# Potential Effects of Omega-3 Fatty Acids on Type 1 Diabetes in Preventing Alzheimer's Disease Progression

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## Abstract

The human metabolic syndrome of diabetes is widely reported globally. People with type 1 diabetes (T1D) are at high risk for developing diabetic complications. Increasing evidence in clinical studies and literature reviews suggests that T1D has a strong relation with cognitive impairments, leading to a higher occurrence of dementia and Alzheimer's disease (AD). Research has shown that diet has a significant impact that may delay the onset of diabetes problems. Recent findings have demonstrated that omega-3 fatty acids act as a neuroprotective agent against the development of brain disorders. However, the positive impact of omega-3 fatty acids against diabetes, particularly on T1D, has debatable roles due to data inconsistencies. This review will discuss the mechanism of T1D on AD and the potential role of omega-3 fatty acids in degrading AD risk in patients with T1D. Scientific reports from epidemiological, molecular, and animal models and human studies are highlighted in this study. In conclusion, despite the conflicting results observed in both experimental and clinical studies, omega-3 fatty acids were proven to exhibit anti-inflammatory characteristics and alleviate autoimmune activities. Hence, omega-3 fatty acids are suggested to be considered in the prevention of AD progression, particularly in T1D patients. Nevertheless, the role of omega-3 fatty acids supplementation in T1D patients needs further exploration.

Keywords: dementia, diabetes mellitus, fish oil, hyperglycemia

**Received:** April 29, 2024 **Revised:** November 26, 2024 **Accepted:** January 9, 2025

## INTRODUCTION

Type 1 diabetes (T1D) is a chronic metabolic disorder marked by pancreatic islet inflammation and pancreatic β-cells loss by the immune system, which will lead to insulin deficiency (Baynest, 2015). Diabetes has been linked to disorders in a variety of organs, including gastrointestinal (Zhao *et al*., 2017), kidney (Koye *et al*., 2018), cardiovascular (Strain and Paldánius, 2018), and brain (De Sousa *et al*., 2020). The mechanisms underlying diabetes-related cognitive disorders are extraordinarily complex and comprise diabetes-associated cardiovascular disorders, chronic microvascular dysfunction, and diabetes-associated factors. These mechanisms might potentially play a role in the development and progression of vascular dementia and Alzheimer's disease (AD) (Shalimova *et al*., 2019).

It has been established that long-term administration of omega-3 fatty acids inhibits inflammatory mechanisms, rendering them potential therapeutic and preventative agents for autoimmune disorders (Balić *et al*., 2020). Scientific research has reported the beneficial effects of omega-3 fatty acids through several mechanisms, such as synthesizing anti-inflammatory mediators, fluidity of cell membranes, intracellular signaling, and expression of genes (Avallone *et al*., 2019). However, omega-3 fatty acids supplementation to interfere with human diseases has produced contrary and often dubious data, and invalid or weak conclusions. Hence, gaining a more comprehensive understanding of the potential impact of omega-3 fatty acids on the emergence

and development of T1D will provide insight into the significance of regular consumption of omega-3 fatty acids as a preventive measure against the development of Alzheimer's disease. This current review summarizes the role and mechanism of omega-3 fatty acids in T1D autoimmune disorders.

## DISCUSSION

### Pathogenesis of T1D-induced Alzheimer's Diseases

The interaction of environmental variables and genetic predisposition led to the development of T1D. These events trigger an immunological response that impairs the functioning of the pancreas, i.e.,reducing the production of insulindue to the loss of pancreatic beta-cells (Ramos-Rodríguez *et al*., 2021). In most cases, T1D is caused by immune-mediated T-cell attacks on pancreatic islets. Nevertheless, a small percentage of cases are categorized as idiopathic T1D, with a strong genetic component (Katsarou *et al*., 2017). In addition, research has demonstrated that environmental factors, including an imbalanced of intestinal microbiota (Qi *et al*., 2016), unhealthy diet (van Bussel *et al*., 2011), and exposure to toxins (Bodin *et al*., 2015) can significantly impact T1D development.

