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A systematic review of the therapeutic potential of nicotinamide adenine dinucleotide precursors for cognitive diseases in preclinical rodent models

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Abstract

This systematic review sought to assess the impact of nicotinamide adenine dinucleotide (NAD^+) precursors on cognitive impairments in several diseases in rat/mouse models. Accumulating evidence suggests that inflammation, apoptosis, oxidative stress responses, and mitochondrial dysfunction are potential factors of cognitive deficits in aging, Alzheimer's disease (AD), diabetes, traumatic brain injury (TBI), vascular dementia (VAD), and schizophrenia. NAD^+ precursors have received increased interest due to their unique molecular structure targets antioxidant and inflammatory pathways and mitochondrial function. The PubMed, Scopus, Google Scholar, Embase, and Web of Science databases were searched through May 30, 2024. Studies investigating the effect of NAD^+ precursors on cognitive impairments in rodent models were included. Two reviewers independently extracted and evaluated the data. The PRISMA guidelines for reporting systematic reviews were followed. Thirty preclinical studies were included in the review. Studies have revealed that treatment with NAD^+ rescues cognitive deficits by inhibiting inflammation, oxidative stress, and apoptosis and improving mitochondrial function**.** Preclinical evidence has demonstrated that treatment with NAD^+ precursors may be more effective in learning and memory recovery in AD, TBI, diabetes, aging, VAD, and schizophrenia. The outcomes of this investigation may lead to additional studies on the use of NAD^+ precursors for treating human cognitive decline.

Keywords Memory, Cognitive impairment, Nicotinamide, Inflammation, Oxidative stress, Mitochondrial dysfunction

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Introduction

Cognitive and memory deficits are cardinal features of many neurological disorders, including Alzheimer's disease (AD), Parkinson's disease, and stroke, as well as systemic conditions such as diabetes and cancer. These impairments significantly diminish an individual's quality of life, impacting their ability to work, maintain social relationships, and independently perform daily activities [1–3]. While the underlying mechanisms are complex and multifaceted, converging evidence points towards the involvement of oxidative stress, inflammation, and mitochondrial dysfunction in the pathogenesis of cognitive decline [4, 5].

Nicotinamide adenine dinucleotide (NAD^+), a crucial coenzyme in cellular metabolism, plays a pivotal role in various physiological processes, including energy production, DNA repair, and cellular signaling pathways. Notably, NAD^+ significantly influences brain function, modulating neurotransmission, learning, and memory formation [6, 7]. A decline in NAD^+ levels is observed with advancing age and has been implicated in age-related cognitive decline, increased susceptibility to neurodegenerative diseases, and accelerated aging [8–10]. Furthermore, reduced NAD^+ levels are associated with decreased activity of sirtuin 1 (Sirt1), a key NAD^+-dependent deacetylase that regulates cellular stress responses, including oxidative stress and inflammation [11]. Recent preclinical and clinical studies have explored the therapeutic potential of NAD^+ precursors, such as nicotinamide (NAM), nicotinamide riboside (NR), and nicotinamide mononucleotide (NMN), in ameliorating cognitive impairments. These compounds have demonstrated promising results in animal models of AD [12], traumatic brain injury (TBI) [13], diabetes [14], and vascular dementia (VAD) [15] improving cognitive function and providing neuroprotection against ischemic injury [16].

Beyond their cognitive benefits, NAD^+ precursors exhibit a range of therapeutic effects, including improved mitochondrial function, reduced oxidative stress, and attenuated inflammation [6, 17]. These pleiotropic effects suggest that targeting the NAD^+ salvage pathway may offer a promising therapeutic strategy for mitigating age-related cognitive decline and neurodegenerative diseases. [15, 18, 19]. This systematic review aims to comprehensively assess the existing preclinical evidence on the neurocognitive effects of NAD^+ precursors in various disease models associated with cognitive dysfunction. Specifically, we will investigate the efficacy of different NAD^+ precursors, and explore the underlying molecular mechanisms of their neuroprotective effects.

Methods

Search strategy

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search was conducted across five electronic databases: PubMed, Web of Science, Embase, Scopus, and Google Scholar. The search encompassed published articles from inception to May 30, 2024. Keywords were developed using a combination of Medical Subject Headings (MeSH) terms and free-text terms. The search strategy included the following keywords:

("Aging"[Mesh]) OR "Cognitive Aging"[Mesh]) OR (("Alzheimer Disease"[Mesh]) OR ("Alzheimer's disease") OR (("Brain Injuries, Traumatic"[Mesh]) OR ("Traumatic brain injury").

OR (("Dementia, Vascular"[Mesh]) OR ("Vascular dementia") OR ((((("Diabetes Mellitus"[Mesh]) OR (Diabetes) OR (Diabetic)) AND ((((("Cognitive Dysfunction"[Mesh]) OR ("Cognitive Impairment") OR ("Cognitive decline") OR ("Cognitive function") AND (((((("Nicotinamide Mononucleotide"[Mesh]) OR "NAD"[Mesh]) OR (Nicotinamide) OR ("Nicotinamide adenine dinucleotide") OR ("Nicotinamide riboside").

Furthermore, the bibliographies of relevant articles were manually reviewed to identify additional studies. All search results were imported into EndNote X8 citation management software for further analysis.

Inclusion and exclusion criteria

Studies were included if they met the following criteria:

Investigated the effects of NAD^+ precursors (NAM, NR, NMN) compared to vehicle or no-treatment controls.

Evaluated cognitive function in rodent models of disease-related cognitive impairment.

Published in peer-reviewed journals.

Studies were excluded if they:

Utilized non-rodent models.

Were conducted in vitro.

Investigated non-relevant treatments.

Represented duplicates, reviews, theses, or books.

Data extraction and quality assessment

Two independent investigators screened titles/abstracts and subsequently assessed full-text articles. Disagreements between the investigators were resolved through discussion or consultation with a third senior researcher.

Data extraction focused on the following study characteristics:

Authors and year of publication.

Animal species and sex.

