of anesthesia and analgesics during procedures. Ethical guidelines were followed throughout to maintain high standards of animal welfare. Cervical dislocation was used to sacrifice the rats

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in accordance with ethical guidelines (22).

Blood samples were collected using cardiac punctures. The blood samples were centrifuged, and the separated serum samples were stored in tubes in the freezer at –20°C for one week prior to the test day. The brain tissues were manually homogenized using a mortar and pestle, combined with phosphate buffer, and cleaned with ice-cold normal saline (23). A cold centrifuge was used to separate the brain tissue extracts, which were thereafter transferred into Eppendorf tubes labeled with the group name and stored in a freezer at –80°C for seven days until the test day (24).

Y-maze spontaneous alternation test

The Y-maze test was used to assess the rats' short-term memory. Three similar arms (designated A, B, and C) made up the maze, each measuring 50 cm in length, 15 cm in height, and 15 cm in width and positioned at equal angles. Video was captured over eight-minute sessions in which the rats were permitted to move through the maze (25). The rats' capacity to consistently enter a different arm—known as an alternation choice—was assessed during the test. Two entries into the same arm were regarded as mistakes. Arm entry was considered complete once the rat's rear paw was within the arm. Alternation was defined as the overlapping of successive entries into a triplet set's three arms (e.g., ABC, BCA, ...). Spontaneous alternation percentage (SAP%), total arm entries, and time spent in novel arms were determined. The SAP% indicates a rat's spatial working memory, using its innate interest in investigating previously unexplored arms of a Y-maze (26). Rats are noted to recall previously visited places. After three consecutive arm entrances, the rat reaches a certain arm of the maze, and there is a random alternation. The percentage of spontaneous alternation is calculated using the following formula: SAP%=((number of alternations)/(TAE–2))×100 (27).

Blood pressure measurement

The rats' BPs were measured using the CODA 8 High Throughput Non-Invasive Blood Pressure System. Up to eight mice or rats can have their BPs measured simultaneously using this system. The CODA tail cuff system measures BP by measuring tail blood volume using volume pressure recording. An occlusion tail cuff and a specially made differential pressure transducer were used to measure the total volume of blood in the tail without requiring individual pulse signals. Either awake or sedated mice or rats can be used for measurements. The CODA system composed of a controller, laptop computer, software, cuffs, animal holders, infrared warming pads, and an infrared thermometer (28).

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Biochemical assays

Rat Aβ peptide 42, pMAPT/ptau, AChE, β-secretase, TNF-a, NO, MDA, tau protein, CRP, and IL-6 were assessed utilizing rat-specific ELISA kits.

Statistical analysis

All data were expressed as mean±standard error mean (mean±SEM). Differences for all parameters were assessed using one-way analysis of variance, including for BP, between the control and drug-treated rats using the Statistical Package for Social Science (version 27). To ascertain the precise differences and levels of significance between the treatment groups and the positive control group, post hoc tests were conducted; groups were compared using the Tukey multiple comparison test. Statistical significance was assessed using the P-value <0.05.

Results

Effects of different treatment groups' brain biomarkers

The results, as shown in Table 1, revealed that the positive control group (with induced HTN and AD) had significantly higher brain acetylcholinesterase levels (10.7±0.37 ng/ml) than the negative control group (4.1±0.18 ng/ml; P <0.05). Significant reductions were observed in all treatment groups compared to the positive control group (P <0.05).

Brain A β levels in the positive control rats were significantly higher (37.04±1.6 pg/ml) than in the negative control group (21.46±0.34 pg/ml; P <0.05). Brain A β levels were significantly reduced in all treatment groups (P <0.05).

Brain β -secretase levels in the HTN- and AD-induced rats were significantly higher (41.0±0.93 pg/ml) than in the negative control group (25.5±0.35 pg/ml; P <0.05). Brain β -secretase levels were significantly reduced in all treatment groups (P <0.05) except Group VI, in which the reduction was insignificant.

Levels of pMAPT/ptau were significantly higher in the positive control group than in the negative control group. According to the *post hoc* analysis, brain pMAPT/ptau levels were significantly reduced in all treatment groups (P <0.05).

Levels of MDA in rats pre-treated with scopolamine and L-NAME HCl were significantly higher than those in the negative control group. MDA levels were significantly reduced in all treatment groups (P <0.05).

Brain nitric oxide levels in the positive control group were significantly higher (42.8±2.6 ng/ml) than in the negative control group (16.0.2±0.5 ng/ml; P <0.05). Brain A β levels were significantly reduced in all treatment groups (P <0.05).

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Table 1. Effects of donepezil, telmisartan, amlodipine, bisoprolol, and bumetanide on brain biomarkers: AChE, Aβ42, β-secretase, pMAPT/ptau, malondialdehyde, and nitric oxide

	AChE (ng/ml)	A β (pg/ml)	β –secretase (pg/ml)	pMAPT/ptau (pg/ml)	Malondialdehyde (ng/ml)	Nitric oxide (ng/ml)
Group I (Negative control)	4.1±0.18[a]	21.46±0.34[a]	25.5±0.35[a]	8.4±0.39[a]	50.8±1.7[a]	16.0.2±0.5[a]
Group II (Positive control)	10.7±0.37[d]	37.04±1.6[d]	41.0±0.93[e]	12.9±0.23[d]	72.3±1.7[d]	42.8±2.6[d]
Group III (Donepezil)	4.26±0.34[a]	23.3±0.74[a,b]	30.89±0.63[b]	7.6±0.33[a]	50.66±0.63[a]	15.7±0.5[a]
Group IV (Telmisartan)	6.4±0.25[b]	29.6±1.6[c]	34.6±0.83[c]	9.8±0.58[b]	61.3±0.58b,c	20.9±1.02[b]
Group V (Amlodipine)	6.49±32[b]	31.4±0.71[c]	37.1±0.51[d]	10.1±0.22[b]	58.8±1.4[b]	23.7±1.1[b,c]
Group VI (Bisoprolol)	8.8±0.24[c]	31.2±0.62[c]	39.2±0.22[d,e]	11.5±0.44[c]	62.9±0.7[c]	25.3±0.83[c]
Group VII (Bumetanide)	4.02±0.24[a]	25.5±0.56[b]	32.7±0.6[b,c]	10.3±0.41[b]	59.6±0.8[b,c]	24.7±1.1[b,c]

The values are expressed as mean±SEM.

Statistically significant differences between groups are shown by different letters (P-value <0.05).

