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Review Article

Investigating the therapeutic potential of venom-derived compounds for the management of Alzheimer's disease: a comprehensive review

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ABSTRACT

Alzheimer’s disease is a comprehensive clinical syndrome featuring cognitive, emotional, and volitional function deterioration. Treatment strategies for Alzheimer's disease involve a mix of pharmacological and non-pharmacological approaches. Current treatments focus on palliative care with limited impact on the disease course. Venom-derived substances, known for their neuroactive properties, have emerged as a novel approach to Alzheimer's treatment. Our team conducted a thorough search for electronic literature related to therapeutic venom-derived substances efficacy in Alzheimer’s disease in different databases, including Medline, PubMed, Google Scholar, and Psych INFO, up to May 2024. In this article, the therapeutic effects of various venom-derived substances effects in Alzheimer’s disease are discussed. Various substances grant anti-inflammatory and anti-oxidant effects. The clinical application of venom-derived therapy is still a long way ahead, still, researchers believe that the ongoing work will eventually allow its compounds to be considered definitive candidates in various therapies in upcoming years.

Keywords: Alzheimer’s disease, Pharmacological treatment, Bee venoms, Venom-derived substances, Therapeutic effects

INTRODUCTION

Alzheimer’s disease (AD) originates from the Latin 'de mens,' meaning noticeable mental decline, it is a comprehensive clinical syndrome featuring cognitive, emotional, and volitional function deterioration. It encompasses various profiles and courses, and a diagnosis indicates multiple mental faculties involvement, excluding isolated neuropsychiatric issues like amnesia and aphasia caused by focal brain lesions.[1,2] Globally, approximately 3.9% of individuals aged 60 and above have dementia. It doubles every two decades.[3,4]

Treatment strategies for AD involve a mix of pharmacological and non-pharmacological approaches. Medications like donepezil, rivastigmine, and galantamine, known as acetylcholinesterase inhibitors (AChEI), help improve cognitive symptoms by increasing acetylcholine levels. N-methyl-d-aspartate (NMDA) antagonists, such as memantine, regulate glutamate

activity in the brain to alleviate Alzheimer's symptoms. Monoclonal antibodies, like aducanumab and lecanemab, target amyloid plaques and oligomers in the brain. Non-pharmacological therapies, including cognitive stimulation, exercise, social engagement, and music therapy, enhance the quality of life for Alzheimer's patients.[5]

Although significant progress has been made in understanding dementia's causes, current treatments offer a focus on palliative care with limited impact on the disease course. This highlights the need for innovative therapies, such as investigating venom-derived substances, known for their neuroactive properties, which emerge as a novel approach to Alzheimer's treatment. Our study explores the potential of these compounds, discussing current research and suggesting future directions for AD management.

METHODS

Our team conducted a thorough search for electronic literature related to therapeutic venom efficacy in Alzheimer's disease in different databases, including Medline, PubMed, Google Scholar, and Psych INFO, up to May 2024. We used specific keywords such as "therapeutic venoms and AD" to find relevant studies. The first author carried out independent research, while the first and second authors evaluated the titles, abstracts, and reference lists according to specific eligibility criteria. To be included, studies had to meet specific PICO criteria, such as having a population treated with Therapeutic venoms, being a clinical trial or RCT study on venoms, or a review article on venoms. Additionally, all the selected studies were published in English, and we excluded any studies that did not include therapeutic venoms.

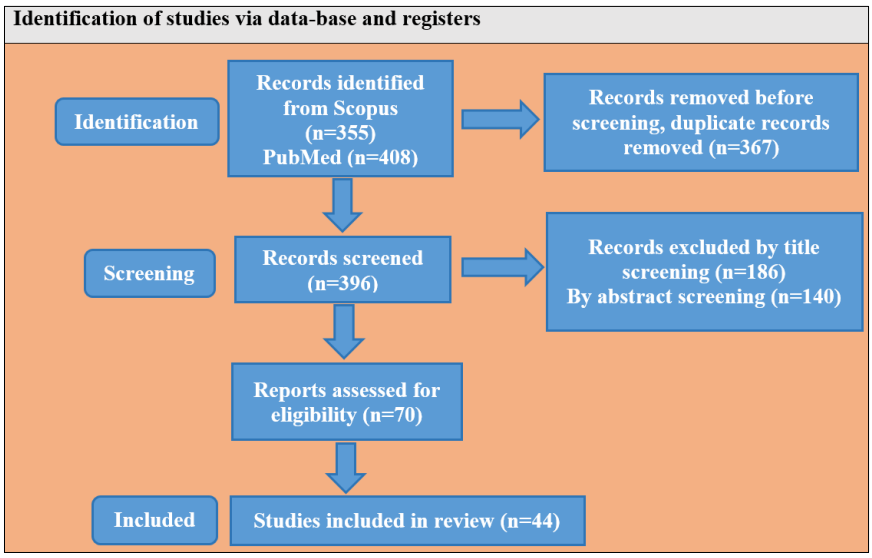

Figure 1: PRISMA flowchart of the study selection.