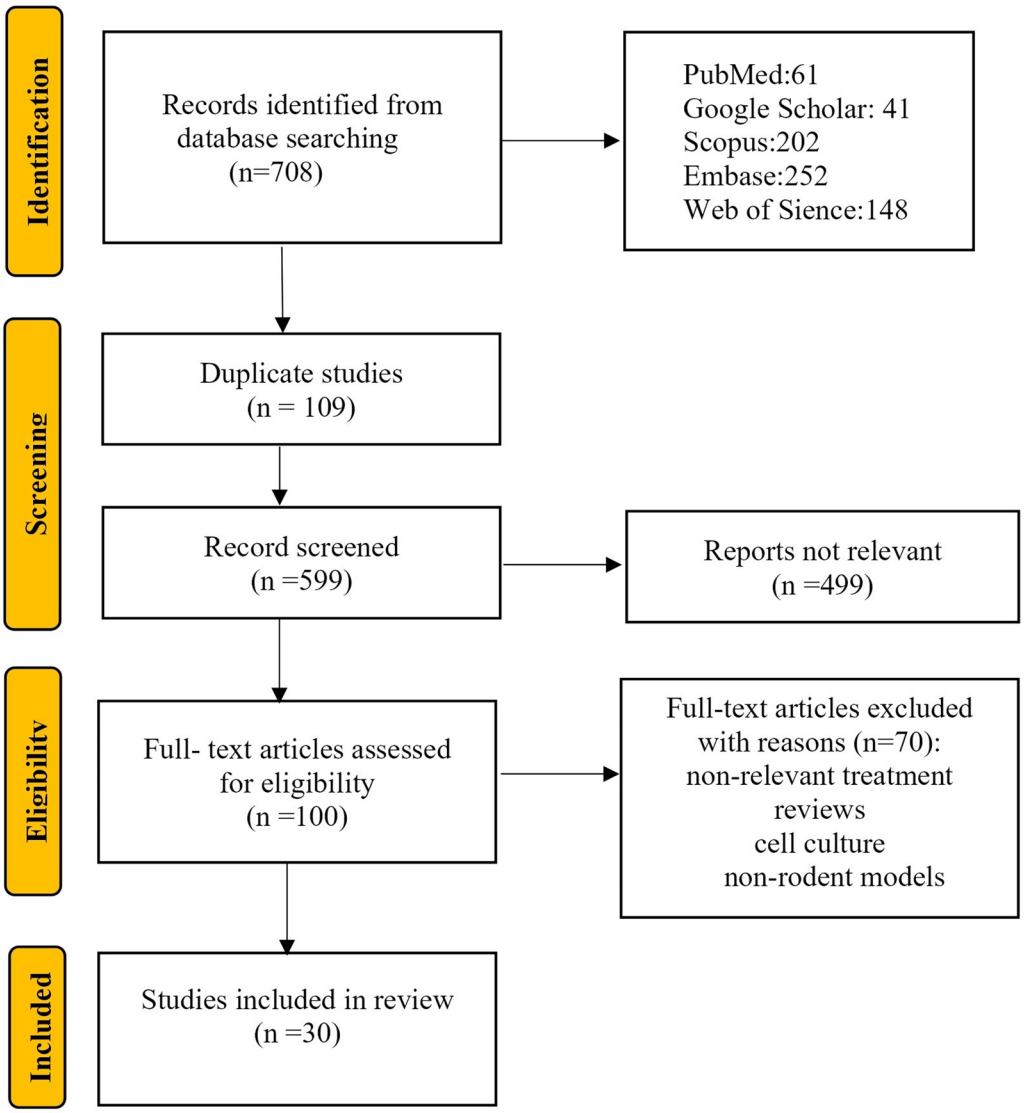

Fig. 1 Study flow diagram

Intervention characteristics (duration of treatment, dosage, and administration route).

Disease model used.

Key findings related to cognitive function.

The methodological quality of the included studies was assessed using the CAMARADES checklist. This checklist evaluates the following criteria:

Publication in a peer-reviewed journal.

Randomization to treatment or control groups.

Allocation concealment.

Blinded assessment of outcomes.

A clear statement of inclusion and exclusion criteria for animals.

Sample size calculation.

Statement of compliance with relevant regulatory requirements.

Declaration of potential conflicts of interest.

Results

Study selection

A comprehensive literature search yielded 708 articles. After removing duplicates and screening titles/abstracts, 608 studies were excluded. Subsequently,100 full-text articles were evaluated based on the predefined inclusion and exclusion criteria. Ultimately, 30 studies met the inclusion criteria and were included in this systematic review. A PRISMA flow diagram illustrating the study selection process is presented in Fig. 1. The

characteristics of the included studies are summarized in Table 1.

Quality of included studies

All included studies were published in peer-reviewed journals.70.63% of studies reported random allocation to treatment groups. 92.85% of studies reported compliance with animal welfare standards, 9.22% reported a blinded assessment of outcomes, and 6.84% explicitly stated the inclusion and exclusion criteria for animals. None of the studies reported sample size calculations. 73.21% of studies included a disclosure statement regarding potential conflicts of interest. The quality assessment results are summarized in Fig. 2.

Cognitive tests used in included studies

All included studies evaluated cognitive tests, commonly used as the MWM test. Nineteen studies evaluated MWM tasks [12, 15, 17, 18, 22–27, 30, 32–38, 42], 8 studies evaluated NOR test [6, 12, 21, 27–29, 39, 40], 4 studies evaluated the Y maze [12, 14, 18, 19], 4 studies evaluated passive avoidance test[25, 27, 31, 41], 3 studies evaluated Barnes [6, 39, 40] and fear conditioning test[12, 20, 28], 2 studies evaluated open field [24, 28] and EPM test [21, 28], and only one study used Radial arms water maze [21] to evaluate the cognitive domains (Table 2).

