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REVIEW

Safety and efficacy of sodium oligomannate in patients with Alzheimer's disease: a systematic review and meta-analysis

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Abstract

Background We aim to evaluate the efficacy and safety of a new marine oligosaccharide drug, sodium oligomannate (GV-971), developed in China to treat Alzheimer's disease (AD).

Methods We researched the following databases: Embase, Web of Science, PubMed, Cochrane library, and Scopus until Sep 2022. We used the Cochrane risk of bias tool to assess the risk of bias and the GRADE scale to assess the quality of the evidence. The meta-analysis was performed using review manager 5.4.

Results We included three randomized controlled trials with 1108 patients. Sodium oligomannate improved the AD assessment scale-cognitive subscale compared to the placebo at 12, 24, and 36 weeks (mean difference (MD) = − 0.69, 95% confidence interval (CI) [− 1.23 to − 0.14], $p = 0.01$), (MD = − 0.68, 95% CI [− 1.26 to − 0.10], $P = 0.02$), and (MD = − 3.84, 95% CI [− 6.40 to − 1.27], and $P = 0.003$), respectively. On the other hand, results showed no significance in terms of adverse events and other assessed scales (Clinician's Interview-Based Impression of Change with caregiver input, AD Cooperative Study-Activities of Daily Living, and Neuropsychiatric Inventory) ($p > 0.05$).

Conclusions Sodium oligomannate is a well-tolerated and promising drug for Alzheimer's patients. However, to better evaluate sodium oligomannate's efficacy in the clinical setting, we need more randomized controlled trials with larger samples and higher quality.

Keywords Sodium oligomannate, GV-971, Alzheimer's disease, Meta-analysis

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that affects older adults. At the beginning of the disease, it is characterized by the inability to store or encode new information and memories. After that, the behaviors and cognitions abilities decline progressively [1]. According to World Health Organization, in 2012, about 36 million people lived with dementia. Moreover, dementia will affect about 115 million people by 2050. AD is the most common cause of dementia [2]. On the other hand, in the United States, AD was estimated to cost $ 305 billion in 2020 [3]. Moreover, caregivers of AD patients suffer from many psychological problems, such as anxiety, sleep problems, and depression [4].

The pathophysiological mechanism of AD is not precise. But the amyloid hypothesis explained the mechanism by the imbalance between Aβ production and clearance, which leads to sequential cleavage of the

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amyloid protein by the γ and β [5]. Unfortunately, in the last decade, the drug targeting the main problem, such as amyloid deposition and tau protein, showed minimal relevant clinical efficacy [6–8]. On the other hand, several medications were investigated to treat AD, but only four were approved [9–12]. According to Cui et al., donepezil improved cognitive dysfunction, and it was better than all other AD medications, but it failed to stop the progression of the disease. Therefore, there has been no effective treatment till now.

A new marine oligosaccharide drug, sodium oligomannate (SO) (GV-971), was developed at the Shanghai Institute of Materia Medica, China [13]. It inhibits the neurotoxicity of Aβ aggregation by inhibiting Aβ accumulation and declines the polymerization of the Aβ [14]. In addition, a small amount of SO can enter the brain and directly block the development of Aβ fibrils while destabilizing already-produced fibrils into nontoxic molecules [15, 16].

This systematic review and meta-analysis aim to collect all information available about SO efficacy and safety. Furthermore, as the SO was only used in China, our work may have a role in reconsidering the drug for trials from other countries and increasing the available evidence.

Methods

We performed this systematic review and meta-analysis depending on the recent updates of the PRISMA statement and Cochrane guidelines [17, 18].

Literature search and data collection

Our research was conducted until 18/9/2022 using the following databases: Embase, PubMed, Cochrane library, Scopus, and Web of Science. Our research term was ("Sodium oligomannate" OR "Sodium oligo-mannurarate" OR "GV-971") AND ("Alzheimer Syndrome" OR "Alzheimer-Type" OR ATD OR "Alzheimer Type" OR "Alzheimer Dementia" OR "Alzheimer's Disease" OR "Alzheimer Sclerosis" OR "Alzheimer Disease" OR "Alzheimers Disease" OR "Familial Alzheimer Disease" OR FAD).

