Neuroprotective Agents from *Syzygium* from Alzheimer's Perspective

Subjects: Pharmacology & Pharmacy

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Alzheimer's disease (AD) is the most prevalent type of dementia worldwide, constituting 70–80% of cases, primarily among the elderly. This irreversible neurodegenerative disorder progressively impairs memory and other cognitive functions. The molecular mechanisms of *Syzygium* species in neuroprotection include the inhibition of acetylcholinesterase (AChE) to correct cholinergic transmission, suppression of pro-inflammatory mediators, oxidative stress markers, reactive immediate species (RIS) production, enhancement of antioxidant enzymes, the restoration of brain ions homeostasis, the inhibition of microglial invasion, the modulation of ß-cell insulin release, the enhancement of lipid accumulation, glucose uptake, and adiponectin secretion via the activation of the insulin signaling pathway. Additional efforts are warranted to explore less studied species, including the Australian and Western *Syzygium* species. The effectiveness of the *Syzygium* genus in neuroprotective responses is markedly established, but further compound isolation, in silico, and clinical studies are demanded.

Syzygium | medicinal plants | Alzheimer's disease | multi-target | neuroprotection | anti-cholinesterase | anti-diabetic | anti-inflammatory | antioxidant

1. Anti-Cholinesterase Activity

Anti-cholinesterase activity remains the primary test used to screen anti-AD drug candidates. **Table 1** summarizes the anti-cholinesterase activities reported from *Syzygium* species. They are often tested in vitro based on Ellman's method using acetylcholinesterase (AChE) extracted from electric eel and butyrylcholinesterase (BChE) from equine serum. Nonetheless, efforts were made to determine in vitro activity using the parasite *Cotylophoron cotylophorum* [1] and the fruit fly *Drosophila melanogaster* [2]. Ex vivo AChE activity was also measured, revealing no significant activity from *S. cumini* [3]. Apart from that, in vivo AChE and BchE activities were determined in alloxan-induced diabetic rats [4] and scopolamine-induced memory-impaired rats [5]. Both studies showed a significant reduction in enzyme activity.

To the researchers' best knowledge, about 10 *Syzygium* species were investigated for their anti-cholinesterase potential. *S. aromaticum* (clove) represents the most studied *Syzygium* species, followed by *S. cumini* for this activity. Not only alcohol extracts were explored, but essential oils were also examined. Methanol and ethanol were widely used to extract *Syzygium* species, while leaves were the most studied plant part for this bioactivity. Eugenol compound from clove demonstrated more potent inhibitory activity than its essential oil and extract, indicating this

compound might provide major inhibition from this plant [6]. Darusman et al. reported no significant activity from the leaf extract of *S. cumini* [7], but other studies showed a disagreement. A reduction in cholinesterase activity was demonstrated from the essential oil, polyphenol-rich leaf extract as well as the seed extract of *S. cumini* [4][5][8]. The inhibitory activity observed from essential oils of *Syzygium coriaceum*, *S. cumini*, *S. aromaticum*, and *S. samarangense* proposes their economic importance in therapy and nutrition [8][9][10].

The aqueous extract of *S. jambos* leaves revealed no significant activity [11]. Similarly, the aqueous extract of clove buds exhibited very weak activity with >250 µg/mL of IC_{50} [12], suggesting the unsuitability of water as a solvent for this analysis. Amir Rawa et al. reported the highest number of *Syzygium* species (*Syzygium grande*, *Syzygium lineatum*, *S. jambos*, and *S. polyanthum*) exhibiting above 80% cholinesterase inhibition at 200 µg/mL concentration in one experiment [13]. Among them, *S. polyanthum* leaf extract showed the lowest IC_{50} at 8.28 and 6.54 µg/mL against AchE and BchE, respectively. Further fractionation revealed that polar bioactive constituents (tannins and polyphenols) were accountable for the enzyme inhibition. It is noteworthy that the ethanol bud extract from *S. aromaticum* corrected the AchE rate in cerium chloride ($CeCl_3$)-induced memory-impaired mice [14]. This research revealed a clear association between memory and AchE activity, where improved cholinergic neural transmission alleviated the state of memory in mice. Additional studies are required to confirm the bioactivity from other less known species of *Syzygium*, but the potency of inhibiting cholinesterase from this genus is well established.