Description of the included studies

Aging

Of all included studies, six articles evaluated the aging process with different types of treatment. Three studies used NMN, and three different studies used NR, NADH, and NAM. In this group of diseases, the most frequently used cognitive test was the MWM test. The method of intervention in most of the studies was i.p., and the results showed that high doses of different NAD^+ precursors led to improvement in the cognition domains. In the Morris water maze (MWM), aging rats show a reduction in cognitive abilities and impaired motor functions. Treatment with NADH did not affect age-associated motor deficits, while NADH treatment (10, 50, and 100 mg/kg, i.p.) for 10 days improved the performance of old animals in the acquisition phase and of spatial probes in the MWM test [22]. KOPPEN, et al. reported that NAM increased the release of acetylcholine. Nevertheless, NAM did not improve learning or memory. They used just a single dosage of NMN (1.2 g/kg) and also the intervention was through s.c. injection. These factors could be the probable reason for no improvement in cognitive features [23]. Hosseini et al. evaluated the effect of NMN on cognition and mitochondrial dysfunction in aged rats. They reported that NMN therapy for 28 days with the dosage of 100 mg/kg, i.p. improved learning and memory impairment induced by aging and decreased mitochondrial dysfunction and the number of apoptotic cells in both the prefrontal cortex and hippocampus [6]. In a study performed by Tarantini et al., the administration of NMN (500 mg /kg, i.p) for two weeks had a protective effect on aging-induced microvascular endothelial dysfunction and cognitive dysfunction in mice [21]. This research highlights that the administration of NMN diminishes endothelial oxidative stress, improves endothelial function, and rescues neurovascular coupling responses. According to Xie et al., three months using 2.5 g/kg NR in food improved short-term spatial memory and inhibited body weight gain in aged mice. NR supplementation downregulated CD11b expression (a microglial marker) and GFAP in the subcortex of aged mice [28]. NMN treatment (300 mg/kg for 15 weeks) results in enhanced learning and memory, reduced oxidative stress and mitochondrial dysfunction, and decreased inflammation in SAMP8 mice [17].

Alzheimer's disease (AD)

Nine of the 30 studies assessed the effects of NAD^+ precursors on cognitive function in AD models. Four studies were used NAM, three were used NR, and NAM was used in two studies. In this group of diseases, the most frequently used cognitive test was the MWM test. The most frequently used intervention method was adding to drinking water.

In addition, NAM and NR were demonstrated to improve AD-related dementia by reducing β-amyloid (Aβ) generation and tau phosphorylation [18, 24, 28, 29]. Neuroinflammation and oxidative stress are known to be major contributors to AD pathogenesis. The results of the included articles showed that NAD^+ precursors abrogated Aβ-induced inflammation by suppressing c-Jun N-terminal kinase (JNK), poly (ADP-ribose) polymerase-1 (PARP-1), and glial cell activation [12, 18, 25]. JNKs participate in regulating various cellular mechanisms, such as gene expression, neuronal plasticity, regeneration, and cell death [43].

A study by Liu et al. [24] reported that long-term (eight months) NAM administration (40 μg/g, drinking water) could increase the time spent in the target quadrant and decrease goal latencies and path lengths in the MWM task, indicating improved learning and memory ability. They found that NAM treatment of 3xTgAD mice attenuated p-tau levels and Aβ accumulation in the cerebral cortex, CA1 region of the hippocampus, and subiculum [24]. NAM treatment reduced autophagosome accumulation by increasing lysosome/autolysosome acidification, which improved the autophagy-lysosome process. NAM has been shown to normalize mitochondrial dynamics and activate neuroplasticity-related kinases (p-Akt,

Table 1 Characteristics of the studies included in the systematic review

Author's	Species/sex	Diseases	Treatment	Duration	Dose/Route	Cognitive Behavioral tests	Findings
Tarantini et al. [21]	Male C57BL/6 Mice	Aging	NMN	14 days	500 mg /kg, i.p	Radial arms water maze, EPM, and NOR	Restoring endothelial NO mediation, mitochondrial oxidative stress ↓ and improved mitochondrial bioenergetics
Rex et a. [22]	Male Wistar Rat	Aging	NADH	10 days	10, 50, and 100 mg/kg, i.p	MWM	Cognitive function↑
Koppen et a. [23]	Male Wistar Rat	Aging	NAM	Single	1.2 g/kg, s.c	MWM	Did not improve learning and memory
Hosseini et al. [6]	Male Wistar Rat	Aging	NMN	28 days, every other day	100 mg/kg, i.p	Barnes maze and NOR tests	Memory impairment and apoptosis↓
Li et al. [17]	Male SAMP8 Mice	Aging	NMN	15 weeks	300 mg/kg	MWM	Decreased oxidative stress and mitochondrial dysfunction, learning and memory deficits, and inflammation
Liu et al. [24]	3xTgAD Mice	AD	NAM	8 months	40 µg/g, drinking water	MWM Open field	Increased levels of activated neuroplasticity-related kinases, and cognitive function↑
Yao et al. [25]	APPswe/PS1dE9 transgenic Mice	AD	NMN	Every other day for 28 days	100 mg/kg s.c	MWM and Passive Avoidance	Inhibited JNK activation, Aβ and cognition deficits↓
Vakilinezhad et al. [26]	Male Sprague–Dawley Rat	AD	NAM	Every other day	i.p	MWM	Cognition impairment ↓
Green et al. [27]	3xTg-AD Mice	AD	NAM	4 months	200 mg/kg. drinking water	MWM, NOR, and Passive Avoidance	Not affect Aβ pathology, Thr231, phosphorylated tau, and monoubiquitinated tau ↓, improve spatial learning
Rehman et al. [18]	Male C57BL/12N Mice	AD	NAM	7 days	250 mg/kg i.p	MWM and Y-Maze	Memory impairments ↓, oxidative stress ↓, neuronal cell, and inflammation ↓
Xie et al. [28]	Male Mice	AD	NR	3 months	2.5 g/kg food	Open field, Y-Maze test, EPM, NOR, and Fear-conditioning	Improved the short-term spatial memory of aged mice, and the contextual fear memory of AD mice, accumulation of Aβ ↓ and the migration of astrocytes to Aβ ↓, activation of astrocytes ↓, and elevation of serum NAMPT of aged mice
Gong et al. [29]	Tg2576 Mice	AD	NR	3 months	250 mg/kg, drinking water	NOR	NAD^+ and PGC-1a ↑, improved synaptic plasticity, BACE1 levels and Aβ production

