



A systematic review on biosynthesis, bioactivities, and therapeutic potential of Spinosin

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Abstract Spinosin, a flavone C-glycoside commonly found in the Fabaceae family and other flowering plants, has gained increasing attention for its diverse bioactivities and therapeutic potential. Spinosin biosynthesis likely follows the shikimic acid pathway, involving key enzymes such as phenylalanine ammonia-lyase, cinnamate 4-hydroxylase (C4H), 4-coumarate-CoA ligase (4CL), and chalcone synthase. The primary source of spinosin is *Ziziphus jujuba* Mill. var. *spinosa*, chief traditional Chinese medicine recognized for its sedative and hypnotic properties, with increasing evidence supporting its role in treating neurological disorders. Recent studies reveal spinosin's potential as an Alzheimer's disease

drug alongside its anti-inflammatory, hypoglycemic, cardioprotective, pigmentation, and anti-liver fibrosis effects. In vitro bioassays have highlighted its pharmacological properties, with less evidence from in vivo research, focusing on its effects on insulin resistance, sedation, cognitive improvement, and anti-cancer activity. This review provides a comprehensive exploration of spinosin in the context of its plant sources, biosynthesis, pharmacokinetics, bioactivity, toxicity, and safety. Such a compilation of literature identifies future prospects for the medicinal, agricultural, and biotechnological applications of spinosin to aid in maximizing its broader therapeutic effects.

Keywords Spinosin · Bioactivity · Biosynthesis · *Semen Ziziphi Spinosae* · Mechanism

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Introduction

Flavonoids are extensively found in plants and play many roles in biological processes like growth, flowering, and fruit development (Hostetler et al. 2017). Over 5000 natural flavonoids have been identified in plants, they take C6-C3-C6 as the basic structural skeleton. Based on structural variations, they are categorized into flavonoids, flavonols, flavanols, chalcones, anthocyanins, and isoflavonoids based on their structural subtypes (Hossain et al. 2016;

Liu et al. 2021). Natural flavonoids mostly occur as glycosides and can comprise a variety of flavonoid glycosides due to differences in the type, number, linkage position, and type of sugars (Xiao et al. 2016; Yang et al. 2018).

Semen Ziziphi Spinosae, derived from the dried mature seeds of *Ziziphus jujuba* Mill. var. *spinosa*, is a traditional Chinese medicine historically utilized for sedation and insomnia treatment (Fan et al. 2022). It was documented in ancient Chinese medical texts such as Golden Chamber Essentials, written by Zhang Zhongjing in the early third century, and the Compendium of Materia Medica, written by Li Shizhen (Wang et al. 2023; Yang et al. 2011). Recent research has shown that spinosin is the primary active compound responsible for the sedative and hypnotic properties of *Semen Ziziphi Spinosae* (Zhou et al. 2018). The seeds of *Ziziphus jujuba* Mill. var. *spinosa* is the major known natural source of spinosin, reports on other natural sources of spinosin were still scarce.

Spinosin, a flavone C-glycoside, is well-known for its classical sedative and hypnotic effects, biological activities, and mechanisms in anti-inflammatory (Zucolotto et al. 2009), anticancer (Shan et al. 2020), cardioprotective (Ismail 2023), and improvement of memory and cognitive abilities are being widely studied (Jung et al. 2014). Progress has also been made towards the investigation of spinosin action mechanisms. For instance, the cardioprotective activity of spinosin may be related to its preventive effect against oxidative stress and inflammation, while its role in enhancing cognitive and memory function is likely associated with its antioxidative, anti-inflammatory, and anti-apoptotic properties (Xu et al. 2019).

The physiological functions of spinosin and other flavonoids are closely linked to their metabolic processes. Several studies have investigated the pharmacokinetics and metabolism of spinosin using both animal and cellular models (Kuang et al. 2022). For example, 8 metabolites of spinosin were detected after co-incubation with human liver microsomes, and other studies have shown that spinosin effectively penetrates via the blood–brain barrier in rats, leading to a pharmacologic impact on the central nervous system (Qiao et al. 2016; Zhang et al. 2020b). Furthermore, gut microbes have an important influence on the metabolism of spinosin, suggesting that it may lead to a decrease in its in vivo bioavailability (Jiao et al. 2017). This review provides a comprehensive

overview of spinosin distribution, physicochemical properties, biosynthesis pathways, biotransformations, and in-depth insights into its biological activities in vivo and in vitro, alongside its toxicity and safety.