It is widely acknowledged that the pathogenesis of T1D contributes to the development and progression of AD via multiple mechanisms. For instance, according to Bluestone *et al*. (2010), T1D arises due to disrupted immunological control, leading to the proliferation of autoreactive CD4+, CD8+, T cells, autoantibody-secreting B lymphocytes, and the activation of the innate immune system, which collectively target and destroy insulin-producing β-cells.Insufficient insulin will result in hyperglycemia, characterized by a high concentration of glucose in the blood. This long-term hyperglycemia condition is linked to the deterioration of a variety of organs and tissues, including brain tissue (Berbudi *et al*., 2019; Hamid *et al*., 2022). Several preclinical and clinical investigations have demonstrated the pivotal significance of this systemic inflammation in the etiology of AD (Holmes, 2013). Prolonged elevation of blood sugar levels will stimulate the excessive production of reactive oxygen species (ROS), leading to oxidative stress and the disruption of regulating matrix metalloproteinase (MMPs) activity (Brook *et al*., 2019). Moreover, the presence of chronic hyperglycemia will also stimulate the production of advanced glycation end products (AGEs), which possess notable pro-inflammatory and pro-oxidant properties, ultimately resulting in cellular and molecular damage (Man *et al*., 2020).

In addition, the inflammation caused by high blood sugar levels can lead to an increase in the buildup of amyloid-beta in the brain, trigger oxidative stress, initiate neuroinflammation, disrupt the functioning of mitochondria, and harm the integrity of neurons (Potenza *et al*., 2021). Neuronal cells in the brain are vulnerable to oxidative stress, and the ROS generated within the brain have the potential to induce numerous neurodegenerative disorders (Anwar, 2022). The cortical neuron cells, the amygdala, and the hippocampus are the neuron regions that are most frequently and significantly affected by the progression of AD (Smith, 2002). Thus, the initial type of memory that would be affected in AD patients is short-term memory, which is located in the hippocampus (Mu and Gage, 2011).

### Therapeutic Approaches of Omega-3 Fatty Acids on Diabetes in Animal, Cell Culture, and Human Research

The investigation into the causative variables of T1D has primarily centered on viruses and components that could impact the gut immune system, such as hygiene and diet (Warshauer *et al*., 2020). Prior studies conducted in vivo and in vitro have demonstrated the advantageous effects of omega-3 fatty acids supplementation. For example, omega-3 fatty acids, especially fish oil, have the potential to inhibit pathological alterations in the pancreas, resulting in elevated insulin levels in rats subjected to a high-fructose diet (Soltan, 2012). Briefly, omega3 fatty acids are assumed to protect pancreatic cells from T1D pathogenesis by reducing oxidative stress (Lucena *et al*., 2015), preserving the structural

integrity of pancreatic cells (Basta *et al*., 2007), or stimulating the regeneration of potent islet progenitor cells from ductal cells (Habib, 2013).

Interestingly, similar study in human generated conflicting results. A systematic review and meta-analysis study of over 95,000 participants, both with and without diabetes, recommended that omega-3 fatty acids should not be encouraged to prevent or treat diabetes (Brown *et al*., 2019). Another investigation found that supplementation with omega-3 fatty acids did not reduce fasting and postprandial blood glucose levels (Chauhan *et al*., 2017), affect glycated hemoglobin (HbA 1c) (Chewcharat *et al*., 2020), and improve insulin sensitivity (Poudyal *et al*., 2011). On the other hand, a study demonstrated contradictory findings. Delpino *et al*. (2021) found that omega-3 fatty acids had a substantial impact on lowering insulin resistance and fasting blood glucose levels, but they did not affect HbA 1c.A further retrospective analysis, which utilized cod liver oil as a source of omega-3 fatty acids, demonstrated that the consumption of omega-3 fatty acids could reduce the likelihood of children with an increased risk of developing autoantibodies against the insulin-producing beta-cells by approximately 55% (Norris *et al*., 2007).