Studies selection and eligibility criteria

Randomized control trials (RCTs) were only included in our research with the following criteria (1) population: patients with AD; (2) intervention: sodium oligomannate; (3) comparator: placebo; (4) outcomes: safety and efficacy outcomes as listed below. After the research was done, first, we removed the duplicates using EndNote. After that, we performed title and abstract screening, followed by the full-text screening based on our eligibility criteria. Moreover, the references of the included studies were reviewed by two independent reviewers for any

missed relevant articles. Two authors have done these steps, and a third reviewer resolved any conflicts between both authors.

Quality assessment

The Cochrane risk of bias tool (version 1) has evaluated our included studies [19]. The following domains make up this tool: (1) detection selection bias and other biases; (2) allocation of arms; (3) participant and investigator blinding; (4) assessment of outcomes and their blinding; and (5) randomization of the population. The possibility of bias in judgment can be a high, low, or ambiguous risk of bias. We used the grading of recommendations assessment, development and evaluation (GRADE) methodology (GRADEpro, version 20. McMaster University, 2013) to assess the quality of evidence of the analyzed outcomes [20].

Data extraction

We retrieved the data in an Excel sheet. The extraction sheets contained the following: (1) summary data: study arms, trial registration, inclusion criteria, main outcomes. (2) baseline characteristics of the selected population: age, gender, education, disease time, Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS cog), the Clinician's Interview-Based Impression of Change with caregiver input (CIBIC+), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), and Neuropsychiatric Inventory (NPI). (3) outcomes: adverse events, ADAS cog, CIBIC+, ADCS-ADL, and NPI.

Data synthesis

Data synthesis was done using Review Manager software version 5.4. We reported risk ratios (RR) and 95% confidence intervals (95% CI) in case the data were dichotomous. If the data were continuous, we mentioned mean differences (MD) and 95% CI. Heterogeneity was tested using the I-square test (I^2) and the Chi-square test. The difference was reported as significant if the p-value < 0.5. According to heterogeneity, the studies were considered heterogeneous if the p-value of Chi-square was < 0.1 and the I^2 value was above 50%. If the data were heterogeneous, we pooled them in the random effects model, while for homogeneous data pooled them in the fixed effect model. Finally, we performed a subgroup analysis for ADAS cog based on the follow-up periods.

Results

Literature search and study selection

Relied on our strategy for strategy, we found 46 articles after removing duplicates. After title and abstract screening, four studies were available for full-text screening.

Then, three studies met our inclusion criteria and were suitable for the quantitative analysis (Fig. 1).

Study characteristics

We included three RCT articles [21–23] with a total sample size of 1108 participants, 603 (54.4%) individuals received SO, whereas 505 (45.6%) received placebo or donepezil. All studies were conducted in China. The SO dose differed between studies from 450 mg to 600 and 900 mg twice daily. Most of the patients were females, and the mean age was between 60 and 70 in all groups (Table 1).

The quality of the included studies

Two studies had a low risk of bias [22, 23]. However, Zhang et al. [21] were unclear regarding performance and detection biases with a high risk of other biases (Fig. 2). The GRADE tool revealed very low to moderate overall evidence quality (Additional file 1).