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Effects on serum biomarkers across groups

As Table 2 shows, the rats in the positive control group had significantly higher Aβ levels (11.3±0.41pg/ml) than those in the negative control group (5.2±0.23 pg/ml; P <0.05).

A *post hoc* test was performed to discover the exact differences and significance levels between the positive control group and the study groups. Serum A β levels were considerably lower in all treatment groups compared to the positive control group.

Table 2. Effects of donepezil, telmisartan, amlodipine, bisoprolol, and bumetanide on serum biomarkers: Aβ42, total tau protein, TNF-α, IL-6, and CRP

	Aβ (pg/ml)	Total tau protein (pg/ml)	TNF-α (ng/L)	IL-6 (ng/L)	CRP (ng/ml)
Group I (Negative control)	5.2±0.23^{a}	82.8±1.5^{a}	17.04±0.84^{a}	14.7±0.31^{a}	18.1±0.9^{a}
Group II (Positive control)	11.3±0.41^{d}	107.5±1.3^{d}	65.03±5.2^{c}	37.9±0.51^{d}	37.7±1.2^{d}
Group III (Donepezil)	5.6±0.34^{a}	82.06±2.1^{a}	23.9±1.8^{a,b}	18.8±0,61^{b}	23.5±1.3^{b}
Group IV (Telmisartan)	7.3±0.45^{b,c}	84.3±1.2^{a,b}	23.3±1.2^{a,b}	21.1±0.92^{b}	22.1±0.84^{a,b}
Group V (Amlodipine)	7.1±0.26^{b}	88.1±1.7^{b,c}	29.5±0.69^{b}	20.1±1.1^{b}	24.6±1.15^{b}
Group VI (Bisoprolol)	8.2±0.37^{c}	91.3±1.01^{c}	36.7±1.1^{c}	25.6±1.33^{c}	26.2±1.3^{b}
Group VII (Bumetanide)	7.1±0.36^{b}	83.5±1.2^{a}	40.8±1.7^{c}	28.1±0.82^{c}	31.6±1.1^{c}

The values are expressed as mean±SEM.

Statistically significant differences between groups are shown by different letters (P-value <0.05).

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Serum levels of total tau protein were considerably higher in the positive control group (107.5±1.3 pg/ml) than in the negative control group (82.8±1.5 pg/ml; P <0.05). All treatment groups demonstrated a significant reduction (P >0.05) in comparison to the positive control group.

Additionally, the findings demonstrate that TNF-α levels in the positive control group were noticeably higher (65.03±5.2 ng/L) than in the negative control group (17.04±0.84 ng/L; P <0.05). A*post hoc* analysis showed that all treatment groups had significantly lower levels than the positive control group (P <0.05), except for Groups VI and VII, for which the reduction was not statistically significant (P >0.05) in comparison to the samples in the positive control group.

The serum IL-6 levels of the rats that received scopolamine and L-NAME HCl were significantly higher (37.9±0.51 ng/L) than those of the control group (14.7±0.31 ng/L; P <0.05). All treatment groups exhibited statistically significant reductions in comparison to the positive control group (P <0.05).

Lastly, the findings indicate that serum CRP levels were considerably elevated in the positive control group (37.7±1.2 ng/ml) in comparison to the negative control group (18.1±0.9 ng/ml; P <0.05). There was a significant decrease for each treatment group as compared to the positive control group (P <0.05).

Effects of different treatment groups on the Y-maze behavioral test

The rats pre-treated with scopolamine and L-NAME HCl had a lower SAP% (39.42±3.66%) than those in the control group (63.82±3.37%; P <0.05) as showed in the Table 3. A *post hoc* analysis showed that, in comparison to the positive control group, all examined groups exhibited a substantial increase (P <0.05).

The results show that the TAE of the positive control group was substantially lower (21.16±2.98) than that of the negative control group (35.66±1.86; P <0.05). All treatment groups showed a substantial increase in TAE compared to the positive control group (P <0.05).

Lastly, rats in the positive control group spent less time in the new arms (3.21±0.27 min) than those in the negative control group (4.64±0.34 min; P <0.05). According to a *post hoc* analysis, rats in every treatment group were in the novel arms for longer than those in the positive control group (P <0.05).

Effects of different treatment groups on systolic and diastolic blood pressure

The findings show that systolic BP values were substantially higher for the rats in the positive control group (188.6±1.4 mmHg) than for those in the negative control group (116.5±1.3 mmHg; P <0.05) as showed by the Table 4. When compared to the positive

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control group, a significant decrease in systolic BP was noted in each treatment group (P >0.05).

The findings also show that the rats in the positive control group had significantly higher diastolic BP levels (116±0.89 mmHg) than those in the negative control group (82±1.4 mmHg; P <0.05). All treatment groups showed significant decreases in diastolic BP compared to the positive control group (P <0.05).

Table 3. Effects of donepezil, telmisartan, amlodipine, bisoprolol, and bumetanide on the Y-maze behavioral test

Group	Parameter		
	Spontaneous alternation (%)	Total arm entries (n)	Time spent in novel arm (min)
Group I (Negative control)	63.82±3.37^{c}	35.66±1.86^{e}	4.64±0.34^{d}
Group II (Positive control)	39.42±3.66^{a}	21.16±2.98^{a}	3.21±0.27^{a}
Group III (Donepezil)	71.02±6.04^{d}	34.50.2.42^{d}	5.42±0.26^{f}
Group IV (Telmisartan)	58.87±2.91^{b}	39.83±3.76^{f}	4.42±0.27^{c}
Group V (Amlodipine)	63.98±1.05^{c}	31.83±1.47^{c}	4.00±0.13^{b}
Group VI (Bisoprolol)	54.54±1.60^{b}	26.50±1.87^{b}	3.66±0.19^{a}
Group VII (Bumetanide)	73.66±1.62^{d}	57.66±3.32^{h}	5.083±0.45^{e}

The values are expressed as mean±SEM.
Different letters mean statistically significant difference between groups (P-value <0.05).

Table 4. Effects of donepezil, telmisartan, amlodipine, bisoprolol, and bumetanide on systolic and diastolic blood pressure

Group	Parameter	
	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Group I (Negative control)	116.5±1.3^{a}	82±1.4^{b}
Group II (Positive control)	188.6±1.4^{d}	116±0.89^{f}
Group III (Donepezil)	170.1±1.7^{c}	106.1±2^{e}
Group IV (Telmisartan)	120.3±1.8^{a}	74.1±1.3^{a}
Group V (Amlodipine)	135.1±1.07^{b}	93.1±1.19^{c,d}
Group VI (Bisoprolol)	140±0.89^{b}	90.1±0.87^{c}
Group VII (Bumetanide)	140.3±1.11^{b}	95.6±0.84^{d}

The values are expressed as mean ± SEM.
Different letters mean statistically significant difference between groups (P-value <0.05).

