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REVIEW

Alzheimer's disease from a diabetic brain: Exploring the molecular process to determine the potential therapy target from marine sources

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Abstract

Background: The prevalence of Alzheimer's Disease (AD) among Type 2 Diabetes Mellitus (T2D) patients has reached almost 30%. Despite the rapid development, treatments for patients with T2D have not succeeded in controlling the neurodegenerative processes that occur in these patients' brains, leading to AD pathology. Several studies have demonstrated that marine sources can inhibit several AD pathogenesis pathways from T2D patients. This review aimed to determine the effect of marine species-sourced compounds at the molecular level in inhibiting and preventing the pathogenesis of AD in T2D patients. **Method:** Combinations of several terms were used to search for peer-reviewed literature published in PubMed, Scopus, and Google Scholar. **Result:** Marine organisms-sourced compounds inhibited various target signaling pathways between T2D and AD, such as an inhibitor of β-site-amyloid precursor protein cleaving enzyme 1 (BACE1) also known as β-secretase, glycogen synthase kinase-3 beta (GSK3B), insulin degradation enzyme (IDE), the mammalian target of rapamycin (mTOR), nuclear factor kappa-light-chain-enhancer (NF-κb), and nuclear factor erythroid 2-related factor 2 (Nrf2). **Conclusion:** Marine sources can be considered as a potential therapy to prevent or slow AD progression in T2D patients.

Introduction

A major risk factor for cognitive impairment is type 2 diabetes (T2D). Alzheimer's disease (AD) is classified as severe dementia, and this type of cognitive impairment is most common among T2D patients (Yu *et al.*, 2020). There are about 6.5 million elderly individuals suffering from AD. This number is projected to double by 2060 (Alzheimer's Association, 2022). A recent study, that has attempted to discover AD's pathophysiology, revealed that AD is closely related to T2D (Matos *et al*., 2017). Insulin resistance, neuroinflammation, and oxidative stress are found in the brains of T2D patients (Nguyen *et al*., 2020). Therefore, T2D is considered the basic mechanism that causes the accumulation of amyloid β (Aβ) plaque and neurofibrillary tangles (NFT) in AD (Nguyen *et al*., 2020).

Several studies have demonstrated that marine sources possess compounds that can inhibit several AD pathogenesis pathways from T2D (Li *et al*., 2013; Gogineni & Hamann, 2018; Ahmad *et al.*, 2019; Lee & Jun, 2019; Arya *et al*., 2020; Guo *et al*., 2021). Each of the compounds discovered from marine sources, such as sponges, fungi, algae, tunicates, and coral, has a unique structure and pharmacological activity, and a target to reduce the incidence and severity of AD (Li *et al*., 2013; Gogineni & Hamann, 2018; Ahmad *et al*., 2019; Lee & Jun, 2019; Arya *et al*., 2020; Guo *et al*., 2021). Therefore, this review aimed to determine the effect of marine compounds at the molecular level in inhibiting and preventing the pathogenesis of AD in T2D.

Methods

Combinations of the search terms "*Type 2 Diabetes*", "*T2D*", "*Diabetes Mellitus*", "*Alzheimer's Disease*", "*AD*", "*marine source*", "*pathogenesis*", "*therapy*" and "*mechanism*" were used to search for peer-reviewed literature published between 2001 and 2022 in PubMed, Scopus, and google scholar. The reference lists of the retrieved articles were examined for additional pertinent articles that were not discovered during the initial search. The initial search found 19 articles, which consisted of randomised controlled trials (RCTs), original articles, systematic reviews, and meta-analyses.

Results

Diabetic individuals have a greater risk of getting AD. Elevated plasma insulin levels are present in both disorders T2D and AD. This event shows that insulin relates to increased plasma Aβ levels, leading to the formation of Aβ plaque in the brain (Wrighten *et al*., 2009). The more specific mechanism of action of marine compounds as anti-Alzheimer can be seen in Table I. Figures 1 to 2 depict the molecular pathways of AD pathogenesis in T2D and the action points of marine source substances in inhibiting the progression of AD in T2D.

