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Role of *Cinnamomum verum* leaves in the management of Vascular dementia: A comprehensive overview

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Abstract

Spices are utilized for both culinary and medicinal purposes and have been for a very long time originating from Sri Lanka and southern India, *Cinnamomum verum* may also be found in other Asian, Caribbean, Australian, and African countries. The principal compounds contained are Cinnamaldehyde and Eugenol, both of which have unique medicinal qualities in the leaves of *Cinnamomum verum*. Cinnamonaldehyde (CA), a bioactive phytochemical offer therapeutic advantages against the beginning of cardiovascular illnesses. Eugenol is an organic compound found in the leaves of *Cinnamomum verum.* Eugenol has antihypercholesterolemic and antiatherogenic effects. Eugenol's smooth muscle relaxant effect is due to its inhibition of receptor-operated and voltage-sensitive channels. Endothelial cells create nitric oxide (NO), which relaxes blood vessels. Eugenol has substantial anti-inflammatory properties. The antipyretic activity of eugenol is well recognized, since it reduces fever by reducing prostaglandin and sodium archidonate synthesis. Eugenol's hydrophobic nature allows it to pass the blood-brain barrier and enter the brain. Eugenol protects neuronal cells against the oxidative and excitotoxic effects of N-methyl-D-aspartate (NDMA). Eugenol has neuroprotective properties in hippocampal tissues due to its capacity to reduce brain-derived neurotrophic factor (BDNF) and postpone amyloid β -peptide (A- β) induced cell death via abnormal Ca2+ blocking. Anti-hypertensive property of Eugenol is known as it has the ability to activate TRPV channels and to relax endothelium-depleted arteries. Eugenol, which is found in *Cinnamomum verum* leaves, has been shown to be beneficial in the control of hypertension and so may be beneficial in the management of vascular dementia.

Keywords: *Cinnamomum verum*; Cinnamon; Eugenol; Anti-hypertensive; Neuroprotective; Vascular dementia

1 Introduction

Spices are vital food components that play an important function in meal preparation. Around the world, over a hundred plant species are utilized as spices and condiments. They are fragrant, dried plant pieces derived from seeds, fruits, leaves, roots, and bark, among other things. Since ancient times, they have been used to add flavor to dishes and improve food quality [1]. A variety of spices also serve as great preservatives, extending the shelf life of food by delaying the rotting process [2]. Furthermore, spices, as a rich reservoir of physiologically active chemicals, have antioxidant, antibacterial, anti-inflammatory, anti-diabetic, and anticancer effects, among others [3].

Cinnamon is a spice derived from the inner bark of many plants of the genus *cinnamomum*. Cinnamon is known in German as ceylonzeimt/kaneel, in hindi as dal-chini, and in Italian as cannella [4]. Cinnamomum is one of the earliest spices known to have been used in cooking. Though several species in this genus are sold as cinnamon, the inner dried bark of *Cinnamomum verum* J. Presl (family lauraceae) has traditionally been regarded as the authentic cinnamon. Its medicinal and culinary benefits have been widely documented in ancient literature extending back 4000 years [1].

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The principal varieties of cinnamon grown for commerce are:

Cinnamomum burmannii is a tiny tree or shrub that belongs to the lauraceae family. It is sometimes referred to as indonesian cassia, batavia cassia, and padang cassia. The plant is found across Southeast Asia and is grown in some areas of Indonesia and the Philippines. It has glossy green, oblong-elliptical leaves that are placed in opposition and an ovoid, 1-cm-long fruit. The plant's dried bark, which is used for flavoring and cooking, is sold on the market in the forms of rolls and quills [5].The essential oil (0.4%) found in *C. burmannii* leaves was thought to be mostly composed of cinnamonaldehyde (45–62%) and eugenol (10%) [6]. *C. Burmannii* has biological activity that includes antibacterial, anti-inflammatory, analgesic, anti-diabetic, antioxidant, anti-tumor, and anti-thrombotic properties, among others [7] .

Figure 1 *Cinnamomum burmanii* leaves [8]

Cinnamomum cassia peral is a lauraceae family tropical fragrant evergreen tree that is frequently utilized in traditional Chinese medicine [9]. Cinnamomum cassia Presl is found in China, India, Vietnam, Indonesia, and other countries; in China, production is centered in Guangxi, Guangdong, Fujian, and Hainan provinces [10]. From C. cassia, more than 160 compounds have been isolated and identified. Terpenoids, phenylpropanoids, glycosides, and other compounds are the primary ingredients of C. cassia. Modern research indicates C. cassia's antitumor, anti-inflammatory and analgesic, anti-diabetic and anti-obesity, antibacterial and antiviral, cardiovascular protective, cytoprotective, neuroprotective, immunoregulatory effects, anti-tyrosinase activity, and other effects [9].

Figure 2 *Cinnamomum* cassia peral tree [10]

Cinnamomum verum has long been used as a spice for both medicinal and culinary purposes. It is indigenous to Sri Lanka and southern India, although it is also found in a number of Asian, Caribbean, Australian, and African nations [1]. Typically, the Palani Hills in Tamil Nadu and the Malabar Coast are home to cinnamon verum in India [11, 12]. *Cinnamomum verum* (lauraceae) is cultivated in a number of Asian nations, most notably Sri Lanka and Southern India. Cinnamon is an ancient folk herb found in Korea, China, and Russia. Cinnamon has been utilized for centuries by numerous civilizations all over the world. Cinnamomum zeylanicum (CZ) and Cinnamon cassia (CC) are two types of cinnamon derived from the inner bark of the tropical evergreen shrub Cinnamomum zeylanicum (CZ). *Cinnamomum*

verum shoots from underneath the parenchyma of their outer cork is used to create the medicine. The surface is striated longitudinally, and the fracture is short and splintery [13]. Research has found Cinnamomum zeylanicum (a synonym for *Cinnamomum verum*) to be high in cinnamaldehyde and its derivatives, followed by linalool, caryophyllene, and eugenol. As a result, it is conceivable that the composition difference between C. verum's leaf and flower essential oils is responsible for the observed differences in activity [14]. Because of its numerous therapeutic characteristics, including astringent, aphrodisiac, antiseptic, aperitif, fragrant, carminative, digestive, stimulant, hypertensive, sedative, tonic, and vasodilator [15] diabetic, antinociceptive, astringent, and diuretic properties [16] this species has been employed in traditional medicine.

Table 1 Taxonomical rank and toxon of the *cinnamon verum* [17]

Taxonomical rank	Taxon
Domain	Eukaryota
Kingdom	Plantae
Phylum	Spermatophyta
Subphylum	Angiospermae
Class	Dicotyledonae
Family	Lauraceae
Genus	Cinnamomum
Species	*Cinnamomum verum*

2 Chemical constituents of cinnamon in various parts

2.1. Bark

Cinnamon Verum bark comprises a minimum of 12 millilitres of essential oil produced by steam distillation per kilogramme. It has a unique perfume that is fragrant as well as pleasant. It tastes pungently spicy, mildly sweet, and mucilaginous, with barely a hint of roughness. Cinnamon bark contains up to 4% essential oil, with the majority of it being cinnamaldehyde (60-75%), cinnamyl acetate (1-5%), eugenol (1-10%), caryophyllene (1-4%), linalool (1-3%), and 1.8-cineole (1-2%). pentacyclic diterpenes cinnzeylanol and its acetyl derivative cinnzeylanine, sugars mannitol,5 L-arabino-Dxylanose, L-arabino-Dxylose, D-xylose, D-glucane, and mucilage polys Several studies have shown that cinnamon has anti-inflammatory, anti-microbial, blood glucose, cardiovascular, cognitive function, and anticarcinogenic properties. Cinnamon is recognized as a powerful neuroprotective agent in traditional Chinese medicine as well as a medication to treat type 2 diabetes mellitus [13] .

Figure 3 *Cinnamom verum* bark

2.2. Leaf and flower

The yield of leaf (LEO) and flower (FEO) essential oil by steam distillation was 1.44 ± 0.09 and 1.07 ± 0.12%. Both the essential oils possessed similar volatile components, with a different percentage composition. The common compounds among these two essential oils were the cinnamaldehyde, eugenol, and linalool. The most abundant (< 10%) compounds in the LEO were (E) Cinnamaldehyde (35.6%), linalool (18.92%), eugenol (18.69%), and (E) Cinnamyl acetate (12.5%). In the FEO, compounds with highest abundance were (E) Cinnamaldehyde (42.88%), eugenol (21.33%), and linalool (15.62%) [14].

Figure 4 *Cinnamon verum* leaves

Table 2 GC-MS analysis of *Cinnamomum verum* LEO and FEO essential oils

No.	Compound	Kovats Index (KI)	% [a]	
			LEO [b]	FEO [c]
1	Camphene	945	0.24	0.41
2	*β*-pinene	967	0.33	0.14
3	Sabinene	972	0.85	0.22
4	Myrcene	988	1.54	1.99
5	1,4-Cineole	1010	0.52	0.13
6	Limonene	1020	0.38	0.64
7	*Cis-β*-Ocimene	1024	0.08	0.11
8	*trans-β*-Ocimene	1028	0.07	0.15
9	*p*-Cymene	1018	1.88	2.68
10	Linalool	1095	18.92	15.62
11	*γ*-Terpinene	1054	0.19	0.55
12	*α*-Terpineol	1296	0.84	1.33
13	Piperitone	1247	0.22	0.41
14	Geraniol	1254	0.62	0.18
15	(*E*)-Cinnamaldehyde	1262	35.6	42.88
16	(*Z*)-Cinnamaldehyde	1271	0.65	0.88
17	Eugenol	1358	18.69	21.33

18	(*E*)-Cinnamyl acetate	1443	12.5	8.26
19	Eugenyl acetate	1496	1.38	0.74
20	Benzyl benzoate	1754	0.25	0.22

a Relative area = relative contents expressed as percentages of the total oil composition. b LEO—essential oil obtained from leaves. c FEO—essential oil obtained from flowers [14].