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Discussion

The association between AD and cardiovascular disease is gaining widespread recognition. However, a substantial portion of this theory is predicated on ongoing research on cognition and dementia, including AD, vascular dementia, and other disorders. Prior research suggests that HTN may indirectly contribute to the pathophysiology of AD by causing intracranial atherosclerosis through the reduction of cerebral blood flow and/or perivascular clearance. In animal studies, HTN increases tau hyperphosphorylation and Aβ accumulation (29). In animal models, L-NAME HCl-induced HTN increases Aβ deposition and tau phosphorylation (30). Although the exact mechanisms remain unknown, the elevation of β- and γ-secretase activity due to HTN may be influential, as these enzymes cause amyloid precursor protein (APP) processing to shift toward β-amyloidogenesis (31).

Hypertension contributes to AD through a variety of pathways, including cerebral hypoperfusion, blood–brain barrier dysfunction, neuroinflammation, oxidative stress, and Aβ accumulation. Chronic hypertension causes endothelial dysfunction and vascular remodeling, lowering cerebral blood flow. Cerebral hypoperfusion then accelerates neurodegeneration and hampers neuronal metabolism.

The pathophysiology of AD is influenced by decreased perfusion in the cortex and hippocampus, two important areas involved in memory and cognition (32).

Because hypertension damages endothelial cells and increases permeability, it compromises the integrity of the blood–brain barrier. This exacerbates neuronal damage by allowing toxins, inflammatory mediators, and Aβ peptides to build up in the brain (33).

AD is characterized by a buildup of Aβ. Reduced interstitial fluid flow and arterial stiffening brought on by hypertension hinder perivascular drainage routes, which are responsible for the clearance of Aβ. Studies have linked high BP with increased cerebral amyloid angiopathy (CAA), a disorder in which Aβ builds up in the brain's blood vessels, causing microvascular damage and cognitive impairment (34).

Additionally, hypertension changes enzymatic processing to favor the creation of Aβ and increases the production of APP. These pathogenic alterations are linked to gradual cognitive decline, neuronal death, and synaptic dysfunction (31).

Neurodegeneration is worsened by hypertension, which encourages a persistent inflammatory state. Microglial activation and elevated levels of pro-inflammatory cytokines, such as TNF-α and IL-6, lead to synaptic dysfunction and neuronal injury (35).

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Hypertension is linked to elevated levels of oxidative stress as a result of the overproduction of reactive oxygen species. Neuronal mitochondria are damaged by oxidative stress, resulting in apoptotic cell death and energy deficits. The pathological features of AD, such as Aβ aggregation and tau hyperphosphorylation, are significantly influenced by dysfunctional mitochondria (36).

Scopolamine's high blood–brain barrier permeability makes it a popular choice for creating experimental models of neurological conditions. It causes Aβ buildup and cholinergic impairment. It is an antagonist of muscarinic receptors, inhibiting muscarinic acetylcholine receptors and leading to synaptic malfunction and cognitive decline (37). Additionally, scopolamine increases tau protein phosphorylation. It raises amounts of hyperphosphorylated tau by intensifying GSK3-β expression (38). Moreover, scopolamine induces oxidative stress in rats by lowering their levels of antioxidants such as catalase and superoxide dismutase (39).

L-NAME HCl, an analog of L-arginine, is frequently used to induce hypertension and other cardiovascular disorders by inhibiting nitric oxide synthase (40). L-NAME HCl-induced HTN is caused by a mechanism that involves more than merely blocking nitric oxide synthesis and lowering vasorelaxant action. However, the primary causes of elevated BP are decreased vascular relaxation and increased contraction in various vascular bed regions. Studies have demonstrated that other mechanisms of L-NAME HCl-induced HTN include elevating the renin-angiotensin-aldosterone system and sympathetic nervous system activity (41).

The enzyme AChE is found in postsynaptic neuromuscular junctions, particularly in nerves and muscles. AChE activity is elevated in AD tissues, according to several studies. Numerous investigations have explored whether variations in AChE levels may serve as biochemical indicators of AD (42). In this investigation, brain AChE levels sharply increased after HTN and AD were induced, and the AChE levels of each treatment group were significantly reduced in comparison to those of the positive control group. Bumetanide, donepezil, telmisartan, and amlodipine were the most successful in restoring the levels to almost normal, consistent with previous research findings (43, 44).

It is generally known that Aβ causes amyloid plaque buildup on nerve cells in AD patients' brains. Studies have shown that Aβ accumulation contributes to the pathophysiology and progression of AD. Aβ accumulation occurs through the increased activity of β-secretase—an enzyme that cleaves APP into the 42-amino-acid Aβ sequence. In particular, it has been determined that the main

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brain enzyme promoting the formation of Aβ is the β-secretase BASE1 (45). Our study found that HTN and AD inductionled to considerable increases in Aβ levels in serum and brain tissues as well as β-secretase BASE1 in brain tissue. Aβ and β-secretase BASE1 levels were significantly lower in all treatment groups than in the positive control group, especially those treated with bumetanide and donepezil. Other treatment groups also had significantly reduced Aβ and β-secretase BASE1 levels, albeit to a lesser extent than in the bumetanide- and donepezil-treated groups. These results align with previous studies suggesting that bumetanide, telmisartan, and amlodipine may constitute potential treatment approaches in managing AD (46-48).

Tau, a microtubule-associated protein (MAP), is essential for preserving the structural integrity of the cytoskeleton, as it stabilizes microtubules in neurons (49). Studies have shown that both tau phosphorylation and Aβ accumulation contribute to the etiology and pathogenesis of AD (50). Previous research has indicated that HTN exacerbates tau hyperphosphorylation (51). A characteristic of AD is the development of neurofibrillary tangles, which are linked to hyperphosphorylation of tau (pMAPT) (52). This study found that the amount of pMAPT noticeably increased upon HTN and AD induction, although all treatment groups had significantly reduced pMAPT levels compared to the positive control group. However, pMAPT was not reduced to normal levels in either group, except with donepezil, the only treatment that could bring pMAPT levels back to normal. This outcome is consistent with prior investigations (53-55).