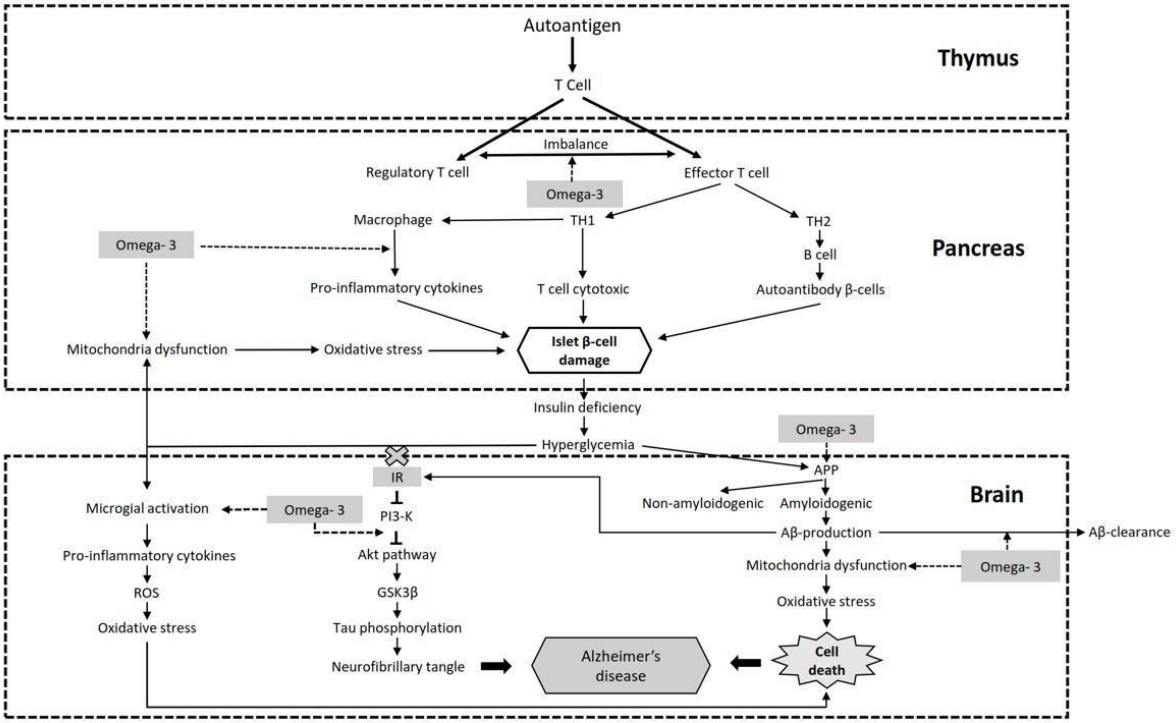


**Figure 1.** Summary of several potential mechanisms by omega 3-fatty acid preventing AD progression in T1D. Omega-3 fatty acids have the capability to restore regulatory T cell activity which suppresses autoreactive effector T cells. Omega-3 fatty acids can affect macrophages and microglia as part of the innate immune systemto reduce oxidative stress and inflammation. Omega-3 fatty acids restore mitochondrial dysfunction and inhibit ROS and oxidative stress production. Meanwhile, in the brain, omega-3 fatty acids inhibit amyloidogenic pathway, promote the non-amyloidogenic pathway and amyloid-beta oligomers clearance from the brain. Omega-3 fatty acids ameliorate impaired insulin signaling pathways via activation of Akt pathway.