RESULTS

Researchers have been exploring the potential benefits of venom-derived substances in the treatment of AD. It has shown promise in providing relief to patients through different mechanisms. *Protobothrops flavoviridis* specific peptides and proteins in the venom have demonstrated neuroprotective properties and the ability to target key pathways involved in Alzheimer's pathogenesis. One area of interest is the venom's metalloproteinases, which show anti-inflammatory effects and the ability to modulate amyloid beta aggregation, a hallmark of AD.[6] A study conducted by Jeong et al investigated the effects of long-term administration of *Vespa velutina nigrithorax* venom a nuclear factor kappa inhibitor on a transgenic mice model called 5xFAD, which exhibits histopathological and cognitive symptoms akin to Alzheimer's disease due to human APP and human presenilin 1 overexpression. The study observed improvements in learning and memory function, reduced histologic damage and amyloid-beta (AB) deposition in the hippocampus, as well as decreased neuroinflammation and oxidative stress post-treatment with *Vespa velutina nigrithorax* venom.[7] A study conducted by Li et al examined the effects of administering sea cucumber-derived cerebrosides in a rat model of AD. The research revealed that oral intake of sea cucumber cerebrosides led to improved cognitive function in rats, as evidenced by various tests including the Morris water maze.[8] PLA2 and hyaluronidase found in bee venom play a key role in immune modulation and modulate drug delivery to the blood-brain barrier (BBB) respectfully.[9,10] Some studies suggest that Kv1.3 channels are involved in neuronal apoptosis (cell death) and excitotoxicity, which are implicated in AD pathogenesis. Blocking these channels by venom (sea anemone peptide ShK) exerts neuroprotective effects by reducing neuronal excitability, preventing excessive calcium influx, and mitigating cell death.[11] The summary of the effects of various venom-derived substances through different mechanisms is given in Table 1.

Table 1: Summary of venom-derived substances effect on Alzheimer's disease.

Venoms mechanisms	Effects
Protobothrops flavoviridis: metalloproteinases	Modulate amyloid beta aggregation and anti-inflammatory effects
***Vespa velutina nigrithorax*: nuclear factor kappa inhibitor**	Reduces histologic damage, reduces AB deposition in the hippocampus, and decreases neuroinflammation, and oxidative stress
Sea cucumber-derived cerebrosides	Improved cognitive function in rats
Bee venom: PLA2	Immune modulation
Bee venom: hyaluronidase	Modulate drug delivery to the blood-brain barrier
Sea anemone peptide ShK: Kv1.3 channels blockage	Reduce neuronal excitability, preventing excessive calcium influx, and mitigating cell death

DISCUSSION

AD is characterized by a gradual decline in behavioral and cognitive skills like memory, understanding, language, focus, reasoning, and decision-making. Symptoms vary by disease stage and are categorized as preclinical, mild cognitive impairment (MCI), and moderate and severe dementia based on the severity of cognitive decline.[12-15] In the preclinical AD stage, minor memory impairment and initial brain pathophysiological changes occur, yet daily functions remain unaffected, and no Alzheimer's indicators show.[12,16,17] In the mild phase of (AD), patients exhibit subtle symptoms, including functional impairment, reduced attention and memory, spatial and temporal disorientation, emotional alterations, and potential depressive onset.[12,15,16] Cognitive decline, such as reduced executive control, motivation, and organizational skills, can lead to difficulties with simultaneous task performance and complex thought processes.[12-14]

In the moderate AD phase, the illness involves cerebral cortex regions, leading to major memory deficits, challenges recognizing familiar faces and acquaintances, diminished impulse control, and difficulties in language processing, including reading, writing, and speech.[12,16]

