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Neuroprotective Effects of Zerumbone on Cognitive Functions: A Scoping Review

(Kesan Neuropelindung Zerumbon terhadap Fungsi Kognitif: Suatu Ulasan Skop)

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ABSTRACT

Zerumbone (ZER) is a sesquiterpenoid compound derived from the rhizome of *Zingiber zerumbet* (L.) Smith, also known as Lempoyang ginger. Evidence suggests that ZER may help manage cognitive disorders. Its unique chemical structure and effects on the central nervous system make it a promising candidate for treating neurodegenerative diseases. This review analyzes nine preclinical studies, including six rodent and three cell-based models, which demonstrate ZER's neuroprotective properties. The studies show that ZER has strong anti-inflammatory and antioxidant effects, with six out of nine reporting increased antioxidant enzyme activity. Other mechanisms include cholinesterase inhibition, stimulation of neural stem cell proliferation, and regulation of key signalling pathways. ZER's lipophilic nature allows it to cross the blood–brain barrier and act within the central nervous system. In all six animal studies, ZER improved behavioral and cognitive outcomes in models of Alzheimer's disease, vascular dementia, scopolamine-induced amnesia, and age-related cognitive decline. These results support further development of ZER as a natural therapeutic for neurodegenerative diseases and cognitive impairment. However, additional research, especially well-designed clinical trials, is needed to confirm its safety and efficacy in humans.

Keywords: Cognitive function; neurodegenerative diseases; neuroprotective; sesquiterpenoid; zerumbone

ABSTRAK

Zerumbon (ZER) ialah sebatian seskuiterpenoid yang berasal daripada rizom *Zingiber zerumbet* (L.) Smith, juga dikenali sebagai Lempoyang. Bukti menunjukkan bahawa ZER boleh membantu menguruskan gangguan kognitif. Struktur kimia dan kesannya yang unik pada sistem saraf pusat menjadikannya bahan aktif yang berpotensi untuk merawat penyakit neurodegeneratif. Ulasan ini menganalisis sembilan kajian praklinikal, termasuk enam model berasaskan tikus dan tiga model berasaskan sel yang menunjukkan sifat neuropelindung ZER. Kajian menunjukkan bahawa ZER mempunyai kesan anti-radang dan antioksidan yang kuat, dengan enam daripada sembilan melaporkan peningkatan aktiviti enzim antioksidan. Mekanisme lain termasuk perencatan kolinesterase, rangsangan percambahan sel stem saraf dan pengawalaturan laluan isyarat utama. Sifat lipofilik ZER membolehkannya melintasi penghalang darah-otak dan bertindak dalam sistem saraf pusat. Dalam keenam-enam kajian haiwan, ZER meningkatkan hasil tingkah laku dan kognitif dalam model penyakit Alzheimer, demensia vaskular, amnesia yang disebabkan oleh skopolamin dan penurunan kognitif berkaitan usia. Keputusan ini menyokong perkembangan selanjutnya ZER sebagai terapeutik semula jadi untuk penyakit neurodegeneratif dan gangguan kognitif. Walau bagaimanapun, kajian tambahan, terutamanya ujian klinikal yang direka bentuk dengan baik, diperlukan untuk mengesahkan keselamatan dan keberkesanannya pada manusia.

Kata kunci: Fungsi kognitif; neuropelindung; penyakit neurodegeneratif; seskuiterpenoid; zerumbon

INTRODUCTION

Neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), and vascular dementia represent significant public health challenges. These disorders are characterized by progressive cognitive and motor decline, frequently linked to oxidative stress, chronic inflammation and neurotransmitter dysregulation. Natural compounds with multitarget mechanisms are under increasing investigation as potential therapeutic agents for these conditions. Among these, zerumbone (ZER), a bioactive monocyclic sesquiterpene isolated from the rhizome of *Zingiber zerumbet* (L.) Smith has emerged as a promising phytochemical due to its diverse pharmacological activities and favorable pharmacokinetic profile (Hwang et al. 2020).