Outcomes

Adverse events

All studies [21–23] were pooled in this outcome, and the total sample size was 1108. The results showed no significant difference in adverse events between the SO group and the placebo group (RR=0.79, 95% CI [0.61–1.03],
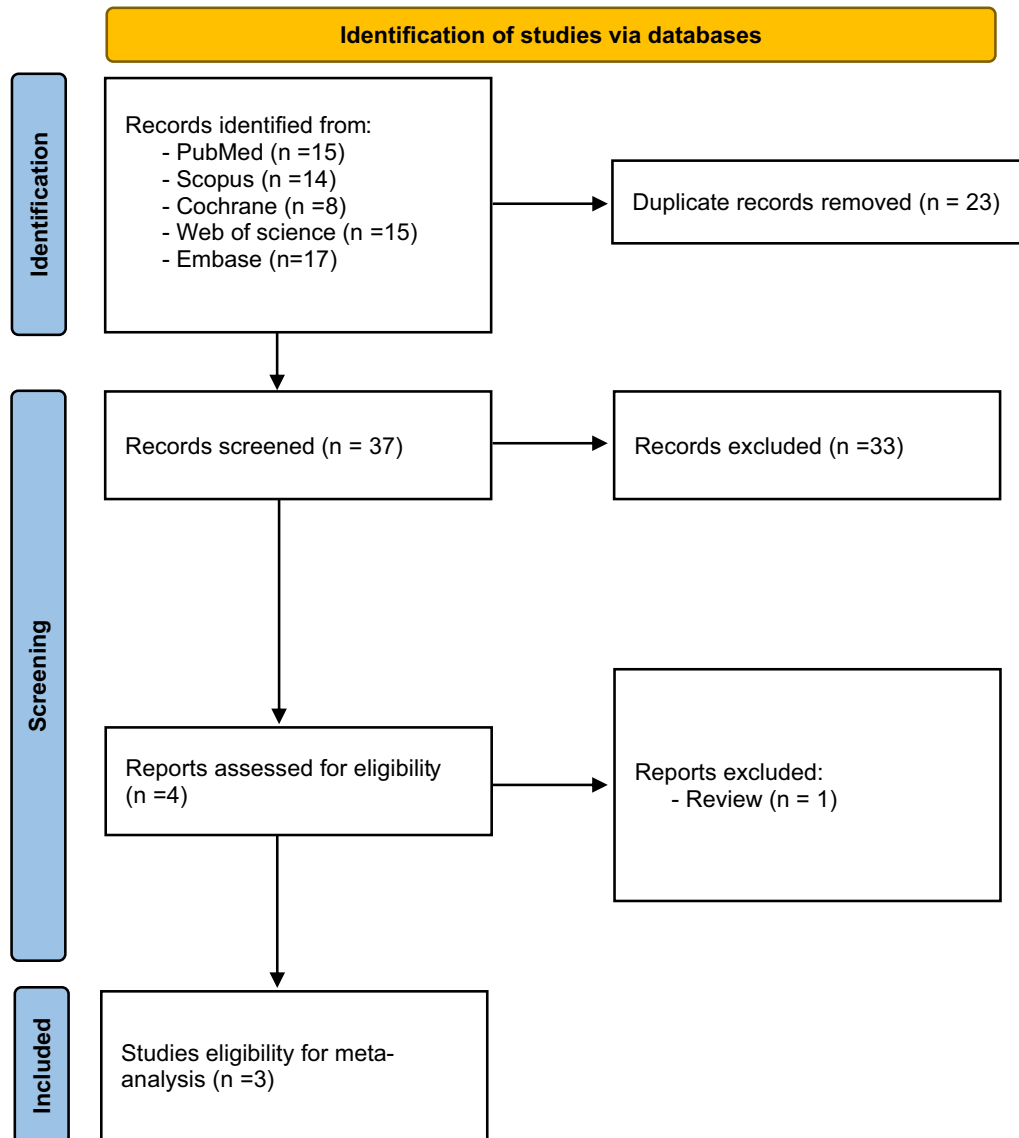

Identification of studies via databases

Identification

Records identified from:
- PubMed (n =15)
- Scopus (n =14)
- Cochrane (n =8)
- Web of science (n =15)
- Embase (n=17)

Duplicate records removed (n = 23)

Screening

Records screened (n = 37)

Records excluded (n =33)

Reports assessed for eligibility (n =4)

Reports excluded:
- Review (n = 1)

Included

Studies eligibility for meta-analysis (n =3)

