REVIEW
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Neuroprotective effects of *Boswellia* extract in animal models of ischemic stroke, Parkinson's disease, and Alzheimer's disease: a systematic review and meta-analysis

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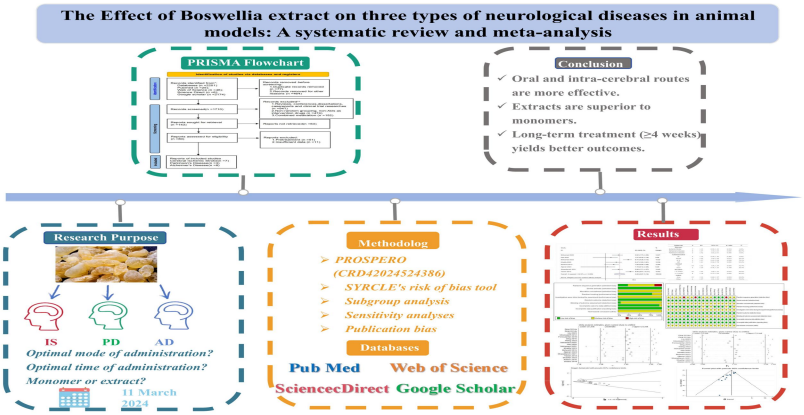
Abstract

Background: Neurological disorders (NDs), including ischemic stroke (IS), Parkinson's disease (PD), and Alzheimer's disease (AD), are major contributors to global morbidity and mortality. *Boswellia* extract has demonstrated neuroprotective properties, yet a comprehensive systematic review assessing its efficacy remains absent. This study aims to evaluate the efficacy of *Boswellia* extract in treating NDs, with a particular focus on its effects in AD and its potential for long-term neurorestoration, thereby supporting further investigation into *Boswellia*'s therapeutic role in ND management. **Methods:** A systematic literature search was performed in PubMed, Web of Science, ScienceDirect, and Google Scholar for English-language studies published up to March 2024. Eighteen studies met the inclusion criteria and were included in the meta-analysis. The study protocol was registered on PROSPERO (CRD42024524386). Eligible studies involved rodent models of IS, PD, or AD with post-operative interventions using *Boswellia* extract. Data extraction focused on mechanisms of action, dosages, treatment durations, and therapeutic outcomes. Studies were excluded if they involved non-ND models, combined treatments, or had incomplete data. Two researchers independently conducted literature screening and data extraction. Statistical analyses were conducted using Stata (version 17) and RevMan (version 5.4), employing fixed or random-effects models based on heterogeneity assessments. **Results:** *Boswellia* extract significantly improved the mean effect size for NDs (ES = 1.28, 95% CI (1.05, 1.51), $P < 0.001$). Specifically, it reduced cerebral infarct volume in IS (SMD = −2.87, 95% CI (−3.42, −2.32)) and enhanced behavioral outcomes in AD (SMD = 3.26, 95% CI (2.07, 5.14)) and PD (SMD = 5.37, 95% CI (3.93, 6.80)). Subgroup analyses revealed that *Boswellia* extract exhibited superior efficacy in AD when administered orally and via intra-cerebroventricular injection. Long-term treatment with *Boswellia* extract suggested potential neurorestorative effects. Additionally, *Boswellia* extract was more effective than its monomeric constituents, highlighting its promising role in ND treatment. **Conclusion:** *Boswellia* extract demonstrates significant neuroprotective effects across various NDs, particularly in AD and in promoting long-term neurorestoration. These findings support the need for further research into *Boswellia*'s potential as a therapeutic agent in the management of neurological disorders.

Keywords: Boswellic acid; *Boswellia* extract; ischemic stroke; Parkinson's disease; Alzheimer's disease; meta-analysis



Author contributions

Zhang MY conceptualized the study, created visualizations, and wrote the original draft. Liao YC provided resources, reviewed and edited the manuscript. Liang S conducted formal analysis and developed the methodology. Yu JP contributed to conceptualization and provided resources. Meng Q performed formal analysis, developed the methodology. Wang YW contributed to conceptualization and methodology. Zhang XF conducted formal analysis and developed the methodology. Wei Q reviewed and edited the manuscript, validated the results, and managed the project. Shi YJ validated the results. Ding Y reviewed and edited the manuscript and managed the project. All authors read and approved the final manuscript.

Competing interests

The authors declare no conflicts of interest.

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Peer review information

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Abbreviations

NDs, Neurological diseases; AD, Alzheimer's disease; PD, Parkinson's disease; IS, ischemic stroke; CI, confidence intervals; AKBA, Acetyl-11-keto-β-Boswellic acid; KBA, 11-keto-β-Boswellic acid; ES, effect sizes; SMD, standardized mean differences; I.P, intraperitoneal injection; P.O, oral; I.C.V, intra-cerebroventricular injection; SOD, superoxide dismutase; MDA, malondialdehyde; GPX, glutathione peroxidase; TUNEL, TdT-mediated dUTP-biotin nick end labeling; MCAO, middle cerebral artery occlusion.

Citation

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Highlights

A meta-analysis of eighteen studies revealed *Boswellia* extract's potential therapeutic efficacy on ischemic stroke, Parkinson's disease, and Alzheimer's disease in animal models across three neurological outcomes.

Boswellia extracts with oral and intra-cerebroventricular routes show greater efficacy for behavioral improvement in NDs.

Boswellia extract was superior to its monomeric forms in mitigating NDs.

Boswellia extract has the best therapeutic effect on AD among the three neurological disorders, and long-term treatment (≥ 4 weeks) correlated with enhanced neurobehavioral recovery.

Medical history of objective

Boswellia extract, commonly known as frankincense, has been utilized for its therapeutic properties since ancient times. As documented in the classic Chinese medical text *Compendium of Materia Medica* (compiled in 1593 C.E.) by Shizhen Li of the Ming Dynasty, *Boswellia* extract is renowned for its "blood-activating and pain-relieving" effects, making it a crucial remedy for conditions such as carbuncles, sores, and abdominal pain. Additionally, supplement to *Bencao Beiyao* (compiled in 1694 C.E.) by Ang Wang of the Qing Dynasty notes that *Boswellia* extract can "treat edema and detoxify", and is effective for "urticaria and itching caused by toxins". These historical applications and therapeutic uses of *Boswellia* extract have not only been widely recognized in traditional medicine but have also been further validated and expanded upon in modern medical research.

Introduction

Neurological disorders (NDs) have become a leading contributor to global morbidity and mortality, with ND-related fatalities increasing by 37% since 1990 [1]. Globally, the primary causes of ND-related deaths include cerebrovascular accidents, which account for 67.4%, Alzheimer's disease (AD) and other forms of dementia, constituting 20.3%, and Parkinson's disease (PD), representing 2.5% of total ND-related deaths [1]. Cerebral infarction, a major contributor to cerebrovascular accidents, is categorized into hemorrhagic stroke and ischemic stroke (IS), with IS accounting for approximately 80% of all stroke cases [2]. The demographic shift towards an aging population has elevated NDs as prominent causes of mortality and disability, resulting in substantial economic and social impacts on healthcare and welfare systems [3, 4]. Consequently, the increasing incidence of NDs underscores the urgent need for effective therapeutic strategies. However, few curative drugs are currently available, highlighting the critical demand for novel ND treatments.