ZER, also known as 2,6,9,9-tetramethyl-[2E,6E,10E]-cycloundeca-2,6,10-trien-1-one (Gopalsamy et al. 2020) is primarily extracted from the rootstocks of *Zingiber zerumbet* (L.) Smith. It can also be sourced from other *Zingiber* species, such as *Zingiber cassumunar* Roxb (Kishore & Dwivedi 1992) and *Zingiber officinale* (Oh et al. 2018). However, ZER from *Zingiber cassumunar* Roxb. is not considered a viable treatment for AD (Han et al. 2021). The compound was first isolated in 1960, and its structure was elucidated in 1965 (Damodaran & Dev 1965; Dev 1960). ZER is a carbon-15 crystalline monocyclic sesquiterpene composed of three isoprene units, with a unique chemical structure that includes an α, β-unsaturated carbonyl group and a triple bond configuration at carbon-2 (isolated double bond), as well as conjugated double bonds at carbon-6 and carbon-9 (Figure 1). Its pharmacological activities, such as anti-inflammatory and antioxidant effects, are attributed to its distinctive structure (Haque, Jantan & Harikrishnan 2018). This structure also confers favourable bioavailability and enables effective penetration of the blood-brain barrier (BBB) and entry into the central nervous system (CNS) (Hwang et al. 2020). Terpenoids such as ZER have been shown to activate the β5 subunit activities of proteasome, thereby exhibiting neuroprotective effects (Ohnishi et al. 2013).

ZER exhibits significant antioxidant activity by reducing oxidative damage through the upregulation of antioxidant enzymes and HO-1 (Chen et al. 2024). Furthermore, ZER mitigates inflammatory responses by downregulating NF-κB pathway (Zhang & Xu 2023). In models of Alzheimer'sdisease, ZER inhibits acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), enzymes that degrade acetylcholine, a neurotransmitter critical for learning and memory (Hwang et al. 2020).

This scoping review systematically examines the preclinical regarding the neuroprotective potential of ZER in neurodegenerative processes and cognitive impairments. It synthesizes recent findings to clarify how ZER may address the critical relationships among oxidative stress, chronic inflammation, neuronal damage and cognitive dysfunction, which are hallmarks of neurodegenerative disease. This review provides a comprehensive overview of ZER's impact on cognitive function, adhering to PRISMA-ScR guidelines and incorporating recent updates to the scoping review protocol.

This review addresses two primary objectives. First, it seeks to consolidate evidence regarding ZER's cognitive and neuroprotective effects, which is currently dispersed across various preclinical models despite extensive investigation of its pharmacological activities. Second, it applies recent methodological advances from the Joanna Briggs Institute (JBI) and the Population, Concept, and Context (PCC) framework to systematically map this evidence. The review aims to identify ZER's principal neuroprotective mechanisms, delineate the current research landscape, and highlight gaps for future investigation.

MATERIALS AND METHODS

The methodological approach employed in this scoping review is guided by the updated recommendations provided by the Joanna Briggs Institute (JBI) for scoping reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). This section outlines the inclusion and exclusion criteria, search strategy, study selection process, data extraction procedures, and strategies for data analysis.

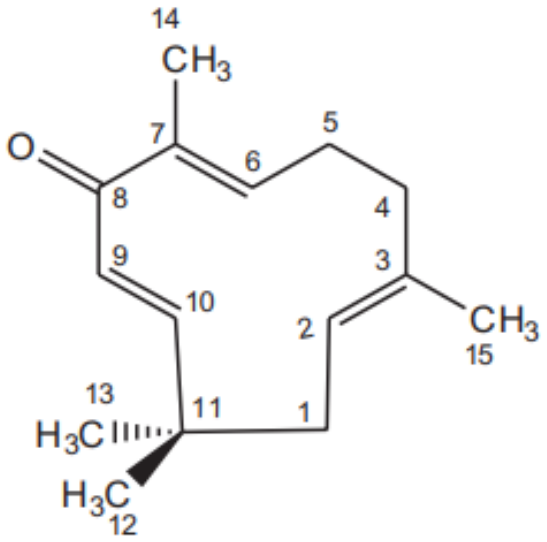

FIGURE 1. Zerumbone's cyclic structure with carbon numbering (Wiart 2012)

INCLUSION CRITERIA

The inclusion criteria were defined using the PCC framework as follows:

Population Preclinical models (e.g., *in vitro* cell models and *in vivo* animal models) utilized to investigate neurodegenerative processes and cognitive functions. The review focuses on studies involving rodents, cell lines, or relevant biological models that replicate key aspects of cognitive impairment.