Research progress of spinosin

Such a potential and key flavonoid as “spinosin” has been the subject of extensive research from various viewpoints over the last 24 years with an obvious increase in research papers from just 2 records in 2000 to reach 80 in 2024 (Fig. 1a) due to its wide range of applications mostly for its health benefits in phytomedicine as retrieved by searching SCOPUS database for literature using keywords of spinosin in title (Fig. 1a). Six main clusters in literature could be visualized using VOSviewer (Fig. 1b) as such: Cluster 1 of 289 items colored red represented mostly by the item occurrence, plant, analysis, and formulations cluster 2 of 181 items colored blue represented mostly by the item biological effects especially central nervous system (CNS) effects, binding and enzyme inhibition, cluster 3 comprised of 138 items colored green including keywords related to the human cell, animal, anti-inflammatory and cytotoxicity and cluster 4 of 106 items colored yellow including keywords related to other flavonoid names mostly to binding and pharmacokinetics studied mostly in the biological field. Overlay visualization in VOSviewer was used to show developments over time with items colored differently based on the year of publication (average for the cluster). In this case, those terms that appeared recently (average year of publication is 2019) are more yellow Fig. 1c. A color bar shown in the corner has the same explanation; the scores of the items are determined by the time since publication revealing that oxidative stress, cytotoxicity, and action mechanisms are the recent trends in spinosin research among others. Further, papers grouped by subject areas revealed that the largest reports of spinosin are in pharmacology (25%), biochemistry (17%), and chemistry (15%) as depicted in Fig. 1d.

Spinosin distribution

Flavonoids are widely present in plants and possess strong antioxidant capabilities (Hidalgo et al. 2010).

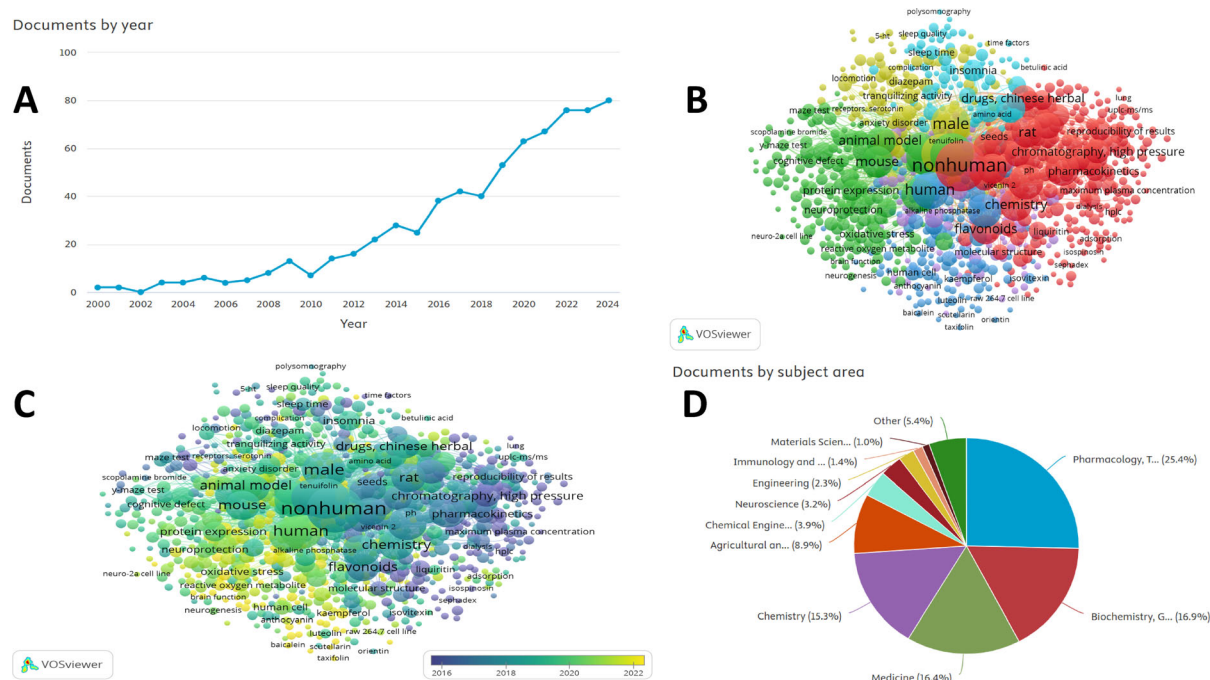


Fig. 1 Bibliographic data for searching spinosin in Scopus databases for its most relevant fields. **a** Research trends for publications retrieved by searching the Scopus database for the keyword spinosin as from the year 2000 till 2024. **b** Analysis of relevant keywords of spinosin in research during 2000–2024 from Scopus (collected on January 16th, 2025) revealing most applications were related to biochemistry and medicine. Irrelevant literature was removed by manual inspection and visualized using VOSviewer. The circular nodes of the same

color in the graph represent the same type of keywords. The larger the node radius and font size, the higher the frequency of the keyword, and the connection between the nodes represents the relationship between the two keywords. **c** Overlay visualization of most frequent terms (Constructed via VOSviewer v.1.6.10), where the score of the item is the time since publication from 2016 till 2022. **d** Pie chart showing papers retrieved by subject area by searching Scopus database for spinosin from 2000 till 2024

Spinosin is a naturally occurring flavone C-glycoside mostly derived from the seeds of *Ziziphus jujuba* Mill. var. *spinosa* (Rhamnaceae) (Zhang et al. 2015). Spinosin has also been isolated from other flowering plants such as *Clutia abyssinica* (Peraceae) (Zerihun et al. 1987), *Cayaponia tayuya* roots (Cucurbitaceae) (Aquila et al. 2009), and the petals of *Iris Nertshinskia* (Iridaceae) (Hirose et al. 1981). An overview of the plant resources of spinosin is shown in Fig. 2.