In this context, the exploration of natural products and their derivatives has gained significant attention in pharmaceutical research [5, 6]. Active medicinal compounds derived from natural sources are crucial for the development of new pharmaceuticals. An analysis spanning from 1981 to 2019 revealed that out of 1,881 new drugs approved globally, approximately 23.5% were derived from natural products or their derivatives, underscoring their importance in drug discovery [7]. Recent studies further emphasize the essential role of natural medicinal compounds in the pathology and management of NDs [8]. Among these, *Boswellia* extract, with its rich pharmacological profile, emerges as a promising candidate for ND therapy. The gum/resin of *Boswellia*, abundant in bioactive phytochemicals, has demonstrated potential in treating various conditions, including NDs [9]. For instance, Baram's randomized controlled trial provided evidence that Boswellic acids reduce inflammatory plasma biomarkers, supporting their therapeutic potential in early-stage IS [10]. Additionally, a randomized, parallel, double-blind, placebo-controlled clinical trial involving 70 elderly subjects investigated the cognitive-enhancing effects of a tablet formulation containing *Boswellia* extract on memory and cognitive impairment in the elderly population [11]. Additionally, Boswellic acid has been utilized in clinical trials. A randomized, parallel, double-blind, placebo-controlled clinical trial involving 70 elderly participants investigated the cognitive-enhancing effects of tablets containing frankincense extract on memory and cognitive impairment in the elderly population [11]. Moreover, in patients with IS, *Boswellia* has been shown to improve early clinical outcomes following stroke, accompanied by changes in plasma inflammatory markers [10].

A synthesis of existing literature using systematic search methods indicates that *Boswellia* extract has the potential to treat a wide range of diseases, including three primary NDs: IS, PD, and AD. Therefore, this study presents a systematic review and meta-analysis to elucidate the effects of *Boswellia* extract on these NDs. Current literature has identified the mechanisms by which *Boswellia* extract exerts its effects on various ND models, particularly through its anti-inflammatory properties. Inflammation is a critical factor in both acute and chronic nervous system pathologies [12]. Notably, *Boswellia* extract, particularly Acetyl-11-keto-β-Boswellic acid (AKBA), has shown efficacy in mitigating inflammation by targeting the 5-lipoxygenase enzyme, a pivotal pathway in ND treatment [13]. Inflammatory stress is increasingly recognized as a key contributor to the pathogenesis of NDs [14, 15]. While existing studies provide valuable insights into the therapeutic mechanisms of *Boswellia* extract in NDs, they employ diverse treatment methodologies and yield evidence of varying quality, limiting their utility in guiding clinical treatment decisions. Thus, this study aims to conduct a comprehensive systematic review and meta-analysis of the effects of *Boswellia* extract in the treatment of NDs.

Preclinical research is essential for providing safety, efficacy, and mechanistic data necessary for transitioning therapies from bench to bedside with minimized risk and maximized clinical efficacy [16]. However, within the domain of *Boswellia* extract for NDs, no analogous meta-analyses have been conducted to date. Our study aims to fill this gap by elucidating the specific efficacy of *Boswellia* extract against each ND, evaluating different administration routes and dosage forms, and exploring its role in long-term neurorestorative processes.

Materials and methods

This meta-analysis was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. The study protocol was registered with PROSPERO (CRD42024524386).

Search strategy

A comprehensive literature search was performed across four databases: PubMed, Web of Science, ScienceDirect, and Google Scholar. The search included studies published in English up to March 2024, with no restrictions on publication date. Search terms combined keywords related to *Boswellia* extract and the NDs of interest (IS, PD, and AD). The search strategy employed for PubMed is detailed in Table 1. To minimize bias, the search was independently replicated by two researchers.

Inclusion and exclusion criteria

Studies were selected based on the following inclusion criteria:

- Population: rodent models of IS, PD, or AD.
- Intervention: post-operative administration of *Boswellia* extract.
- Outcomes: mechanisms of action, optimal dosages, treatment duration, and therapeutic effects, including cerebral infarct volume for IS and behavioral outcomes for AD and PD.
- Study design: peer-reviewed animal studies published in English.

Exclusion criteria were:

- Studies involving non-neurological disease models.
- Combined treatments with other therapeutic agents.

Table 1 PubMed search strategy

	Search terms
1	*Boswellia* OR *Boswellia* extract OR 3-O-Acetyl-11-keto-beta-Boswellic acid OR Frankincense OR *Boswellia* serrata OR *Boswellia* carteri OR *Boswellia* frereana OR Ruxiang OR Boswellic acid OR Lanconone
2	Ischemic stroke OR cerebral ischemic injury OR cerebral ischemic reperfusion OR cerebral infarct OR middle cerebral artery occlusion
3	Parkinsonian disorders OR Parkinson's disease OR Parkinsonism OR Lewy body dementia OR multiple system atrophy OR progressive supranuclear palsy OR corticobasal syndrome OR corticobasal degeneration
4	Alzheimer OR Alzheimer disease OR Alzheimer's Disease OR Presenile Alzheimer Dementia OR Alzheimer Sclerosis OR Alzheimer Type Dementia
5	1 AND 2
6	1 AND 3
7	1 AND 4
8	5 AND 6 AND 7

- Studies lacking full-text availability, adequate data, or originality.

Data extraction

Two independent researchers conducted literature screening and data extraction using EndNote X9 (Thomson Corporation, Stanford, CT, USA). Discrepancies were resolved through discussion or consultation with a third reviewer. Extracted data included:

- Basic metadata: title, primary author, publication year, animal model, weight, and experimental conditions.
- Intervention details: name of the pharmaceutical agent, dosage, route of administration, and timing of intervention.
- Outcome metrics: quantitative data on cerebral infarct volume, behavioral assessments, and relevant physiological and biochemical markers.
- Data from graphs: for studies presenting data graphically, numerical values were extracted using GetData Graph Digitizer software.

Quality assessment

The risk of bias in the included studies was evaluated using the Systematic Review Centre for Laboratory Animal Experimentation risk of bias tool [18]. This tool assesses various domains, including selection bias, performance bias, detection bias, attrition bias, and reporting bias, categorizing each domain as low, high, or unclear risk.

Data analysis

Statistical analyses were performed using Stata (Statacorp, College Station, TX, USA) and Review Manager (Cochrane Collaboration, London, UK). Effect sizes were expressed as standardized mean differences (SMD) with 95% confidence intervals (CI). A fixed-effects model was applied when heterogeneity was low ($I^2 \leq 50\%$, $P \geq 0.1$), and a random-effects model was used when heterogeneity was substantial ($I^2 > 50\%$, $P < 0.1$).

Subgroup analyses were conducted to explore sources of heterogeneity based on disease type (IS, PD, AD), administration routes (oral, intraperitoneal, intra-cerebroventricular), and dosage forms. Sensitivity analyses were performed to assess the robustness of the results by excluding studies with high risk of bias or extreme effect sizes.