Table 1 (continued)

Author's	Species/sex	Diseases	Treatment	Duration	Dose/Route	Cognitive Behavioral tests	Findings
Hou et al. [12]	Male and female adult Mice	AD	NR	6 months	12 mM in their drinking water	MWM, NOR, Y-Maze, and Fear-conditioning	Neuroinflammation, pTau,DNA damage, and synaptic dysfunction↓ and sirtuins activity↑
Wang et al. [30]	Male Wistar Rat	AD	NMN	10 days	500 mg/kg, i.p	MWM and Open field	Cognition function, neuron survival, and energy metabolism ↑ , ROS↓
Yang et al. [31]	Male Mice	VAD	NAM	0, 2, 6 or 12 h after the first and second injections of MPTP	500 mg/kg i.p	Step-down passive avoidance test and Step-through active avoidance test	Restored learning and memory
Zhao et al. [15]	Male Sprague–Dawley Rat	VAD	NAD^+	8 weeks	250 µg/g i.p	MWM	Cognitive deficits and neuroinflammation ↓
Peterson et al. [32]	Male Sprague–Dawley Rat	TBI	NAM	3 days	75 mg/kg, i.p	MWM	Diminished tissue loss in the injured cortex and ipsilateral
Hoane et al. [33]	Sprague–Dawley Rat	TBI	NAM	15 min, 4 h, or 8 h post-injury, followed by five boosters at 24 h intervals	50 mg/kg, i.p	MWM	Improved working memory
Swan et al. [34]	Male Sprague–Dawley Rat	TBI	NAM	Single dose after CCI	500 mg/kg or 50 mg/kg, i.p	MWM	NAM (50 mg/kg) appeared to have no effect, 500-mg/kg dose worsened performance, not reduce reactive gliosis and edema
Haar et al. [35]	Male Sprague–Dawley Rat	TBI	NAM	30 days	50 mg/kg s.c	MWM	Improved reference memory and decreased lesion size
Haar et al. [36]	Male Long-Evans Rat	TBI	NAM	Starting at 2 h post-surgery and then at 12, 24, 36, 48, 60 and 72 h	150 mg/kg, i.p	MWM	Improved retraining on the discrimination task
Shear et al. [37]	Male Sprague–Dawley Rat	TBI	NAM	15 min and 24 h after injury	50 or 500 mg/kg i.v	MWM	Reduced GFAP levelsand improve working memory
Hoane et al. [38]	Sprague–Dawley Rat	TBI	NAM	15 min and 24 h post-FPI	500 or 50 mg/kg; i.p	MWM	High dose prevented of behavioral deficits and decreased GFAP expression
Hao et al. [39]	Wistar Rat	Schizophrenia	NAM	30 days	100 mg/kg, i.p	NOR and Barnes maze test	IL-1β, TNF-α, and IL-6 expression, and microglial activation↓

Table 1 (continued)

Author's	Species/sex	Diseases	Treatment	Duration	Dose/Route	Cognitive Behavioral tests	Findings
Hao et al. [40]	Wistar Rat	Schizophrenia	NAM	30 days	100 mg/kg gavage	NOR and Barnes maze test	Neuronal apoptosis and microglial over-activation ↓ and cognition function↑
Hee Jae Lee and Soo Jin Yang. [19]	ICR Male Mice	Diabetes	NR	Six weeks	400 mg/kg, gavage	Y-Maze	Brain inflammation ↓ and Cognitive function↑
Jangra et al. [41]	Sprague–Dawley Rat	Diabetes	NAM	14 days	300 and 1000 mg/kg, s.c	Passive avoidance and open field	Oxidative stress–PARP overactivation ↓, Glutamate levels ↑, GABA levels ↓, ameliorated the reduction in hippocampal AChE level
Chandrasekaran et al. [14]	Male Sprague–Dawley Rat	Diabetes	NMN	3 months	100 mg/kg i.p	Y-Maze test	Memory impairment and hippocampal neurodegeneration ↓ and NAD^+ levels↑
Wang et al. [42]	Male Sprague–Dawley Rat	Hypoglycemia	NMN	7 days	500 mg/kg, i.p	MWM	Reduced neuronal cell death, cognitive impairment, ROS, PARP-1 activation, and increased NAD^+ and ATP levels

NR Nicotinamide riboside, *NMN* Nicotinamide mononucleotide, *NAM* Nicotinamide, *MWM* Morris water maze, *i.p* Intraperitoneally, *s.c* Subcutaneous, NAD^+ Nicotinamide adenine dinucleotide, *TBI* Traumatic brain injury, *i.v* Intravenously, *NOR* Novel object recognition, *VAD* vascular dementia, *ROS* Reactive oxygen species