Fig. 1 PRISMA flowchart

Table 1 Summary and baseline characteristics

ID	Trial registration	Inclusion criteria	Main outcomes	Study arms	Sample size	Age, years	Male	Education, years	Disease time, months	ADAS-Cog	ADCS-ADL	CIBIC-plus	NPI
Zhang et.al 2022 [21]	H20190031	1. Age > 18 y old 2. Meet the AD diagnostic criteria of NINCDS-ADRDA 3. Mild-to-moderate cognitive impairment (10 ≤ MMSE score < 27)	Change in ADAS-Cog, ADL, CIBIC-plus, NPI, and adverse events	Sodium oligomannate 450 mg BID	36 (50)	67.67 ± 4.92	16 (44.44)	NR	44.04 ± 18.6	37.22 ± 11.96	90 ± 7.07	19.67 ± 6.60	11.67 ± 4.78
				Donepezil 5 mg QD	24 (33.33)	70 ± 6	16 (66.67)		42 ± 30	46 ± 6	62.5 ± 22.5	17.5 ± 0.5	13 ± 3
				Placebo	12 (16.67)	64.33 ± 7.59	4 (33.33)		15 ± 9	40 ± 10	85 ± 15	9 ± 1	3.5 ± 0.5
Xioa et.al 2021 [22]	NCT02293915	1. Aged 50–85y 2. Met the diagnostic criteria for probable AD of NINCDS-ADRDA 3. Mild-to-moderate AD, with an MMSE score from 11 to 22	Change in ADAS-Cog, ADL, CIBIC-plus, NPI, and adverse events	Sodium oligomannate 450 mg BID	408 (49.87)	69.6 ± 8.12	173 (42.4)	a. > 6y, 337(82.6) b. ≤ 6y, 711(17.4)	30.42 ± 20.59	21.28 ± 10.14	64.0 ± 11.2	NR	5.6 ± 8.0
				Placebo	410 (50.13)	69.7 ± 8.20	177 (43.2)	a. > 6y, 335(81.7) b. ≤ 6y, 75(18.3)	31.46 ± 20.79	20.88 ± 10.00	64.2 ± 10.1		5.9 ± 8.6

Table 1 (continued)

ID	Trial registration	Inclusion criteria	Main outcomes	Study arms	Sample size	Age, years	Male	Education, years	Disease time, months	ADAS-Cog	ADCS-ADL	CIBIC-plus	NPI
Wang et.al 2020 [23]	NCT01453569	1. Aged 50–85y regardless of their gender 2. Met the diagnostic criteria for probable AD of NINCDS-ADRDA 3. Mild-to-moderate AD, with 10 ≤ total MMSE score ≤ 24 4. Should have been educated to primary school level and above	Change in ADAS-Cog, ADL, NPI, and adverse events	Sodium oli-gomannate 600 mg BID	76 (31.4)	70.3 ± 8.4	35 (46.1)	a. > 6y, 22 (29.0) b. ≤ 6y, 54 (71.1)	NR	26.1 (12.4)	50.0 (17.4)	NR	7.3 (10.9)
				Sodium oli-gomannate 900 mg BID	83 (34.29)	70.4 ± 8.5	33 (39.8)	a. > 6 y, 27 (32.5) b. ≤ 6y, 56 (67.5)		26.16 (12.00)	53.7 (16.4)		7.4 (12.2)
				Placebo	83 (34.29)	70.3 ± 8.1	31 (37.4)	a. > 6y, 31 (37.4) b. ≤ 6y, 52 (62.7)		28.1 (12.0)	50.9 (17.4		9.9 (13.7)

Y years, *AD* Alzheimer's disease, *NINCDS-ADRDA* the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, *MMSE* Mini-Mental State Examination, *ADAS cog* Alzheimer's Disease Assessment Scale-cognitive subscale, *CIBIC+* the Clinician's Interview-Based Impression of Change with caregiver input, *ADCS-ADL* Alzheimer's Disease Cooperative Study-Activities of Daily Living scale, *NPI* Neuropsychiatric Inventory, *QD* once a day, *BID* two times a day, *NR* not reported

Data are presented as mean ± standard deviation or number (percentage)

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Fig. 2 Risk of bias summary

p-value = 0.08). the analyzed studies were homogenous with the fixed effect model (*p*-value = 0.85, $I^2 = 0\%$) (Fig. 3).

Change in ADAS cog score

At 12 weeks   Two studies [21, 22] reported this outcome with a total population of 840 participants. The pooled estimate suggested SO group had a significantly lower ADAS cog score than the placebo group (MD = − 0.69, 95% CI [− 1.23 to − 0.14], *p*-value = 0.01). The results were homogeneous (*p*-value = 0.43, $I^2 = 0\%$) (Fig. 4A).