Concept Studies needed to report on the neuroprotective effects of ZER. This includes interventions where ZER is administered as a therapeutic compound and measured outcomes related to neuronal viability, oxidative stress markers, inflammation, synaptic function, or direct behavioral/cognitive performance.

Context The scope was limited to preclinical evaluations that assess cognitive function. Studies excluded were those that focused solely on other pharmacological effects of ZER (e.g., anticancer properties), unless they also reported on markers or tests indicative of cognitive functions.

EXCLUSION CRITERIA

Studies were excluded if they: a) Studies utilizing ZER derived from species other than *Zingiber zerumbet*, b) Focused on clinical populations or human studies, as the review is restricted to preclinical (animal and *in vitro*) evidence, c) Primarily investigated pharmacological effects of ZER unrelated to neuroprotection or cognitive impairment and d) Did not report sufficient methodological details regarding the cognitive or neuroprotective outcomes.

SEARCH STRATEGY AND STUDY SELECTION

A computer-assisted scoping review was conducted utilizsing PubMed, Scopus, and WoS to identify primary research articles examining the neuroprotective and therapeutic effectss of zerumbone (ZER) in neurodegenerative diseases. The database search employed the terms [‘zerumbone’ AND (Alzheimer* OR Parkinson* OR dementia OR cognitive OR memory OR neuro* OR astrocyt* OR microglia)]. The search strategy emphasized transparency, with comprehensive documentation of inclusion and exclusion criteria and all screening procedures.

The study selection process was conducted in two stages:

Title and Abstract Screening against by Two independent reviewers initially assessed each article for relevance based on the inclusion criteria. Any discrepancies were resolved through consensus.

Full-Text Review Articles meeting the initial screening criteria underwent comprehensive full-text analysis to confirm eligibility.

The literature search conducted on November 28, 2024, identified 148 articles across Scopus (n=77), Web of Science (WoS) (n=42), and PubMed (n=29). Following the removal of 55 duplicate references, 93 articles remained for eligibility assessment. Of these, nine (9) original research articles met the inclusion criteria and were selected for review, while 84 articles were excluded (78 for irrelevance and 6 for focusing on neuropathic pain). The study selection process is illustrated in a flow diagram (Figure 1) in accordance with PRISMA-ScR guidelines.

DATA EXTRACTION

Data extraction was performed using a standardized form that was piloted before implementation. Critical data elements included: a) Author(s) and publication year, b) Study design and model type (*in vitro* or *in vivo*); c) Intervention details such as dosage, mode of delivery, and duration of exposure to ZER; d) Cognitive-related outcome measures (e.g., behavioural tests, biochemical markers, histopathological assessments); and e) Key findings concerning neuroprotection and cognitive improvements.

DATA ANALYSIS

Given the exploratory nature of scoping reviews, the analysis primarily involved descriptive statistics and thematic synthesis. The extracted data were organized in tables to map study characteristics and results and identify common trends and gaps in the literature. Statistical analysis is not expected for this scoping review, but the analytical value is strengthened by including descriptive quantification of study characteristics and outcomes.

RESULTS

The review included a total of nine (9) preclinical studies that met the inclusion criteria. These studies predominantly used rodent models and *in vitro* systems to investigate the neuroprotective aspects of ZER.

STUDY CHARACTERISTICS AND MODEL HETEROGENEITY

The included studies were published between 2019 and 2024. The evidence base is heavily weighted toward *in vivo* models, comprising 6 studies (66.7%) using rodents (rats or mice), and 3 studies (33.3%) using *in vitro* cell lines. Doses in *in vivo* studies ranged substantially, from 1 mg/kg up to 100 mg/kg administered via various routes. Treatment durations ranged from single acute administration to chronic regimens lasting up to 6 weeks or unspecified long-term dietary exposure. *In vitro* concentrations were consistently limited to the 1–40/uM range. A study characteristics table (Table 1) has been devised to present the key attributes of the included studies.

OPERATIONAL SUMMARY AND COGNITIVE OUTCOMES

To facilitate translational assessment and delineate the operational parameters of ZER efficacy, a summary of study metrics including model type, dose range, duration, and definitive cognitive outcome is presented in Table 2.