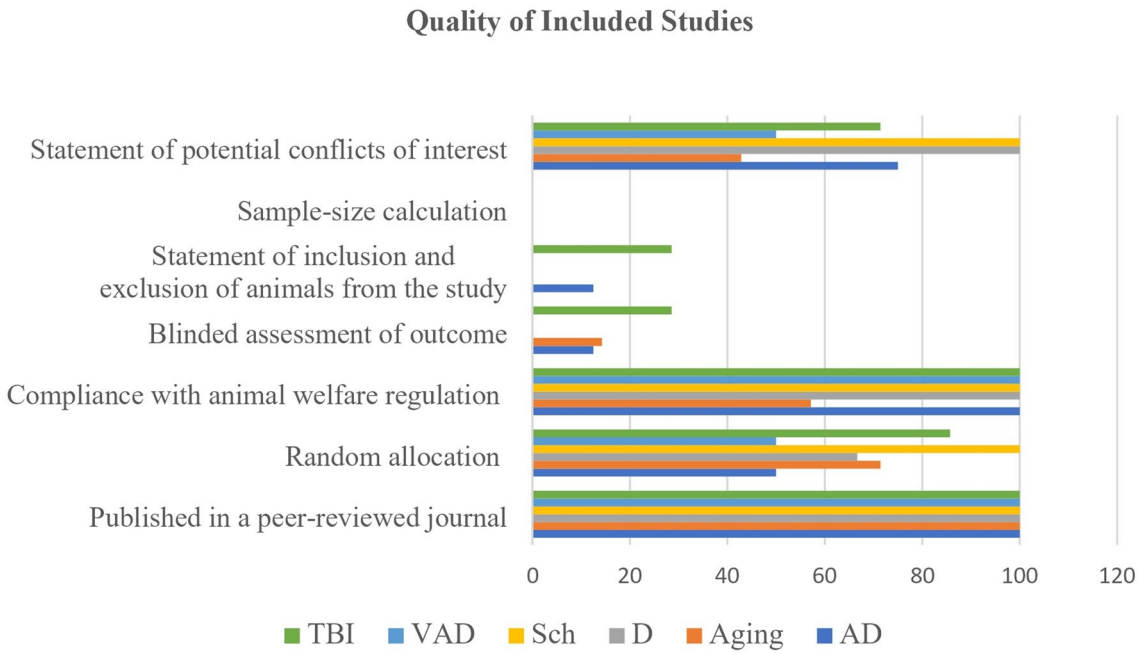

Fig. 2 Evaluation of the included studies based on the modified CAMARADES quality checklist. *AD* Alzheimer's disease, *TBI* Traumatic brain injury, *D* Diabetes, *VAD* Vascular dementia, *Sch* Schizophrenia

MAPK/ERK42, and cyclic AMP response element-binding protein [CREB]) and upregulate Sirt1protein levels [24].

According to Gong et al. [29], NR therapy (250 mg/kg, Drinking water) for 90 days decreased Aβ production and improved recognition memory performance in an AD mouse model through proliferator-activated receptor-γ coactivator 1α (PGC-1α) overexpression, increasing NAD^+ levels, β-secretase 1 degradation and the promotion of energy metabolism gene expression. In another study, Green et al. [27] reported that NAM treatment (200 mg/kg. drinking water) for four months resulted in a significant improvement in spatial memory and reduced contextual fear memory impairments without influencing Aβ pathology. In the novel object recognition test, there was no difference between the vehicle and the 3xTg-AD group that received NAM treatment in the same study. After NAM administration, Thr231-phosphorylated tau levels were decreased, and microtubule-associated protein 2c (MAP2c) expression was increased in 3xTg-AD mice [27]. Similarly, Hou et al. illustrated that although NR treatment (12 mM in their drinking water) for 6 months did not affect Aβ accumulation, p-tau pathology was reduced in AD mice. Impaired spatial learning, recognition, and working memories in AD mice are reversed by NR therapy for six months [12]. In a rat model of AD induced by STZ, NAM-loaded phosphatidylserine-solid lipid nanoparticles reduced tau hyperphosphorylation and ameliorated spatial learning and memory impairments [26]. Xie et al. reported that the NR regimen can improve contextual fear memory but not cue fear or short-term memories in APP/PSA1 mice [28]. A large number of GFAP-positive cells were observed in the cortex of APP/PS1 mice without NR treatment. Surprisingly, NR reversed the decrease in the density of GFAP-positive cells in the hippocampal CA1 region of APP/PS1 mice [28]. Additionally, in the dentate gyrus and cortex, the NR did not affect the density of IBA1-positive cells. Xie et al. [28] also reported that supplementation with NR inhibited Aβ accumulation in the cortex of AD mice.

According to a study performed by Yao et al. [25], NMN treatment (100 mg/kg, s.c.) administrated every other day for 28 days is capable of reversing learning deficits, noticeably lowering proinflammatory cytokines, and ameliorating synaptic loss in transgenic AD mice at least partially through the inhibition of JNK activation. Similarly, another study revealed that NMN restored cognition in AD animals [37]. Rehman and colleagues reported that NAM treatment (250 mg/kg, i.p) for 7 days counteracted memory deficits and attenuated Aβ1–42 elevation, p-JNK levels, neuroinflammation, apoptotic marker proteins, and oxidative stress in adult mouse brains [18]. In the study conducted by Wang et al., they showed that in AD model rats, treatment of intracerebroventricular Aβ oligomer with NMN (500 mg/kg, i.p.) led to sustained

Table 2 The effects of different NAD^+ precursors on cognitive domains

Study	Diseases	Treatment	Working, Spatial and long-term memory	Learning capacity	Recognition memory	Anxiety	Contextual memory
Dan et al. [20]	Aging	NR					Fear context discrimination
Tarantini et al. [21]	Aging	NMN	Radial arms water maze	EPM	NOR		
Rex et al. [22]	Aging	NADH	MWM				
Koppen et al. [23]	Aging	NAM	MWM				
Hosseini et al. [6]	Aging	NMN	Barnes		NOR		
Li et al. [17]	Aging	NMN	MWM				
Liu et al. [24]	AD	NAM	MWM			Open field	
Yao et al. [25]	AD	NMN	MWM				Passive Avoidance
Vakilinezhad et al. [26]	AD	NAM	MWM				
Green et al. [27]	AD	NAM	MWM		NOR		Passive Avoidance
Rehman et al. [18]	AD	NAM	MWM, Y-Maze				
Xie et al. [28]	AD	NR	Y-Maze		NOR	Open field and EPM	Fear-conditioning
Gong et al. [29]	AD	NR			NOR		
Hou et al. [12]	AD	NR	MWM, Y-Maze		NOR		Fear-conditioning
Wang et al. [30]	AD	NMN	MWM				
Yang et al. [31]	VAD	NAM					Passive Avoidance
Zhao et al. [15]	VAD	NAD^+	MWM				
Peterson et al. [32]	TBI	NAM	MWM				
Hoane et al. [33]	TBI	NAM	MWM				
Swan et al. [34]	TBI	NAM	MWM				
Haar et al. [35]	TBI	NAM	MWM				
Haar et al. [36]	TBI	NAM	MWM				
Shear et al. [37]	TBI	NAM	MWM				
Hoane et al. [38]	TBI	NAM	MWM				
Hao et al. [39]	Schizophrenia	NAM	Barnes maze test		NOR		
Hao et al. [40]	Schizophrenia	NAM	Barnes maze test		NOR		
Hee Jae Lee and Soo Jin Yang. [19]	Diabetes	NR	Y-Maze				
Jangra et al. [41]	Diabetes	NAM					Passive Avoidance
Chandrasekaran et al. [14]	Diabetes	NMN	Y-Maze				
Wang et al. [42]	Hypoglycemia	NMN	MWM				

NR Nicotinamide riboside, *NMN* Nicotinamide mononucleotide, *NAM* Nicotinamide, *MWM* Morris water maze, NAD^+ Nicotinamide adenine dinucleotide, *TBI* Traumatic brain injury, *NOR* Novel object recognition, *MWM* Morris water maze

improvement in cognitive function as measured by the Morris water maze [30].