At 24 weeks   The pooled studies (sample size = 1014) showed that there was no significant difference in ADAS cog score between the intervention and control group (MD = − 2.01, 95% CI [− 5.09 to 1.07], *p*-value = 0.20). The results were heterogeneous (*p*-value < 0.00001, $I^2 = 98\%$) with random effect model (Fig. 4A).

After removing Zhang et al. [21], the heterogeneity was resolved (*p*-value = 0.85, $I^2 = 0\%$). Moreover, the data significantly favored the SO group over the placebo group (MD = − 0.68, 95% CI [− 1.26 to − 0.10], *p*-value = 0.02) (Fig. 4B).

At 36 weeks   The studies measured this outcome at 36 weeks with a total sample size of 732. The ADAS cog score declined significantly in the SO group compared to the placebo group with a (MD = − 3.84, 95% CI [− 6.40 to − 1.27], and *p*-value = 0.003). The results were heterogeneous (*p*-value < 0.00001, $I^2 = 96\%$) (Fig. 4A).

Change in ADL score (from baseline to the last follow-up period)

The pooled results (sample size = 968) showed that there was no difference between the placebo and SO group (MD = 0.34, 95% CI [− 0.65 to 1.32], *p*-value = 0.50). The results were homogeneous (*p*-value = 0.78, $I^2 = 0\%$) (Fig. 5).

Change in CIBIC scale (from baseline to the last follow-up period)

Two studies [21, 22] reported this outcome with a sample size of 728. The analysis suggested no significant difference between the intervention and placebo group (MD = − 2.44, 95% CI [− 7.21 to 2.34], *p*-value = 0.32). The results were heterogeneous (*p*-value < 0.00001, $I^2 = 95\%$) (Fig. 6).

Change of NPI score (from baseline to the last follow-up period)

The results (sample size = 968) concluded no variation in NPI score between the SO and placebo groups (MD = − 2.19, 95% CI [− 8.59 to 4.21], *p*-value = 0.50) (Fig. 7A). The heterogeneity (*p*-value < 0.00001, $I^2 = 98\%$) was resolved after removing Zhang et al. [21] (*p*-value = 0.28, $I^2 = 15\%$). The results remained
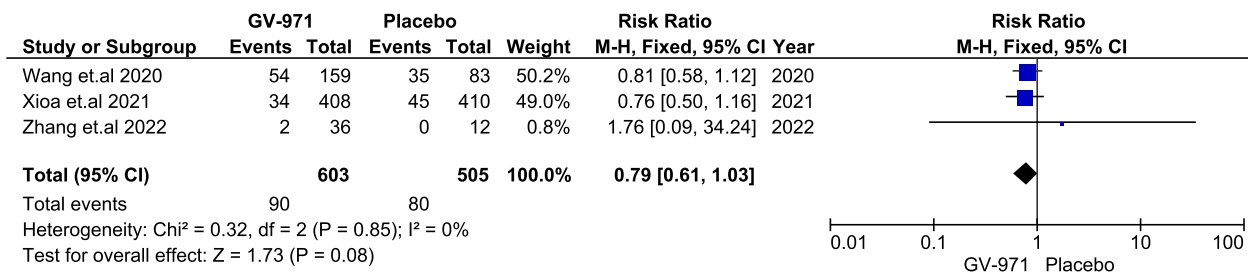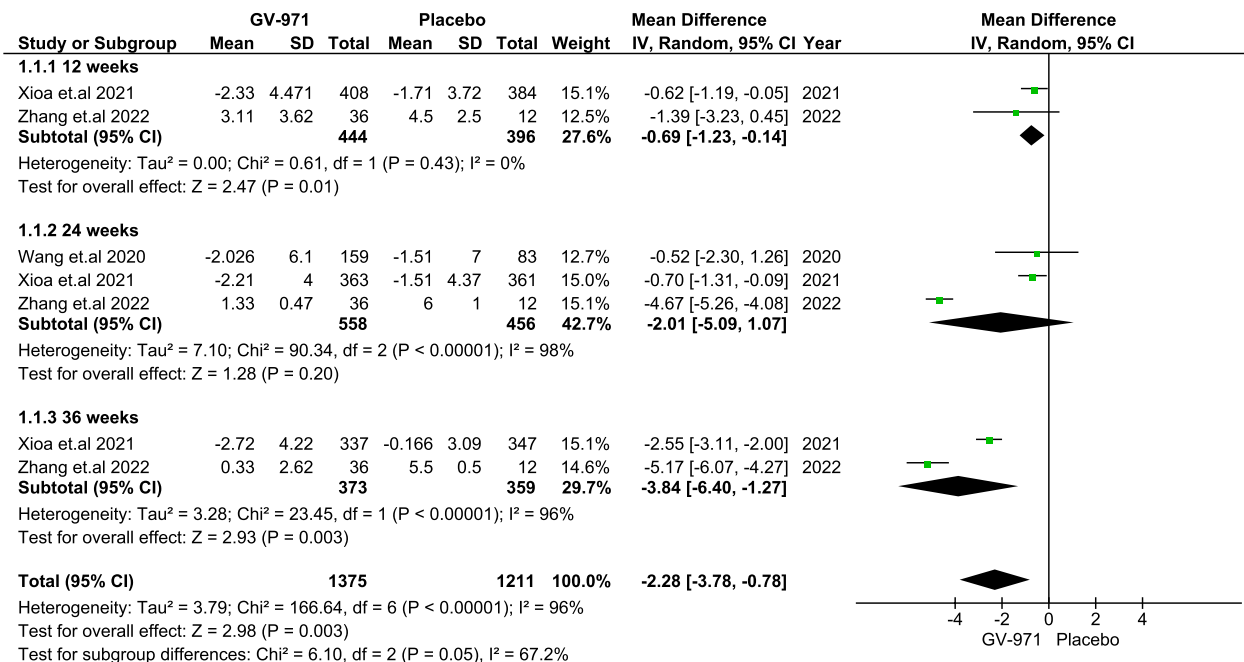