Our experimental medications decreased tau and Aβ levels, which may suggest a disease-modifying effect, especially in the early stages of Alzheimer's. Reduced tau levels may indicate fewer tangles and higher nerve cell stability, whereas decreased Aβ may indicate fewer plaques and enhanced neuronal health. Improved memory, cognitive function, and general brain health may result from these modifications, but proof of real behavioral and functional gains is needed.

MDA is created when polyunsaturated fatty acids peroxidate. It has been used as a biomarker to evaluate oxidative stress in a range of biological samples from patients with varying diseases (56), including AD(57). We observed that MDA levels rose significantly after HTN and AD induction, in all treatment groups, with donepezil, bumetanide and amlodipine bringing levels back to almost normal. This result accords with the results of prior research (58, 59).

A physiological component of the human body is nitric oxide, which works

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as a signaling molecule, dilates blood vessels, promotes hormone release, and controls neurotransmission (60). Inducible nitric oxide synthase (iNOS) triggers nitric oxide overproduction in response to inflammatory stimuli during neuroinflammation, which causes AD to worsen and progress. Therefore, identifying potent iNOS inhibitors can aid in preventing and delaying the advancement of AD (61). In all treatment groups, we observed that donepezil and telmisartan could return NO levels to normal, which agrees with the findings of earlier investigations (62, 63). While the NO levels in all treatment groups were significantly lower than those in the positive control group, the level of reduction was less than in the groups treated with donepezil and telmisartan.

TNF-α is a cytokine that has pleiotropic effects on different cell types. Although it was first identified as a factor contributing to tumor necrosis, it has since been demonstrated to play significant roles as a pathogenic component of various disorders. Previous research has illustrated that TNF-α plays a crucial role in coordinating chronic inflammation, influencing the production of Aβ plaques and neurofibrillary tangles, thereby amplifying the advancement of AD pathogenesis (64). AD patients have been shown to have greater plasma levels of TNF-α compared to healthy individuals (65). In this study, TNF-α levels were drastically increased by HTN and AD and, compared to the positive control group, significantly reduced by the administration of donepezil and telmisartan. This conclusion aligns with the findings of earlier studies (66,67).

The cytokine IL-6 is released as part of the inflammatory response by activated monocytes and macrophages. Cognitive performance is negatively correlated with higher plasma IL-6 levels. The risk of dementia from all causes is approximately 30% higher in those with elevated IL-6 levels. High levels of circulating IL-6 are found in AD patients, and elevated brain IL-6 may result from systemic or local generation (68). Serum IL-6 levels appeared to be considerably lowered in this trial for all therapy groups, with donepezil, telmisartan, and amlodipine exhibiting the highest efficacy in this regard. This outcome is consistent with previous research findings (67, 69, 70).

Patients with AD have elevated levels of CRP, a nonspecific indicator of inflammation, in their brains and sera. Several previous studies have linked this elevation to an increased risk of dementia(93).Our study found all treatment groups to have considerably decreased serum CRP levels, with amlodipine, donepezil, and telmisartan displaying the greatest effects. This outcome supports the findings of previous studies (62, 73, 74).

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A typical indicator of neurodegenerative illness is total tau (t-tau). Serum t-tau proteins are beneficial indicators in the diagnosis and tracking of AD development (75). All the treatment groups in our investigation exhibited a considerable decrease in t-tau protein; donepezil, telmisartan, and bumetanide restored the levels to nearly normal. This result aligns with the conclusions of earlier studies (76, 77).

The Y-maze test is typically employed in rodent models of AD to evaluate short-term memory. Rats' natural interest in investigating previously unexplored places enables the assessment of spontaneous alternation, which measures spatial working memory as they investigate the maze's three arms. Additionally, studies typically utilize arm entries to evaluate rats' locomotor activity. The amount of time that rats spend in the novel arm during Y-maze tests constitutes a measure of their spatial recognition recall and novelty preference (78). In comparison to the positive group, all treatment groups in our study demonstrated a significant increase in the proportion of spontaneous alternation, time spent in novel arms, and number of TAEs. Compared to other groups, the groups treated with donepezil, bumetanide, and amlodipine had the highest percentage of spontaneous alternation. However, rats in the groups treated with telmisartan and bumetanide traveled in more arms than the rats in the other groups. Finally, rats in the groups treated with donepezil, bumetanide, and telmisartan spent more time in the new arms than those in the other treatment groups. These outcomes are in line with earlier research (33, 77, 79, 80).

According to the literature, telmisartan shows remarkable neuroprotective qualities via numerous mechanisms. One important mechanism is the drug's capacity to inhibit the angiotensin II type 1 receptor, which lowers vascular dysfunction, inflammation, and oxidative stress—all of which are connected to neurodegenerative processes. Telmisartan contributes to an improved neuronal environment by increasing cerebral blood flow and minimizing blood–brain barrier disruption. Telmisartan also functions as a partial agonist of peroxisome proliferator-activated receptor gamma, which promotes synaptic plasticity, decreases neuronal apoptosis, and improves mitochondrial function (81).

Bumetanide may have a neuroprotective effect in AD by lowering excessive neuronal stimulation. Increased excitability and neuroinflammation are caused by changes in the chloride gradient between neurons in AD, according to research. Bumetanide aids in reestablishing the appropriate chloride gradient in neurons by acting on the NKCC1 transporter, a chloride importer.

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This may lessen neurotoxic signaling and hyperexcitability, which are linked to AD neurodegeneration (46). Additionally, bumetanide plays a critical role in inhibitory neurotransmission through its impact on GABA receptors. Bumetanide may help balance excitation and inhibition in the brain by improving GABAergic signaling, which could lessen some AD symptoms, including behavioral abnormalities and memory impairment (82).

Conclusion

All the HTN medications examined in this investigation, particularly bumetanide and telmisartan, were demonstrated to effectively reduce the majority of plasma and brain biomarkers when administered at the recommended dosages. According to this study, telmisartan and bumetanide, either alone or in combination with donepezil, may constitute beneficial medication options for neuroregeneration and risk mitigation in AD patients who also have HTN.

Competing interest

The authors declare that they have no competing interests.

References

1. Chertkow H, Feldman HH, Jacova C, Massoud F. Definitions of dementia and predementia states in Alzheimer's disease and vascular cognitive impairment: consensus from the Canadian conference on diagnosis of dementia. Alzheimers Res Ther. 2013;5:S2. https://doi.org/10.1186/alzrt198.