In individuals with AD, there is a notable increase in the expression and activation of JNK3 in both brain tissue and cerebrospinal fluid [44]. JNK is activated by Aβ peptides and is correlated with cognitive loss. It has been demonstrated that in AD mice, genetic depletion of JNK3 leads to a decrease in Aβ42 peptide levels and an increase in the number of neurons and ameliorates cognitive dysfunction [45].

A growing body of research indicates that the generation of Aβ and p-tau and mitochondrial dysfunction are finally triggered by oxidative stress, resulting in neuronal damage and cognitive deficits [46]. In both the cortex and hippocampus of the mouse brain, NAM significantly increased Nrf2/HO-1 levels, which were initially suppressed by Aβ1–42. These findings highlight the antioxidative potential of NAM [18]. Besides, studies conducted on AD animals have demonstrated a decrease in reactive oxygen species (ROS) levels following treatment with NA or NMN [47]. NAM has been found to increase the activity of antioxidant enzymes and decrease MDA in both the prefrontal cortex and hippocampus [47]. Research has revealed that NMN

treatment can improve the balance of fission and fusion (mitochondrial dynamics) in nerve cells affected by AD [48].

Traumatic brain injury (TBI)

All seven included studies in the TBI model used NAM as treatment and for cognitive assessment, all used the MWM test. The most frequently used NAM intervention method was i.p. [49]. NAM has been found to improve memory and cognition in TBI animals [32, 33, 38, 50]. However, several studies reported contrary results [34, 35, 37], which may be related to injury location, administration method, and/or dose of the drug.

One study investigated the preclinical efficacy of NAM following unilateral cortical contusion injury (CCI) in middle-aged rats. They reported that the injection of 50 mg/kg NAM at 1 h and 24 h following injury had no effect. In addition, 500 mg/kg NAM worsened cognitive performance. NAM treatment did not significantly diminish reactive gliosis or the blood–brain barrier and did not affect injury size at acute time points. Their findings showed low efficacy of NAM administration following TBI in middle-aged rats and suggested conducting future studies on more aged TBI animal models [34]. Haar et al. reported that NAM administration (50 mg/kg) for seven days could improve behavioral recovery and reduce lesion size following TBI [35]. In another study, they found that administration of NAM (150 mg/kg) improved reference memory [36]. Shear et al.[37] reported that low-dose NAM (50 mg/kg, 15 min and 24 h after injury) had no significant effect on cognitive function, but high-dose NAM improved motor function and reduced tissue injury in a CCI model of TBI. In addition, NAM (500 mg/kg) improved working memory and reduced GFAP levels [37]. Similarly, NAM (500 mg/kg, 15 min and 24 h after injury) downregulated GFAP expression in the hippocampus and cortex of TBI rats. Moreover, high-dose NAM had a preventive effect on behavioral deficits [38].

According to the findings of Peterson et al., treatment with NAM (75 mg/kg) combined with continuous infusion for 3 days at 4 h post-CCI improved reference memory acquisition and reversal learning in the MWM test compared with the vehicle group. NAM therapy can also decrease tissue loss in the ipsilateral hippocampus and cortex [32]. Hoane et al. [33] investigated the effects of the NAM regimen (50 mg/kg, i.p.) at 15 min, 4 h, or 8 h after injury, followed by five boosters at 24 h intervals in TBI rats. NAM treatment (at either the 15-min or 4-h time points) meaningfully improved the performance of a reference memory task and working memory and preserved cortical tissue loss.

Diabetes

Among the retrieved articles, two investigated the effect of NMN (i.p), and two different studies investigated NR (gavage), and NAM (s.c.) on cognitive function. Chandrasekaran et al.[14] reported that in diabetic rats, NMN treatment (100 mg/kg, i.p.) for three months prevented neuronal loss, elevated brain NAD^+ triggered the Sirt1 pathway, maintained mitochondrial oxidative phosphorylation function, and preserved cognitive function. A study by Lee and colleagues revealed that 6 weeks of NR treatment (400 mg/kg, stomach gavage) improved spatial recognition memory and locomotor activity in diabetic mice, as evaluated by the Y-maze and construction tests. NR supplementation can prevent hyperglycemia-related dementia by suppressing neuroinflammation and amyloidogenesis [19]. Another study reported that 14 days of treatment with NAM (300 and 1000 mg/kg, P.O) decreased the time running on the rotarod, increased the avoidance response, and improved supported and unsupported rears in comparison with those in the diabetic group. This study also revealed that NAM reduced GABA and malondialdehyde levels and elevated NAD and glutamate levels and acetylcholinesterase activity in the hippocampus of diabetic rats [41].

In diabetic patients, the dangerous side effects of insulin therapy and hypoglycemia-induced brain injury are common. While maintaining blood glucose control helps reduce the risk of diabetes-related complications, it also substantially increases the likelihood of severe hypoglycemia [51], which triggers a cascade of events such as oxidative stress and the activation of PARP-1 in neurons. These events cause neuronal death and cognitive deficits even after glucose is restored to normal levels. ROS production leads to DNA damage and activation of PARP-1, causing a depletion of NAD^+ and ATP, ultimately resulting in brain damage [52]. Wang et al. [42] reported that the administration of NMN (500 mg/kg, i.p.) for seven days resulted in a reduction in spatial learning and memory deficits caused by severe hypoglycemia. Additionally, it decreased ROS generation, suppressed the activation of PARP-1, and restored the NAD^+ and ATP levels in the hippocampus. Decreased hippocampal long-term potentiation was significantly recovered in the rats treated with NMN.