Fig. 3 Forest plot of adverse events

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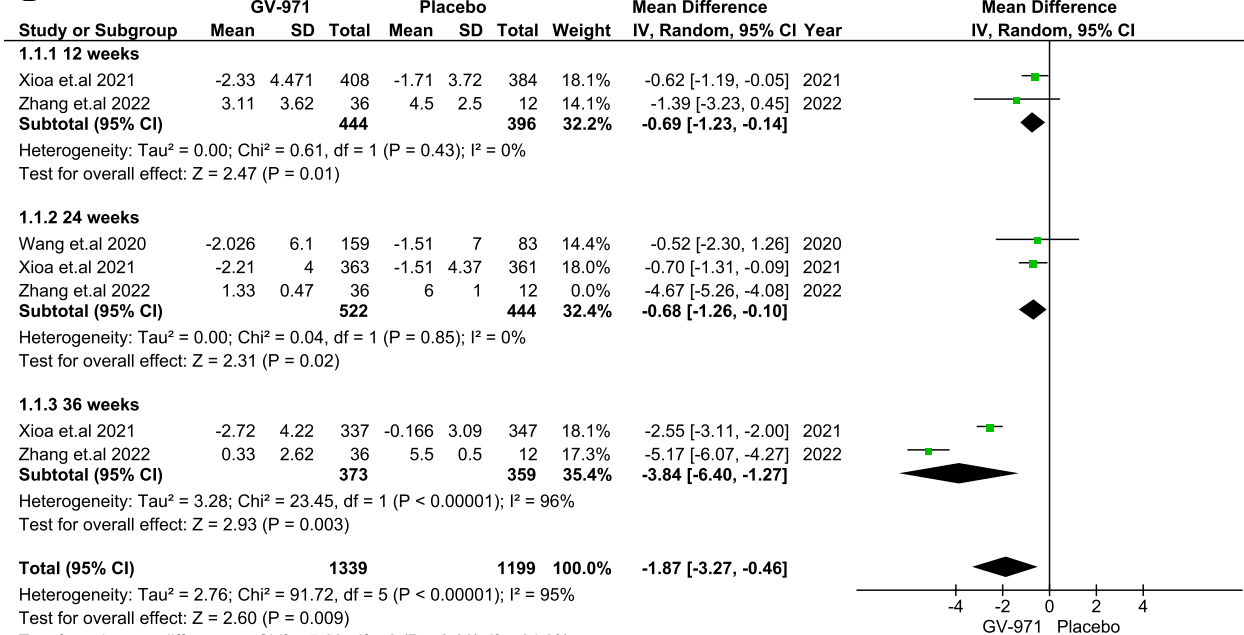
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A

B

Fig. 4 **A** Forest plot of change in ADAS cog score. **B** Forest plot of change in ADAS cog score after sensitivity analysis

insignificant (MD = 0.48, 95% CI [− 0.78 to 1.73], *p*-value = 0.45) (Fig. 7B).