Furthermore, combined therapies involving omega-3 fatty acids and other substances demonstrated encouraging outcomes. For instance, the supplementation of probiotics and omega-3 fatty acids in individuals with type 2 diabetes (T2D) resulted in improved glycemic profile and decreased insulin resistance (Kobyliak *et al*., 2020). Thoha and colleagues (2019)

discovered a similar finding, revealing that a combination of curcumin and omega-3 fatty acid supplementation lowered the risk of developing T2D in people with a high risk of T2D by reducing triglyceride levels and improving insulin sensitivity. Meanwhile,the administration of vitamin D and omega-3 fatty acids supplementation in T1D patients demonstratedan anti-inflammatory effect that might slow or stop the progression of T1D (Cadario *et al*., 2018).

**Molecular Mechanism of Omega-3 Fatty Acids on T1D Associated with AD**

Omega-3 fatty acids, which belong to the polyunsaturated fatty acids group (PUFAs), are characterized by the initial carbon bond situated at the third position from the chain's terminus (Nettleton, 1995). Alpha-linolenic acid (ALA), an omega-3 fatty acid derived from plants, is abundant in oils derived from plants, including flaxseed, hazelnuts, canola, and soybeans. Fish and seafood, which are sources of omega-3 fatty acids derived from animals, are particularly abundant in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Mali *et al*., 2016). In addition, research has shown that the fatty acid composition of the feed strongly influences fish fatty acid composition, leading to farmed fish having similar or even more omega-3 fatty acids than wild-caught fish (Hossain, 2011). Meanwhile, another research study indicated that higher consumption of fish is associated with a reduced incidence of dementia (Bakre *et al*., 2018). Likewise, several in vitro and in vivo investigations have documented the possible beneficial effect of omega-3 fatty acid supplementation in preventing complications associated with diabetes, including nephropathy (Chewcharat *et al*., 2020), cardiomyopathy (McEwen *et al*., 2010), retinopathy (Gorusupudi *et al*., 2019), and neuropathy (Wang *et al*., 2020). The advantageous effects of omega-3 fatty acids in T1D can be attributed to at least two primary mechanisms—autoimmunity suppression and antiinflammatory activity (Purdel *et al*., 2021)—as shown in Figure 1.

**Omega-3 Fatty Acid-Suppressing Autoimmunity in T1D Diseases**

Omega-3 fatty acids have the most potent immunomodulatory activity, and among the major varieties of omega-3, fish oil-derived DHA and EPA are stronger than ALA. Some influences of omega-3 fatty acids in autoimmune diseases are due to the modulation of eicosanoids formed and other effects caused by eicosanoid-independent mechanisms (Simopoulos, 2002). It is common knowledge that eicosanoids, a family of bioactive lipids, are capable of inducing inflammation. Eicosanoids derived from omega-6, specifically arachidonic acid (AA), exhibit pro-inflammatory characteristics. AA produces a metabolite Prostaglandin E2 (PGE2), which will affect the polarization of immune cells. The PGE2 activates E prostanoid receptor 3 to negatively regulate pancreatic beta-cell function and proliferation. Conversely, eicosanoids derived from omega-3 fatty acids, including EPA and DHA, demonstrate anti-inflammatory properties (Cas *et al*., 2020). Further evidence showed that increasing the ratio of omega-3 to omega-6 in the diet of non-obese diabetic (NOD) rodents resulted in decreased inflammation and the pancreatic islet infiltration scores (Peter *et al*., 2019).

It is widely recognized that the NOD mice model presents a powerful approach to investigating immunoregulation and autoimmune diabetes development (Aoki *et al*., 2005). Dietary omega-3 fatty acids sharply decreased T1D incidence in NOD mice by suppressing Th1 and Th17 cells and escalating Th2 cells and regulatory T cells (Tregs) (Bi *et al*., 2017). A dietary intervention study obtained similar results, i.e., EPA-diet reduced Th1 and PGE2, but dramatically increased Th17 (Peter *et al*., 2019). Another study using EPA-enriched diet for 12 weeks in NOD female mice showed significantly increased Th1 and Tregs, but no effect on Th17. In addition, PGE2 metabolite (PGEM) levels were decreased by around 80% in the EPAenriched diet, and in the AA-enriched diet were increased by 30% (Fenske *et al*., 2021). The discrepancies in the findings between these studies are likely related to variations in dietary composition and EPA dosage, as variability in the

mixture or concentration of EPA in the diet may produce varying effects. The study by Peter *et al*. (2019) analyzed the effects of AA or EPA on the diet, while the study by Fenske *et al*. (2021) explored the effects of different dietary ratios combining AA and EPA in the diet.