2. Mayeux R, Stern Y. Epidemiology of Alzheimer Disease. Cold Spring Harb Perspect Med. 2012;2:a006239–a006239. https://doi.org/10.1101/cshperspect.a006239.

3. A. Armstrong R. Risk factors for Alzheimer's disease. Folia Neuropathol. 2019;57:87–105. https://doi.org/10.5114/fn.2019.85929.

4. Herrup K. Reimagining Alzheimer's Disease—An Age-Based Hypothesis. J Neurosci. 2010;30:16755–62. https://doi.org/10.1523/JNEUROSCI.4521-10.2010.

5. Varkey BP, Joseph J, Haokip HR, Sharma SK, Mathews E, Ameen S, et al. The Prevalence of Comorbidities and Associated Factors among Patients with Dementia in the Indian Setting: Meta-analysis of Observational Studies. Indian J Psychol Med. 2023;45:338–44. https://doi.org/10.1177/02537176221130252.

6. Mulligan MD, Murphy R, Reddin C, Judge C, Ferguson J, Alvarez-Iglesias A, et al. Population attributable fraction of hypertension for dementia: global, regional, and national estimates for 186 countries. eClinical Medicine. 2023;60:102012. https://doi.org/10.1016/j.eclinm.2023.102012.

https://doi.org/10.15218/zjms.2026.018

7. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. Clin Epidemiol. 2014;6:37–48. https://doi.org/10.2147/CLEP.S37929.

8. Yao Q, Jiang K, Lin F, Zhu T, Khan NH, Jiang E. Pathophysiological Association of Alzheimer's Disease and Hypertension: A Clinical Concern for Elderly Population. Clin Interv Aging. 2023; 18:713–28. https://doi.org/10.2147/CIA.S400527.

9. Forcaia G, Formicola B, Terribile G, Negri S, Lim D, Biella G, et al. Multifunctional Liposomes Modulate Purinergic Receptor-Induced Calcium Wave in Cerebral Microvascular Endothelial Cells and Astrocytes: New Insights for Alzheimer's disease. Mol Neurobiol. 2021;58:2824–35. https://doi.org/10.1007/s12035-021-02299-9.

10. Bowman GL, Dayon L, Kirkland R, Wojcik J, Peyratout G, Severin IC, et al. Blood-brain barrier breakdown, neuroinflammation, and cognitive decline in older adults. Alzheimers Dement. 2018;14:1640–50. https://doi.org/10.1016/j.jalz.2018.06.2857.

11. Park L, Zhou P, Koizumi K, El Jamal S, Previti ML, Van Nostrand WE, et al. Brain and Circulating Levels of Aβ1–40 Differentially Contribute to Vasomotor Dysfunction in the Mouse Brain. Stroke 2013;44:198–204. https://doi.org/10.1161/STROKEAHA.112.670976.

12. De La Torre J. The Vascular Hypothesis of Alzheimer's Disease: A Key to Preclinical Prediction of Dementia Using Neuroimaging. J Alzheimers Dis. 2018;63:35–52. https://doi.org/10.3233/JAD-180004.

13. Sung JH, Jo YS, Kim SJ, Ryu JS, Kim MC, Ko HJ, et al. Effect of Lutein on L-NAME-Induced Hypertensive Rats. Korean J Physiol Pharmacol Off J Korean Physiol Soc Korean Soc Pharmacol. 2013;17:339–45. https://doi.org/10.4196/kjpp.2013.17.4.339.

14. Berzinji B, Dizaye K. Investigating the effect of Fenofibrate on biomarkers of vascular inflammation in L-NAME induced hypertensive rats. Pharmacia. 2022;69:459–65. https://doi.org/10.3897/pharmacia.69.e81078.

15. Hafez HS, Ghareeb DA, Saleh SR, Abady MM, El Demellawy MA, Hussien H, et al. Neuroprotective effect of ipriflavone against scopolamine-induced memory impairment in rats. Psychopharmacology (Berl). 2017;234:3037–53. https://doi.org/10.1007/s00213-017-4690-x.

16. Lazarova M, Stefanova M, Denev P, Taseva T, Vassileva V, Tasheva K. Neuroprotective Effect of Marrubium vulgare Extract in Scopolamine-Induced

https://doi.org/10.15218/zjms.2026.018

Cognitive Impairment in Rats: Behavioral and Biochemical Approaches. Biology. 2024;13:426. https://doi.org/10.3390/biology13060426.

17. Ali SK, Ali RH. Effects of antidiabetic agents on Alzheimer's disease biomarkers in experimentally induced hyperglycemic rat model by streptozocin. PLOS ONE. 2022;17:e0271138. https://doi.org/10.1371/journal.pone.0271138.

18. Sueta D, Koibuchi N, Hasegawa Y, Toyama K, Uekawa K, Katayama T, et al. Telmisartan Exerts Sustained Blood Pressure Control and Reduces Blood Pressure Variability in Metabolic Syndrome by Inhibiting Sympathetic Activity. Am J Hypertens. 2014;27:1464–71. https://doi.org/10.1093/ajh/hpu076.

19. Azouz AA, Abdel-Nassir Abdel-Razek E, Abo-Youssef AM. Amlodipine alleviates cisplatin-induced nephrotoxicity in rats through gamma-glutamyl transpeptidase (GGT) enzyme inhibition, associated with regulation of Nrf2/HO-1, MAPK/NF-κB, and Bax/Bcl-2 signaling. Saudi Pharm J. 2020;28:1317–25. https://doi.org/10.1016/j.jsps.2020.08.022.

20. Watanabe K, Ohta Y, Inoue M, Ma M, Wahed MII, Nakazawa M, et al. Bisoprolol Improves Survival in Rats with Heart Failure: J Cardiovasc Pharmacol. 2001;38:S55–8. https://doi.org/10.1097/00005344-200110001-00012.

21. Han KS, Lee SH, Lee MG, Kim ND. Pharmacokinetics and pharmacodynamics of bumetanide after intravenous and oral administration to spontaneously hypertensive rats and DOCA-salt induced hypertensive rats. Biopharm Drug Dispos. 1993;14:533–48. https://doi.org/10.1002/bdd.2510140609.

22. Leary S, Pharmaceuticals F, Underwood W, Anthony R, Cartner S, Johnson CL, et al. AVMA Guidelines for the Euthanasia of Animals: 2020 Edition. 2020.