Publication bias was evaluated using funnel plots and Egger's test. A funnel plot asymmetry was considered indicative of potential publication bias if Egger's test was significant ($P < 0.05$).

All statistical tests were two-tailed, and significance was set at $P < 0.05$.

Results

Study inclusion

Our comprehensive search across multiple databases yielded 2,251 potentially relevant articles. Following rigorous screening based on the PRISMA flowchart criteria, 18 studies were deemed eligible for inclusion in our meta-analysis. The literature screening process and results are illustrated in Figure 1. These comprised 7 studies on IS, 8 on AD, and 3 on PD, demonstrating a broad investigational spectrum of *Boswellia* extract effects on NDs [19–36].

Study characteristics

The meta-analysis encompassed a total of 728 animals, with individual study sizes ranging from 18 to 90 subjects. The majority of the studies (12 out of 18) originated from Asia, reflecting global interest in exploring natural compounds like *Boswellia* extract for ND treatment. The experimental models primarily involved rats (14 studies) and mice (4 studies), with weights spanning 22 g–300 g. The most frequently used animal strains included Sprague-Dawley, Wistar, C57BL/6, and albino, highlighting a diverse genetic backdrop for the investigations. Administration routes varied, with intraperitoneal injection (I.P) being the most common, followed by combined I.P and oral (P.O), intra-cerebroventricular injection (I.C.V), and oral only, indicating a range of methodologies in delivering *Boswellia* extract in ND research. The detailed basic characteristics of the enrolled studies are presented in Table 2.

Methodological quality

The methodological quality of the 18 included studies revealed variability in the rigor of randomization procedures. Four studies utilized a random number table for group assignment, ensuring a high level of methodological integrity. In contrast, ten studies vaguely referenced "random grouping" without further elaboration, and four studies failed to mention randomization entirely, potentially compromising their validity. Notably, none of the studies described their allocation concealment methods, a critical aspect of avoiding selection bias. Despite these limitations, all studies adequately reported baseline characteristics and outcomes, although data extraction from graphical representations introduced a potential source of bias. The risk of bias profiles for the included studies are depicted in Figure 2.

***Boswellia* extract for IS**

Cerebral infarction volume. Analysis of seven studies revealed that *Boswellia* extract significantly reduced cerebral infarction volume in IS models (SMD = −2.87; 95% CI = (−3.42, −2.32), $P < 0.0001$), demonstrating low heterogeneity ($I^2 = 9.1\%$, $P = 0.360$) (Figure 3A) [19–25]. This robust finding underscores *Boswellia* extract's potential as a neuroprotective agent against ischemic damage.

TUNEL (TdT-mediated dUTP-biotin nick end labeling) analysis. Five studies evaluated the impact of *Boswellia* extract on neuronal apoptosis, revealing a significant reduction (SMD = −3.36; 95% CI = (−4.25, −2.47), $P < 0.0001$) with moderate heterogeneity ($I^2 = 24.6\%$) (Figure 3B) [20–23, 26]. This suggests *Boswellia* extract may mitigate cell death following ischemic events.

SOD levels. Four studies examining superoxide dismutase (SOD) activity indicated that *Boswellia* extract inhibits oxidative stress markers induced by IS (SMD = 2.76; 95% CI = (0.91, 4.60), $P < 0.0001$), albeit with significant heterogeneity ($I^2 = 83.6\%$) (Figure 3C) [19–22]. This suggests variability in *Boswellia* extract's

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Table 2 Basic characteristics of included studies

Study	Country	Animal species	Animal weights	Animal model	Main experimental groups	Administration	Intervention time	Anesthetic agent
Ding 2014	China	Male SD rats	280–300 g	MCAO (middle cerebral artery occlusion) model	1. Sham group 2. MCAO group 3. MCAO + 20 mg/kg AKBA n = 8 animals per group	I.P	2 h ischemia followed by 48 h reperfusion	isoflurane
Ding 2014	China	Male SD rats	280–300 g	MCAO model	1. Sham group 2. MCAO group 3. MCAO + 25 mg/kg KBA n = 6 animals per group	I.P	2 h ischemia followed by 48 h reperfusion	chloral hydrate
Liu 2023	China	Male C57BL/6 mice	N	MCAO model	1. Sham group 2. MCAO group 3. MCAO + 50 mg/kg KBA 4. MCAO + 50 mg/kg Z-GS 5. MCAO + 25 mg/kg KBA + 25 mg/kg Z-GS 6. MCAO + 5 mg/kg EDA n = 12 animals per group	I.P	2 h ischemia followed by 48 h reperfusion	isoflurane
Moussaieff 2012	Israel	C57BL/6 mice	22–25 g	MCAO model	1. MCAO group 2. MCAO + 1 mg/kg IA 3. MCAO + 10 mg/kg IA 4. MCAO + 50 mg/kg IA n = 6 animals per group	I.P	1 h ischemia followed by 24 h reperfusion	halothane
Forouzanfar 2016	Iran	Male Wistar rats	200–230 g	MCAO model	1. Sham group 2. MCAO group 3. MCAO + 125 mg/kg ABS 4. MCAO + 250 mg/kg ABS 5. MCAO + 500 mg/kg ABS 6. MCAO + 125 mg/kg EBS 7. MCAO + 250 mg/kg EBS 8. MCAO + 500 mg/kg EBS 9. MCAO + 50 mg/kg AKBA n = 8 animals per group	I.P	0.5 h ischemia followed by 24 h reperfusion	chloral hydrate
Ding 2016	China	Male SD rats	192–228 g	OGD Model MCAO Model	1. Sham group 2. MCAO group 3. MCAO + 10 mg/kg AKBA n = 8 animals per group	I.V	1 h ischemia followed by 48 h reperfusion	chloral hydrate
Wang 2022	China	Male SD rats	N	MCAO model	1. Sham group 2. MCAO group 3. MCAO + 10 mg/kg β-BA 4. MCAO + 20 mg/kg β-BA 5. MCAO + 40 mg/kg β-BA n = 6 animals per group	I.P	2 h ischemia followed by 24 h or 48 h reperfusion	chloral hydrate

Table 2 Basic characteristics of included studies (*continued*)