2.3. Leaves

After being hydro-distilled, C. verum leaves produced 1.5% (v/w-on a dry weight basis) of colorless essential oil. Ninety-seven percent of the examined sample, or 19 components, were identified. Eugenol (81.7%), linalool (3.8%), and benzyl benzoate (3.9%), together with their respective biological functions, were the main constituents found.

Table 3 Constituents of the essential oil extracted from leaves of C. verum

SL. No	RI[a]	Name	Area %[b]	Method of identification
1.	933	α-Thujene	0.1	RI,MS
2.	936	α-Pinene	0.5	RI,MS
3.	952	Camphene	0.2	RI,MS
4.	981	β-Pinene	0.2	RI,MS
5.	1005	α-Phyllandrene	0.3	RI,MS
6.	1027	ρ-Cymene	0.4	RI,MS
7.	1031	β-Phellandrene	0.5	RI,MS
8.	1034	1,8-Cineole	0.1	RI,MS
9.	1100	Linalool	3.8	RI,MS
10.	1171	Borneol	0.1	RI,MS
11.	1192	α-Terpeneol	0.1	RI,MS
12.	1274	(*E*)-Cinnamaldehyde	0.8	RI,MS
13.	1363	Eugenol	81.7	RI,MS
14.	1422	(*E*)-Caryophyllene	1.7	RI,MS
15.	1440	γ-Elemene	1.1	RI,MS
16.	1455	(*E*)-Isoeugenol	0.3	RI,MS
17.	1579	Caryophyllene oxide	1.2	RI,MS
18.	1591	Humulene epoxide II	0.6	RI,MS
19.	1764	Benzyl benzoate	3.9	RI,MS
		Total identified		

a.Retention indices as tested on HP-5 column using the homologous series of C8-20 n-alkanes ; b.Relative percentages of components based on GC-FID peak areas [11]

3 Pharmacological activities of cinnamon

Different components contain some primary elements, namely cinnamaldehyde and trans-cinnamaldehyde (Cin), which are present in the essential oil of its bark and contribute to the aroma and varied biological activity [18]. Several MDR pathogenic microorganisms are inhibited by eugenol (leaf) [19]. Its leaf and bark have digestive, blood purifier, astringent, carminative, warming stimulant, antiseptic, antibacterial, antifungal, and antiviral qualities, as well as the ability to lower cholesterol and blood sugar levels [20].

3.1. Anti-oxidant activity

Antioxidants have been considered the most important drivers in the progress and existence of humans, as they respond to free radicals and damage in metabolic diseases and age-related syndromes of humans and other animals [21, 22] Cinnamon flavonoids have free-radical scavenging and antioxidant effects [23]. The essential oils and key chemicals found in cinnamon, such as (E)-cinnamaldehyde, eugenol, and linalool, were studied in terms of peroxynitrite-induced nitration and lipid peroxidation. Eugenol and essential oils outperformed the other two chemicals [24]. A rat study found that administering 10% bark powder of C. verum for 90 days exhibited antioxidant activity as measured by cardiac and hepatic antioxidant enzymes, lipid conjugate dienes, and glutathione (GSH) [25].

3.2. Anti-inflammatory activity

Several investigations on medicinal plants and their constituents have revealed that cinnamon has anti-inflammatory properties [26, 27]. Several studies have found that cinnamon and its essential oils have anti-inflammatory properties [28, 29]. To date, various flavonoid compounds with anti-inflammatory properties have been identified (e.g., gossypin, gnaphalin, hesperidin, hibifolin, hypolaetin, oroxindin, and quercetin) [30, 31].

3.3. Anti-diabetic activity

Cinnamon contains a component known as "insulin-potentiating factor" (IPF) [32]. Methylhydroxychalcone polymer (MHCP) is a pure hydroxychalcone polymer that can promote glucose oxidation [33, 34]. A novel molecule derived from hydroxycinnamic acid derivatives known as naphthalenemethyl ester has been found as having blood glucose-lowering properties [35]. Several studies have also found that cinnamon extracts reduce blood glucose and cholesterol levels [36, 37].

3.4. Anti-microbial activity

Cinnamon and its oils have been shown to have antibacterial properties in multiple investigations [38-40]. According to Hili et al., cinnamon oils may have antibacterial (Pseudomonas aeruginosa, Staphylococcus aureus, and Escherichia coli) and yeast (Torulopsis utilis, Schizosaccharomyces pombe, Candida albicans, and Saccharomyces cerevisiae) activity [41].

3.5. Anti-cancer activity

The aqueous extract and the HPLC fraction of cinnamon suppress vascular endothelial growth factor subtype 2 (VEGFR2) kinase activity, consequently decreasing cancer angiogenesis. According to the study's findings, cinnamon might potentially be employed in cancer prevention [42]. Cinnamaldehydes have been produced and investigated as anti-angiogenesis agents [43]. CB403's antitumor and growth-inhibitory activities in animal and cell culture tests show that cinnamon has the potential to be employed as an anticancer drug [44].

3.6. Cardiovascular disease management

Cinnamaldehyde has hypotensive properties [45]. A recent study showed that cinnamaldehyde expands rat vascular smooth muscle in an endothelium-independent manner. The ability of cinnamaldehyde in vasodilatory function may be because it impedes both Ca2+ influx and Ca2+ release [46] Cinnamaldehyde averts the progress of hypertension in types 1 and 2 diabetes by abridging vascular contractility, in addition to its insulinotropic effect in insulin deficiency [47].

3.7. Cholesterol and lipid lowering activity

Administration of Cinnamon to mice improved the lipid profile by lowering high density lipoprotein (HDL), cholesterol levels and plasma triglycerides [35]. A research found that taking cinnamon at 1, 3, and 6 g dosages per day reduced blood glucose, triglyceride, total cholesterol, and LDL cholesterol levels in adults [48].

4 Eugenol and Its Uses

Eugenol is a natural chemical present in dietary plants such as cinnamon, cloves, basil and nutmeg [49]. Eugenol is a pale yellow to transparent liquid with an oily viscosity and a pungent scent. It is only slightly soluble in water but very soluble in organic solvents [50]. Eugenol, also known as phenylpropanoid or C10H12O2, is an aromatic chemical that is a member of the phenol group. Natural essential oils of plants belonging to the Lamiaceae, Lauraceae, Myrtaceae, and Myristicaceae families are typically used to obtain it [51].

Eugenol has limited chemical stability and is susceptible to oxidation and other chemical reactions. When taken orally, it is quickly absorbed by multiple organs and processed in the liver. As a result, encapsulation of eugenol appears to be the ideal strategy for preventing early absorption, improving its water solubility, and hence increasing its activity [50, 52]. Eugenol is well recognized for its pharmacological properties, antimicrobial, anticancer, antioxidant, anti-inflammatory, and analgesic. Different derivatives of eugenol are used in medication as a local anesthetic and antiseptic [53] eugenol also used in management of hypertension and digestive complications [54].

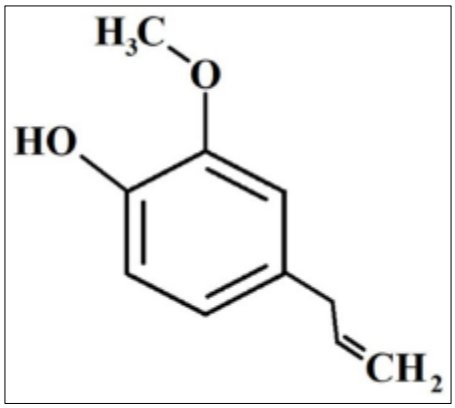

Figure 5 Chemical structure of eugenol [51]

4.1. Cardiovascular protective property of eugenol

Hyperlipidemia is the most frequent social problem in the general population, and it is the root cause of cardiovascular disease (CVD) and lipid-related disorders [55]. Less physical activity and a high fatty acid consumption are the root causes of CVDs and hyperlipidemic diseases [56]. High levels of low-density lipoprotein cholesterol (LDL-c) cause toxicity in vascular tissues and atherosclerosis/atherogenesis, eventually leading to diabetes, obesity, and hypertension [57]. Eugenol possesses powerful anti hypercholesterolemic and antiatherogenic properties [58] [59]. The smooth muscle relaxant activity of eugenol is owing to its inhibiting action on receptor-operated and voltage-sensitive channels. Nitric oxide (NO) produced by endothelial cells relaxes the blood vessels [60]. A recent study employing a hyperlipidemic zebra fish model found that eugenol significantly reduced triglyceride (80%) and cholesterol (68%) levels in blood samples [61].

4.2. Anti-inflammatory and analgesic activity of eugenol

Inflammation is the body's adaptive immune response to unpleasant stimuli, tissue infection, and damage [62]. It can be either chronic or acute [63]. Many modern anti-inflammatory medicines have negative side effects [64] Eugenol, which has no adverse effects, has a significant anti-inflammatory potential [65]. In one research, male Swiss albino mice treated with eugenol had lower LOP and higher levels of inflammatory markers such as COX-2, iNOS, and the cytokine tumor necrosis factor (TNF-α), as well as antioxidant enzymes [66]. It is also known to inhibit pro-inflammatory mediators such as IL-1 and IL-6, tumor necrosis factor alpha (TNF-α), prostaglandin E2 (PGE2), expression of inducible oxide nitrate synthase (iNOS), cyclooxygenase-2 (COX-2) and leukotriene C4 and 5-lipoxygenase (5-LOX) [67].