Tregs have a crucial role in controlling immune tolerance and inhibiting autoimmune disorders (Zhang *et al*., 2020). Therefore, it is crucial to repair Tregs activity to block autoimmune development and inflammatory attacks against pancreatic beta-cells (Bi *et al*., 2017). In human research, the therapeutic potential of omega-3 fatty acids suppressing autoimmunity in children with high genetic risk for T1D development has been reported via measuring erythrocyte membranes fatty acids and islet autoantibodies (e.g., insulin autoantibody, glutamic acid decarboxylase, or insulinoma-associated antigen-2). A study conducted on 1,770 children revealed that omega-3 fatty acids supplementation could lower the percentage of islet autoimmunity and autoantibody titers (Norris *et al*., 2007). Current longitudinal cohort research on 8,676 children also showed similar results. This study suggested taking omega-3 fatty acids in early infancy to reduce the risk of islet autoimmunity in children (Niinistö *et al*., 2021). On the contrary, another research revealed that supplementation of omega-3 fatty acids did not prevent 45 of 167 children from developing persistent islet autoimmunity. The study also demonstrated no relationship between the conversion to T1D and omega-3 fatty acid levels in erythrocyte membranes (Miller *et al*., 2011). Further research in this area is necessary to justify the effectiveness of omega-3 fatty acids in inhibitting T1D progression.

**Omega-3 Fatty Acids Inhibit Inflammation in Pancreas Cells**

An increase in plasma glucose will result in an imbalance between NADH and NAD+, ultimately causing dysfunction in the mitochondria and triggering ROS (Wu and Yan, 2015). The intracellular reactive ROS can also arise from various signaling pathways, including increased flux in the polyol pathway, activation of the protein kinase C (PKC) pathway, enhanced formation of advanced glycation end products (AGEs), excessive activity in the hexosamine pathway, and elevated production of angiotensin II (Panigrahy *et al*., 2016). In addition, macrophages also correspond with the development of diabetes and provoke inflammation via pro-inflammatory cytokines and protease production (Rendra *et al*., 2019). Increased ROS via these pathways leads to beta-cell dysfunction and insulin resistance, which are responsible for the damage and apoptosis of beta-cells (Keane *et al*., 2015). In vitro research of omega-3 fatty acids demonstrated the prevention of apoptosis in pancreatic acinar cells, indicated by the inhibition of apoptotic gene expression (e.g., p53, Bax, apoptosis-inducing factor) and blocked DNA fragmentation. It also suppressed inflammatory cytokines (e.g., IL-1β and IL-6) through the inhibition of activators protein-1 (Park *et al*., 2009). Cytokine expression in macrophages following treatment with omega-3 fatty acids was suppressed through deacetylation of NF-κB, which happens via AMPK/SIRT1 pathway activation (Xue *et al*., 2012). The lack of these inflammatory cells and collagen fiber deposition in pancreatic cell microstructure emphasizes the capability of omega-3 fatty acids to prevent inflammation (Habib, 2013). In addition, omega-3 fatty acids also preserved the islet and acinar cell's normal appearance and enhanced the regeneration of potent islet progenitor cells, which eventually impacted normal glucose and insulin levels (Soltan, 2012). Omega-3 fatty acids inhibited lymphocyte infiltration of regenerated islets and enhanced pancreatic beta-cell markers expression and the transcription factor for pancreatic development, such as Pdx1, Pax4, and Arx (Bi *et al*., 2017).