Discussion

Our analysis concluded a significant difference between the SO group and placebo group in the ADAS cog score at 12, 24, and 36 weeks. Moreover, there was no difference between the SO and placebo groups in adverse events. On the other hand, the results were insignificant

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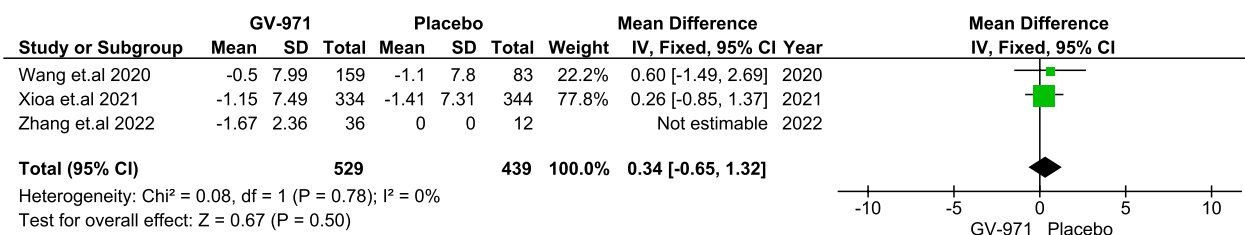
Fig. 5 Forest plot of change in ADL score (from baseline to the last follow-up period)
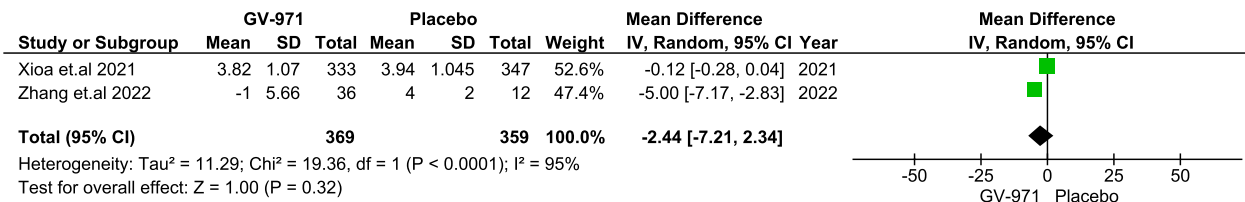

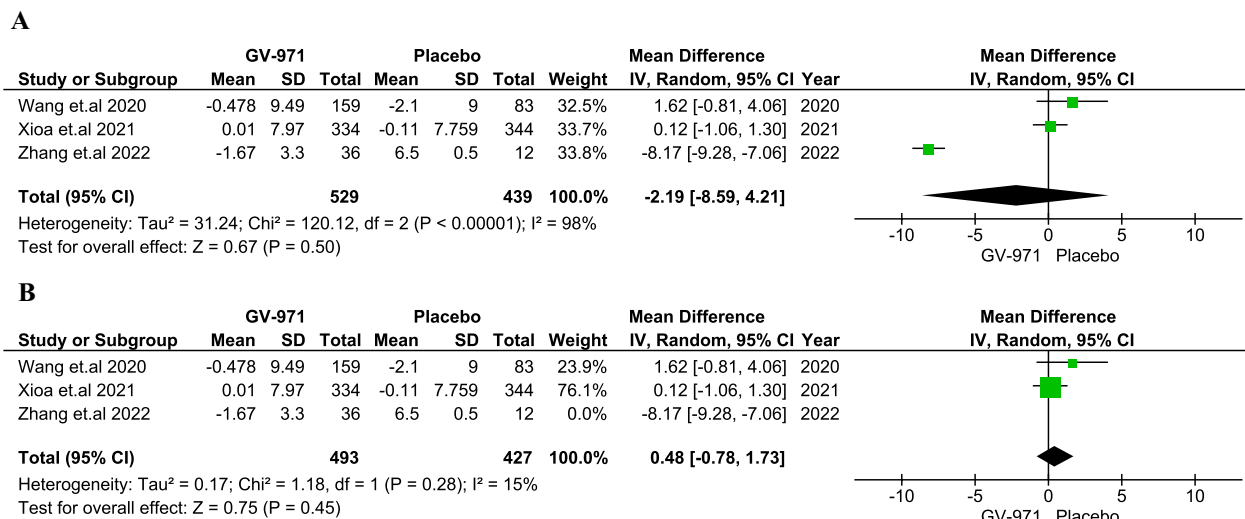**Fig. 6** Forest plot of change in CIBIC scale (from baseline to the last follow-up period)