Table 1. Summary of anti-cholinesterase activities exerted from *Syzygium* species.

	Species	Plant Part/Compound	Test	Activity	Reference
1	*Syzygium cumini* (L.) Skeels.	Ethanol leaf extract	In vitro AChE	44.54 µg/mL of IC_{50}	[3]
			Ex vivo AChE	No significant effect	
		Leaf essential oil	In vitro AChE	32.9 µg/mL of IC_{50}	[8]
		Polyphenol-rich leaf extract	In vitro AChE and BChE	Significant reduction in cholinesterase activities; bound polyphenolic extract showed better inhibitory activity than free polyphenolic extract	[4]
		Polyphenol-rich leaf extract	In vivo AChE and BChE from alloxan-induced diabetic rats	Enzyme activities were significantly reduced after 14 days (400 mg/kg oral dose)	[4]
		Methanol seed extract	In vivo AChE from scopolamine-induced rats	Significant reduction in AChE activity (400 mg/kg oral dose)	[5]

	Species	Plant Part/Compound	Test	Activity	Reference
		Leaf extract	In vitro AChE	No significant activity	[7]
2	*Syzygium aqueum* Alston	Methanol leaf extract	In vitro ACHE and BChE	16.04 µg/mL and 13.95 µg/mL of IC_{50}, respectively	[15]
3	*Syzygium polyanthum* (Wight) Walp.	Methanol and ethyl acetate extracts from leaves	In vitro ACHE	47.30 and 45.10 µg/mL of IC_{50}, respectively	[7]
		Methanol leaf and stem extracts	In vitro ACHE and BChE	>80% inhibition at 200 µg/mL concentration (8.28 and 6.54 µg/mL of IC_{50} in the leaf extract, respectively)	[13]
4	*Syzygium aromaticum* (L.) Merrill and Perry	Methanol, ethyl acetate, and hexane extracts from leaves; methanol bud extract	In vitro ACHE	42.10, 55.9, and 62.05 µg/mL of IC_{50}, respectively (leaves); 45.25 µg/mL of IC_{50} (bud)	[7]
		Methanol extract, clove oil, and eugenol	In vitro ACHE and BChE using TLC bioautography	Eugenol (42.44 and 63.51 µg/mL of IC_{50}) showed better inhibition than extract (61.5 and 103.53 µg/mL of IC_{50}) and oil (49.73 and 88.14 µg/mL of IC_{50}), respectively	[6]
		Clove bud essential oil	In vitro ACHE and BChE	1.5 µL/L and 18.2 µL/L of IC_{50}, respectively	[9]
		Ethanol extract	HPTLC-densitometry	Showed efficiency in AChE inhibition	[16]
		Ethanol bud extract	In vitro AChE isolated from human erythrocytes	No inhibitory effect	[17]
		Ethanol bud extract	In vitro AChE of parasite *C. cotylophorum*	86.86% inhibition at 0.5 mg/mL after 8 hr exposure	[1]
		Clove oil (eugenol) encapsulated with a nanostructured lipid carrier	In vitro ACHE and BChE from *D. melanogaster* tissue	4.3 and 3.5 mM of IC_{50}, respectively	[2]
		Aqueous and hydroalcoholic	In vitro AChE	253.29 µg/mL of IC_{50} in aqueous extract	[12]