In human study, the mechanism of omega-3 fatty acids that prevented inflammation in pancreatic cells was reported through measurement of biomarker inflammation in blood samples. In a study among women with gestational diabetes, intake of combined vitamin D and omega-3 fatty acids containing EPA and DHA for six weeks showed significantly reduced inflammation and oxidative stress biomarkers (e.g

hs-CRP and MDA) and increased total antioxidant capacity (TAC) and glutathione (GSH). However,the supplementation did not affect nitric oxide (NO) levels in fasting blood samples (Razavi *et al*., 2017; Suryadiningrat *et al*., 2021). Different results were obtained on patient intake of omega-3 fatty acids from flaxseed oil for 12 weeks, which showed no significant effects on hs-CRP, NO, TAC, GSH, and MDA compared with the placebo (Soleimani *et al*., 2017). Although several studies have proposed the potential effect of omega-3 fatty acids on reducing inflammatory biomarkers (Natto *et al*., 2019), studies revealed that no effects were seen on the inflammatory status and oxidative stress in participants with different metabolic disorders or healthy person (Stella *et al*., 2018). These inflicting data needs long-term follow-up studies and a larger sample size before drawing a conclusion concerning omega-3 fatty acids' impact toward pancreatic cells.

**Omega-3 Fatty Acids Prevent Neuroinflammation and AD Development**

Prior studies on rodents have identified two primary mechanisms driving the development of diabetes-related AD: amyloidogenesis and brain insulin resistance. Further interconnected processes include neuroinflammation, oxidative stress, and mitochondrial dysfunction (Lee *et al*., 2018). Elevated blood glucose levels stimulated the production of inflammatory cytokines, altered expression of genes associated with apoptosis, and apoptosis of neurons in the hippocampus (Wang *et al*., 2021). Interferon-γ (IFN-γ) triggers the activation of microglia, leading to an increase in the production of inflammatory cytokines, such as tumor necrosis factor-α (TNF-α). In addition, TNF-α induces elevated ROS levels, leading to neuronal death (Yun *et al*., 2021). As the brain-resident macrophage, microglial is a therapeutic approach to coping with this neuroinflammation (Sevenich, 2018).

In contrast, omega-3 fatty acids have been demonstrated to decrease inflammation in neurons and hinder the decline of cognitive function, which plays a crucial part in the development of AD (Devassy *et al*., 2016). Omega-3 fatty acids have been shown to effectively inhibit the NF-κB stress response by decreasing the production of TNF-α and IL-6, as evidenced by in vitro studies utilizing microglial cell lines (Inoue *et al*., 2017). In addition, omega-3 fatty acids successfully decreased the levels of iNOS and COX-2 produced by IFN-γ, while also promoting the increase of heme oxygenase-1 (HO-1) expression (Lu *et al*., 2010). In turn, these inflammatory responses inhibition may diminish brain cell damage and concomitant cognitive decline.

Another problem with high glucose conditions in the body is amyloidogenesis stimulation. Hyperglycemia enhances the level of amyloid-beta precursor protein (APP) by inhibiting the breakdown of APP and promoting the development of amyloid-beta (Yang *et al*., 2013). It is common knowledge that APP is normally processed by α- and γ- secretase to form harmless peptide fragments in the non-amyloidogenic pathway, whereas APP in the amyloidogenic pathway is cleaved by β- and γ-secretase, resulting in whole-length amyloid-beta peptides. Contrarily, research has demonstrated that omega-3 fatty acids can prevent the production of amyloid-beta by reducing and altering the activities of β- and γ-secretase enzymes while also encouraging a non-amyloidogenic pathway (Avallone *et al*., 2019). Likewise, a study on cell cultures found that supplementing with omega-3 fatty acids decreased the quantity of amyloid-beta peptides by more than 30% (Amtul *et al*., 2011; Solikhah *et al*., 2022). Additionally, omega-3 fatty acids could significantly enhance the clearance of amyloid beta from the brain into the circulation through the restoration of expression of low-density lipoprotein receptor-related protein 1 (LRP-1) in APP transgenic mice (Yan *et al*., 2020). Moreover, amyloid-beta is believed to be the cause of insulin resistance in the brains of AD patients (De Sousa *et al*., 2020) and is often associated with T2D (Umegaki, 2012). However, dysregulation of insulin occurs in both T1D and T2D (Morales-Corraliza *et al*., 2016). In addition, consuming a continuous high-fat diet could also alter brain insulin signaling and cognitive