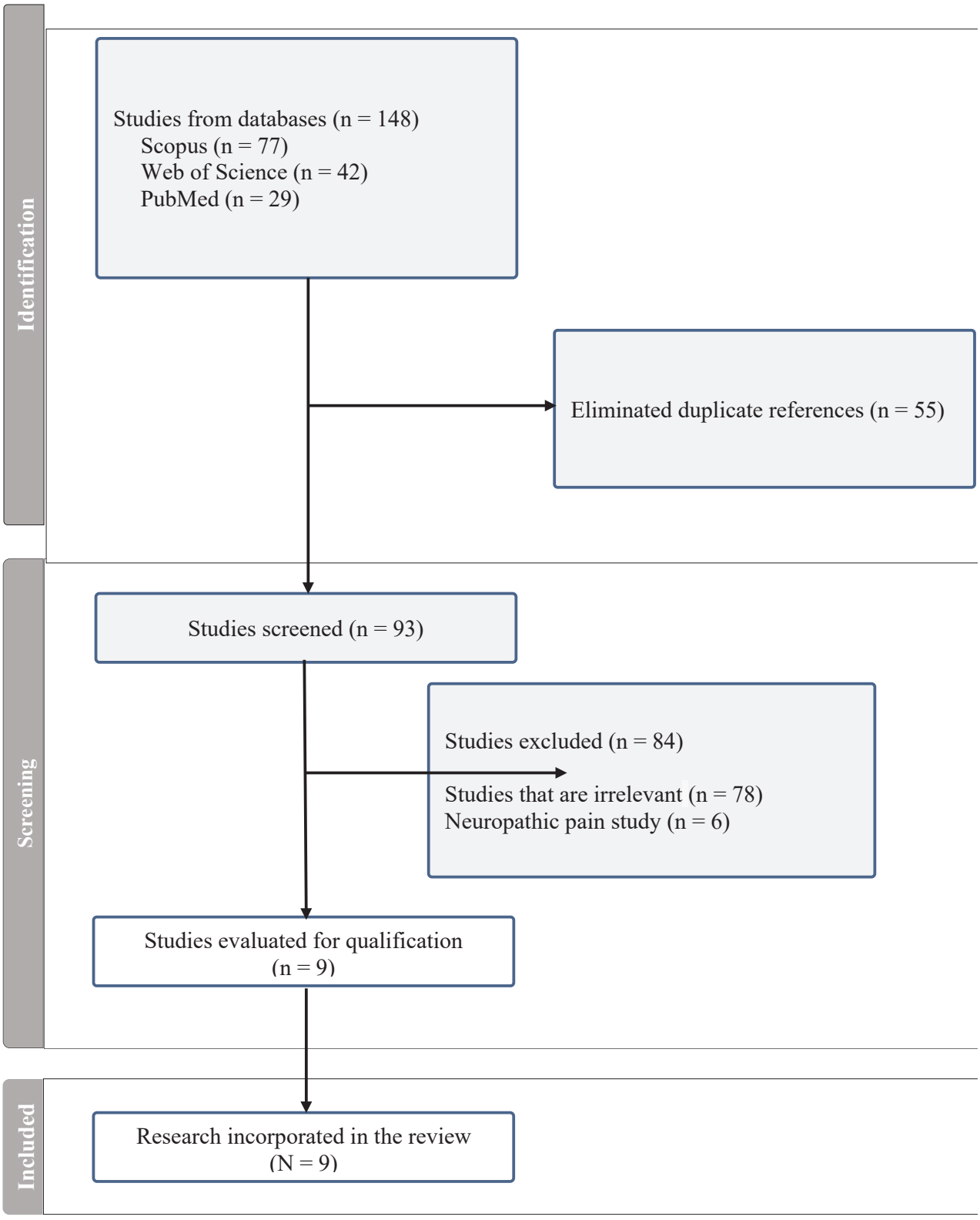

FIGURE 2. Schematic flowchart following PRISMA-ScR guidelines (2018) illustrating the process of literature search and study selection

A critical finding is the consistency of translational efficacy. Assessment of the 6 *in vivo* studies demonstrated universal cognitive improvement across diverse models, regardless of the underlying pathological trigger (AD, vascular dementia, scopolamine-induced amnesia, hyperlipidemia, or aging). Behavioral improvements were confirmed using validated tasks such as the Morris Water Maze (MWM), Novel Object Recognition (NOR), Y-Maze, and Elevated Plus Maze (EPM), consistently showing improved memory, learning, and reduced anxiety-like behaviors in ZER-treated groups. Furthermore, a positive dose-response relationship between ZER administration and observed effect size was explicitly reported in 4 studies (44.4% of the evidence base).