Eugenol is extremely effective in relieving pain by reducing the pain-related reactions. It inhibits numerous reactions to histamine, norepinephrine, and periarterial sympathetic nerve stimulation [69] as well as inhibiting prostaglandin synthesis [70]. Its analgesic action is connected to the suppression of voltage-dependent Na+, K+, and Ca2+ channels [71, 72]. TRPV-1 receptors are implicated in pain stimulation. According to one study, eugenol suppressed TRPV-1 via inhibiting voltage-activated Na+ and Ca2+ channels [49, 73]. Eugenol is a common pain reliever and anesthetic used in dentistry. In numerous investigations, including one using a rat model, it was discovered to block voltage-gated sodium channels (VGSC) in primary supply neurons of the teeth [72, 74].

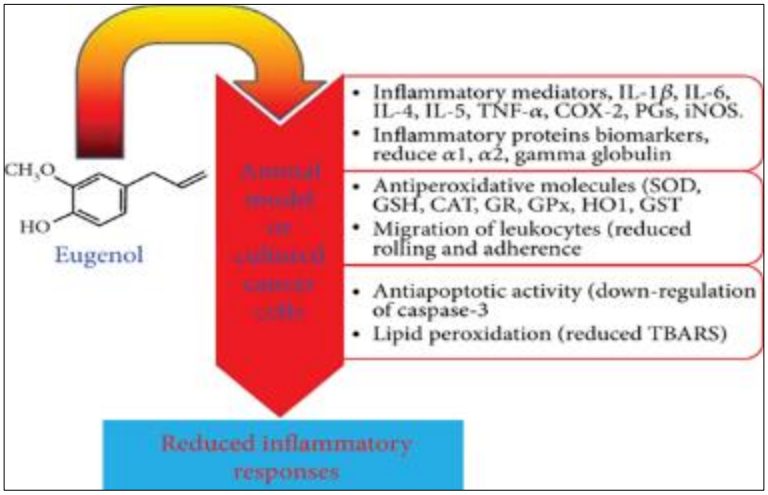

Figure 6 The anti-inflammatory effect of eugenol[68]

4.3. Antipyretic activity of eugenol

Feng and associates investigated the antipyretic effectiveness of eugenol [75]. Where they discovered that EUG had an antipyretic effect against acetaminophen, a well-known antipyretic, in rabbits produced feverish by IL-1β, when administered intragastrically, centrally, and intravenously, it has a greater antifever effect than acetaminophen. In contrast to acetaminophen, eugenol generates mild hypothermia when administered intravenously. Acetaminophen lowered fever by 68% at a dose of 1.3 mM/kg, but eugenol reduced fever by 68% at a significantly lower dosage. When administered peripherally, it significantly reduces fever. When administered intravenously, rabbits' respiration and vasodilatation in the ears increased. Increased respiration indicates that eugenol has a favorable effect on the central nervous system (CNS). If prostaglandins and sodium archidonate cause fever in the CNS, acetaminophen and eugenol can suppress fever by inhibiting prostaglandin and sodium archidonate production. Both of these medications have the same antipyretic effect, although eugenol is more powerful when compared to acetaminophen [76].

4.4. Effects of Eugenol on the Central Nervous System (CNS)

Eugenol acts not just on the periphery but also in the central nervous system. The hydrophobic feature of eugenol allows it to cross the blood-brain barrier and enter the brain [77]. Eugenol protects neuronal cells from N-methyl-D-aspartate (NDMA)induced oxidative and excitotoxic damage [78]. Eugenol has a neuroprotective potential in hippocampus tissues due to its ability to diminish brain-derived neurotrophic factor (BDNF) and to delay amyloid-β peptide (A-β) caused cell death via aberrant Ca2+ blockage (as a result of A-β) [79]. Eugenol increases the functions of a few glutathione-related proteins in cell models and protects critical brain cells from oxidative and excitotoxic effects [80, 81]. The inhibitory impact of eugenol on 5-lipoxygenase has been observed, as well as an enhanced action in response to excitotoxic and ROS-injured neuron cells [82].

Depression, a neurological condition, causes frequent psychiatric problems, and it affects 10-20% of the general population. Eugenol had a significant antidepressant effect in the force swimming test (FST) and tail suspension test (TST), equivalent to the antistress medication imipramine [78]. These two medications have distinct mechanisms of action. Real-time PCR (RT-PCR) revealed that metallothionein-III (MT-III) was associated with the antidepressive action of eugenol in a way that imipramine was not. If patients acquire resistance to standard medications, this becomes the basis of an alternate treatment. Eugenol has antiepileptic properties. It works by inhibiting long-term potentiating and synaptic transmission in neurons [83]. Eugenol can help with Alzheimer's disease (AD) and depression. Furthermore, Eugenol regulates BDNF gene expression in the hippocampus. It also inhibits monoamine oxidase A (MAO-A) and occasionally restores monoamines that are depleted in the brains of depressive people [77]. Eugenol has been shown to be beneficial in the treatment of stress-induced irritable bowel syndrome (IBS) [84].

4.5. Antihypertensive activity of eugenol

Eugenol is a naturally occurring chemical found in plants such as cloves, basil, cinnamon, and nutmeg [49]. These plants exhibit antihypertensive effects, albeit the molecules that mediate this action have not been identified [85-87]. Eugenol and capsaicin have a vanillyl group, which is critical for bioactivity. As a result, eugenol, like capsaicin, can activate TRPV channels [88]. TRPV1 channels in trigeminal ganglion neurons and TRPV3 channels in keratinocytes and endothelial cells are activated by eugenol [89-92]. Eugenol lowers blood pressure and produces bradycardia in normotensive and

deoxycorticosterone acetate-salt hypertensive rats. Both investigations hypothesized that eugenol-induced hypotension was caused by vasorelaxation [59, 93]. Eugenol also eased endothelium-depleted arteries. One reason for this action is because eugenol inhibits voltage-dependent Ca2+ channels in arterial smooth muscle cells, causing vasodilation [94]. HC-067047, a selective TRPV4 channel blocker, reduced eugenol-induced relaxation in endothelium-depleted arteries, indicating that TRPV4 channels in cells other than endothelial cells are implicated in this reaction. TRPV4 channel activation in arterial smooth muscle cells activates BK channels, resulting in membrane hyperpolarization and vasodilation, which is one explanation for this conclusion [95].

Eugenol decreases systemic blood pressure by activating TRPV4 channels. In anaesthetized rats, the effect of eugenol on systemic blood pressure was examined in vivo. An intravenous dose of eugenol resulted in a biphasic reaction consisting of an initial transitory decrease in blood pressure and lasting hypotension [96].

4.6. Eugenol's role in Brain Ischemia-Reperfusion Injury

One of the most dangerous illnesses endangering people's health and lives is stroke, which is brought on by cerebral artery blockage and the ensuing hypoperfusion that results [97]. Stroke is the second most prevalent cause of death and dementia in those over 60, and it is also the most common cause of lasting impairments [98]. Autophagy is a fundamental biological process involved in several physiological and pathological processes. It breaks down and recycles damaged organelles and intracellular macromolecules. It has been established that autophagy contributes to the development of a number of illnesses, including neurological conditions [99], diabetes, obesity and so on.

Significantly, mounting data suggests that autophagy may have a role in a variety of ischemic illnesses, such as cerebral ischemia reperfusion injury, renal ischemia reperfusion injury, and myocardial infarction. Although autophagy may be induced during an ischemic stroke, its significance in relation to stroke is currently debatable. According to a number of studies, autophagy has both advantageous and detrimental effects on brain neurons in response to an ischemic stimulation [100].

Eugenol may be able to prevent hepatic ischemia-reperfusion damage, according to a research [101]. Significantly, research indicates that eugenol may be effective in treating cerebral ischemia damage [102]. Furthermore, it has been shown that methyleugenol, a related substance, reduces brain ischemia damage by preventing oxidative stress, inflammation, and apoptosis [103].

Via the experiment conducted by (Sun et al., 2020) it was coming to know that, In MCAO rats, eugenol therapy successfully reduced the neurological impairment. Additionally, eugenol treatment clearly decreased the infarct volume in rats given MCAO. Reduced neurological score due to eugenol induction, Eugenol treatment resulted in a reduction in the brain's water content. TUNEL was also used to assess the apoptosis in brain tissues. Eugenol significantly reduced the number of apoptotic cells in the brain tissues' ischemic penumbra region.Eugenol treatment increased the level of Bcl-2 while decreasing the amounts of cleaved caspase-3 and Bad.

After MCAO challenge, the p-AMPKα/AMPKα ratio increased, whereas the p-mTOR/mTOR and p-P70S6K/P70S6K ratios decreased, according to research on the molecular mechanisms of eugenol in cerebral I/R damage. Eugenol therapy may significantly amplify the aforementioned alterations. Eugenol therefore contributed to the protective mechanisms against cerebral I/R damage through the AMPK/mTOR/P70S6K pathway.

The HT22 cell viability was significantly reduced by OGD/R, however this effect was countered by incubating the cells with 30 or 100 μM eugenol. Given that the best result was obtained with 100 μM eugenol. Furthermore, HT22 cells treated with eugenol showed a significant suppression of OGD/R-induced apoptosis, indicating that eugenol reduced OGD/R-induced damage in HT22 cells. Following OGD/R exposure, there was a noticeable rise in Beclin-1 level but a fall in p62 level. Eugenol, as predicted, caused a decrease in p62 and an increase in Beclin-1 when compared to the OGD/R group. The p-AMPKα/AMPKα ratio was increased by eugenol treatment, but the p-mTOR/mTOR and p-P70S6K/P70S6K ratios were decreased. Eugenol, thus, increased HT22 cell viability by triggering autophagy that is reliant on AMPK, mTOR, and P70S6K.

Afterwards, the research came to the conclusion that, when considered collectively, the data demonstrated that autophagy activation through AMPK/mTOR/P70S6K pathway regulation was responsible for eugenol's protective action against cerebral I/R damage [100].

Eugenol and its correlation with levodopa in rats with hemiparkinsonia produced by 6-hydrodopamine.