dysfunction (Kothari *et al*., 2017). Brain insulin resistance is widely recognized as the inability of brain cells to normally respond to insulin. In the normal brain, the activation of insulin signaling stimulates the activation of phosphoinositide 3-kinase (PI3-K), which in turn leads to the activation of the Akt pathway. The Akt pathway activation leads to the inactivation of glycogen synthase kinase-3β (GSK3β) (Kleinridders *et al*., 2014). Meanwhile, the GSK3β is one of the kinases involved in the phosphorylation of tau. Therefore, if insulin dysfunction occurs in diabetic disorders, it will block the Akt pathway and activate GSK3β, which then promotes tau hyperphosphorylation and neurofibrillary tangle (Burillo *et al*., 2021).

Omega-3 fatty acids promote the translocation of Akt and interfere with the phosphorylation and activation of Akt, which then inhibit the activity of GSK3β and consequently prevent the activation of caspase-3 and cell death (Saisho *et al*., 2011). Ina human study, omega-3 fatty acids supplementation for 12 weeks reduced GSK3β and insulin resistance in adult participants with abdominal obesity (Thota *et al*., 2020). Furthermore, in vivo investigations demonstrated the importance of fulfilling daily omega-3 fatty acid requirements. In a study using a rat model of a metabolic syndrome caused by high fructose consumption, a lack of omega-3 fatty acids raised the risk of metabolic dysfunction and poor cognitive performance by modifying insulin receptor signaling and neural plasticity (Agrawal and Gomez-Pinilla, 2012). Meanwhile an adequacy level of omega-3 fatty acids in the diet restored metabolic homeostasis and maintained feasible brain insulin signaling (Simopoulos, 2013).

## CONCLUSION

In general, many studies appeared to support the protective impact of omega-3 fatty acids on maintaining the brain's structure and function. However, conflicting results and different experimental designs, sometimes with inadequate control, render the notion of the positive impact of omega-3 fatty acids on T1D disorder debatable. Many studies have reported that individuals with diabetes indication have an increased risk of developing AD compared to healthy individuals. Impairment of insulin signaling, chronic hyperglycemia, increased levels of ROS, and inflammatory pathways activation are general features of both diseases. Furthermore, omega-3 fatty acids supplementation in the diet might positively inhibit the abnormal mechanism and restore homeostasis. In terms of public health, this present review encourages people with or without diabetes or maybe at risk of developing diabetes to always be attentive to the adequacy of omega-3 daily intake to prevent diabetic complications. Nevertheless, higher doses should only be taken under medical supervision because it may have unintended side effects in some circumstances, such as bleeding, diarrhea, abdominal discomfort, and nausea.

## ACKNOWLEDGEMENTS

The authors would like to express their gratitude to the Ministry of Higher Education Malaysia for granting the MIS Scholarship 2022–2024 and to Universitas Brawijaya for supporting this study. This work is supported by Universiti Putra Malaysia through the Putra Grant Scheme (IPS: 9722900), Malaysia.

## AUTHORS' CONTRIBUTIONS

NT: conceptualization and writing-original draft. HA: conceptualization, review, and editing. AF: review and editing. NS and ISAR: supervision. All authors have read, reviewed, and approved the final manuscript.

## COMPETING INTERESTS

The authors declare that they have no competing interests.

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