THEMATIC SYNTHESIS OF NEUROPROTECTIVE MECHANISMS

The consolidated findings robustly support ZER as a multifaceted neuroprotective compound capable of modulating multiple interrelated pathological processes underlying cognitive impairment. ZER consistently demonstrates the ability to mitigate neurodegeneration through a convergence of four primary mechanisms:

Antioxidant activity Enhancement of endogenous antioxidant defenses (SOD, CAT, GPx, HO-1) was the most consistent mechanistic finding, documented in 6 out of 9 studies.

Anti-inflammatory effects ZER attenuates neuroinflammatory cascades by suppressing microglial activation and down-regulating pro-inflammatory mediators, notably through the NF-kB pathway.

Neurotransmitter modulation ZER exhibits dual inhibitory activity against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), crucial enzymes in the cholinergic system essential for memory.

Cellular signalling and regeneration ZER regulates key cellular survival and pathological pathways, including suppression of MAPK signalling and ER stress (PERK/CHOP), alongside activation of Notch and SIRT1/AMPK pathways to promote neurogenesis and neuronal survival.

A comprehensive summary of the key mechanisms of action is provided in Table 3. The detailed molecular explanations and pathway interactions underpinning these effects are discussed in depth in the discussion section. The proposed molecular and cellular pathways through which ZER exerts its neuroprotective effects are illustrated in Figure 3, highlighting its integrated actions on inflammation, oxidative stress, cholinergic transmission, and neuronal survival.

LIMITATIONS OF THE EVIDENCE BASE

Despite the promising evidence, several limitations are notable:

Study Heterogeneity There is considerable variability in the models used, intervention dosages, and outcome measures, which may affect the generalizability of the findings.

Preclinical Focus All included studies are preclinical. This precludes direct translation of findings to clinical scenarios involving human subjects.

Limited Number of Studies With only nine studies available, the evidence base is relatively restricted, underscoring the need for further research to corroborate these findings and explore underlying mechanisms in greater detail.

These limitations highlight gaps in the current body of research, emphasizing the need for standardized methodologies and subsequent clinical investigations to validate the neuroprotective properties of ZER.

DISCUSSION

Zerumbone (ZER), a naturally occurring sesquiterpene, has emerged as a promising candidate for the treatment of neurodegenerative diseases due to its extensive and multifaceted neuroprotective properties. This comprehensive review, synthesizing nine preclinical studies, confirms ZER's significant efficacy across six distinct *in vivo* disease models, including Alzheimer's disease (AD), vascular dementia, scopolamine-induced amnesia, hyperlipidemia, and aging-related cognitive decline, positioning it as a uniquely comprehensive therapeutic agent. ZER's broad neuroprotective efficacy operates simultaneously across three critical axes of neurodegeneration: Environmental Stress, Neurotransmitter Deficiency, and Cellular Survival/Regeneration.

A pivotal pharmacological advantage supporting ZER's therapeutic potential is its intrinsic lipophilic nature, which critically enhances its ability to cross the blood–brain barrier (BBB) and effectively exert central nervous system (CNS) effects (Kesharwani & Bhat

TABLE 1. Study characteristics

Model type	Intervention details	Key findings
In vivo (rodents)	ZER (varied dosages)	Improves spatial memory and reduced oxidative stress
In vitro (cell line)	ZER treatment	Attenuation of oxidative injury, increased cell survival
In vivo (rodents)	Chronic administration	Long-term cognitive benefits with neuroprotective outcomes

TABLE 2. Quantitative Operational Summary of Included Preclinical Studies (N=9)