Chemically known as 2-methoxy-4-(2-propenyl-phenol) or 4-allyl-2-methoxy-phenol, eugenol is a derivative of phenylpropanoid [104]. In both neuronal cells and in vivo 6-hydroxydopamine (6-OHDA) models in mice, eugenol has demonstrated neuroprotective properties [82, 105].

4.7. Hypertension and stroke linkage

There are several ways in which hypertension can result in stroke. In intracerebral arteries, a high intraluminal pressure will cause significant changes in the endothelium and smooth muscle function. Increased permeability across the blood–brain barrier and local or multifocal cerebral oedema might result from the increased stress on the endothelium. Ischemic lesions and localized thrombi development can result from endothelial injury and changed blood cell–endothelium interaction. Focal stenosis and occlusions brought on by fibrinoid necrosis can result in lacunar infarcts. Intracerebral hemorrhages are predisposed by degenerative alterations in smooth muscle cells and endothelium. Moreover, hypertension quickens the arteriosclerotic process, raising the risk of cerebral lesions from stenosis and embolism coming from the heart, the aortic arch, and major extracranial arteries [106].

4.8. Hypertension and cognitive dysfunction linkage

Despite the fact that hypertension is well acknowledged as a cause of vascular dementia (VaD) [107]. Recent research indicates that hypertension has a role in the etiology of Alzheimer's disease (AD). Mild cognitive impairment (MCI) is considered a risk factor for dementia, and early detection is expected to contribute to secondary prevention by lowering the risk of cardiovascular disease. Recent research has found that disturbance of diurnal blood pressure (BP) fluctuation is strongly linked to cognitive impairment [108, 109]. In several clinical trials, BP-lowering with antihypertensive agents was shown to substantially reduce the risk of dementia or cognitive decline [110].

4.9. Hypertension and cerebrovascular dysfunction linkage

Hypertension is the major cause of cognitive decline and dementia, as well as the greatest risk factor for stroke [111]. There is a linear link between blood pressure and stroke mortality, and a 1 mm Hg increase in systolic blood pressure increases stroke fatalities by 2% in people with controlled hypertension [112]. Furthermore, hypertension is a significant risk factor for Alzheimer's disease, the leading cause of dementia in the elderly [113].

Recent breakthroughs in neurovascular control and hypertension pathobiology have provided a better knowledge of how hypertension alters cerebral blood flow. These novel discoveries allow for a current reconsideration of the cerebrovascular consequences of hypertension [114].

Stroke and dementia are two primary brain disorders that are exacerbated by hypertension. Stroke can occur as a result of the obstruction of a major cerebral artery (ischemic infarction) or the rupture of intracerebral arterioles (hemorrhage). Hypertension can also induce berry aneurysms of the circle of Willis to rupture, resulting in bleeding into the subarachnoid space (subarachnoid hemorrhage). Ischemia can cause bleeding by ischemic vascular rupture or extravasation of blood from leaky blood vessels. Hemorrhage, on the other hand, can cause ischemia by squeezing the surrounding tissues and limiting local blood supply. Vascular cognitive impairment (VCI) is caused by the obstruction of tiny arterioles in the subcortical white matter, which disrupts neuronal connections that are important for cognition and memory [115].

By disrupting brain circuits related to memory and cognition, such as the midline thalamus, a single stroke can cause dementia (strategic infarct dementia, SID). several-infarct dementia, or MID, is a kind of dementia brought on by cumulative brain damage from several strokes. Alzheimer's disease is a gradual dementia brought on by a buildup of β-amyloid, and hypertension is one of its risk factors [116].

Although Alzheimer's disease and vascular dementia have always been seen as distinct conditions, new research indicates that they may have shared pathogenic elements that interact [117].

4.10. Hypertension and Aβ accumulation

About 20% of the heart's output is absorbed by the central nervous system, which depends on a complex vascular network for both nutrition delivery and neuronal regulation. Maintaining proper cognitive function depends on the cerebral circulation operating in an appropriate manner. The most common cardiovascular risk factor associated with middle and late life, arterial hypertension, appears to be a major obstacle to the start and progression of dementia. Aging and vascular factors are the primary drivers of cerebrovascular dysfunction.

Specifically, hypertension is a significant risk factor for Alzheimer's disease (AD), which is the most prevalent form of dementia in the elderly. In fact, a growing body of epidemiological studies strongly links vascular risk factors, such as arterial hypertension, with increased probability to develop AD, reducing the boundary between AD and vascular dementia. This is contrary to the long-held belief that AD is distinct from vascular dementia, having a nonvascular origin [118].

Amyloid-β peptide (Aβ) buildup in the brain is a pathogenic characteristic of AD that underlies cognitive impairment and dementia [119], and growing data indicates that Aβ transit across the blood-brain barrier plays a crucial role in regulating Aβ concentrations in the central nervous system, considering peripheral Aβ's capacity to engage with the cerebral vasculature and impact its own accumulation in the brain [119].

The blood-brain barrier (BBB) keeps the intracerebral Aβ pool and the bloodstream pool in the proper proportion [120].

In actuality, the BBB's structural makeup prevents unrestricted transfers of polar solutes like Aβ between the brain and blood or the opposite. Nonetheless, several pathways play a role in the natural entry and exit of amyloid beta into and from the brain. Aβ can be transported from the central nervous system into the circulation or vice versa via specialized receptors at the blood-brain barrier (BBB)[121, 122]. The BBB transport of Aβ into the brain is dominated by the receptor for advanced glycation end products (AGE; RAGE) among these receptor systems. Thus far, the onset of diabetes mellitus has been linked to RAGE activation. More recently, it has been shown that RAGE is activated in mouse models of AD where the disease originates in the nervous system, such as transgenic models [121]. Nevertheless, conclusive data is lacking regarding the possibility that a blood pressure challenge might initiate and maintain Aβ precipitation in the brain by activating RAGE in brain arteries.

Use of specific mouse model of arterial hypertension obtained by transverse aortic coarctation, or TAC that is predisposed to develop AD-related brain disease in order to shed light on this problem. It has previously been shown that cerebral amyloid deposition occurred as early as 4 weeks after TAC's hemodynamic stress to the brain, preceded by neuroinflammation and hypoperfusion. The cortex and hippocampus are two examples of specific brain regions that affect cognitive functioning where the resultant brain damage was mostly focused. Additionally, we have demonstrated that the production of soluble oligomers and intermediate amyloids is increased in TAC-induced hypertension [123, 124], the Aβ types that are most neurotoxic. It's interesting to note that oligomer levels in the brain, rather than the overall Aβ load, have been shown to correlate more strongly with the severity of the cognitive deficit in AD [125, 126].

It was coming to know that hypertension activates a biological target called RAGE, which leads to amyloid accumulation and cognitive decline that are hallmarks of Alzheimer's disease. Specifically, we have discovered that elevated blood pressure triggers oxidative stress, which in turn controls the AGEs that circulate and activate RAGE in brain capillaries. Ultimately, we demonstrate that blocking RAGE or the oxidant stress-related AGE/RAGE axis can stop amyloid buildup and cognitive decline brought on by TAC's prolonged hemodynamic strain to the brain. Long-term hypertension causes memory decline in the Morris water maze test, which evaluates hippocampal functioning, and in the NOR test, which evaluates cortical function, closely reflecting changes typical of Alzheimer's disease.

Memory impairment fully characterize this experimental condition as a model of vascular-induced AD, along with the earlier observations showing that TAC-induced hypertension also reproduces other typical features of AD, such as brain amyloid deposition, hypoperfusion, and neuroinflammation [118].

4.11. RAGE signaling contributing in amyloid-β transport and neuronal dysfunction

Aβ, an intracellular peptide, has been linked to neuronal death in Alzheimer's disease. Aβ is mostly released into the extracellular environment, although its transport routes at the neuronal cell membrane are not entirely understood. Our findings show that the receptor for advanced glycation end products (RAGE) helps transport Aβ from the cell surface to the intracellular region. Mouse cortical neurons exposed to extracellular human Aβ exhibited detectable peptides in the cytosol and mitochondria using confocal microscope and immunogold electron imaging. Cultured neurons from wild-type mice were pretreated with a RAGE-neutralizing antibody, while neurons from RAGE knockout animals showed reduced Aβ absorption and protection from Aβ-induced mitochondrial dysfunction. Aβ activated p38 MAPK but not SAPK/JNK, leading to intracellular absorption of Aβ-RAGE complexes. Transgenic animals producing mutant amyloid precursor protein showed intraneuronal co-localization of Aβ and RAGE in their hippocampus. These data suggest that RAGE plays a role in the translocation of Aβ from the extracellular to the intracellular area, increasing its cytotoxicity [127].

4.12. RAGE and Alzheimer's Disease

RAGE, a member of the immunoglobulin superfamily, acts as a receptor for amyloid-β peptide (Aβ) on neurons, microglia, astrocytes, and arterial wall cells. Alzheimer's disease (AD) causes increased expression of RAGE in brain areas. In vitro, Aβ-RAGE interaction causes cell stress, reactive oxygen species production, and activation of downstream signaling systems such as the MAP kinase pathway. RAGE activates p38 MAP kinase in neurons, inhibiting Aβ-induced long-term potentiation in entorhinal cortex slices. Transgenic mouse models overexpressing RAGE in an Aβ-rich environment exhibit faster and more severe clinical, biochemical, and behavioral problems than mice overexpressing solely mutant amyloid-β protein precursors. In a mouse transgenic model of Aβ accumulation, infusing soluble RAGE inhibits Aβ interaction with RAGE and reduces Aβ content and amyloid burden while increasing learning and memory and synaptic function. These findings show that RAGE might be a potential therapeutic target for Alzheimer's disease.