Table I: Mechanism of action and active compounds of anti-Alzheimer's disease from marine source

Target of therapy	Marine source	Common name	Active compound	Mechanism of action	References
Inhibitor the β-secretase	*Portunus flagicus*	Flower crab	Heparan sulfate	Attached to the core of protein form HS proteoglycans (HSPGs)	Mycroft-West *et al*., 2019
	Sardina pilchardus	While leg shrimp	Glycosaminoglycans	structural destabilisation of BACE1	Mycroft-West *et al.*, 2020
	Ecklonia cava	Brown algae	Eckol, dieckol, 8,8'-bieckol	The side target of BACE1 integrated into the hydroxyl group of the three major phlorotannins formed hydroxyl bonds	Lee & Jun, 2019
	Urechis unicinctus	Innkeeper warm	Hecogenin and cholest-4-en-3-one	-	Naushad *et al.*, 2019
GSK-3 inhibitor	*Ircinia dendrides and Callyspngia truncate*	Marine sponge	Palinurin and Phenylmethylene	Non-competitive inhibitors at the ATP-binding site.	Arya *et al.,* 2020
	Ircinia dendrides	Marine sponge	Manzamine A	The presence of a double bond between positions 15 and 16 increased the capability of manzamine to inhibit the GSK-3	Kubota *et al*., 2020
	Aplidium meridianum	Tunicate	Meridianin	The hydroxyl group in position 4 and the substitution of Br in position 6 in the indole ring inhibited the GSK-3.	Alonso & Martnez, 2006
	Botryotinia fuckeliana	Marine fungus	Pannorin, Alternariol, and Alternariol monomethylether	Their benzocoumarine ring plays a role in transferring electrons to make GSK-3 inhibition more efficient	Wiese *et al*., 2016
Insulin-degradation enzyme (IDE)	*Streptomyces tumescens*	Marine bacteria	Tumescenamides A and B	Induces the reporter gene expression and controls the IDE	Gogineni & Hamann, 2018
Nuclear-factor erythroid 2-related factor	*Erylus formasus*	Marine sponge	Triterpenoid glycoside	Induce the antioxidant response element (ARE)	Li, Himaya & Kim, 2013
	Holothuria scabra	Sandfish (sea cucumber)	Triterpenoid glycoside	Induce the antioxidant response element (ARE)	Li, Himaya & Kim, 2013
NF-κB Inhibitor	*Tridemnum solidum*	Tunicate	Didemnin B (Depsipeptides)	LPS-induced macrophages, and inflammatory mediators	Ankisetty *et al*., 2013; Ahmad *et al*., 2019;; Ghiciuc *et al*., 2021
	Serratia marcescens, Vibrio psychroerythrus, Pseudoalteromonas denitrificans and Zooshikella rubidus	Marine bacterium	Prodigiosin and Cycloprodigisin	Inhibits TNF-α-induced NF-κB activation	Kamata *et al*., 2001; Ahmad *et al*., 2019;

Target of therapy	Marine source	Common name	Active compound	Mechanism of action	References
	Bacillus sp. HC001, *Piscicoccus* sp. 12L081	Marine bacterium	Diketopiperazines	Downregulation of TNF-α, IL-6, NF-κB, and ERK1/2	Ahmad *et al*., 2019
	Axinella verrucosa, Acanthella aurantica and *Stylissa massa*	Sponge	Alkaloids	NF-κB-specific inhibitors, inhibit the production of IL-8, IL-2, and TNF-α	Ahmad *et al*., 2019
	Ishige okamurae	Algae	Diphlorethohydroxycar malol	Suppress the expressions of p-p65 NF-κB	Kim *et al*., 2020
	Ecklonia cava	Algae	Dieckol	Inhibits the increase of inflammatory markers	Barbalace *et al*., 2019
	Ecklonia stolonifera	Algae	Phlorofucofuroeckol B	Inhibited the phosphorylation of Akt, ERK, and JNK	Barbalace *et al*., 2019
	Gracilaria verrucosa	Algae	(E)-9-Oxooctadec-10-enoic-acid and (E)-10-Oxooctadec-8-enoic-acid	Suppress the production of inflammatory biomarkers including NO, IL-6, and TNF-α	Ahmad *et al*., 2019
	Aspergillus insulicola	Hawaiian marine sedimentary fungus	Azonazine (hexacyclic dipeptide)	inhibiting the production of NF-κB	Ahmad *et al*., 2019
	Penicillium paxilli Ma(G)K	Fungi	Pyrenocine A	-	Ahmad *et al*., 2019
mTOR Inhibitor	*Fascaplysinopsis* sp.	Marine Sponge	4-chloro fascaplysin	Inhibited cell survival through PI3K/Akt/mTOR pathway	Sharma *et al*., 2017
	Brown seaweeds	Seaweeds	Fucoxanthin	Inhibitory effect on the Akt/ mTOR signalling	Guo *et al*., 2021
	Sinularia flexibilis	Soft Coral	Sinulariolide	Inhibiting the phosphorylation of PI3K, Akt, and mTOR	Li *et al*., 2013
	Streptomyces hygroscopicus	Marine bacterium	Sirolimus	Binds to FK-bound protein 12 and serine-threonine kinase, mTOR, inhibiting the transduction of IL-2R	Nguyen *et al.*, 2019