Reference (Year)	Model type	ZER dose route/ range (mg/kg/day)	ZER dose range (μM)	Duration	Primary cognitive test (s)	Behavioral/ cognitive outcome
Gu et al. (2020)	*In vitro* (microglia/LPS)	N/A	1–10	Acute	Molecular only	Not assessed
Jafarian et al. (2019)	*In vivo* (rat/ Scopolamine)	1–10 (i.p.)	N/A	Acute/single	EPM, Y-Maze, OFT	Improved
Li et al. (2020)	*In vivo* (APP/PS1 mice/AD)	10 & 20 (oral)	N/A	6 weeks (Chronic)	MWM, NOR	Improved
Sun et al. (2019)	*In vivo* (rat/ vascular dementia)	50–100 (i.p.)	N/A	4 weeks	MWM, NF score	Improved
Uppin et al. (2020b)	*In vivo* (rat/HFD)	Unspecified	N/A	Chronic	N/A (Biochemical focus)	Improved (Prevented decline)
Uppin et al. (2020a)	*In vivo* (rat/HFD + EPA/DHA)	Unspecified	N/A	Chronic	MWM, T-maze, Rotarod	Improved
Yeh et al. (2022)	*In vitro* (macrophage/ LPS)	N/A	5–20	Acute	Molecular only	Not assessed
Moon & Yun (2023)	*In vitro* (SH-SY5Y/H_2O_2)	N/A	1–10	Acute	Molecular only	Not assessed
Yang et al. (2024)	*In vivo* (aged mouse model)	Unspecified (dietary)	N/A	Chronic	MWM, ORT	Improved

APP/PS1; amyloid precursor protein/presenilin 1, ZER; zerumbone, MWM; Morris water maze, ORT; Object recognition test, OFT; open field test, EPM; elevated plus maze, NOR; novel object recognition, NF score; neurological function score, i.p; intraperitoneal, LPS; lipopolysaccharide, HFD; high-fat diet

TABLE 3. Proposed neuroprotective mechanisms of ZER on cognitive function

Mechanism	Description	Supporting evidence
Anti-inflammatory action	Zerumbone inhibits pro-inflammatory cytokines (TNF-α, IL-1β) and suppresses activation of microglia via pathways like NF-κB and MAPK	Gu et al. (2020); Li et al. (2020); Yeh et al. (2022)
Antioxidant defense enhancement	Enhances endogenous antioxidant enzymes (SOD, CAT, GPx) and reduces oxidative stress in neural cells and brain tissue	Moon & Yun (2023); Uppin et al. (2020b); Yeh et al. (2022)
Modulation of neurotrophic factors	Increases neurotrophins like BDNF and NGF, supporting synaptic plasticity and neuronal survival	Uppin et al. (2020a); Uppin et al. (2020b)
Regulation of neural signaling pathways	Suppresses pathological signaling pathways such as MAPK and ER stress (PERK/CHOP); activates SIRT1/AMPK and Notch signaling	Li et al. (2020); Moon & Yun (2023); Sun et al. (2019); Yang et al. (2024)
Promotion of neural stem cell proliferation	Stimulates proliferation and differentiation of endogenous neural stem cells in the hippocampus	Sun et al. (2019)
Reduction of amyloid pathology	Lowers Aβ plaque accumulation and neurodegeneration in Alzheimer's disease models	Li et al. (2020)
Synergistic cognitive enhancement	Enhances cognitive effects when combined with other agents like EPA/DHA through complementary neuroprotective actions	Uppin et al. (2020a)
Behavioral and memory improvement	Improves performance in cognitive tasks (Morris Water Maze, Y-Maze, Object Recognition), particularly in memory, learning, and anxiety models	Jafarian et al. (2019); Li et al. (2020); Yang et al. (2024)