Study	Country	Animal species	Animal weights	Animal model	Main experimental groups	Administration	Intervention time	Anesthetic agent
Mohamed 2020	Egypt	Male albino rats	220–250 g	I.C.V injection of 0.2 μg/μL β amyloid	1. Vehicle group 2. 250 mg/kg Boswellic acid 3. 0.2 μg/μL β amyloid + 250 mg/kg D-galactose 4. 250 mg/kg Boswellic acid + 0.2 μg/μL β amyloid + 250 mg/kg D-galactose 5. 0.2 μg/μL β amyloid + 250 mg/kg D-galactose + 250 mg/kg Boswellic acid n = 10 animals per group	P.O I.C.V I.P	Boswellic acid P.O daily for 3 weeks, injected daily for 8 weeks	ketamine; xylazine
Wei 2020	China	Male APPswe/PS1 dE9 mice	N	APPswe/PS1dE9	1. vehicle-treated wild-type mice 2. wild-type mice + 5 mg/kg AKBA 3. vehicle-treated APPswe/PS1dE9 mice 4. APPswe/PS1dE9 mice + 5 mg/kg AKBA n = 7 animals per group	I.P	once per day for 3 months	N
Mohamed 2022	Egypt	Male SD rats	180–200 g	I.P $AlCl_3$	1. Vehicle group 2. 100 mg/kg $AlCl_3{\cdot}6H_2O$ 3. 100 mg/kg $AlCl_3{\cdot}6H_2O$ + 125 ml/kg BAs 4. 100 mg/kg $AlCl_3{\cdot}6H_2O$ + 250 ml/kg BAs n = 10 animals per group	I.P P.O	once per day for 6 weeks	N
Khalifa 2023	Egypt	Male Wistar rats	250–280 g	I.C.V injection of 3 μg/μL Aβ	1. Vehicle group 2. 20 mg/kg caffeine 3. 400 mg/kg *Boswellia serrata* aqueous extract 4. 3 μg/μL Aβ 5. 3 μg/μL Aβ + 20 mg/kg caffeine 6. 3 μg/μL Aβ + 400 mg/kg *Boswellia serrata* aqueous extract n = 7 animals per group	I.C.V P.O	once per day for 4 weeks	chloral hydrate
Behesht 2015	Iran	Male Wistar rats	230–270 g	I.C.V administration of streptozotocin	1. Vehicle group 2. 1.5 mg/kg STZ 3. 1.5 mg/kg STZ + 50 mg/kg frankincense, 21 days 4. 1.5 mg/kg STZ + 50 mg/kg frankincense, 42 days 5. 1.5 mg/kg STZ + distilled water, 21 days 6. 1.5 mg/kg STZ + distilled water, 42 days n = 8 animals per group	I.C.V	once per day for 21 or 42 days	ketamine; xylazine

Table 2 Basic characteristics of included studies (*continued*)

Study	Country	Animal species	Animal weights	Animal model	Main experimental groups	Administration	Intervention time	Anesthetic agent
Aljarari 2023	Saudi Arabia	Male albino Wister rats	150–200 g	I.P $AlCl_3$	1. Vehicle group 2. 100 mg/kg $AlCl_3$ 3. 100 mg/kg $AlCl_3$ + 200 mg/kg *B. papyrifera* 4. 100 mg/kg $AlCl_3$ + 200 mg/kg *S. aromaticum* 5. 100 mg/kg $AlCl_3$ + 200 mg/kg *B. papyrifera* + 200 mg/kg *S. aromaticum* n = 8 animals per group	P.O	once per day for 8 weeks	N
Shasaltaneh 2021	Iran	Male Wistar rats	250–300 g	I.C.V administration of streptozotocin	1. 2.25 mg/kg STZ 2. 2.25 mg/kg STZ + 35 μg/kg BBA 3. 35 μg/kg BBA + 2.25 mg/kg STZ group n = 10 animals per group	I.C.V	STZ I.C.V during days 1 and 3, BBA once per day for 4 days	N
Yassin 2013	Egypt	Male SD rats	150–200 g	I.P $AlCl_3$	1. Vehicle group 2. 17 mg/kg $AlCl_3$ 3. 0.3 mg/kg rivastigmine + 17 mg/kg $AlCl_3$ 4. 45 mg/kg *Boswellia serrata* + 17 mg/kg $AlCl_3$ 5. 90 mg/kg *Boswellia serrata* + 17 mg/kg $AlCl_3$ 6. AD rats + 17 mg/kg $AlCl_3$ 7. AD rats + 0.3 mg/kg rivastigmine 8. AD rats + 45 mg/kg *Boswellia serrata* 9. AD rats + 90 mg/kg *Boswellia serrata* n = 10 animals per group	P.O	$AlCl_3$ P.O for 4 successive weeks, B. serrata P.O for 2 successive weeks	N
Shadfar 2022	Australia	Male C57BL/6 J mice	N	I.P rotenone	1. vehicle A + vehicle B 2. 500 mg/kg *Boswellia* extract + vehicle B 3. vehicle A + 4 mg/kg rotenone 4. 500 mg/kg *Boswellia* extract + 4 mg/kg rotenone n = 7 animals per group	I.P P.O	P.O vehicle A or *Boswellia* extract, 1 week; injected with rotenone 2 weeks	N
Ameen 2016	Egypt	Male albino rats	120–146 g	S.C rotenone	1. Vehicle group 2. 1 mg/kg rotenone 3. 1 mg/kg rotenone + 125 mg/kg BAs 4. 1 mg/kg rotenone + 250 mg/kg BAs n = 6 animals per group	S.C P.O	S.C 9 doses of rotenone every 48 ± 2 h, BAs once per day for 17 days	N
Doaee 2018	Iran	Male Wistar rats	200–250 g	I.C.V injection of 6-OHDA	1. sham group 2. 12.5 μg 6-OHDA 3. 12.5 μg 6-OHDA + 125 mg/kg BS 4. 12.5 μg 6-OHDA + 250 mg/kg BS 5. 12.5 μg 6-OHDA + 500 mg/kg BS n = 7 animals per group	I.C.V I.P	extract I.P from 14 days before to 7 days after the surgery	ketamine; xylazine

MCAO, middle cerebral artery occlusion; P.O, oral; I.C.V, intra-cerebroventricular injection; S.C, subcutaneous injection; I.V, intravenous injection; AKBA, Acetyl-11-keto-β-Boswellic acid; KBA, 11-keto-β-Boswellic acid; I.P, intraperitoneal injection; EDA, edaravone; EBS, B. serrate; β-BA, β-Boswellic acid; STZ, streptozotocin; BBA, Beta Boswellic acid; BAs, Boswellic acids; Z-GS, Z-Guggulsterone; IA, Incensole acetate; Aβ, amyloid β; 6-OHDA, 6-Hydroxydopamine Hydrochloride.