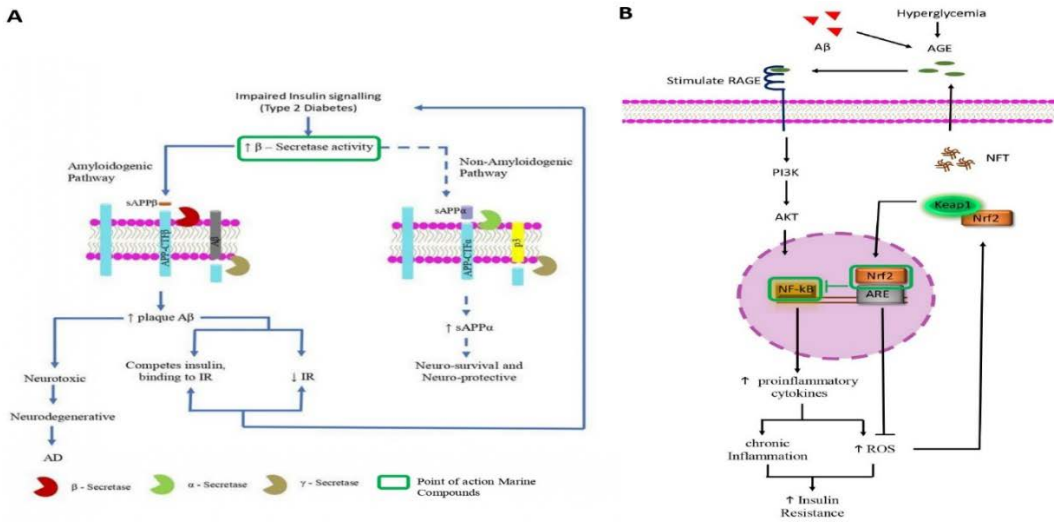

Figure 1: A) The basic mechanism between T2D and AD. Marine compounds act as β-secretase inhibitors. B) Molecular Pathway Effect of T2D on increased oxidative stress and proinflammatory cytokines. Marine compounds act as NFkB inhibitors and Nrf2 inducers. Insulin Receptor (IR); Alzheimer's Disease (AD), Amyloid β (Aβ); soluble Amyloid Precursor Protein by α secretase (sAPPα); soluble Amyloid Precursor Protein by β secretase (sAPPβ); Advanced Glycation End Products (AGE); Receptor for Advanced Glycation Endproducts (RAGE); Nuclear-factor erythroid 2-related factor (NRf-2); Reactive Oxygen Species (ROS); Antioxidant Responsive Element (ARE); Kelch-like ECH associated-protein 1 (Keap1); Neurofibrillary tangles (NFTs)