4.13. RAGE and cognitive decline

RAGE, also known as a pattern recognition receptor, is a multiligand cell surface protein that was first discovered in the bovine lung. This receptor binds a variety of inflammatory ligands, including N-carboxymethyl-lysine-modified protein (CML/AGE) (Kislinger et al., 1999) and high-mobility group box 1 (HMGB1). As a result, RAGE is not only implicated in diabetes-related AGE degradation, but it also plays a crucial role in inflammatory control. RAGE is expressed in microglia, monocytes, and endothelium and may enhance the inflammatory process in the brain. RAGE is also recognized as a key component in the pathogenesis of metabolic diseases [128]. RAGE knockout mice have been shown to be protected from HFD-induced adipocyte hypertrophy, obesity, and insulin resistance [128, 129]. RAGE has also been demonstrated to govern the evolution of atherosclerosis, endothelial inflammation, and obesity via regulating the inflammatory process [128].

Soluble RAGE (sRAGE) is an isoform of RAGE generated by the proteolytic cleavage of RAGE on cell surfaces by metalloproteinase [130]. TNF-α stimulates RAGE shedding via JNK and ATF4 pathways [131]. Endogenous secretory RAGE (esRAGE) is a splice variation that controls the production of RAGE proteins without the transmembrane and signaling domains [132]. The serum sRAGE and esRAGE levels are regarded as a potential protective factor against cognitive decline for APOE ε4 carriers or MCI patients.

Because of its tight link to metabolism and inflammation, we hypothesized that RAGE coordinates latent chronic inflammation, intracerebral inflammation, and cognitive impairment [128].

4.14. Aβ causing decrease in the Cholinergic functioning and transmission

According to many studies, when Aβ peptides are given to the brain, they can cause dopaminergic hypofunction [133].In the absence of toxicity, injection of Aβ25-35/1-40 into the rat medial septum reduces the amount of ACh released from the hippocampus. By employing a similar method, Harkany et al.39 shown that Aβ1-42 is harmful to cholinergic neurons by showing a decrease in ChAT-immunoreactive cell bodies in the basal forebrain and fibers in the cerebral cortex [134]. Additional research has demonstrated that adult rats' lateral ventricles infused with Aβ exhibit a comparable learning and memory impairment to that of glutamatergic inhibition [135-137]. Also it has been established that Aβ inhibits the release of ACh in rat and guinea pig cortical synaptosomes, [138] rat retinal neurons [139], and in cholinergic synaptosomes taken from the Narke japonica electric ray's electric organ [140]. These effects may be affected by aging.Aged rats with cognitive impairments had higher levels of Aβ1–40 in their hippocampal regions than did young adult rats, and it's possible that the cholinergic neurons in these older rats are more susceptible to Aβ-mediated inhibition of hippocampal ACh release [140].

4.15. Cholinergic function reduction/ loss causing neuronal degradation (Brain atrophy)

A decrease in cholinergic function may be caused by abnormalities in the expression of muscarinic and nicotinic acetylcholine receptors, changes in acetylcholine release, high-affinity choline uptake, and imbalances in the expression of NGF, its precursor proNGF, and the high and low NGF receptors, trkA and p75NTR, respectively. These findings provide credence to the theory that the cholinergic system plays a significant role in the physiological mechanisms leading to AD. Pharmacological intervention in cholinergic and neurotrophic signaling cascades has been demonstrated to improve the cholinergic deficit in the early stages of the illness and halt its course, making it possible to treat cholinergic system dysfunction. Unlike many other dementing disorders, AD's cholinergic dysfunctions are accompanied by the presence of two major histopathological hallmarks: neurofibrillary tangles and β-amyloid plaques. This raises the question of whether these hallmarks have a specific role in mediating or causing cholinergic dysfunction in AD. It is widely known that β-amyloid can cause cholinergic dysfunction via binding to α7 nicotinic acetylcholine

receptors, altering NGF signaling, facilitating tau phosphorylation, interacting with acetylcholinesterase, and having a particular impact on the proteome of cholinergic neurons [141].

4.16. AD and Vascular Dementia

The two most prevalent types of dementia are Alzheimer's disease (AD) and vascular dementia (VaD). Cerebrovascular disease (CVD)-related dementia is currently being evaluated for therapy with cholinergic medications, which have shown strong, long-lasting, and comprehensive effectiveness in AD. These two kinds of dementia share many pathological, clinical, and neurochemical aspects. Recent research has revealed that dementia in the elderly is a continuum of diseases, with "mixed" dementia (AD with CVD) occurring in between and perhaps accounting for the majority of cases, and pure AD and VaD being the two extremes. However, because most diagnostic techniques lean toward a diagnosis of AD, "mixed" dementia is seldom identified in clinical settings [142].

4.17. Vascular dementia (VaD) and Cardiovascular Risk Factors

VaD can result after a stroke that affects brain regions important for memory processing,[143, 144] Subcortical small vessel disease is known to be related with VaD in the elderly. Microvascular injury occurs when tiny brain arteries are exposed to greater blood pressure, pulsatile pressure, and flow.[145]The progress of multiple infarction dementia is gradual yet unpredictable, depending on the magnitude, placement, and number of ischemia insults [144]. Stroke survivors had a 2.0-2.8-fold higher incidence of dementia than controls in a case-control study nested inside the Framingham cohort [146].

4.18. Alzheimer’s disease and Cardiovascular Risk Factors

The extraneuronal and intraneuronal accumulation of amyloid β-peptide (Aβ) starts a pathogenetic cascade that results in neurotoxicity among AD patients, toxicity begins in the entorhinal cortex and spreads to neurons in other locations. The second histological feature of Alzheimer's disease is neurofibrillary tangles, which are made up of hyperphosphorylated microtubule-associated protein Tau [147]. These tangles form pairs of filaments known as paired helical filaments, which influence the nutrition of axon terminals and dendrites [110].

4.19. The mechanism that underpins the link between cardiovascular disease risk and cognitive impairment

Neuroimaging [148], as well as postmortem histopathology [149],According to research, up to one-third of AD patients have some degree of vascular pathology, and AD lesions are also present in a comparable proportion of VaD patients [110].Treatments with cholinesterase inhibitors increase regional cerebral blood flow (CBF) in individuals with AD or VaD [150]. A constricts the cerebral arteries of human [150]. A inhibits the rise in neocortical CBF in response to somatosensory stimulation and attenuates endothelium-mediated dilatation in the cerebral arteries via producing reactive oxygen radicals.[151] CBF is reduced in transgenic mice that overexpress mutant types of amyloid precursor protein, which is the source of misfolded A β [151, 152] and a reduced autoregulation of the cerebral circulation [153].The APOE4 allele is important in plaque formation [154],These pathophysiological similarities and interactions between AD and VaD were summarized by Staessen et al. [116].

VaD and Alzheimer's disease have the same pathogenesis. Each vascular and cholinergic component is linked to decreased cerebral blood flow. This might be a contributing cause of silent brain damage, such as leukoaraiosis or brain shrinkage. Alzheimer's disease (AD); vascular dementia (VaD) [110].

Figure 7 VaD and Alzheimer's disease have a same pathogenesis. Each vascular and cholinergic component is linked to decreased cerebral blood flow. This might be a contributing cause to silent brain damage, such as leukoaraiosis or brain shrinkage. Alzheimer's disease (AD); vascular dementia (VaD) [110]

5 Conclusion

Based on evidences from several sources, it is obvious that Eugenol, a prominent chemical ingredient found in *Cinnamomum verum* leaves, is an effective antihypertensive. As hypertension causes stroke through a variety of mechanisms, it can result in local or multifocal cerebral oedema. It is also a big cause of Aβ-accumulation, which puts a significant danger in the factor of Alzheimer's disease. This buildup reduces chollinergic functionality and transmission. This decrease in cholinergic transmission leads to neuronal degeneration and, as a result, brain shrinkage. Which plays an important part in the physiological mechanism that leads to dementia. AD, VAD, or mixed dementia were the three types of dementia. Despite the literature's emphasis on the dualism of Vascular dementia, Alzheimer's disease and Parkinson's disease, rational states the role of cardiovascular risks in the genesis of Vascular Dementia. So, while it is possible to hypothecate that consumption of Cinnamon leaves might be beneficial in the prevention of Hypertension, Cognitive dysfunction and ultimately Vascular dementia, it is concluded that more research on a larger scale is required to understand the mechanism of action on *Cinnamomum verum* leaves.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Singh, N., et al., Phytochemical and pharmacological review of *Cinnamomum verum* J. Presl-a versatile spice used in food and nutrition. Food Chemistry, 2021. **338**: p. 127773.

[2] Asimi, O.A., N. Sahu, and A. Pal, Antioxidant activity and antimicrobial property of some Indian spices. International Journal of Scientific and Research Publications, 2013. **3**(3): p. 1-8.

[3] Premakumara, G., et al., Antioxidant, anti-amylase and anti-glycation potential of brans of some Sri Lankan traditional and improved rice (Oryza sativa L.) varieties. Journal of cereal science, 2013. **58**(3): p. 451-456.

[4] Shreaz, S., et al., Cinnamaldehyde and its derivatives, a novel class of antifungal agents. Fitoterapia, 2016. **112**: p. 116-131.

[5] Tan, H.T., Herbs & Spices of Thailand. 2005: Marshall Cavendish.

[6] Rowaan, P., The essential oil from the leaf of the Padang-cinnamon tree. Chem Weekbl, 1936. **33**: p. 698-9.

[7] Al-Dhubiab, B.E., Pharmaceutical applications and phytochemical profile of Cinnamomum burmannii. Pharmacogn Rev, 2012. **6**(12): p. 125-31.

[8] Yang, H.-W., et al., Discriminating morphologically similar species in Genus Cinnamomum (Lauraceae) using machine vision. 2018.