In diabetes, oxidative stress can induce PARP overactivation, ultimately activating proinflammatory signals and altering neurotransmitters. Overactivation of PARP attenuates NAD^+ and ATP levels, resulting in energy failure and apoptosis [53]. On the other hand, less ATP causes a decrease in the amount of glutamate released as a result of depolarization. Alterations in GABA-glutamate homeostasis are potential factors contributing

to cognitive deficits and impairments in avoidance responses in diabetic animals [54]. The neuroprotective effect of NAM is attributed to the inhibition of oxidative stress–PARP overactivation in diabetic animals [41]. NR treatment reduced NLRP3 and proinflammatory cytokines, including IL-1, TNF-α, and IL-6, in the brains of diabetic mice [19].

Vascular dementia (VAD)

Two of the 30 studies assessed the effects of NAM in VAD. Yang and colleagues studied the effects of the intraperitoneal administration of 500 mg/kg NAM on 1-methyl-4-phenyl-l,2,3,6-tetrahydropyridine (MPTP)-induced learning and memory impairment in mice. Improvements in learning and memory deficits were observed in MPTP-treated mice treated with NAM 2 h after the second MPTP injection [31]. Zhao et al. [15] conducted an animal study to examine the neuroprotective effects of NAD^+ in male rats with VAD caused by chronic cerebral hypoperfusion (CCH). Treatment with NAD^+ (250 μg/gi.p) for two months mitigated cognitive deficits and alleviated microglial activation, proinflammatory factor expression, and neuronal death in CCH models. Besides, NAD^+ attenuated ROS generation and mitochondrial damage via activation of the Sirt1/PGC-1α pathway. Additionally, NAD^+ ameliorated neuronal damage in the cortex and hippocampal area, resulting in improved cognitive function [15]. Both of the included studies used the i.p. method for treatment intervention.

Schizophrenia

Two investigations focused on the impact of NAM on cognitive impairments related to schizophrenia. The findings demonstrated that NAM administration significantly reduced microglial inflammation and neuronal apoptosis through the NAD^+-Sirt3-superoxide dismutase 2 (SOD2) pathway in a model of schizophrenia-like behavior induced by maternal separation [40]. Furthermore, NAM improved recognition and remote memories in schizophrenic mice [39]. Both include studies used NAM with the same dosage with different intervention methods.

Discussion

This systematic review provides evidence for the effectiveness of NAD^+ precursors in improving both behavioral and neuroprotective outcomes related to cognitive impairments in different diseases. The current review shows that treatment with the mediator NAD^+ increased spatial memory [12, 24–27], contextual learning, and freezing behavior [12, 28] in rodents. Our study indicated that most of the studies used NAM (n = 19), followed by NMN (n = 9), NR (n = 6), NAD^+ (n = 1), and NADH (n = 1) treatment for investigating cognitive function. Also, the results showed that the most frequently used cognitive test was the MWM test. Of the included studies, the number of AD articles was higher than other mentioned diseases.

NAD^+ serves as an essential coenzyme that plays a pivotal role in numerous cellular functions, such as energy metabolism, DNA repair, and cellular signaling. The decline in NAD^+ levels has been implicated in age-related cognitive decline and neurodegenerative diseases. Supplementation with NAD^+ precursors, such as NR and NMN, has emerged as a promising strategy to enhance NAD^+ levels and promote cognitive recovery [27]. NAD^+ is essential for the functioning of mitochondrial enzymes involved in oxidative phosphorylation, the primary pathway for ATP production. By increasing NAD^+ availability through supplementation with its precursors, mitochondrial function is enhanced, leading to improved ATP synthesis. This increase in energy availability supports neuronal health and function, which is crucial for cognitive processes [29]. Elevated levels of NAD^+ can activate sirtuins, a family of NAD^+-dependent deacetylases that play a protective role against oxidative stress. Sirtuins help regulate antioxidant defenses by modulating the expression of genes involved in the cellular stress response. By enhancing the antioxidant capacity of neurons, NAD^+ precursors can mitigate oxidative damage, which is often associated with cognitive impairments [55]. Moreover, chronic inflammation in the brain is a hallmark of many neurodegenerative diseases. NAD^+ precursors may help reduce neuroinflammation by promoting the activity of sirtuins and other signaling pathways that regulate inflammatory responses. This reduction in inflammation can lead to a more favorable environment for neuronal survival and function, thereby supporting cognitive recovery [56].

NAD^+ plays a pivotal role in DNA repair mechanisms, particularly in response to oxidative damage. By increasing NAD^+ levels, precursors can enhance the activity of PARPs, which are involved in detecting and repairing DNA strand breaks. Effective DNA repair is critical for maintaining neuronal integrity and function, especially in aging and neurodegenerative conditions [56]. NAD^+ also influences various signaling pathways that are crucial for synaptic plasticity—the ability of synapses to strengthen or weaken over time, which is essential for learning and memory. By enhancing NAD^+ levels, precursors may facilitate synaptic remodeling and improve cognitive functions that are often impaired in neurodegenerative diseases [56]. In summary, NAD^+ precursors enhance mitochondrial function and reduce oxidative stress and inflammation—critical factors that contribute to cognitive impairments in various diseases. This multifaceted

approach underscores the therapeutic potential of NAD^+ precursors in promoting brain health and cognitive recovery.

NAD^+ precursors and age-related cognitive decline

The aging process is associated with a progressive decline in brain function, which manifests as impairments in memory, learning, exploration, coordination, and motor abilities. These phenomena heighten the vulnerability of the aging brain to neurodegenerative disorders and stroke [36]. Age-related cognitive deficits are a tremendous public health and socioeconomic burden and hence a major problem for health systems [57].