	Species	Plant Part/Compound	Test	Activity	Reference
		extract of clove buds			
		Clove oil	In vitro AChE from $AlCl_3$-induced rats	Significant reduction in AChE activity	[18]
		Ethanol bud extract	In vivo AChE from $CeCl_3$-induced memory-impaired rats	Corrected the AChE rate caused by $CeCl_3$ toxicity and improved cholinergic neural transmission	[14]
		Eugenol derivatives	In vitro ACHE and BChE	4-Allyl-2-methoxyphenyl-4-ethyl benzoate inhibited AChE with 5.64 µg/mL of IC_{50}	[19]
		Isoeugenol	In vitro ACHE	77 nM of IC_{50}	[20]
5	*Syzygium antisepticum* (Blume) Merr. and L.M.Perry	Methanol leaf extract; ursolic acid; gallic acid	In vitro ACHE	61.9% at 300 µg/mL concentration; 81.64% at 200 µg/mL concentration; 73.39% at 200 µg/mL concentration	[21]
6	*Syzygium samarangense* (Blume) Merr. and L.M.Perry	Essential oil	In vitro ACHE and BChE	4.83 and 5.69 mg GALAE/g, respectively	[10]
		Dihydrochalcone	In vitro ACHE and BChE	98.5% inhibition at 0.25 mM and 68% inhibition at 0.20 mM, respectively	[22]
7	*Syzygium coriaceum* Bosser and J. Guého	Essential oil	In vitro ACHE and BChE	4.79 and 7.10 mg GALAE/g, respectively	[10]
8	*Syzygium jambos* (L.) Alston	Aqueous leaf extract	In vitro ACHE from homogenized tissue of rat brain	No significant activity	[11]
		Methanol stem and leaf extracts	In vitro ACHE and BChE	>80% inhibition at 200 µg/mL concentration (16.05 and 15.25 µg/mL of IC_{50} from stem extract, respectively)	[13]
9	*Syzygium grande* (Wight) Walp.	Methanol leaf extract	In vitro ACHE and BChE [23]	>80% inhibition at 200 µg/mL concentration	[13]

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plants that can stimulate insulin secretion would benefit diabetic as well as AD patients.

Zulcafli et al. extensively reviewed the anti-diabetic potential of eight *Syzygium* species [24]. It's reported that the inhibition of enzymes involving carbohydrate metabolisms such as α-glucosidase, maltase, and α-amylase is the

	Species	Plant Part/Compound	Test	Activity [24]	Reference
10	*Syzygium lineatum* (DC.) Merr. and L.M.Perry	Methanol leaf extract [26]	In vitro AChE and BChE [25]	>80% inhibition at 200 µg/mL concentration (20.69 µg/mL of IC_{50} for BChE)	[13]

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evident in 30 newly diagnosed type 2 diabetic patients when *S. cumini* seed powder was administered [27]. The treatment of high-fat diet/streptozotocin (HFD/STZ)-induced diabetic rats with the aqueous seed extract of *S. cumini* at 400 mg/kg decreased the levels of serum glucose, insulin, and other diabetic markers [28].

2. Anti-Diabetic Activity

A study by Shen et al. demonstrated a clear connection between insulin resistance and inflammation in TNF-α-treated FL83B cells [29]. The suppression of c-Jun N-terminal kinase (JNK) inhibited an inflammatory response as the cells were treated with the fruit extract of *S. samarangense*. As a result, insulin resistance induced by TNF-α was alleviated via the activation of phosphatidylinositol-3 kinase–protein kinase B (PI3K–Akt/PKB) signaling [29]. *S. aqueum* leaf extract, on the other hand, reduced glucose levels, increased insulin secretion, and decreased the collagen deposition associated with its anti-inflammatory and antioxidant responses in STZ-induced diabetic rats [30]. It decreased the levels of toll-like receptor 4 (TLR-4), myeloid differentiation primary response 88 (MYD88), TNF receptor-associated factor 6 (TRAF-6), and TNF-α correlated to pancreatic inflammatory cell infiltration. Malondialdehyde, a sensitive biomarker of ROS-induced lipid peroxidation, was also reduced [30].