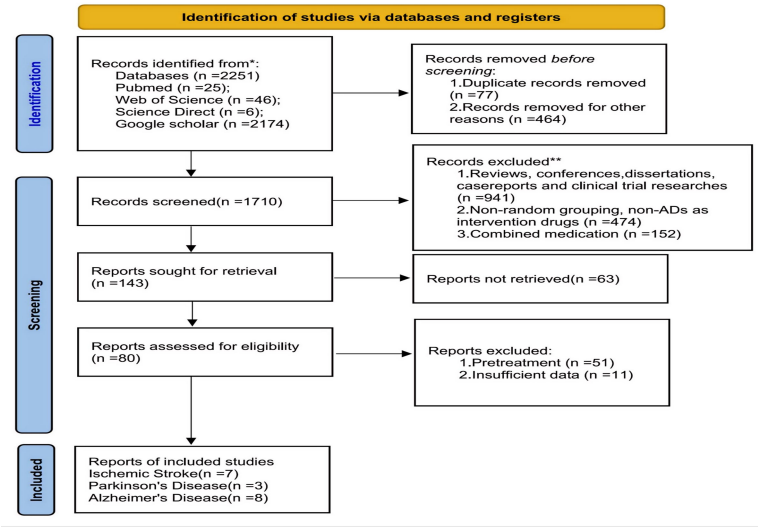

Figure 1 Flow diagram of the reporting items for systematic reviews and meta-analyses

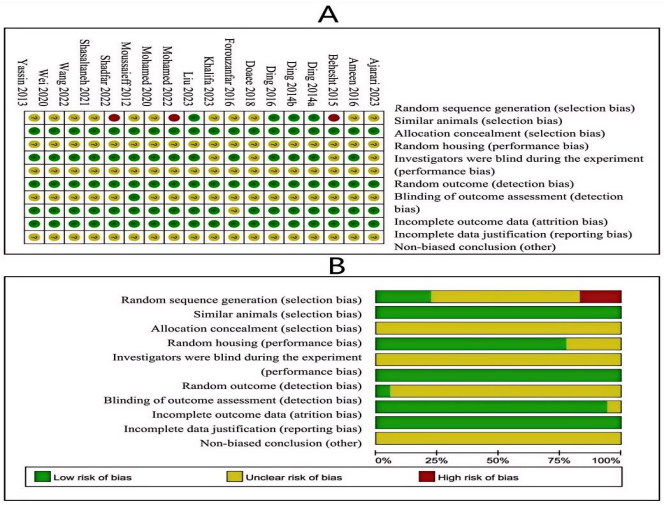

Figure 2 Methodologic quality assessment of the risk of bias. (A) Risk of bias summary; (B) Risk of bias graph.

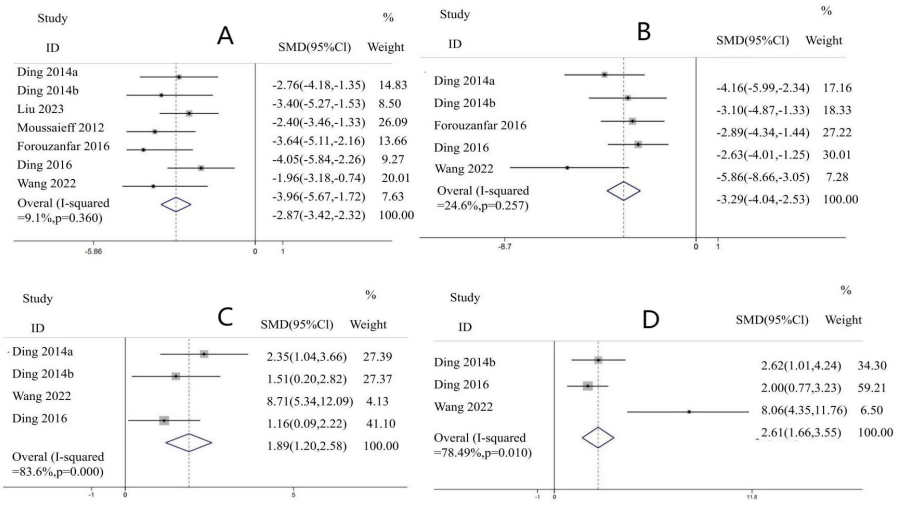

Figure 3 The forest plots: the effects of Boswellic extract for improving IS compared with the control group. (A) Cerebral infarction volume; (B) TUNEL% analysis; (C) SOD levels; (D) GPX levels. SMD, standardized mean differences; CI, confidence intervals; IS, ischemic stroke; TUNEL, TdT-mediated dUTP-biotin nick end labeling; SOD, superoxide dismutase; GPX, glutathione peroxidase.

antioxidative efficacy across different experimental setups.

GPX levels. Three studies evaluating glutathione peroxidase (GPX) expression highlighted an increase in GPX levels following *Boswellia* extract treatment (SMD = 3.54; 95% CI = (1.17, 5.91), $P < 0.0001$), despite high heterogeneity ($I^2 = 78.4\%$) (Figure 3D) [19, 21, 25]. This enhancement in antioxidative defense mechanisms further supports *Boswellia* extract's neuroprotective role.

Boswellia extract for AD

Behavioral effects. Analysis of eight studies demonstrated that *Boswellia* extract significantly improved behavioral outcomes in AD models, with a substantial effect size (SMD = 3.26; 95% CI = (2.07, 5.14), $P < 0.00001$), albeit amid considerable heterogeneity ($I^2 = 82.0\%$) (Figure 4A) [26–33].

MDA levels. Four studies quantified malondialdehyde (MDA) expression levels. The observed heterogeneity was minimal ($P = 0.258$, $I^2 = 25.6\%$), warranting the application of a fixed-effects model for analysis [26, 28–30, 32]. The findings indicate that *Boswellia* extract can diminish the expression of MDA in AD models (SMD = −2.21; 95% CI = (−2.68, −1.56), $P < 0.0001$) (Figure 4B).

SOD and GPX levels. Four studies reported SOD levels, and three studies reported GPX levels. Significant increases in antioxidant enzymes SOD (SMD = 3.50; 95% CI = (2.66, 4.35), $P < 0.0001$) (Figure 4C) and GPX (SMD = 3.55; 95% CI = (1.81, 5.29), $P < 0.0001$) (Figure 4D) were observed, underscoring *Boswellia* extract's potential neuroprotective effects against AD [26, 28, 30, 32].

Boswellia extract for PD

Behavioral effects. Three studies reported behavioral effects. In PD models, *Boswellia* extract significantly enhanced behavioral performance (SMD = 5.37; 95% CI = (3.93, 6.80), $P < 0.0001$), with studies showing low heterogeneity ($I^2 = 0.0\%$) (Figure 5A) [34–36].

Anti-inflammatory and dopamine levels. Two studies reported anti-inflammatory levels and dopamine levels. *Boswellia* extract increased anti-inflammatory levels (SMD = 2.55; 95% CI = (0.28, 4.82), $P = 0.028$) (Figure 5B) and dopamine content (SMD = 3.35; 95% CI = (1.94, 4.76), $P < 0.0001$) (Figure 5C), indicating its therapeutic potential in mitigating PD pathology [34, 36].

Subgroup analysis. To elucidate the sources of heterogeneity and address secondary objectives, we stratified the included studies by disease type, treatment duration, study location, drug delivery modalities, animal type, and dosage form (Table 3).

Disease type: significant heterogeneity was observed across disease categories, with AD exhibiting the highest variability ($I^2 = 82.0\%$, $P < 0.001$). In contrast, studies on IS and PD revealed no heterogeneity ($I^2 = 0.0\%$).

Drug delivery modalities: intraperitoneal administration showed uniform effects ($I^2 = 0.0\%$), whereas P.O (ES = 1.41; 95% CI = (0.04, 2.78), $P < 0.001$) and I.C.V (ES = 1.27; 95% CI = (0.45, 2.08), $P = 0.008$) routes displayed considerable heterogeneity, suggesting that the mode of *Boswellia* extract administration significantly influences outcome variability.