23. Akataobi US, Unanaowo BE, Michael OC, Arong WO. Brain Response to Intraperitoneal and Oral Administration of Monosodium Glutamate in Wistar Rats. Niger J Exp Clin Biosci. 2021;9:61–7. https://doi.org/10.4103/njecp.njecp_38_20.

24. Bao J, Potts BD. Quantitative determination of olanzapine in rat brain tissue by high-performance liquid chromatography with electrochemical detection. J Chromatogr B Biomed Sci App. 2001;752:61–7. https://doi.org/10.1016/S0378-4347(00)00518-1.

25. Kim J, Kang H, Lee Y-B, Lee B, Lee D. A quantitative analysis of spontaneous alternation behaviors on a Y-maze

https://doi.org/10.15218/zjms.2026.018

reveals adverse effects of acute social isolation on spatial working memory. Sci Rep. 2023;13:14722. https://doi.org/10.1038/s41598-023-41996-4.

26. Weiss C, Shroff A, Disterhoft JF. Spatial learning and memory in aging C57BL/6 mice. Neurosci Res Commun. 1998;23:77–92. https://doi.org/10.1002/(SICI)1520-6769(199809/10)23:2<77::AID-NRC2>3.0.CO;2-Y.

27. Ijomone OM, Olaibi OK, Mba C, Biose IJ, Tete SA, Nwoha PU. Chronic nicotine administration does not alter cognitive or mood associated behavioural parameters. Pathophysiology. 2015;22:57–63. https://doi.org/10.1016/j.pathophys.2014.12.004.

28. Daugherty A, Rateri D, Hong L, Balakrishnan A. Measuring blood pressure in mice using volume pressure recording, a tail-cuff method. J Vis Exp JoVE. 2009:1291. https://doi.org/10.3791/1291.

29. Pacholko A, Iadecola C. Hypertension, Neurodegeneration, and Cognitive Decline. Hypertension. 2024;81:991–1007. https://doi.org/10.1161/HYPERTENSIONAHA.123.21356.

30. Cifuentes D, Poittevin M, Bonnin P, Ngkelo A, Kubis N, Merkulova-Rainon T, et al. Inactivation of Nitric Oxide Synthesis Exacerbates the Development of Alzheimer Disease Pathology in APPPS1 Mice (Amyloid Precursor Protein/Presenilin-1). Hypertension. 2017;70:613–23. https://doi.org/10.1161/HYPERTENSIONAHA.117.09742.

31. Faraco G, Park L, Zhou P, Luo W, Paul SM, Anrather J, et al. Hypertension enhances A β -induced neurovascular dysfunction, promotes β -secretase activity, and leads to amyloidogenic processing of APP. J Cereb Blood Flow Metab. 2016;36:241–52. https://doi.org/10.1038/jcbfm.2015.79.

32. Park J-H, Hong J-H, Lee S-W, Ji HD, Jung J-A, Yoon K-W, et al. The effect of chronic cerebral hypoperfusion on the pathology of Alzheimer's disease: A positron emission tomography study in rats. Sci Rep. 2019;9:14102. https://doi.org/10.1038/s41598-019-50681-4.

33. Kerkhofs D, Helgers R, Hermes D, Steinbusch HPJ, Van Essen H, Leenders P, et al. Amlodipine limits microglia activation and cognitive dysfunction in aged hypertensive mice. J Hypertens. 2023;41:1159–67. https://doi.org/10.1097/HJH.0000000000003445.

34. Kim SH, Ahn JH, Yang H, Lee P, Koh GY, Jeong Y. Cerebral amyloid angiopathy aggravates perivascular clearance impairment in an Alzheimer's disease mouse model. Acta Neuropathol Commun. 2020;8:181.

https://doi.org/10.15218/zjms.2026.018

https://doi.org/10.1186/s40478-020-01042-0.

35. Zhao Z, Zhang J, Wu Y, Xie M, Tao S, Lv Q, et al. Plasma IL-6 levels and their association with brain health and dementia risk: A population-based cohort study. Brain BehavImmun. 2024;120:430–8. https://doi.org/10.1016/j.bbi.2024.06.014.

36. Wang W, Zhao F, Ma X, Perry G, Zhu X. Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances. Mol Neurodegener. 2020;15:30. https://doi.org/10.1186/s13024-020-00376-6.

37. Bajo R, Pusil S, López ME, Canuet L, Pereda E, Osipova D, et al. Scopolamine effects on functional brain connectivity: a pharmacological model of Alzheimer's disease. Sci Rep. 2015;5:9748. https://doi.org/10.1038/srep09748.

38. Tang KS. The cellular and molecular processes associated with scopolamine-induced memory deficit: A model of Alzheimer's biomarkers. Life Sci. 2019;233:116695. https://doi.org/10.1016/j.lfs.2019.116695.

39. Bhuvanendran S, Kumari Y, Othman I, Shaikh MF. Amelioration of Cognitive Deficit by Embelin in a Scopolamine-Induced Alzheimer's Disease-Like Condition in a Rat Model. Front Pharmacol. 2018;9:665. https://doi.org/10.3389/fphar.2018.00665.

40. Kopincová J, Púzserová A, Bernátová I. L-NAME in the cardiovascular system – nitric oxide synthase activator? Pharmacol Rep. 2012;64:511–20. https://doi.org/10.1016/S1734-1140(12)70846-0.

41. Pechanova O, Vrankova S, Cebova M. Chronic L-Name-Treatment Produces Hypertension by Different Mechanisms in Peripheral Tissues and Brain: Role of Central eNOS. Pathophysiol Off J Int Soc Pathophysiol. 2020;27:46–54. https://doi.org/10.3390/pathophysiology27010007.

42. McHardy SF, Wang H-YL, McCowen SV, Valdez MC. Recent advances in acetylcholinesterase Inhibitors and Reactivators: an update on the patent literature (2012-2015). Expert Opin Ther Pat. 2017;27:455–76. https://doi.org/10.1080/13543776.2017.1272571.

43. Şen S, Hacıosmanoğlu E. Comparing the Neuroprotective Effects of Telmisartan, Perindopril, and Nebivolol Against Lipopolysaccharide-Induced Injury in Neuron-Like Cells. Cureus. 2022. https://doi.org/10.7759/cureus.27429.

44. Çelik T, Kayir H, Ceyhan M, Demirtaş S, Coşar A, Uzbay IT. CPP and amlodipine alter the decrease in basal acetylcholine and choline release by audiogenic stimulus in hippocampus of

https://doi.org/10.15218/zjms.2026.018

ethanol-withdrawn rats in vivo. Brain Res Bull. 2004;64:243–9. https://doi.org/10.1016/j.brainresbull.2004.07.003.