In advanced stages, neuropsychiatric manifestations such as apathy, social detachment, disinhibition, aggression, psychosis, and disoriented ambulation are prevalent. Motor skill execution difficulties (dyspraxia), impaired olfaction, sleep disturbances, extrapyramidal motor signs, and Parkinsonian symptoms emerge later. Subsequently, primitive reflexes and urinary and fecal incontinence with complete reliance on nursing care ensure.[12-14,16,18]

THERAPEUTIC EFFECTS OF VENOMS

Protobothrops flavoviridis

Protobothrops flavoviridis, commonly known as the Habu snake, is a venomous pit viper found in Japan, Taiwan, and nearby areas. Their venom contains various enzymes, such as metalloproteinases, serine proteinases, and phospholipase A2, which contribute to the venom's cytotoxic, hemotoxic, and neurotoxic effects.[19,20] Additionally, it contains toxins that affect blood clotting and tissue damage through its factor and prothrombin activation, inhibition of platelet activation and aggregation, and breakdown of fibrin fibers, leading to symptoms such as pain, swelling, bleeding, and potential organ failure.[6,19] Another study by Tijti et al focused on the neurotoxic properties of protobothrops flavoviridis venom. They isolated and characterized a peptide that showed activity blocking neuronal inflammatory response, suggesting a potential application in neurological disorders.[22] Additionally, studies have highlighted the potential of venom phospholipase A2 in promoting neurogenesis and enhancing synaptic plasticity, which is an essential process for cognitive function and memory.[6]

These properties of venom components have paved the way for its use in developing several essential medicines. Among these are antihypertensive drugs like captopril, antiplatelets like tirofiban, and analgesics like alpha-cobratoxin.[6,20] Similarly, peptides exhibiting neuroprotective effects hold potential applications in treating neurodegenerative diseases or neurological conditions like Alzheimer's.[6]

Sea anemone peptide ShK venom

Sea anemone produces a variety of bioactive compounds, including peptides, which can have potent effects on biological systems. *Stichodactyla* toxin K (ShK), derived from sea anemone *Stichadactyla helianthus* venom. ShK has garnered attention due to its ability to selectively block a specific type of potassium channel known as Kv1.3 channels. The mechanism of action of ShK venom primarily revolves around its ability to block voltage-gated potassium Kv1.3 channels, predominantly found in immune cells. When ShK interacts with kv1.3 channels, it binds to specific sites on the channel protein, thereby blocking the ion conduction pore. This blockage prevents potassium ions from flowing through the channel, essential for maintaining resting membrane potential and regulating cell excitability. ShK-mediated inhibition on the Kv1.3 channel can dampen pro-inflammatory cytokine production and reduce immune cell migration and activation, contributing to anti-inflammatory effects.[21]

AD is characterized by chronic neuroinflammation involving the activation of microglia and astrocytes,

leading to the release of pro-inflammatory cytokines and oxidative stress. Kv1.3 channels are also expressed in microglia and play a role in their activation. It is hypothesized that ShK venom, by blocking the Kv1.3 channel in microglia, could potentially modulate neuroinflammation and reduce neuronal damage associated with AD.[22] Furthermore, there is speculation that modulating immune responses through Kv1.3 channel inhibition could indirectly influence the beta-amyloid clearance mechanism in the brain.[21]

Bee venom

Hyaluronidase

Hyaluronidase is an enzyme that breaks down hyaluronic acid, a substance found in connective tissue, skin, and in the fluid found in the eye. It is indeed one of the common enzymes present in bee venom, that act by hydrolysis the bonds present in hyaluronic acid found in several body cells. This enzymatic activity helps the venom to spread more effectively in the victim's body and increases the flow of blood to the involved area, contributing to the pain, inflammation, and other effects associated with bee stings.[9]

As of now, hyaluronidase is not directly involved in the treatment of AD. However, researchers are exploring various avenues in which hyaluronidase, or its related mechanism could potentially be harnessed to benefit Alzheimer's patients. Since inflammation is a contributing factor in AD, hyaluronidase through modulation of inflammatory response could lead to strategies for managing neuroinflammation in these patients. In Alzheimer's disease, the BBB can become compromised, limiting the effectiveness of the medication, therefore, hyaluronidase by temporarily modulating BBB permeability might facilitate the delivery of therapeutic agents to the brain. In preclinical studies, hyaluronidase has been investigated for its potential neuroprotective and neurodegenerative effects.[9,10]

It is important to note that while these potential roles of hyaluronidase are intriguing, they are mostly speculative or based on preclinical studies. Clinical studies and rigorous testing would be necessary to determine the safety and efficacy of its use in the context of AD treatment.[10]

PLA2

Phospholipase A2 (PLA2) is an enzyme that catalyzes the hydrolysis of the sn-2 position of phospholipase, specifically phosphatidylcholine, to release free fatty acids and lysophospholipids. The presence of melittin along with PLA2 in bee venom further synergies the action of PLA2 by increasing the exposure of cell membrane phospholipases to the enzyme, resulting in inflammation, pain, and immune response.[23] Overall, PLA2 enzymes and their lipid products play a multifaceted role in immune modulation, spanning from the initiation and propagation of inflammatory responses to the resolution of inflammation and maintenance of immune homeostasis. There is a need for further exploration of the potential role of PLA2 in the management of AD.