Treatment duration: treatments starting at 4 weeks or later showed a significant effect (ES = 1.18; 95% CI = (0.37, 1.64), $P < 0.001$) with a high level of heterogeneity ($I^2 = 82.0\%$). This suggests that the timing of treatment initiation is critical.

Dosage form: the analysis highlights the importance of dosage form, with the extract form of *Boswellia* showing a significant effect (ES = 1.62; 95% CI = (1.47, 1.77), $P < 0.001$) and a considerable degree of heterogeneity ($I^2 = 71.6\%$).

Modeling of AD: the aluminum-induced model demonstrated a stronger effect compared to the β amyloid-injected model (ES = −2.809, 95% CI = (−3.58, −2.02), $P < 0.001$), with a substantial degree of heterogeneity observed ($I^2 = 90.0\%$).

Animal model and study location: these factors contributed less to the overall heterogeneity, although regional differences and animal models showed some influence on study outcomes.

The subgroup analysis underscores disease type and drug delivery mode as primary contributors to the observed heterogeneity, highlighting the complexity of *Boswellia* extract effects in ND treatment.

Sensitivity analyses

Sensitivity analysis, conducted in response to high heterogeneity ($I^2 > 70\%$), involved the exclusion of certain studies (Figure 6) [29, 33, 35]. This adjustment altered the significance of *Boswellia* extract's effects on NDs (SMD = 0.53; 95% CI = (0.01, 1.07), $P < 0.05$), indicating these studies as potential sources of heterogeneity.

Publication bias

Publication bias was assessed using funnel plot analysis (Figure 7A) and Egger's test (Figure 7B) ($P = 0.16$) for the primary outcomes. The symmetrical distribution of the funnel plots suggests no apparent publication bias in the studies examining *Boswellia* extract effects on NDs.

Discussion

Boswellia extract for IS

Stroke remains a leading cause of morbidity and mortality worldwide, with IS accounting for approximately 61.4% of all stroke incidents [37]. The progression of IS is closely linked to oxidative stress, which exacerbates neuronal damage following vascular occlusion [37]. Research indicates that *Boswellia* extracts can penetrate the blood-brain barrier, promoting neurite outgrowth and dendritic arborization within the hippocampal region [38]. Additionally, *Boswellia* extract has been shown to reduce oxidative stress, enhance memory performance, and decrease peritumoral edema in the brain [39]. The neuroprotective effects of Boswellic acids (BAs) are primarily attributed to their antioxidant properties, positioning *Boswellia* extract as a promising therapeutic agent for mitigating cerebral ischemia/reperfusion injury and managing NDs [40].

Our meta-analysis revealed that *Boswellia* extract significantly reduced infarct volume in IS models ($P < 0.05$), a critical indicator of cerebral ischemia. Furthermore, levels of GPX and SOD, enzymes essential for degrading peroxides and protecting cellular membranes from oxidative damage, were significantly upregulated in the *Boswellia*-treated groups compared to controls [37]. TUNEL staining indicated a notable reduction in apoptotic neurons in the experimental cohorts, suggesting that *Boswellia*'s neuroprotective effects are mediated through its antioxidant capabilities. These findings collectively demonstrate that *Boswellia* extract effectively protects against ischemic brain injury, underscoring its potential as a therapeutic agent for neurological conditions.

Boswellia extract for AD

AD is the most prevalent neurodegenerative disorder, characterized by progressive cognitive decline and pathological features such as amyloid-beta (Aβ) aggregation into neuritic plaques, tau protein neurofibrillary tangles, and significant neuronal loss [41, 42]. Neuroinflammation and oxidative stress are pivotal in AD pathogenesis [43]. Aβ aggregation initiates a cascade of events, including the overproduction of proinflammatory cytokines like TNF-α and IL-1β, which further exacerbate Aβ accumulation [44]. *Boswellia* extract has been shown to inhibit Aβ aggregation and reduce levels of TNF-α and IL-1β, highlighting its potential therapeutic applications in AD [45]. The anti-amyloidogenic properties of *Boswellia* extract are likely due to its antioxidant capacity and anti-inflammatory mechanisms, offering therapeutic intervention points for mitigating disease progression [46].

Our study highlights the therapeutic potential of *Boswellia* extract in ameliorating cognitive impairments, reducing oxidative stress, and attenuating inflammatory processes in AD murine models. Behavioral assessments, including the Morris water maze and rotarod tests, demonstrated significant improvements in cognitive and motor functions. Biochemical analyses revealed that *Boswellia* extract effectively reduced MDA levels, a biomarker of lipid peroxidation and oxidative damage, while increasing antioxidant enzymes SOD and

GPX. These results indicate that *Boswellia* extract not only enhances behavioral performance but also modulates biochemical pathways to reduce oxidative stress and inflammation, thereby preserving neuronal health in AD [47].

***Boswellia* extract for PD**

PD is the second most common neurodegenerative disorder, characterized by the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta, leading to a significant reduction in striatal dopamine levels [48]. The multifactorial etiology of PD has impeded the development of definitive preventive or curative treatments [49]. However, studies have demonstrated that *Boswellia* extract can significantly alleviate neurodegenerative features associated with PD in animal models [38]. Boswellic acid, a principal