[9] Zhang, C., et al., Cinnamomum cassia Presl: A Review of Its Traditional Uses, Phytochemistry, Pharmacology and Toxicology. Molecules, 2019. **24**(19).

[10] Zhang, C., et al., Cinnamomum cassia Presl: A Review of Its Traditional Uses, Phytochemistry, Pharmacology and Toxicology. Molecules, 2019. **24**(19): p. 3473.

[11] Chakraborty, A., et al., Chemical analysis of leaf essential oil of *Cinnamomum verum* from Palni hills, Tamil Nadu. Tic, 2015. **3**(e10): p. x10.

[12] C. K. Kokate, A.P.P., S.B. Gokhale Pharmacognosy 57th Edition 57th ed. 2021: Nirali parskashan

[13] Pathak, R. and H. Sharma, A review on medicinal uses of *Cinnamomum verum* (Cinnamon). Journal of Drug Delivery and Therapeutics, 2021. **11**(6-S): p. 161-166.

[14] Narayanankutty, A., et al., Chemical Composition of *Cinnamomum verum* Leaf and Flower Essential Oils and Analysis of Their Antibacterial, Insecticidal, and Larvicidal Properties. Molecules, 2021. **26**(20).

[15] Silva, K.B., et al., Tolerância à dessecação de sementes de Cinnamomum zeylanicum Ness. Semina: Ciências Agrárias, 2012. **33**(2): p. 587-594.

[16] Hassan, S.A., et al., Aqueous bark extract of cinnamomum zeylanicum: a potential therapeutic agent for streptozotocin-induced type 1 diabetes mellitus (T1DM) rats. Tropical Journal of Pharmaceutical Research, 2012. **11**(3): p. 429-435.

[17] Bakewell-Stone, P., *Cinnamomum verum* (cinnamon).

[18] Yeh, H.-F., et al., Methods for thermal stability enhancement of leaf essential oils and their main constituents from indigenous cinnamon (Cinnamomum osmophloeum). Journal of agricultural and food chemistry, 2013. **61**(26): p. 6293-6298.

[19] Suresh, P., V. Ingle, and V. Vijayalakshmi, Antibacterial activity of eugenol in comparison with other antibiotics. Journal of food science and technology (Mysore), 1992. **29**(4): p. 254-256.

[20] Lee, J., et al., Analysis of the trans-cinnamic acid content in Cinnamomum spp. and commercial cinnamon powder using HPLC. Journal of Agricultural Chemistry and Environment, 2015. **4**(04): p. 102.

[21] Halliwell, B., Free radicals and antioxidants–quo vadis? Trends in pharmacological sciences, 2011. **32**(3): p. 125-130.

[22] Halliwell, B., Reactive species and antioxidants. Redox biology is a fundamental theme of aerobic life. Plant physiology, 2006. **141**(2): p. 312-322.

[23] Okawa, M., et al., DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical scavenging activity of flavonoids obtained from some medicinal plants. Biological and Pharmaceutical Bulletin, 2001. **24**(10): p. 1202-1205.

[24] Chericoni, S., et al., In vitro activity of the essential oil of Cinnamomum zeylanicum and eugenol in peroxynitrite-induced oxidative processes. Journal of agricultural and food chemistry, 2005. **53**(12): p. 4762-4765.

[25] Dhuley, J., Anti-oxidant effects of cinnamon (*Cinnamomum verum*) bark and greater cardamom (Amomum subulatum) seeds in rats fed high fat diet. 1999.

[26] Lin, J., et al., Preliminary screening of some traditional zulu medicinal plants for anti-inflammatory and anti-microbial activities. Journal of Ethnopharmacology, 1999. **68**(1-3): p. 267-274.

[27] Matu, E.N. and J. Van Staden, Antibacterial and anti-inflammatory activities of some plants used for medicinal purposes in Kenya. Journal of Ethnopharmacology, 2003. **87**(1): p. 35-41.

[28] Chao, L.K., et al., Study on the antiinflammatory activity of essential oil from leaves of Cinnamomum osmophloeum. Journal of agricultural and food chemistry, 2005. **53**(18): p. 7274-7278.

[29] Tung, Y.-T., et al., Anti-inflammatory activities of essential oils and their constituents from different provenances of indigenous cinnamon (Cinnamomum osmophloeum) leaves. Pharmaceutical biology, 2010. **48**(10): p. 1130-1136.

[30] García-Lafuente, A., et al., Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease. Inflammation research, 2009. **58**(9): p. 537-552.

[31] Cho, N., et al., Cognitive-enhancing effects of Rhus verniciflua bark extract and its active flavonoids with neuroprotective and anti-inflammatory activities. Food and chemical toxicology, 2013. **58**: p. 355-361.

[32] Khan, A., et al., Insulin potentiating factor and chromium content of selected foods and spices. Biological trace element research, 1990. **24**: p. 183-188.

[33] Jarvill-Taylor, K.J., R.A. Anderson, and D.J. Graves, A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. Journal of the American College of Nutrition, 2001. **20**(4): p. 327-336.

[34] Anderson, R., et al., Isolation and characterization of chalcone polymers from cinnamon with insulin like biological activities. American Journal of Clinical Nutrition, 2006. **84**(3): p. 1432-1436.

[35] Kim, S.H., S.H. Hyun, and S.Y. Choung, Anti-diabetic effect of cinnamon extract on blood glucose in db/db mice. Journal of ethnopharmacology, 2006. **104**(1-2): p. 119-123.

[36] Blevins, S.M., et al., Effect of cinnamon on glucose and lipid levels in non-insulin-dependent type 2 diabetes. Diabetes care, 2007. **30**(9): p. 2236-2237.

[37] Safdar, M., et al., Effect of various doses of cinnamon on blood glucose in diabetic individuals. Pakistan Journal of Nutrition, 2004. **3**(5): p. 268-272.

[38] Gende, L.B., et al., Antimicrobial activity of cinnamon (Cinnamomum zeylanicum) essential oil and its main components against Paenibacillus larvae from Argentine. Bulletin of insectology, 2008. **61**(1): p. 1.

[39] Prabuseenivasan, S., M. Jayakumar, and S. Ignacimuthu, In vitro antibacterial activity of some plant essential oils. BMC complementary and alternative medicine, 2006. **6**(1): p. 1-8.

[40] Becerril, R., et al., Combination of analytical and microbiological techniques to study the antimicrobial activity of a new active food packaging containing cinnamon or oregano against E. coli and S. aureus. Analytical and bioanalytical chemistry, 2007. **388**: p. 1003-1011.

[41] Hili, P., C. Evans, and R. Veness, Antimicrobial action of essential oils: the effect of dimethylsulphoxide on the activity of cinnamon oil. Letters in applied microbiology, 1997. **24**(4): p. 269-275.

[42] Lu, J., et al., Novel angiogenesis inhibitory activity in cinnamon extract blocks VEGFR2 kinase and downstream signaling. Carcinogenesis, 2010. **31**(3): p. 481-488.

[43] Kwon, B.-M., et al., Synthesis and biological activity of cinnamaldehydes as angiogenesis inhibitors. Bioorganic & Medicinal Chemistry Letters, 1997. **7**(19): p. 2473-2476.

[44] Jeong, H.-W., et al., Antitumor effect of the cinnamaldehyde derivative CB403 through the arrest of cell cycle progression in the G2/M phase. Biochemical pharmacology, 2003. **65**(8): p. 1343-1350.

[45] HARADA, M. and S. YANO, Pharmacological studies on Chinese cinnamon. II. Effects of cinnamaldehyde on the cardiovascular and digestive systems. Chemical and pharmaceutical bulletin, 1975. **23**(5): p. 941-947.

[46] Xue, Y.-L., et al., Vasodilatory effects of cinnamaldehyde and its mechanism of action in the rat aorta. Vascular health and risk management, 2011: p. 273-280.

[47] El-Bassossy, H.M., A. Fahmy, and D. Badawy, Cinnamaldehyde protects from the hypertension associated with diabetes. Food and chemical toxicology, 2011. **49**(11): p. 3007-3012.

[48] Khan, A., et al., Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes care, 2003. **26**(12): p. 3215-3218.

[49] Kamatou, G.P., I. Vermaak, and A.M. Viljoen, Eugenol—from the remote Maluku Islands to the international market place: a review of a remarkable and versatile molecule. Molecules, 2012. **17**(6): p. 6953-6981.

[50] Marchese, A., et al., Antimicrobial activity of eugenol and essential oils containing eugenol: A mechanistic viewpoint. Critical reviews in microbiology, 2017. **43**(6): p. 668-689.

[51] Ulanowska, M. and B. Olas, Biological Properties and Prospects for the Application of Eugenol—A Review. International Journal of Molecular Sciences, 2021. **22**(7): p. 3671.

[52] Mak, K.-K., et al., A comprehensive review on eugenol's antimicrobial properties and industry applications: A transformation from ethnomedicine to industry. Pharmacognosy Reviews, 2019. **13**(25): p. 1-9.

[53] Sharma, A., et al., Chapter 9 - Eugenol, in Nutraceuticals and Health Care, J. Kour and G.A. Nayik, Editors. 2022, Academic Press. p. 177-198.

[54] Rauscher, F.M., R.A. Sanders, and J.B. Watkins III, Effects of isoeugenol on oxidative stress pathways in normal and streptozotocin-induced diabetic rats. Journal of biochemical and molecular toxicology, 2001. **15**(3): p. 159-164.

[55] Morsy, M.A. and A.A. Fouad, Mechanisms of gastroprotective effect of eugenol in indomethacin-induced ulcer in rats. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives, 2008. **22**(10): p. 1361-1366.

[56] Khalil, A.A., et al., Essential oil eugenol: Sources, extraction techniques and nutraceutical perspectives. RSC advances, 2017. **7**(52): p. 32669-32681.