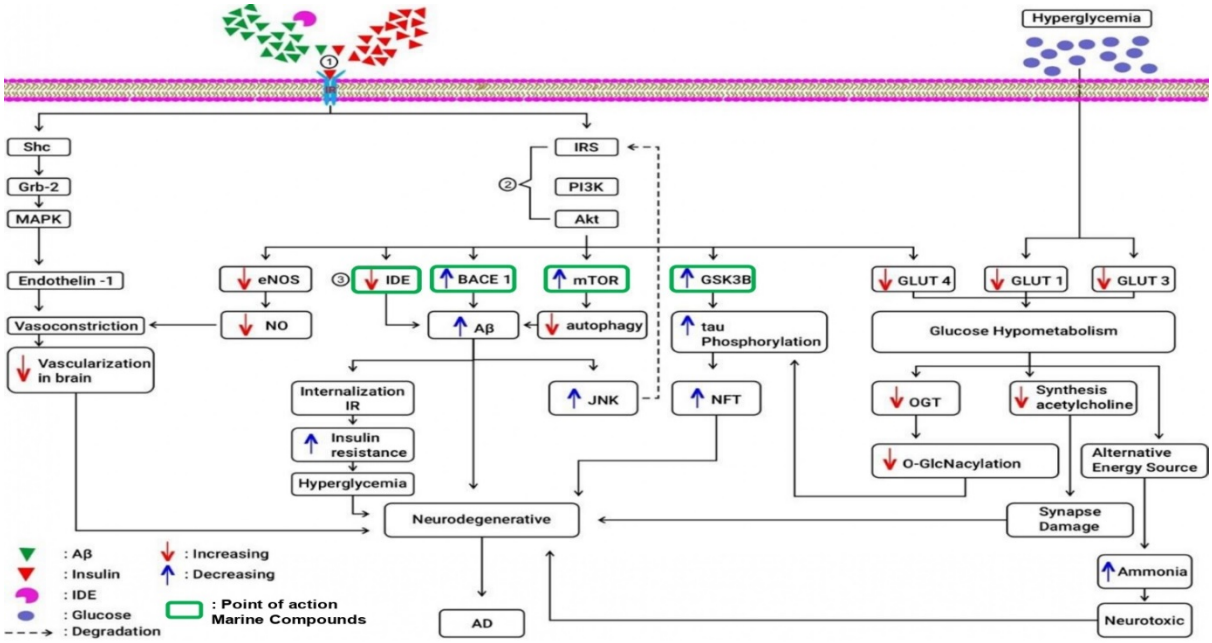

Figure 2: Molecular pathway of impaired Insulin Signaling and glucose metabolism in T2D and AD. Marine species-sourced compounds act as β-secretase inhibitors, mTOR inhibitors, and GSK3B inhibitors, and increase IDE expression. Insulin receptor (IR); insulin receptor substrate (IRS); phosphatidylinositol 3-kinase (PI3K); protein kinase B (Akt); insulin-degrading enzyme (IDE); beta secretase-1 (BACE1); Amyloid β (Aβ); mammalian target of rapamycin (mTOR); glycogen synthase kinase-3 beta (GSK3B); glucose transporter (GLUT); *c-Jun N-terminal kinase (*JNK); *neurofibrillary tangle (*NFT); *endothelial nitric oxide synthase* (eNOS); nitric oxide (NO); src homology and collagen protein (Shc); growth factor receptor bound protein 2 (Grb-2); mitogen-activated protein kinase (MAPK); Alzheimer's disease (AD)

Discussion

Accumulation of Aβ, a peptide derived from amyloid precursor protein (APP), is one of the hallmarks of Alzheimer's disease (AD). There are two pathways for APP degradation; amyloidogenic and non-amyloidogenic (Figure 1A). Normally, most APP is cleaved by non-amyloidogenic pathways (Najem *et al*., 2016). Insulin was shown to enhance the non-amyloidogenic pathway by stimulating α-secretion activity. Additionally, sAPPα, a protein resulting from non-amyloidogenic pathways, is involved in neuronal survival and protection (Shieh *et al*., 2020; Soriano *et al*., 2001).

In diabetic individuals, impaired insulin signalling results in an increase in β-secretase activity and a decrease in α-secretase activity (Shieh *et al*., 2020). Thus, the APP breakdown pathway becomes more amyloidogenic than non-amyloidogenic. This event will cause a decrease in sAPPα, a neuroprotective protein, and an increase in Aβ oligomers (Shieh *et al*., 2020). Aβ oligomers have been shown to impair synaptic plasticity in neurons by inhibiting long-term potentiation (LTP) and long-term depression (LTD). Additionally, the accumulation of Aβ oligomers facilitates the formation of neurotoxic Aβ plaques, resulting in neuronal death and synaptic injury (Lei *et al*., 2016; Varga *et al*., 2015).

Many marine sources were reported to inhibit the β-secretase or disease-relevant β-secretase 1 (BACE1) (Table I). The four species have each active compound with a mechanism action in BACE1. The active compounds were glycoside, flavonoid and steroid groups. Nevertheless, the final action of these compounds was to inhibit the BACE1 activity. It could reduce the accumulation of the Aβ plaque and the progression of AD.

Aβ oligomers also worsen insulin signalling impairment in T2D by degrading the Insulin Receptor Substrate (IRS), decreasing the number of Insulin receptors (IR) (Figure 2), and competing with insulin to bind to the insulin receptor. Shieh et al. (2020) and Tumminia et al. (2018) showed that disruption of the insulin signalling pathway in T2D impairs the PI3K-Akt cascade's activation**.** This impaired insulin signalling results in several events that aggravate AD (Figure 2), some of

which are: 1) decreased secretion of insulin-degrading enzyme (IDE); 2) abolishment of the inhibitory effect of Glycogen Synthase Kinase 3 Beta (GSK3B); 3) elimination of insulin's inhibitory action on mammalian target of rapamycin (mTOR). IDE plays a role in Aβ degradation. Thus, decreased IDE secretion leads to further Aβ accumulation (Tumminia *et al*., 2018; Nguyen *et al*., 2020).