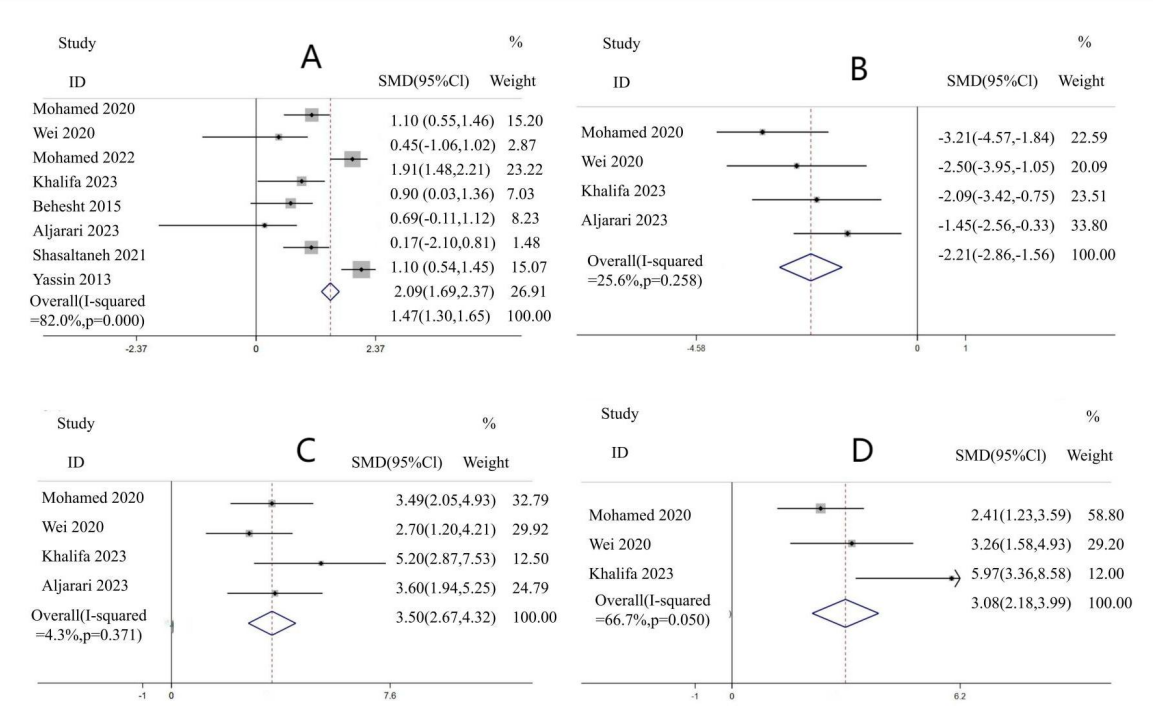

Figure 4 The forest plots: the effects of Boswellic extract for improving AD compared with the control group. (A) Behavioral effects; (B) MDA levels; (C) SOD levels; and (D) GPX levels. SMD, standardized mean differences; CI, confidence intervals; AD, Alzheimer's disease; MDA, malondialdehyde; SOD, superoxide dismutase; GPX, glutathione peroxidase.

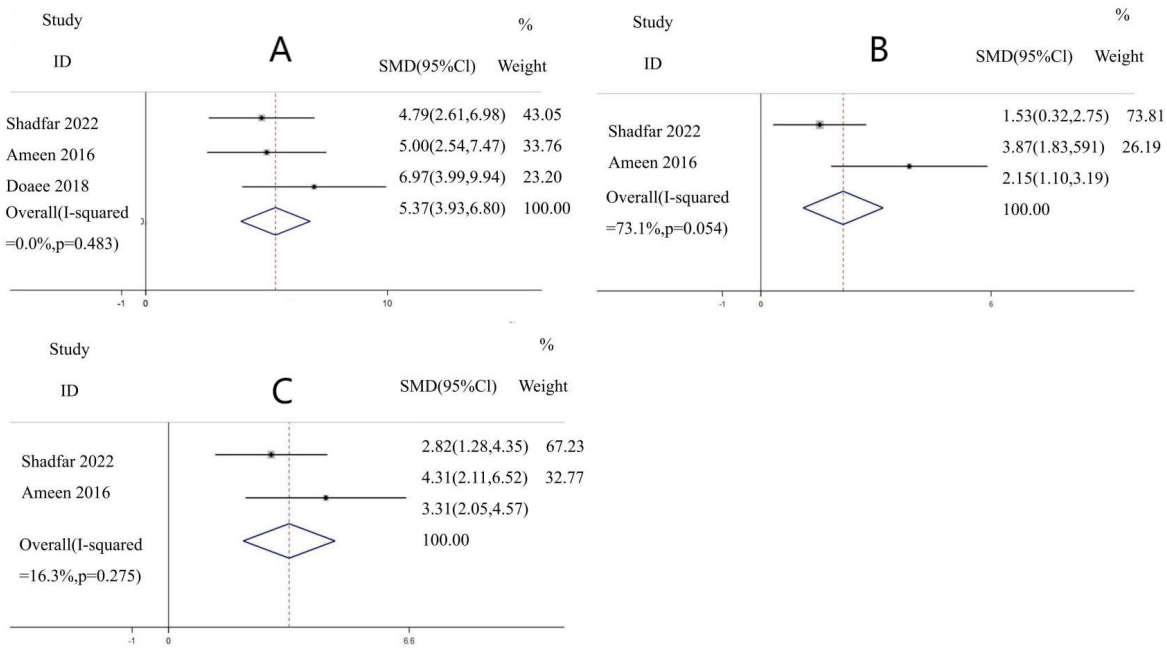

Figure 5 The forest plots: the effects of Boswellic extract for improving PD compared with the control group. (A) Behavioral effects; (B) Anti-inflammatory levels; and (C) Dopamine levels. SMD, standardized mean differences; CI, confidence intervals; PD, Parkinson's disease.

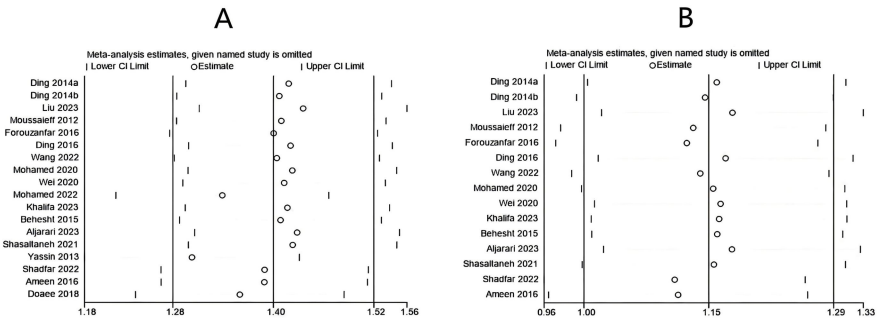

Figure 6 Sensitive analysis results of NDs. (A) All studies; (B) Exclusion of certain studies. CI, confidence intervals.

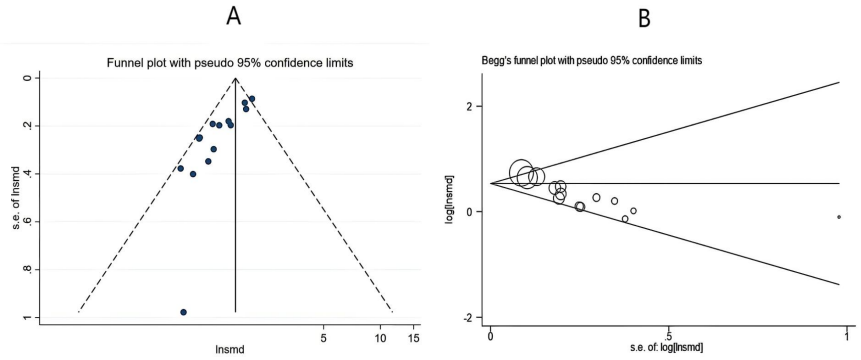

Figure 7 Publication bias. (A) funnel plot; (B) Begg's funnel plot.