45. Corbo CP, Alonso ADC. Therapeutic Targets in Alzheimer's Disease and Related Tauopathies. Prog. Mol. Biol. Transl. Sci., vol. 98, Elsevier; 2011, P. 47–83. https://doi.org/10.1016/B978-0-12-385506-0.00002-8.

46. Boyarko B, Podvin S, Greenberg B, Momper JD, Huang Y, Gerwick WH, et al. Evaluation of bumetanide as a potential therapeutic agent for Alzheimer's disease. Front Pharmacol. 2023;14:1190402. https://doi.org/10.3389/fphar.2023.1190402.

47. Kurata T, Lukic V, Kozuki M, Wada D, Miyazaki K, Morimoto N, et al. Long-term Effect of Telmisartan on Alzheimer's Amyloid Genesis in SHR-SR After tMCAO. Transl Stroke Res. 2015;6:107–15. https://doi.org/10.1007/s12975-013-0321-y.

48. Lovell MA, Abner E, Kryscio R, Xu L, Fister SX, Lynn BC. Calcium Channel Blockers, Progression to Dementia, and Effects on Amyloid Beta Peptide Production. Oxid Med Cell Longev. 2015;2015:787805. https://doi.org/10.1155/2015/787805.

49. Medeiros R, Baglietto-Vargas D, LaFerla FM. The role of tau in Alzheimer's disease and related disorders. CNS Neurosci Ther. 2011;17:514–24. https://doi.org/10.1111/j.1755-5949.2010.00177.x.

50. Basheer N, Smolek T, Hassan I, Liu F, Iqbal K, Zilka N, et al. Does modulation of tau hyperphosphorylation represent a reasonable therapeutic strategy for Alzheimer's disease? From preclinical studies to the clinical trials. Mol Psychiatry. 2023;28:2197–214. https://doi.org/10.1038/s41380-023-02113-z.

51. Kim T, Yi D, Byun MS, Ahn H, Jung JH, Kong N, et al. Synergistic interaction of high blood pressure and cerebral beta-amyloid on tau pathology. Alzheimers Res Ther. 2022;14:193. https://doi.org/10.1186/s13195-022-01149-7.

52. Moloney CM, Lowe VJ, Murray ME. Visualization of neurofibrillary tangle maturity in Alzheimer's disease: A clinicopathologic perspective for biomarker research. Alzheimers Dement. 2021;17:1554–74. https://doi.org/10.1002/alz.12321.

53. Kurata T, Lukic V, Kozuki M, Wada D, Miyazaki K, Morimoto N, et al. Telmisartan Reduces Progressive Accumulation of Cellular Amyloid Beta and Phosphorylated Tau with Inflammatory Responses in Aged Spontaneously Hypertensive Stroke Resistant Rat. J Stroke Cerebrovasc Dis. 2014;23:2580–90.

https://doi.org/10.15218/zjms.2026.018

https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.05.023.

54. Guan P-P, Cao L-L, Wang P. Elevating the Levels of Calcium Ions Exacerbate Alzheimer's Disease via Inducing the Production and Aggregation of β-Amyloid Protein and Phosphorylated Tau. Int J Mol Sci. 2021;22:5900. https://doi.org/10.3390/ijms22115900.

55. Hamano T, Shirafuji N, Sasaki H, Ishi-da A, Ueno A, Yen S, et al. P1–401: Donepezil reduces phosphorylation levels of tau protein in a cellular model of tauopathy. Alzheimers Dement. 2013;9. https://doi.org/10.1016/j.jalz.2013.05.629.

56. Cordiano R, Di Gioacchino M, Mangifesta R, Panzera C, Gangemi S, Minciullo PL. Malondialdehyde as a Potential Oxidative Stress Marker for Allergy-Oriented Diseases: An Update. Molecules. 2023;28:5979. https://doi.org/10.3390/molecules28165979.

57. Nie Y, Chu C, Qin Q, Shen H, Wen L, Tang Y, et al. Lipid metabolism and oxidative stress in patients with Alzheimer's disease and amnestic mild cognitive impairment. Brain Pathol Zurich Switz. 2024;34:e13202. https://doi.org/10.1111/bpa.13202.

58. Mahajan AS, Babbar R, Kansal N, Agarwal SK, Ray PC. Antihypertensive and antioxidant action of amlodipine and vitamin C in patients of essential hypertension. J Clin Biochem Nutr. 2007;40:141–7. https://doi.org/10.3164/jcbn.40.141.

59. Ongnok B, Khuanjing T, Chunchai T, Kerdphoo S, Jaiwongkam T, Chattipakorn N, et al. Donepezil provides neuroprotective effects against brain injury and Alzheimer's pathology under conditions of cardiac ischemia/reperfusion injury. BiochimBiophys Acta BBA - Mol Basis Dis. 2021;1867:165975. https://doi.org/10.1016/j.bbadis.2020.165975.

60. Kiani AK, Bonetti G, Medori MC, Caruso P, Manganotti P, Fioretti F, et al. Dietary supplements for improving nitric-oxide synthesis. J Prev Med Hyg. 2022;63:E239–45. https://doi.org/10.15167/2421-4248/jpmh2022.63.2S3.2766.

61. Mariwan Ahmed S, Tugcu G, Koksal Akkoc M. THE PROMISING ROLE OF iNOS INHIBITORS IN ALZHEIMERS DISEASE. Ank Univ Eczacilik Fak Derg. 2023;48:4–4. https://doi.org/10.33483/jfpau.131490.

62. Imenshahidi M, Roohbakhsh A, Hosseinzadeh H. Effects of telmisartan on metabolic syndrome components: a comprehensive review. Biomed Pharmacother. 2024;171:116169. https://doi.org/10.1016/j.biopha.2024.116169.

63. Kim J, Lee H, Park SK, Park J-H, Jeong H-R, Lee S, et al. Donepezil

https://doi.org/10.15218/zjms.2026.018

Regulates LPS and Aβ-Stimulated Neuroinflammation through MAPK/NLRP3 Inflammasome/STAT3 Signaling. Int J Mol Sci. 2021;22:10637. https://doi.org/10.3390/ijms22191063.

64. Plantone D, Pardini M, Righi D, Manco C, Colombo BM, De Stefano N. The Role of TNF-α in Alzheimer's Disease: A Narrative Review. Cells. 2023;13:54. https://doi.org/10.3390/cells13010054.