[57] S Jain, K., R. R Kulkarni, and D. P Jain, Current drug targets for antihyperlipidemic therapy. Mini Reviews in Medicinal Chemistry, 2010. **10**(3): p. 232-262.

[58] Venkadeswaran, K., et al., Antihypercholesterolemic and antioxidative potential of an extract of the plant, Piper betle, and its active constituent, eugenol, in triton WR-1339-induced hypercholesterolemia in experimental rats. Evidence-Based Complementary and Alternative Medicine, 2014. **2014**.

[59] Interaminense, L.F.L., et al., Pharmacological evidence of calcium-channel blockade by essential oil of Ocimum gratissimum and its main constituent, eugenol, in isolated aortic rings from DOCA-salt hypertensive rats. Fundamental & clinical pharmacology, 2007. **21**(5): p. 497-506.

[60] Damiani, C.E.N., L.V. Rossoni, and D.V. Vassallo, Vasorelaxant effects of eugenol on rat thoracic aorta. Vascular pharmacology, 2003. **40**(1): p. 59-66.

[61] Jin, S. and K.-H. Cho, Water extracts of cinnamon and clove exhibits potent inhibition of protein glycation and anti-atherosclerotic activity in vitro and in vivo hypolipidemic activity in zebrafish. Food and Chemical Toxicology, 2011. **49**(7): p. 1521-1529.

[62] Medzhitov, R., Origin and physiological roles of inflammation. Nature, 2008. **454**(7203): p. 428-435.

[63] Ferrero-Miliani, L., et al., Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1β generation. Clinical & Experimental Immunology, 2007. **147**(2): p. 227-235.

[64] Saraiva, R.A., et al., Topical anti-inflammatory effect of Caryocar coriaceum Wittm.(Caryocaraceae) fruit pulp fixed oil on mice ear edema induced by different irritant agents. Journal of ethnopharmacology, 2011. **136**(3): p. 504-510.

[65] Barboza, J.N., et al., An overview on the anti-inflammatory potential and antioxidant profile of eugenol. Oxidative medicine and cellular longevity, 2018. **2018**.

[66] Kaur, G., M. Athar, and M.S. Alam, Eugenol precludes cutaneous chemical carcinogenesis in mouse by preventing oxidative stress and inflammation and by inducing apoptosis. Molecular Carcinogenesis: Published in cooperation with the University of Texas MD Anderson Cancer Center, 2010. **49**(3): p. 290-301.

[67] das Chagas Pereira de Andrade, F. and A.N. Mendes, Computational analysis of eugenol inhibitory activity in lipoxygenase and cyclooxygenase pathways. Scientific reports, 2020. **10**(1): p. 16204.

[68] Nisar, M.F., et al., Pharmacological Properties and Health Benefits of Eugenol: A Comprehensive Review. Oxidative Medicine and Cellular Longevity, 2021. **2021**: p. 2497354.

[69] Hume, W., Effect of eugenol on constrictor responses in blood vessels of the rabbit ear. Journal of dental research, 1983. **62**(9): p. 1013-1015.

[70] Dewhirst, F. and J. Goodson. Prostaglandin synthetase inhibition by eugenol, guaiacol and other dental medicaments. in Journal of Dental Research. 1974. AMER ASSOC DENTAL RESEARCH 1619 DUKE ST, ALEXANDRIA, VA 22314.

[71] Chung, G., et al., Modulation of CaV2. 3 calcium channel currents by eugenol. Journal of dental research, 2008. **87**(2): p. 137-141.

[72] Park, C.-K., et al., Eugenol inhibits sodium currents in dental afferent neurons. Journal of dental research, 2006. **85**(10): p. 900-904.

[73] Inoue, M., et al., Presynaptic enhancement by eugenol of spontaneous excitatory transmission in rat spinal substantia gelatinosa neurons is mediated by transient receptor potential A1 channels. Neuroscience, 2012. **210**: p. 403-415.

[74] Hwang, S.-M., et al., Co-application of eugenol and QX-314 elicits the prolonged blockade of voltage-gated sodium channels in nociceptive trigeminal ganglion neurons. Biomolecules, 2020. **10**(11): p. 1513.

[75] Feng, J. and J. Lipton, Eugenol: antipyretic activity in rabbits. Neuropharmacology, 1987. **26**(12): p. 1775-1778.

[76] Brodin, P. and A. Røed, Effects of eugenol on rat phrenic nerve and phrenic nerve-diaphragm preparations. Archives of Oral Biology, 1984. **29**(8): p. 611-615.

[77] Irie, Y., Effects of eugenol on the central nervous system: its possible application to treatment of Alzheimer's disease, depression, and Parkinson's disease. Current Bioactive Compounds, 2006. **2**(1): p. 57-66.

[78] Anuj, G. and S. Sanjay, Eugenol: a potential phytochemical with multifaceted therapeutic activities. Pharmacologyonline, 2010. **2**: p. 108-120.

[79] Irie, Y. and W.M. Keung, Rhizoma acori graminei and its active principles protect PC-12 cells from the toxic effect of amyloid-β peptide. Brain research, 2003. **963**(1-2): p. 282-289.

[80] Bupesh, G., et al., Molecular properties and insilico neuroprotective activity of eugenol against glutamate metabotrophic receptors. Int. J. Pharm. Sci. Rev. Res, 2016. **40**: p. 318-323.

[81] Prabhu, J., et al., Molecular properties and insilico neuroprotective activity of eugenol against glutamate metabotrophic receptors. International Journal of Pharmaceutical Sciences Review and Research, 2016. **40**(1): p. 318-323.

[82] Kabuto, H., M. Tada, and M. Kohno, Eugenol [2-methoxy-4-(2-propenyl) phenol] prevents 6-hydroxydopamine-induced dopamine depression and lipid peroxidation inductivity in mouse striatum. Biological and Pharmaceutical Bulletin, 2007. **30**(3): p. 423-427.

[83] Müller, M., et al., Effect of eugenol on spreading depression and epileptiform discharges in rat neocortical and hippocampal tissues. Neuroscience, 2006. **140**(2): p. 743-751.

[84] Garabadu, D., et al., Eugenol as an anti-stress agent: modulation of hypothalamic–pituitary–adrenal axis and brain monoaminergic systems in a rat model of stress. Stress, 2011. **14**(2): p. 145-155.

[85] Grover, J., et al., Pharmacological studies on Myristica fragrans--antidiarrheal, hypnotic, analgesic and hemodynamic (blood pressure) parameters. Methods and findings in experimental and clinical pharmacology, 2002. **24**(10): p. 675-680.

[86] Umar, A., et al., Antihypertensive effects of Ocimum basilicum L.(OBL) on blood pressure in renovascular hypertensive rats. Hypertension research, 2010. **33**(7): p. 727-730.

[87] Ranasinghe, P., et al., BMC Medicinal Properties of True Cinnamon (Cinnamomum zeylanicum): a. Systematic Review. Complementary and Alternative Medicine, 2013.

[88] Calixto, J.B., et al., Contribution of natural products to the discovery of the transient receptor potential (TRP) channels family and their functions. Pharmacology & therapeutics, 2005. **106**(2): p. 179-208.

[89] Yang, B., et al., Activation of vanilloid receptor 1 (VR1) by eugenol. Journal of dental research, 2003. **82**(10): p. 781-785.

[90] Xu, H., et al., Oregano, thyme and clove-derived flavors and skin sensitizers activate specific TRP channels. Nature neuroscience, 2006. **9**(5): p. 628-635.

[91] Earley, S. and J.E. Brayden, Transient receptor potential channels and vascular function. Clinical Science, 2010. **119**(1): p. 19-36.

[92] Earley, S., A.L. Gonzales, and Z.I. Garcia, A dietary agonist of transient receptor potential cation channel V3 elicits endothelium-dependent vasodilation. Molecular pharmacology, 2010. **77**(4): p. 612-620.

[93] Lahlou, S., et al., Cardiovascular effects of eugenol, a phenolic compound present in many plant essential oils, in normotensive rats. Journal of cardiovascular pharmacology, 2004. **43**(2): p. 250-257.

[94] Peixoto-Neves, D., J.H. Leal-Cardoso, and J.H. Jaggar, Eugenol dilates rat cerebral arteries by inhibiting smooth muscle cell voltage-dependent calcium channels. Journal of cardiovascular pharmacology, 2014. **64**(5): p. 401.

[95] Earley, S., et al., TRPV4 forms a novel Ca2+ signaling complex with ryanodine receptors and BKCa channels. Circulation research, 2005. **97**(12): p. 1270-1279.

[96] Peixoto-Neves, D., et al., Eugenol dilates mesenteric arteries and reduces systemic BP by activating endothelial cell TRPV4 channels. British Journal of Pharmacology, 2015. **172**(14): p. 3484-3494.

[97] Roger, V.L., et al., Executive summary: heart disease and stroke statistics-2012 update: a report from the American Heart Association. Circulation, 2012. **125**(1): p. 188-197.

[98] Chamorro, Á., et al., Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. The Lancet Neurology, 2016. **15**(8): p. 869-881.

[99] Kumar, A., et al., Autophagy and mitochondria: targets in neurodegenerative disorders. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders), 2018. **17**(9): p. 696-705.

[100] Sun, X., et al., Eugenol attenuates cerebral ischemia-reperfusion injury by enhancing autophagy via AMPK-mTOR-P70S6K pathway. Frontiers in Pharmacology, 2020. **11**: p. 84.

[101] Abd El Motteleb, D.M., S.A. Selim, and A.M. Mohamed, Differential effects of eugenol against hepatic inflammation and overall damage induced by ischemia/re-perfusion injury. Journal of immunotoxicology, 2014. **11**(3): p. 238-245.

[102] Won, M.H., et al., Postischemic hypothermia induced by eugenol protects hippocampal neurons from global ischemia in gerbils. Neuroscience letters, 1998. **254**(2): p. 101-104.