Table 3 Pooled estimates for Boswellic extract on NDs in subgroup analysis

Subgroup	n	ES	95% CI	*P* value	I^2
Diseases					
IS	7	1.15	0.95, 1.35	0.553	0.0%
AD	8	1.47	1.30, 1.65	0.000	82.0%
PD	3	1.72	1.44, 2.01	0.490	0.0%
Administration					
I.P	9	1.12	0.94, 1.30	0.580	0.0%
I.P, P.O	4	1.56	1.18, 1.94	0.077	56.1%
I.C.V	3	1.27	0.45, 2.08	0.008	79.5%
P.O	2	1.41	0.04, 2.78	0.000	93.4%
Animal					
Rat	14	1.32	1.04, 1.59	0.000	72.7%
Mice	4	1.16	0.76, 1.55	0.108	50.7%
Duration					
< 4 weeks	10	1.32	1.09, 1.55	0.052	46.4%
≥ 4 weeks	8	1.18	0.73, 1.64	0.000	82.0%
Region					
Asia	12	1.13	0.89, 1.37	0.024	50.0%
Other	6	1.57	1.21, 1.93	0.002	73.2%
Dosage Form					
Monomer	8	1.03	0.83, 1.23	0.790	0.0%
Extract	10	1.62	1.47, 1.77	0.000	71.6%
Methods					
β amyloid	2	−2.767	−3.74, −1.79	0.584	0.0%
$AlCl_3$	4	−2.809	−3.58, −2.02	0.000	90.0%
Other	2	−1.909	−2.74, −1.07	0.037	77.0%

NDs, Neurological diseases; ES, effect sizes; CI, confidence intervals; AD, Alzheimer's disease; PD, Parkinson's disease; IS, ischemic stroke; I.P, intraperitoneal injection; P.O, oral; I.C.V, intra-cerebroventricular injection.

constituent of *Boswellia* extract, has been shown to enhance neurite elongation, arborization, and modulate tubulin polymerization dynamics. Its well-documented antioxidant properties contribute to cerebrovascular protection [50].

In this study, we conducted a comprehensive assessment of the neuroprotective properties of *Boswellia* extract in PD models. The extract activated AMP-activated protein kinase and related neuroprotective pathways, effectively safeguarding nigrostriatal dopaminergic neurons from rotenone-induced degeneration. This neuroprotection was evidenced by improved behavioral performance, reduced inflammation, and normalized dopamine levels. Given dopamine's crucial role in various physiological processes, these findings suggest that *Boswellia* extract holds significant therapeutic potential for managing PD symptoms and enhancing neuroactivity.

Effect size and heterogeneity analysis

Our meta-analytic approach employed effect sizes (ES) with thresholds of 0.2, 0.5, and 0.8 delineating small, moderate, and large effects, respectively. The pooled effect sizes for structural outcomes were substantial, indicating a strong favorable impact of *Boswellia* extract. However, significant heterogeneity across studies necessitates cautious interpretation of these findings. The presence of publication bias, although not strongly evident, underscores the potential overestimation of efficacy and highlights the importance of comprehensive literature inclusion to mitigate bias. But to ensure methodological consistency and the reliability of our findings within the existing literature, it is essential that the meta-analysis adheres to stringent inclusion criteria. The studies by Zhang, et al. 2025, and Miao, et al. 2020 combination therapies were utilized [51, 52]. The concurrent use of frankincense with other herbal compounds precluded the definitive determination of the independent effects of frankincense. Additionally, the studies Roy, et al. 2019 and Fathi, et al. 2017 lacked sufficient data to draw definitive conclusions. Therefore, we must exclude them from our analysis [53, 54].

Subgroup analyses provided several insightful revelations regarding the therapeutic potential of *Boswellia* extract in NDs:

Disease type: AD models exhibited the highest variability (I^2 = 82.0%, $P < 0.001$), suggesting targeted effects of *Boswellia* extract in this complex disorder. The ability to ameliorate cognitive deficits in AD, where current treatment options are limited, represents a significant advancement in neurology.

Drug delivery modalities: intraperitoneal administration showed uniform effects (I^2 = 0.0%), while P.O (ES = 1.41; 95% CI = (0.04, 2.78), $P < 0.001$) and I.C.V (ES = 1.27; 95% CI = (0.45, 2.08), P = 0.008) routes exhibited considerable heterogeneity. This suggests that the mode of *Boswellia* extract administration significantly influences outcome variability, potentially guiding the development of more efficient delivery systems to enhance bioavailability and efficacy.

Treatment duration: treatments initiated at 4 weeks or later demonstrated significant effects (ES = 1.18; 95% CI = (0.37, 1.64), $P < 0.001$) with high heterogeneity (I^2 = 82.0%), indicating that the timing of treatment initiation is critical for achieving optimal neurobehavioral outcomes. To investigate the neurorestorative effects of frankincense and its extracts with treatment durations ≥ 4 weeks, we reviewed and supplemented relevant literature. Boswellic acids were suggested to exert neuroprotective effects by modulating the Wnt/β-catenin pathway and inhibiting GSK-3β activity. They also upregulated BDNF levels, enhancing learning and memory. AKBA significantly reduced LPS-induced neuroinflammation by modulating miRNA-155 [46]. Components in frankincense extracts increased *CaMKII* mRNA expression, promoting neurodevelopment, and reduced neuroinflammation by inhibiting NF-κB activity and GFAP expression, with additional antidepressant effects [55].

Dosage form: the extract form of *Boswellia* showed a significant effect (ES = 1.62; 95% CI = (1.47, 1.77), $P < 0.001$) with considerable heterogeneity (I^2 = 71.6%), suggesting enhanced therapeutic benefits compared to monomeric forms.

The observed heterogeneity, particularly concerning administration routes and disease types, underscores the complexity of *Boswellia*'s therapeutic effects. The absence of significant publication bias (Egger's test, P = 0.16) suggests a balanced representation of study outcomes, although the inherent variability calls for cautious interpretation.

Strengths and limitations

This meta-analysis consolidates extensive data on the effects of *Boswellia* extract across multiple NDs, marking a pioneering effort to evaluate its efficacy comprehensively. The rigorous sensitivity and subgroup analyses identified sources of heterogeneity, ensuring the robustness and stability of the results. Predefining animal models and outcome indicators minimized selection bias, enhancing the translational value of our findings from preclinical research to potential clinical applications.

However, the study has several limitations. The exclusive inclusion of English-language studies may introduce selection bias and limit the generalizability of the findings. Additionally, the absence of reported adverse effects of Boswellic extract could contribute to publication bias, although our analysis did not indicate significant asymmetry. The methodological quality of the included studies varied, with only a few detailing their randomization processes, potentially affecting the reliability of the results. These limitations necessitate cautious interpretation of the findings and highlight the need for further research.

Despite these limitations, this meta-analysis provides valuable insights into the therapeutic potential of *Boswellia* extract in neurodegenerative disorders. Future studies should include non-English publications and unpublished data to offer a more comprehensive understanding of *Boswellia* extract's efficacy in treating neurological diseases. Additionally, standardized methodologies and detailed reporting in future research will enhance the reliability and applicability of the findings.

Conclusion

This study systematically evaluated the neuroprotective effects of *Boswellia* extract across three major NDs: IS, AD, and PD. The findings indicate that *Boswellia* extract significantly reduces cerebral infarct volume in IS, improves behavioral outcomes in AD and PD, and enhances antioxidant enzyme levels across these models. Subgroup analyses highlighted the importance of disease type, administration route, treatment duration, and dosage form in influencing the efficacy of *Boswellia* extract. Despite significant heterogeneity, the overall evidence supports the potential of *Boswellia* extract as a promising therapeutic agent for NDs. These results not only contribute to the growing body of evidence supporting the use of natural compounds in neurodegenerative diseases but also pave the way for future studies to explore synergistic effects and optimize treatment protocols.

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