A large body of evidence has shown that working, reference, and recognition memories are disrupted in aged rodents [58–60]. The functions of the CNS are closely linked to energy metabolism in neurons. Aging progression leads to decreased NAD^+ levels, which causes mitochondrial dysfunction. Mitochondrial disturbances are associated with a wide spectrum of human illnesses, including neurodegenerative diseases and aging [61]. Aging causes alterations in the morphology and function of mitochondria, as well as a decrease in the activity of proteins and enzymes and a reduction in biogenesis, which consequently impairs the oxidative phosphorylation system [62]. In addition, aging promotes neuronal apoptosis and inflammation [63].

Numerous studies have investigated the effects of NAD^+ precursors on cognitive function in animal models of aging. The results of these studies suggest that NAD^+ precursors may have beneficial effects on cognitive function in aged animals. For example, a study by Xie et al. demonstrated that the administration of 2.5 g/kg NR in the diet for three months led to improvements in short-term spatial memory and a reduction in body weight gain among aged mice. Additionally, the supplementation of NR resulted in a downregulation of CD11b and GFAP expression in the subcortex of aged mice [28].

NAD^+ precursors and AD

AD is a neurodegenerative disorder that advances with age, characterized by pathological neuroinflammation, neuronal loss, and impaired cognitive function that severely affects daily living. Its characteristic pathological features are Aβ plaque deposition and neurofibrillary tangle (NFT) accumulation [64]. Several studies have investigated the effects of NAD^+ precursors on cognitive function in AD models. The results of these studies suggest that NAD^+ precursors may have beneficial effects on cognitive function in AD animals. For example, a study by Liu et al. [24] reported that long-term (eight months) NAM administration (40 μg/g, drinking water) could increase the time spent in the target quadrant and decrease goal latencies and path lengths in the MWM task, indicating improved learning and memory ability. They found that NAM treatment of 3xTgAD mice attenuated p-tau levels and Aβ accumulation in the CA1 region of the hippocampus, subiculum, and cerebral cortex [24].

NAD^+ precursors and TBI

TBI has become a main cause of mortality and long-term disability among young adults and children in developed countries. The pathology of TBI includes primary and secondary injuries characterized by cellular and biochemical processes, including neuroinflammation, autophagy, impaired mitochondrial function, and apoptosis [65]. Impairments in cognitive function are primary contributors to the disability and decreased quality of life of TBI survivors [65].

Several studies have investigated the effects of NAD^+ precursors on cognitive function in TBI models. The results of these studies suggest that NAD^+ precursors may have beneficial effects on cognitive function in TBI animals. For example, a study by Peterson et al. [32] found that treatment with NAM (75 mg/kg) combined with continuous infusion for 3 days at 4 h post-CCI improved reference memory acquisition and reversal learning in the MWM test compared with the vehicle group. NAM therapy can also decrease tissue loss in the ipsilateral hippocampus and cortex [32].

NAD^+ precursors and Diabetes

Diabetes is linked to lower brain NAD^+ levels and predisposes to cognitive decline that leads to dementia [14]. Several studies have investigated the effects of NAD^+ precursors on cognitive function in diabetic animals. The results of these studies suggest that NAD^+ precursors may have beneficial effects on cognitive function in diabetic animals. For example, a study by Chandrasekaran et al. [14] reported that in diabetic rats, NMN treatment (100 mg/kg, i.p.) for three months prevented neuronal loss, elevated brain NAD^+ triggered the Sirt1 pathway, maintained mitochondrial oxidative phosphorylation function, and preserved cognitive function [14].

NAD^+ precursors and VAD

Dementia is an irreversible disease that leads to a progressive decline in cognitive function. It has emerged as a significant health concern. VAD is the second most common cause of dementia during aging after AD. VAD is characterized by cognitive decline resulting from hemorrhagic or ischemic brain lesions due to vascular disease [66]. The pathogenic mechanisms of VAD are unclear, but they appear to be associated with several conditions, including oxidative stress, inflammation, disruption of

zinc homeostasis, cholinergic hypofunction, and neurovascular unit destruction [67, 68].

Limited studies have investigated the effects of NAD^+ precursors in VAD models. Yang and colleagues studied the effect of NAM on MPTP-induced learning and memory impairment in mice, observing improvements in cognitive function [31]. Zhao et al. [15], examined the neuroprotective effects of NAD^+ in a rat model of CCH, demonstrating that NAD^+ treatment mitigated cognitive deficits, alleviated microglial activation and neuroinflammation, and attenuated oxidative stress and mitochondrial damage through activation of the Sirt1/PGC-1α pathway [15]. These findings suggest that NAD^+ precursors may offer potential therapeutic avenues for mitigating cognitive decline in VAD. However, further research is needed to confirm these findings in larger studies and translate them to clinical settings.

Schizophrenia

Two studies evaluated the effects of NAM on schizophrenia-induced cognitive deficits. NAM administration reduced microglial inflammation and neuronal apoptosis via the NAD^+-Sirt3-SOD2 pathway in a model of maternal separation-induced schizophrenia-like behavior [40]. Moreover, NAM improved recognition and remote memories in schizophrenic mice [39]. These findings suggest that NAM may have potential therapeutic benefits in ameliorating cognitive impairments associated with schizophrenia. However, further research is needed to elucidate the underlying mechanisms and determine the optimal dosage and treatment regimen for clinical translation.

Conclusions

The findings of this systematic review suggest that nicotinamide could attenuate cognitive impairments through the prevention of ATP depletion by elevating NAD^+ levels, attenuating apoptosis, and reducing mitochondrial dysfunction, inflammation, and oxidative stress. The supplementation of NAD^+ precursors can enhance mitochondrial function, reduce oxidative stress and inflammation, improve DNA repair mechanisms, and support synaptic plasticity. These interconnected pathways contribute to cognitive recovery and highlight the potential of NAD^+ precursors as therapeutic agents for enhancing brain health.

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M.A.Q, L.H, F.F, F.O, and N.A contributed to the screening and quality assessment of studies and data extraction. L.H contributed to the literature review and wrote the article. L.M.N, H.S.P, and R.N.S provided critical revision and final approval of the finalized manuscript. All authors have read and approved the final manuscript.

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Data availability
The data from this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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