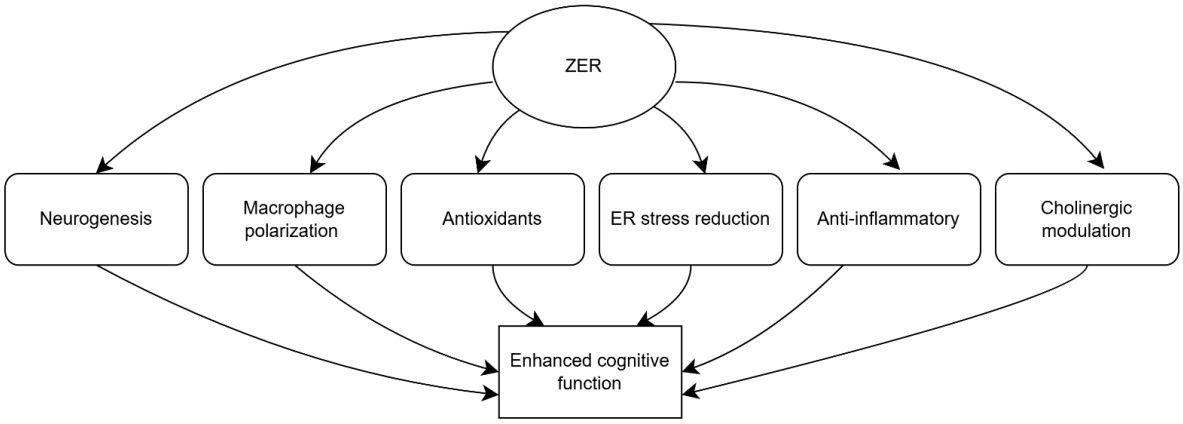

FIGURE 3. Proposed neuroprotective mechanisms of ZER on cognitive function

2020). This characteristic ensures that ZER can interact with various neural targets implicated in AD and other cognitive disorders, a property further supported by computational ADMET profiling demonstrating favourable pharmacokinetic and physicochemical properties conducive to CNS drug delivery (Kesharwani & Bhat 2020).

This intrinsic BBB permeability contrasts favourably with other phytochemicals like curcumin, which suffers from inherent instability in biological systems, including rapid metabolism, low solubility, and poor CNS access (Moldoveanu et al. 2024), often requiring chemical adjuvants such as piperine to enhance its BBB penetration (Genchi et al. 2024; Rotimi et al. 2024). ZER, by comparison, offers a more pharmacologically stable profile, strongly suggesting superior translational potential for neurological applications.

The foundation of ZER's action lies in the Environmental Stress Axis, where it consistently modulates redox and inflammatory homeostasis, a mechanism documented in six out of nine studies. ZER mitigates oxidative damage by upregulating endogenous antioxidant enzymes, including superoxide Dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1), effectively reducing reactive oxygen species (ROS) and lipid peroxidation products in neural and glial cells.

Complementary to this, the anti-inflammatory effects involve potent suppression of microglial activation and subsequent neuroinflammatory cascades, evidenced by the downregulation of the NF-κB and MAPK pathways and inhibition of critical pro-inflammatory mediators such as TNF-α, IL-1β, iNOS, COX-2, and nitric oxide (Haque, Jantan & Harikrishnan 2018; Ohnishi et al. 2013).

Moreover, ZER modulates neuroimmune responses by promoting M2-type microglial polarization, thereby maintaining immune homeostasis and limiting neuroinflammation - an essential aspect of neurodegenerative pathogenesis (Darwish et al. 2023; Yeh et al. 2022). While curcumin also influences immune pathways, its effects are largely limited to suppression of M1-related pro-inflammatory mediators, lacking ZER's broader regulatory capacity.

Regarding the Neurotransmitter Deficiency Axis, ZER exhibits dual inhibitory activity against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), enzymes implicated in cholinergic dysfunction associated with AD, thereby restoring cholinergic neurotransmission essential for cognition (Hwang et al. 2020).

Furthermore, a distinctive and therapeutically advantageous aspect of ZER's potential is its synergistic effect when combined with omega-3 fatty acids (EPA and DHA). This specific combination significantly enhances both memory performance and neurotrophic signalling in hyperlipidemic models, offering a novel approach to dietary interventions for neuroprotection (Uppin et al. 2020a). Such synergism is relatively rare among natural compounds and sets ZER apart from other plant-derived neuroprotectants.

The Cellular Survival and Regeneration Axis further underscores ZER's comprehensive versatility, distinguishing it from phytochemicals such as 6-gingerol and 6-shogaol, which largely exert limited anti-inflammatory or antioxidant effects. ZER modulates key pathological pathways across various models: in an AD mouse model (APP/PS1 transgenic mice), ZER significantly improved cognitive performance and attenuated neuropathological markers (Li et al. 2020).

Specifically, ZER attenuated neuropathology by suppressing the MAPK signalling pathway while reducing amyloid-beta (Aβ) aggregation and attenuating tau hyperphosphorylation. In models of vascular dementia, ZER promoted the proliferation and differentiation of endogenous neural stem cells by regulating the Notch signalling pathway, further underscoring its regenerative potential (Sun et al. 2019).