In another study, vescalagin isolated from *S. samarangense* ameliorated insulin resistance in high-fructose diet-induced hyperglycemic rats [31]. Myricitrin isolated from the *S. malaccense* leaf extract exhibited insulin-like effects by enhancing lipid accumulation, glucose uptake, and adiponectin secretion via the activation of the insulin signaling pathway [32]. The aqueous extract of *Syzygium paniculatum* fruits alleviated hepatic insulin resistance at a 100 mg/kg dose by reducing the blockage of the insulin signaling pathway via the improvement of insulin receptor (IR and IRS-1) function in HFD-induced diabetic rats [33]. In addition, the IR mRNA levels were restored to the control level in type-2 diabetic rats treated with *Syzygium jambolanum* homeopathic remedies, suggesting improvement in insulin secretion [34].

3. Anti-Inflammatory Activity

Nearly all pathological events, including endoplasmic reticulum stress and autophagy dysfunction, can trigger inflammatory responses in AD [23]. Moroever, insulin resistance and diabetes have been shown to correlate well with inflammation. For example, the bark extract of *S. jambos* improved the insulin receptor substrate-2/protein kinase B/glucose transporter-4 (IRS-2/AKT/GLUT4) insulin signaling pathway in the liver while improving glycemic parameters by suppressing inflammation, oxidative stress, and apoptosis in STZ-induced rats [35]. Inflammation is defined as a physiological defense mechanism by the immune system to combat health hazards, causing pain to occur [23]. It was demonstrated that microglia accumulate in higher quantities near Aß plaques than in the healthy brain. Amyloid plaques and other factors can activate microglia to initiate neuroinflammation [23]. Anti-inflammatory drugs enable the central nervous system (CNS) to impede pain signaling in the brain, therefore, reducing

inflammation in AD pathogenesis. Recent anti-inflammatory activities reported from *Syzygium* were summarized in **Table 2**.

The levels of pro-inflammatory mediators such as IL-6, IL-1β, and TNF-α were generally measured to determine the anti-inflammatory activity (**Table 2**). The inflammation was induced by a toxic chemical or drug such as alloxan and STZ to stimulate inflammatory diabetes in model rats. LPS- or HFD-induced inflammation in diabetic rats was also conducted to observe the anti-inflammatory potential of *Syzygium*. So far, one study has demonstrated a close correlation between inflammation and memory loss in AD model rats. The memory-related learning ability of $A\beta_{1-40}$-infused AD model rats was improved as pro-inflammatory TNF-α and lipid peroxide (LPO) were suppressed when *S. cumini* seed extract was administered [36]. The leaf, fruit, pulp, and seed extracts of *S. cumini* exerting anti-inflammatory activity suggested that almost all parts are bioactive (**Table 2**).

S. malaccense leaf extract exerted neuroinflammatory protection against LPS-induced neuroinflammation on murine BV-2 microglial cell lines by reducing nitric oxide production [37]. Nitric oxide (NO) is one of the pro-inflammatory mediators released by microglia; reducing the NO levels can minimize immune outrage caused by microglia [23]. Other less studied *Syzygium* species have also been observed to exert anti-inflammatory activities, including *Syzygium caryophyllatum*, *Syzygium mundagam*, *Syzygium calophyllifolium*, and *S. samarangense* (**Table 2**).

Table 2. Summary of anti-inflammatory activities reported from *Syzygium* species.

	Species	Plant Part/Compound	Test	Activity	Reference
1	*S. malaccense* (L.) Merr. and L.M. Perry	Methanol leaf extract	In vitro LPS-induced neuroinflammatory assay on murine BV-2 microglial cells; in vivo croton oil-induced ear edema test	Neuroprotective activity by a reduction in nitric oxide production in vitro; decreased mice ear edema in vivo	[37]
2	*S. cumini*	Methanol fruit extract	In vitro membrane stabilization, egg albumin denaturation, and bovine serum albumin denaturation assays; in vivo murine models of carrageenan, formaldehyde, and PGE_2 induced paw edema.	Showed inflammatory activities both in vitro and in vivo	[38]
		Betulinic acid	In vivo Fx1A antiserum-induced	Ameliorated mRNA and protein expression of NF-κB,	[39]