Fig. 7 **A** Forest plot of change of NPI score (from baseline to the last follow-up period). **B** Forest plot of change of NPI score after sensitivity analysis

according to the following outcomes: ADL, CIBIC, and NPI at the last follow-up.

The SO proposed has two mechanisms of action. First, it prevents Aβ from aggregating and breaks down Aβ aggregates into harmless conformers [14, 15]. Second, it inhibits neuroinflammation by reconstituting gut microbiota and decreasing metabolite-driven peripheral immune cell influx into the nervous system [24].

Compared to the placebo and donepezil, the SO improved the ADAS cog scale, which means that the SO may have a role in enhancing the AD patients' condition daily [25]. This scale measured 12 essential tasks: word recall, commands, orientation, remembering test

instructions, and word-finding difficulty. These tasks are the most critical in AD patients' life. Therefore, improving the ADAS cog may improve the quality of life of patients and their caregivers.

A previous meta-analysis concluded that galantamine, donepezil, and rivastigmine improved the ADAS cog scale [26]. Our results remarkably resemble the effects of these cholinesterase inhibitors. Moreover, the mean difference and effect size increased with the drug's period. Therefore, our drug is a good candidate for treating AD patients.

SO was a safe and well-tolerated drug. Most adverse events were infections, gastrointestinal tract disorders,

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or nervous system problems. Furthermore, none of the adverse events were more common in the SO group compared to the placebo group and donepezil group. Finally, according to safety and efficacy, SO is similar to the already approved drug and is a good candidate for further research.

Our results were insignificant in three scales (CIBIC, ADL, and NPI). The insignificance might be attributed to the size of the sample being relatively small, culture variation, and behavioral evaluation may depend on the different interpretations of cultures [27].

Our study is the first meta-analysis of SO medication, collecting all available evidence. Moreover, all studies are randomized controlled studies. On the other hand, it has limitations. First, the number of patients is relatively small. Second, all studies conducted in the same country may be liable to selection and racial bias. Third, the absence of a diagnostic amyloid biomarker leads to including some patients with non-amyloid-related dementia. Finally, the study period was slightly short, which may mask some delayed side effects.

Three other studies with a sample size of 3450 patients are being conducted now [28, 29]. The results of these studies may give more evidence about the SO medication and may affect the outcomes measured in this study. Therefore, for further research, we recommend more RCTs on the SO with larger sample sizes and different doses in different places and situations. Moreover, we need to evaluate the drug with various comorbidities to know how it will affect elderly patients if used for a long time.

Conclusions

Sodium oligomannate is a promising drug for Alzheimer's patients and does not cause significant adverse events. However, to better evaluate the efficacy of SO in the clinical setting, we need more randomized controlled trials with larger samples and higher quality.

Abbreviations

AD	Alzheimer's disease
SO	Sodium oligomannate
RCTs	Randomized controlled trials
GRADE	The Grading of Recommendations Assessment, Development and Evaluation
ADAS cog	Alzheimer's Disease Assessment Scale-cognitive subscale
CIBIC+	The Clinician's Interview-Based Impression of Change with caregiver input
ADCS-ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living
NPI	Neuropsychiatric inventory
RR	Risk ratio
MD	Mean difference
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41983-023-00682-y.

Additional file 1. The quality of evidence of the analyzed outcomes using the GRADE tool.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
None.

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