Additionally, ZER provided protection against age-related cognitive decline by inhibiting the endoplasmic reticulum (ER) stress pathway (PERK/CHOP) (Yang et al. 2024). In oxidative stress models, ZER promoted

neuronal survival and autophagy by activating the SIRT1/AMPK signalling pathway (Moon & Yun 2023). ZER also supports neurogenesis, modulates brain lipid metabolism, enhances synaptic plasticity, and modulates key markers of learning and synaptic function, such as BDNF and CREB, distinguishing it from compounds like 6-paradol or gingerols, which lack specific neurobiological targets (Uppin et al. 2020a). This comprehensive breadth of action positions ZER as a more versatile agent than others like bacosides or resveratrol, which often exhibit narrow mechanism specificity (Boondam et al. 2024; Shaito et al. 2020; Zeng et al. 2023).

Crucially, preclinical data consistently indicate that ZER is well-tolerated at neurotherapeutic doses (50–100 mg/kg), with no major neurotoxic or adverse effects reported across all included studies. This robust safety profile contrasts with compounds like curcumin or resveratrol, which may cause gastrointestinal or metabolic disturbances at higher concentrations and exhibit complex interactions with cellular signalling pathways (Bertoncini-Silva et al. 2024; Shaito et al. 2020). In summary, ZER presents a compelling pharmacological profile as a highly versatile neuroprotective agent. Its confirmed efficacy across diverse *in vivo* disease models, combined with its lipophilicity, CNS bioavailability, multi-targeted mechanisms, synergy with dietary compounds, and favourable safety profile, strongly support its potential for therapeutic application in neurodegenerative conditions, especially Alzheimer's disease and vascular dementia.

However, while the current body of evidence is highly promising, some limitations currently remain: mechanistic studies, such as those by Gu et al. (2020) and Yeh et al. (2022), provide valuable *in vitro* data but notably lack corresponding behavioral assessments, which are crucial for translating biological findings to tangible cognitive outcomes. Consequently, human clinical studies focused on long-term safety, optimal dosing, and definitive efficacy must still be conducted.

CONCLUSIONS

This scoping review consolidates compelling preclinical evidence supporting ZER's neuroprotective effects on cognitive function, drawing from N=9 studies, predominantly *in vivo* rodent models (66.7%). ZER demonstrates promise in improving cognitive outcomes in preclinical models via multi-targeted action, most frequently involving antioxidant defense enhancement (6/9 studies), and the synergistic modulation of key pathological pathways (MAPK, Notch, PERK/CHOP).

Its lipophilic properties facilitate blood-brain barrier (BBB) penetration, enabling neuroprotective actions within the central nervous system (CNS), including cholinesterase inhibition, mitigation of cognitive deficits in Alzheimer's disease models, and promotion of neurogenesis in vascular dementia models.

ZER's multifaceted mechanisms of action, favourable bioavailability, broad-spectrum efficacy demonstrated across all 6 behaviourally tested *in vivo* models, synergistic potential with omega-3 fatty acids, and strong safety profile collectively underscore its promise as a natural neurotherapeutic agent.

Despite converging evidence from rodent and cellular studies, heterogeneity in study designs and the reliance on preclinical models highlight limitations in the current evidence. Future research should prioritize standardized experimental paradigms, dosage optimization, and, critically, phase I clinical trials to validate ZER's safety and efficacy in human populations.

IMPLICATIONS FOR FUTURE RESEARCH

The findings of this scoping review lay the groundwork for several avenues of further research:

Standardization of Preclinical Models Future studies should aim to standardize the experimental models used, including consistent dosing regimens and outcome measures. This would improve comparability across studies and facilitate meta-synthesis.

Mechanistic Studies Detailed investigations into the molecular mechanisms underlying ZER's effects are needed. Such studies should employ advanced techniques (e.g., proteomics, genomics) to elucidate the precise intracellular pathways involved.

Translational Research Given that all studies included in this review are preclinical, there is a clear need for translational research, including phase I clinical trials, to assess the safety and efficacy of ZER in human populations.

Long-Term Efficacy Studies Chronic administration studies are required to evaluate whether the observed cognitive benefits of ZER can be maintained over longer periods and under conditions that mimic neurodegenerative diseases such as Alzheimer's disease.

Combination Therapies Emerging evidence suggests that ZER may have synergistic effects when combined with other bioactive compounds. Future research should explore potential combination therapies that could enhance neuroprotective outcomes.

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