	Species	Plant Part/Compound	Test	Activity	Reference
			passive Heymann nephritis (PHN) in Sprague-Dawley rats	iNOS, TNF-α, Nrf2, HO-1, and NQO1 in the kidney, reducing inflammation	
		Polyphenol-rich leaf extract	In vivo Alloxan-induced diabetic rats	NF-κB and inflammatory cytokines such as TNF-α and IL-1α were regulated	[4]
		Anthocyanins di-glucosides from pulp	In vitro determination of cytokine production in LPS-induced RAW264.7 macrophages	Inhibited pro-inflammatory mediators such as IL-6, IL-1β, and TNF-α	[40]
		Aqueous seed extract	In vivo high cholesterol diet-streptozotocin-induced diabetes in rats	Exhibited significant anti-inflammatory and β-cell salvaging activity via overexpression of PPARγ and PPARα activity and a significant decrease in TNF-α levels when treated with 100, 200, 400 mg/kg/day doses	[41]
		Methanol seed extract	In vitro high glucose (HG) diabetic cardiomyopathy in H9C2 cardiomyoblast cells	HG-induced activation of NF-*κ*B, TNF-*α*, and IL-6 was remarkably reduced	[42]
		Seed extract	In vivo $A\beta_{1-40}$-infused AD model rats	Reduced the levels of Aß burdens and oligomers by suppressing the levels of TNFα and LPO in the corticohippocampal tissues	[36]
3	*Syzygium caryophyllatum* (L.) Alston	Aqueous root extract	In vitro anti-inflammatory test using heat-induced albumin denaturation assay	6.229 µg/mL of IC_{50}	[43]
4	*S. aqueum*	Polyphenol-rich leaf extract	In vitro lipoxygenase inhibitor screening assay, membrane stabilizing activity (hypotonic solution-induced hemolysis), and in vivo carrageenan-	Inhibited LOX, COX-1, and COX-2 with higher COX-2 selectivity reduced the extent of lysis of erythrocytes and markedly reduced leukocyte numbers in rats challenged with carrageenan.	[44]

	Species	Plant Part/Compound	Test	Activity	Reference
			induced hind-paw edema in rats		
		Leaf extract	In vivo STZ-induced oxidative stress and inflammation in pancreatic beta cells in rats	Significantly decreased levels of TLR-4, MYD88, pro-inflammatory cytokines TNF-α, and TRAF-6 in pancreatic tissue homogenates, which correlated well with minimal pancreatic inflammatory cell infiltration	[30]
5	*Syzygium mundagam* (Bourd.) Chithra	Methanol bark extract	In vivo carrageenin- and egg albumin-induced paw edema, cotton pellet implanted granuloma in rats	Effective anti-inflammation at 200 mg/kg dose	[45]
6	*Syzygium calophyllifolium (Wight) Walp.*	Methanol bark extract	In vivo carrageenin- and egg albumin-induced paw edema, cotton pellet implanted granuloma	200 mg/kg dose significantly reduced the paw edema in carrageenan (96.71%) and egg albumin models (54.24%) compared to the control. Chronic inflammation was also inhibited by up to 70.46%	[46]
7	*S. aromaticum*	Ethanol/water extract	In vivo carrageenan-induced paw edema inflammatory in rats	Pretreatment at different doses (100, 200, and 400 mg/kg) produced a significant ($p < 0.001$) reduction in paw inflammation up to 5 h of carrageenan injection	[47]
		Essential oil	In vivo formalin-induced and carrageenan-induced paw edema inflammation in rats	26.9 ± 2.5 µg/paw of EC_{50}	[48]
		Aqueous clove extract	In vivo LPS-induced lung inflammation in mice.	Inhibited matrix metalloproteinases: MMP-2 (15%) and MMP-9 (18%) activity in lung homogenates, reducing inflammation	[49]
		Ethanol extract	In vitro TNF-α induced inflammation in	Prevented the increase in IL-6 levels	[50]