The activation of GSK3B plays a role in *tau* protein phosphorylation and causes *tau* protein accumulation and NFT formation. The accumulation of NFT causes impaired synapse formation, neuronal cytoskeletal collapse, and neurite retraction (Tumminia *et al*., 2018; Nguyen *et al*., 2020). Notably, mTOR activation inhibits normal autophagy processes. At the same time, the autophagy process is needed to degrade various abnormal proteins, including Aβ and *tau* proteins (Cai *et al*., 2015).

The compounds that were reported to have the activity to inhibit the GSK3B activity and induced IDE activity were found in marine sources. *Streptomyces tumescens* was the only reported marine source that induced the IDE activity (Table I). Tumescenamides A was the type of peptide found in *S. tumescens* that can increase the presence of IDE. Tumescenamide A and B can induce the upregulation of the IDE enzyme, a metalloprotease enzyme that is responsible for insulin degradation. It proved to have a role in Aβ degradation which is expected to be a promising treatment of AD (Motohashi *et al*., 2010).

Most species of these marine sources were found in the sponge (Table I), tunicate and marine fungi also contain compounds that can inhibit the activities of the GSK3B (Alonso & Martnez, 2006). The compounds that play the role of inhibiting the GSK3B included the sesquiterpene, alkaloid and polyphenolic groups. The mechanism of action of each compound was different, but the final action was to inhibit the GSK3B activity. Palinurin, a sesquiterpene from types of marine sponges exerts its high selectivity inhibition of the allosteric site of GSK3B (Hafez & Kijjoa, 2021).

Four species that were reported can inhibit the mTOR (Table I). Brown seaweeds and sponges were marine sources that were easy to find in the sea. The type of compounds in these marine sources was alkaloid, macrolide, carotenoid, and diterpene lactone. The mechanism of action of these compounds was to inhibit the upstream mTOR pathways. Fucoxanthinol, the active form of fucoxanthin metabolite from seaweeds has a neuroprotective activity by preventing inflammation, ROS scavenging effect, and activation of mTOR (Song & Zhou, 2022). Sirolimus can be found in the marine bacterium *Streptomyces hygroscopicus* (Nguyen *et al*., 2019).

Stress oxidative and neuroinflammation are other hallmarks that play roles in AD pathogenesis (Figure 1B). Hyperglycemia patient causes the production of advanced glycation end products (AGE) in diabetic patients. AGE is formed when proteins or lipids are glycated with glucose or its metabolites. The binding of AGE with the Receptor for Advanced Glycation End Products (RAGE) will promote the activity of Nuclear Factor kappa B (NF-kB), which will stimulate various proinflammatory cytokines, including IL-β and TNF-α and increase Reactive Oxygen Species (ROS) (Granic *et al*., 2009). Aβ can also become AGEs and bind to RAGE, aggravating oxidative stress and chronic neuroinflammation (He & Sun, 2021).

The NRf-2 has a relationship with antioxidant activity. The increase of NRF-2 can activate the antioxidant transcription. The seaweeds, marine macroalgae, contained sulfated polysaccharides with potent antioxidant activity (Cardoso *et al*., 2016). Byun *et al*. (2018) showed that polysaccharides mediated the Nrf-2 activation (Table I). The species of marine source that inhibited the NFkB was algae (Table I). Various compounds were found in algal species, such as polyphenols and fatty acids. The common mechanism of action of these compounds decreased the release of inflammation mediators (Byun *et al*., 2018).

Conclusion

Marine sources possess potential therapies to prevent or slow AD progression in T2D patients. Marine species-sourced compounds have mechanisms of action that inhibit the progression of Alzheimer's disease in T2D patients. Due to impaired insulin signalling, some of these substances act as beta-secretase inhibitors, inducers of IDE expression, GSK3B inhibitors, and mTOR inhibitors that can prevent AD progression in T2D patients. In addition, these compounds can act as NFkB inhibitors and stimulate Nrf2 activation to inhibit oxidative stress and neuroinflammation, which are major aspects of the pathogenesis of AD in T2D patients.

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