Vespa velutina nigrithorax

Wasp venom contains a range of components, including amines like histamine, tyramine, and serotonin, as well as small peptides such as anoplin, decoralin, eumenitin, eumenitin-R, EpVP, mastoparan, and rumenitin-F, along with proteins like hyaluronidase, α-glucosidase, phosphatase, phospholipase A2, and phospholipase B. Some compounds within wasp venom have been found to possess antibacterial, anti-tumor, and anti-inflammatory properties.

Research on *Vespa velutina nigrithorax*, commonly known as the invasive yellow-legged hornet, indicates that its wasp venom can inhibit the nuclear factor kappa B (NFκB) pathway in vitro, thereby preventing microglial activation. Additionally, it activates the Nrf2/HO-1 signaling pathway, enhancing the antioxidant response.[24]

Echinoderms

Echinoderms are marine organisms that are famous for producing a variety of bioactive compounds.[25]

Echinoderms of the Persian Gulf

The Persian Gulf is home to a wide variety of marine organisms, with untapped potential for biomedical exploration. Of particular interest are echinoderms like the sea urchin (*Echinometra mathaei*) and brittle star (*Ophiocoma erinaceus*), which possess a wealth of bioactive compounds, including toxins crucial for their defense mechanisms. These compounds encompass pyridines, piperidines, indole alkaloids, monoterpenes, xanthophylls, esters, sterols, alkanes, amides, carbohydrates, and more.

Dehghani et al study indicated that these venoms demonstrate strong inhibitory effects on cholinesterase (both AChE and BChE) and possess antioxidant properties, possibly attributed to the presence of proteins. Within these venomous compounds, compound C7, an indole alkaloid, displayed the highest inhibitory activity against both AChE and BChE. Consequently, further investigations are warranted to isolate compound C7 and ascertain its potential as a therapeutic candidate for AD.[25]

Sea cucumber

The sea cucumber, an echinoderm widely consumed as traditional seafood in Asian cultures, is recognized for its rich content of bioactive compounds, especially cerebrosides and phospholipids. Cerebrosides, a type of neutral glycosphingolipids, are abundantly distributed across various life forms including fungi, plants, animals,

and marine organisms' body walls. Remarkably, cerebrosides are prominently found in brain tissue, where they can be converted into ceramides, subsequently giving rise to sphingomyelins, sulfatides, and other glycosphingolipids. These compounds play a crucial role in supporting the regular functioning of the brain.[8]

Tangrodchanapong et al explored the therapeutic potential of compounds derived from the sea cucumber *Holothuria scabra* in treating AD using a transgenic *Caenorhabditis elegans* model. Among the compounds investigated, 2-butoxytetrahydrofuran (2-BTHF) emerged as the most effective in mitigating amyloid-beta (Aβ)-induced paralysis in the nematodes. The mechanism of action involved the reduction of toxic oligomeric Aβ forms and fibril deposits, likely achieved by modulating autophagy-related genes through the heat shock factor 1 (HSF-1) pathway, resulting in decreased levels of reactive oxygen species. Moreover, 2-BTHF exhibited neuroprotective effects by preventing Aβ-induced impairments in chemotaxis behavior. These findings suggest that 2-BTHF from *H. scabra* holds promise as a potential therapeutic agent targeting Aβ aggregation and toxicity in Alzheimer's disease.[26]

CONCLUSION

The use of pharmacological therapy for AD can be traced back for many years. In this article, the therapeutic effects of various venom-derived substances in AD are discussed. Various substances grant anti-inflammatory and anti-oxidant effects. They modulate amyloid beta aggregation and decrease neuronal excitation leading to neuroprotective effects in AD. The clinical application of substances is still a long way ahead, still, researchers believe that the ongoing work will eventually allow its compounds to be considered definitive candidates in various therapies in upcoming years.

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