	Species	Plant Part/Compound	Test	Activity	Reference
			dental pulp stem cells		
		Eugenol	Cytochrome c reduction assay to measure superoxide anion generation in human neutrophils	Inhibited the generation of superoxide anion by neutrophils via the inhibition of Raf/MEK/ERK1/2/p47phox-phosphorylation pathway	[51]
		Eugenol	In vivo ethanol-induced ulcer in rats	Decreased TNF-α and IL-6 cytokine concentrations responsible for inflammation	[52]
		Essential oil	Isbolographic study using the formalin test in rats	*S. aromaticum* in combination with ketorolac, showed an antinociceptive effect in the treatment of inflammatory pain	[53]
8	*S. samarangense*	Polyphenol vescalagin	In vivo methylglyoxal-induced inflammation in diabetic rats	The pancreatic levels of NF-κB, ICAM-1, and TNF-α protein, were reduced	[54]
		Lyophilized fruit powder	In vivo STZ-induced pancreatic beta cells apoptosis in rats	Pancreatic ß-cell apoptosis was alleviated with significantly down-regulated cleaved caspase-3 and Bax and upregulated Bcl-2 and Bcl-xl protein expression	[55]
9	*S. polyanthum*	Leaf extract	In vivo coronary artery ligation-induced myocardial infarction in rats	Reduced levels of C-reactive protein (CRP) and myeloperoxidase (MPO) in the rats started from day 4 after the induction of myocardial infarction.	[56]
10	*S. jambos*	Bark extract	In vivo streptozotocin-induced inflammation in diabetic rats	Significantly reduced TNF-α and increased IL-10 ($p < 0.05$) in pancreatic tissues	[35]

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4. Antioxidant Activity

S. aromaticum (clove) is indeed the most studied *Syzygium* species for its antioxidant capacity. Its economically important essential oil source has brought many interests toward its applications. Alfikri et al. reported that clove produced the least essential oil ingredient at the flowering stage and the most efficient source of antioxidants when the trees are young. [60]. Meanwhile, Teles et al. demonstrated that eugenol (the primary compound of clove oil) exhibited higher antioxidant activity than its essential oil [61]. Various plant parts of the clove have been examined,

especially its bud essential oil (**Table 3**). As for *S. cumini* and *S. malaccense*, their dried peel powders showed higher phenolic compounds, anthocyanin content, and antioxidant activity than their freeze-dried extracts, which can be pharmacologically relevant to their food applications [62].

Table 3. Summary of plant parts or compounds examined for antioxidant activity from *Syzygium* species.

	Species	Plant Part/Compound	Reference
1	*S. cumini*	Leaf	[3][4][63]
		Fruit	[38][62][64]
		Bark	[65]
		Polyphenol-rich extract	[66][67]
		Seed kernels powder	[68]
2	*S. polyanthum*	Leaf	[7]
3	*S. aromaticum*	Flower	[60]
		Bud	[14][69]
		Bud essential oil	[9][60][61][70][71][72]
		Eugenol	[61]
		All parts	[73]
4	*S.antisepticum*	Leaf	[21]
		Gallic acid, myricitrin, and quercitrin	[21]
5	*S. caryophyllatum*	Leaf	[74]
		Fruit	[74][75]
		Fruit pulp healthy snack	[76]
6	*Syzygium paniculatum* Gaertn.	Leaf	[77]
		Fruit	[78]
		Volatile oil from the aerial part	[79]
7	*S. malaccense*	Leaf	[37][62][80]
		Myricetin derivatives	[81]
8	*S. aqueum*	Stem	[82]

	Species	Plant Part/Compound	Reference
		Bark	[82]
9	*S. polyanthum*	Leaf	[83]
10	*S. jambos*	Fruit	[84]
		Bark	[35]
11	*S. samarangense*	Vescalagin	[54]
12	*Syzygiumcymosum* (Lam.) DC.	Leaf	[85]

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