[103] Choi, Y.K., et al., Methyleugenol reduces cerebral ischemic injury by suppression of oxidative injury and inflammation. Free Radical Research, 2010. **44**(8): p. 925-935.

[104] Moreira Vasconcelos, C.F., et al., Eugenol and its association with levodopa in 6-hydroxydopamine-induced hemiparkinsonian rats: Behavioural and neurochemical alterations. Basic & Clinical Pharmacology & Toxicology, 2020. **127**(4): p. 287-302.

[105] Wie, M.-B., et al., Eugenol protects neuronal cells from excitotoxic and oxidative injury in primary cortical cultures. Neuroscience letters, 1997. **225**(2): p. 93-96.

[106] Johansson, B.B., Hypertension mechanisms causing stroke. Clinical and experimental pharmacology and physiology, 1999. **26**(7): p. 563-565.

[107] Ruitenberg, A., et al., Antihypertensive drugs and incidence of dementia: the Rotterdam Study. Neurobiology of aging, 2001. **22**(3): p. 407-412.

[108] Sakakura, K., et al., Exaggerated ambulatory blood pressure variability is associated with cognitive dysfunction in the very elderly and quality of life in the younger elderly. American journal of hypertension, 2007. **20**(7): p. 720-727.

[109] Nagai, M., et al., Ambulatory blood pressure as an independent determinant of brain atrophy and cognitive function in elderly hypertension. Journal of hypertension, 2008. **26**(8): p. 1636-1641.

[110] Nagai, M., S. Hoshide, and K. Kario, Hypertension and Dementia. American Journal of Hypertension, 2010. **23**(2): p. 116-124.

[111] Dahlöf, B., Prevention of stroke in patients with hypertension. The American journal of cardiology, 2007. **100**(3): p. S17-S24.

[112] Palmer, A.J., et al., Relation between blood pressure and stroke mortality. Hypertension, 1992. **20**(5): p. 601-605.

[113] Kelley, B.J. and R.C. Petersen, Alzheimer's disease and mild cognitive impairment. Neurologic clinics, 2007. **25**(3): p. 577-609.

[114] Iadecola, C. and R.L. Davisson, Hypertension and Cerebrovascular Dysfunction. Cell Metabolism, 2008. **7**(6): p. 476-484.

[115] Chui, H.C., Subcortical ischemic vascular dementia. Neurologic clinics, 2007. **25**(3): p. 717-740.

[116] Staessen, J.A., T. Richart, and W.H. Birkenhäger, Less atherosclerosis and lower blood pressure for a meaningful life perspective with more brain. Hypertension, 2007. **49**(3): p. 389-400.

[117] Iadecola, C., Neurovascular regulation in the normal brain and in Alzheimer's disease. Nature Reviews Neuroscience, 2004. **5**(5): p. 347-360.

[118] Carnevale, D., et al., Hypertension induces brain β-amyloid accumulation, cognitive impairment, and memory deterioration through activation of receptor for advanced glycation end products in brain vasculature. Hypertension, 2012. **60**(1): p. 188-197.

[119] Zlokovic, B.V., New therapeutic targets in the neurovascular pathway in Alzheimer's disease. Neurotherapeutics, 2008. **5**: p. 409-414.

[120] Zlokovic, B.V., The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron, 2008. **57**(2): p. 178-201.

[121] Deane, R., et al., RAGE mediates amyloid-β peptide transport across the blood-brain barrier and accumulation in brain. Nature medicine, 2003. **9**(7): p. 907-913.

[122] Zlokovic, B.V., et al., Low-density lipoprotein receptor-related protein-1: a serial clearance homeostatic mechanism controlling Alzheimer's amyloid β-peptide elimination from the brain. Journal of neurochemistry, 2010. **115**(5): p. 1077-1089.

[123] Carnevale, D., et al., Role of neuroinflammation in hypertension-induced brain amyloid pathology. Neurobiology of aging, 2012. **33**(1): p. 205. e19-205. e29.

[124] Gentile, M.T., et al., β-Amyloid deposition in brain is enhanced in mouse models of arterial hypertension. Neurobiology of aging, 2009. **30**(2): p. 222-228.

[125] Selkoe, D.J., Alzheimer's disease is a synaptic failure. Science, 2002. **298**(5594): p. 789-791.

[126] Querfurth, H.W. and F.M. LaFerla, Alzheimer's disease. New England Journal of Medicine, 2010. **362**(4): p. 329-344.

[127] Takuma, K., et al., RAGE-mediated signaling contributes to intraneuronal transport of amyloid-β and neuronal dysfunction. Proceedings of the National Academy of Sciences, 2009. **106**(47): p. 20021-20026.

[128] Ye, D., et al., RAGE in circulating immune cells is fundamental for hippocampal inflammation and cognitive decline in a mouse model of latent chronic inflammation. Brain, Behavior, and Immunity, 2024. **116**: p. 329-348.

[129] Song, F., et al., RAGE regulates the metabolic and inflammatory response to high-fat feeding in mice. Diabetes, 2014. **63**(6): p. 1948-1965.

[130] Zhang, L., et al., Receptor for Advanced Glycation End Products Is Subjected to Protein Ectodomain Shedding by Metalloproteinases*. Journal of Biological Chemistry, 2008. **283**(51): p. 35507-35516.

[131] Yu, M., et al., High mobility group box-1 mediates hippocampal inflammation and contributes to cognitive deficits in high-fat high-fructose diet-induced obese rats. Brain, Behavior, and Immunity, 2019. **82**: p. 167-177.

[132] Sakurai, S., et al., The AGE-RAGE system and diabetic nephropathy. Journal of the American Society of Nephrology, 2003. **14**(suppl_3): p. S259-S263.

[133] Blusztajn, J.K. and B. Berse, The cholinergic neuronal phenotype in alzheimer' s disease. Metabolic brain disease, 2000. **15**: p. 45-64.

[134] Kar, S., et al., Interactions between β-amyloid and central cholinergic neurons: implications for Alzheimer's disease. Journal of Psychiatry and Neuroscience, 2004. **29**(6): p. 427-441.

[135] Giovannelli, L., et al., Differential effects of amyloid peptides β-(1–40) and β-(25–35) injections into the rat nucleus basalis. Neuroscience, 1995. **66**(4): p. 781-792.

[136] Itoh, A., et al., Dysfunction of cholinergic and dopaminergic neuronal systems in β-amyloid protein-infused rats. Journal of neurochemistry, 1996. **66**(3): p. 1113-1117.

[137] Auld, D.S., et al., Alzheimer's disease and the basal forebrain cholinergic system: relations to β-amyloid peptides, cognition, and treatment strategies. Progress in neurobiology, 2002. **68**(3): p. 209-245.

[138] Wang, H.-Y., et al., Galanin inhibits acetylcholine release from rat cerebral cortex via a pertussis toxin-sensitive Giprotein. Neuropeptides, 1999. **33**(3): p. 197-205.

[139] Melo, J.B., P. Agostinho, and C.R. Oliveira, Amyloid beta-peptide 25-35 reduces [3H] acetylcholine release in retinal neurons. Involvement of metabolic dysfunction. Amyloid, 2002. **9**(4): p. 221-228.

[140] Satoh, Y., et al., β-amyloid peptides inhibit acetylcholine release from cholinergic presynaptic nerve endings isolated from an electric ray. Neuroscience letters, 2001. **302**(2-3): p. 97-100.

[141] Schliebs, R. and T. Arendt, The cholinergic system in aging and neuronal degeneration. Behavioural brain research, 2011. **221**(2): p. 555-563.

[142] Kalaria, R., Similarities between Alzheimer's disease and vascular dementia. Journal of the Neurological Sciences, 2002. **203-204**: p. 29-34.

[143] Roman, G.C., Vascular dementia. Advances in nosology, diagnosis, treatment and prevention. Panminerva medica, 2004. **46**(4): p. 207-215.

[144] Pasquier, F. and D. Leys, Why are stroke patients prone to develop dementia? Journal of neurology, 1997. **244**: p. 135-142.

[145] O'ROURKE, M. and M. Safar, Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertens. Dallas Tex 1979 46: 200-204, 2005. 2005.

[146] Ivan, C.S., et al., Dementia after stroke: the Framingham Study. Stroke, 2004. **35**(6): p. 1264-1268.

[147] Blennow, K., M.J. de Leon, and H. Zetterberg, Alzheimer's disease. The Lancet, 2006. **368**(9533): p. 387-403.

[148] Schneider, J., et al., Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. Neurology, 2004. **62**(7): p. 1148-1155.

[149] Snowdon, D.A., et al., Brain infarction and the clinical expression of Alzheimer disease: the Nun Study. Jama, 1997. **277**(10): p. 813-817.

[150] Lojkowska, W., et al., The effect of cholinesterase inhibitors on the regional blood flow in patients with Alzheimer's disease and vascular dementia. Journal of the neurological sciences, 2003. **216**(1): p. 119-126.

[151] Niwa, K., et al., Aβ1–40-related reduction in functional hyperemia in mouse neocortex during somatosensory activation. Proceedings of the National Academy of Sciences, 2000. **97**(17): p. 9735-9740.

[152] Paris, D., et al., Vasoactive effects of A β in isolated human cerebrovessels and in a transgenic mouse model of Alzheimer's disease: role of inflammation. Neurological research, 2003. **25**(6): p. 642-651.

[153] Niwa, K., et al., Cerebrovascular autoregulation is profoundly impaired in mice overexpressing amyloid precursor protein. American Journal of Physiology-Heart and Circulatory Physiology, 2002. **283**(1): p. H315-H323.

[154] Holtzman, D.M., et al., Apolipoprotein E isoform-dependent amyloid deposition and neuritic degeneration in a mouse model of Alzheimer's disease. Proceedings of the National Academy of Sciences, 2000. **97**(6): p. 2892-2897.

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