65. Serafini S, Ferretti G, Monterosso P, Angiolillo A, Di Costanzo A, Matrone C. TNF-α Levels Are Increased in Patients with Subjective Cognitive Impairment and Are Negatively Correlated with β Amyloid-42. Antioxidants. 2024;13:216. https://doi.org/10.3390/antiox13020216.

66. Araújo AA, Souza TO, Moura LM, Brito GAC, Aragão KS, Araújo LS, et al. Effect of telmisartan on levels of IL-1, TNF-α, down-regulated COX-2, MMP-2, MMP-9 and RANKL/RANK in an experimental periodontitis model. J Clin Periodontol. 2013;40:1104–11. https://doi.org/10.1111/jcpe.12160.

67. Arikawa M, Kakinuma Y, Noguchi T, Todaka H, Sato T. Donepezil, an acetylcholinesterase inhibitor, attenuates LPS-induced inflammatory response in murine macrophage cell line RAW 264.7 through inhibition of nuclear factor kappa B translocation. Eur J Pharmacol. 2016;789:17–26. https://doi.org/10.1016/j.ejphar.2016.06.053.

68. Lyra E Silva NM, Gonçalves RA, Pascoal TA, Lima-Filho RAS, Resende EDPF, Vieira ELM, et al. Pro-inflammatory interleukin-6 signaling links cognitive impairments and peripheral metabolic alterations in Alzheimer's disease. Transl Psychiatry. 2021;11:251. https://doi.org/10.1038/s41398-021-01349-z.

69. Tian Q, Miyazaki R, Ichiki T, Imayama I, Inanaga K, Ohtsubo H, et al. Inhibition of Tumor Necrosis Factor-α–Induced Interleukin-6 Expression by Telmisartan Through Cross-Talk of Peroxisome Proliferator-Activated Receptor-γ With Nuclear Factor κB and CCAAT/Enhancer-Binding Protein-β. Hypertension. 2009;53:798–804. https://doi.org/10.1161/HYPERTENSIONAHA.108.126656.

70. Batuo H, Van Der Linden E, Galenkamp H, Moll Van Charante E, Born B-JVD, Chilunga FP. Effects of antihypertensives with and without IL-6 lowering properties on long-term blood pressure control: The prospective HELIUS cohort. Int J Cardiol Cardiovasc Risk Prev. 2025;24:200358. https://doi.org/10.1016/j.ijcrp.2024.200358.

71. Kravitz BA, Corrada MM, Kawas CH. Elevated C-reactive protein levels are associated with prevalent dementia in the oldest-old. Alzheimers Dement J Alzheimers Assoc. 2009;5:318–23.

https://doi.org/10.15218/zjms.2026.018

https://doi.org/10.1016/j.jalz.2009.04.1230.

72. Hegazy SH, Thomassen JQ, Rasmussen IJ, Nordestgaard BG, Tybjærg-Hansen A, Frikke-Schmidt R. C-reactive protein levels and risk of dementia—Observational and genetic studies of 111,242 individuals from the general population. Alzheimers Dement. 2022;18:2262–71. https://doi.org/10.1002/alz.12568.

73. Sun L, Ma L, Ren L. The Impact of Combined Application of Donepezil and Nimodipine on Patients with Comorbid Cerebral Small Vessel Disease and Cognitive Dysfunction: Efficacy and Influence on Nutritional Status. Actas Esp Psiquiatr. 2024;52:533–41. https://doi.org/10.62641/aep.v52i4.1647.

74. Unlu M, Karaman M, Ay SA, Balta S, Cakar M, Demirkol S, et al. The Comparative Effects of Valsartan and Amlodipine on Vascular Microinflammation in Newly Diagnosed Hypertensive Patients. Clin Exp Hypertens. 2013;35:418–23. https://doi.org/10.3109/10641963.2012.739237.

75. Nam E, Lee Y-B, Moon C, Chang K-A. Serum Tau Proteins as Potential Biomarkers for the Assessment of Alzheimer's Disease Progression. Int J Mol Sci. 2020;21:5007. https://doi.org/10.3390/ijms21145007.

76. Yoshiyama Y, Kojima A, Ishikawa C, Arai K. Anti-Inflammatory Action of Donepezil Ameliorates Tau Pathology, Synaptic Loss, and Neurodegeneration in a Tauopathy Mouse Model. J Alzheimers Dis. 2010;22:295–306. https://doi.org/10.3233/JAD-2010-100681.

77. Abo-Youssef AM, Khallaf WA, Khattab MM, Messiha BAS. The anti-Alzheimer effect of telmisartan in a hyperglycemic ovariectomized rat model; role of central angiotensin and estrogen receptors. Food Chem Toxicol. 2020;142:111441. https://doi.org/10.1016/j.fct.2020.111441.

78. Schroeder A, Hudson M, Du X, Wu YWC, Nakamura J, Van Den Buuse M, et al. Estradiol and raloxifene modulate hippocampal gamma oscillations during a spatial memory task. Psychoneuroendocrinology. 2017;78:85–92. https://doi.org/10.1016/j.psyneuen.2017.01.022.

79. Shin CY, Kim H-S, Cha K-H, Won DH, Lee J-Y, Jang SW, et al. The Effects of Donepezil, an Acetylcholinesterase Inhibitor, on Impaired Learning and Memory in Rodents. Biomol Ther. 2018;26:274–81. https://doi.org/10.4062/biomolther.2017.189.

80. Kim HR, Rajagopal L, Meltzer HY, Martina M. Depolarizing $GABA_A$ current in the prefrontal cortex is linked with

https://doi.org/10.15218/zjms.2026.018

cognitive impairment in a mouse model relevant for schizophrenia. Sci Adv. 2021;7:eaba5032. https://doi.org/10.1126/sciadv.aba503.

81. Abdel Rasheed NO, Ibrahim WW. Telmisartan neuroprotective effects in 3-nitropropionic acid Huntington's disease model in rats: Cross talk between PPAR-γ and PI3K/Akt/GSK-3β pathway. Life Sci. 2022;297:120480. https://doi.org/10.1016/j.lfs.2022.120480.

82. Ben-Ari Y, Cherubini E. The GABA Polarity Shift and Bumetanide Treatment: Making Sense Requires Unbiased and Undogmatic Analysis. Cells. 2022;11:396. https://doi.org/10.3390/cells11030396.