Aside from Rhamnaceae, Fabaceae is also one of the natural plant families of spinosin exemplified by *Ohwia caudata* (Bin Kwon et al. 2020; Wei. et al. 2013), and *Desmodium tortuosum* (Lewis et al. 2000). In addition, *Passiflora edulis* of Passifloraceae, enriched in flavonoids in its seeds, leaves, pericarp, and pulp, has been identified as a source of spinosin in the pericarp and leaf extract of *Passiflora edulis* (Sena et al. 2009; Zucolotto et al. 2009), and to likely contribute for its CNS sedative effect among others.

Consequently, searching for flavonoid-rich plants with biological activities such as sedative, hypnotic, anti-inflammatory, and antioxidant that could be used for activity guided isolation attempts of spinosin.

Nevertheless, the majority of previous studies have reported *Ziziphus jujuba* Mill. var. *spinosa* as the major source of spinosin, indicating that there is huge potential for exploitation of spinosin from this species. Due to the increasing demand for plant-derived bioactive molecules, there is a need to increase plant resources for spinosin, alongside improving the recovery yield of spinosin in the future.

Biosynthesis pathway and biotransformation

Flavonoids are plant secondary metabolites synthesized via different biosynthetic pathways (Wang et al. 2018). Flavonoids in higher plants primarily exist as

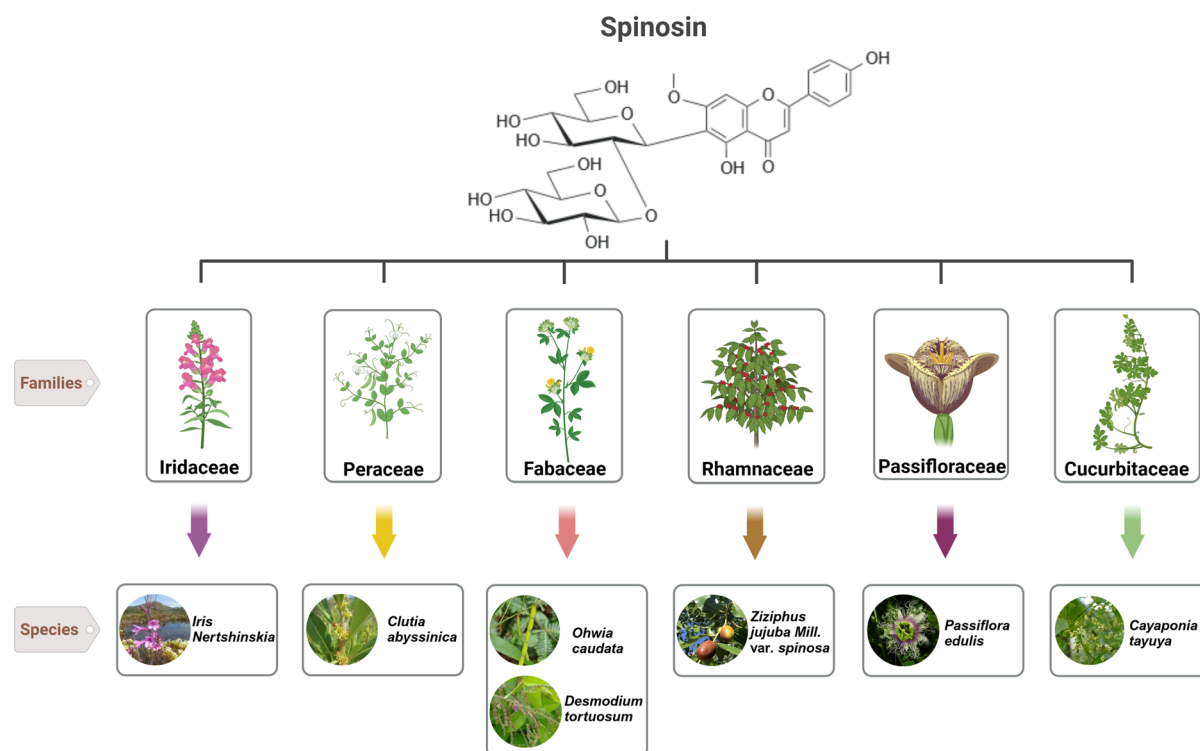


Fig. 2 The plant sources of spinosin. The picture materials are from *iNaturalist* and *Biorender* (www.inaturalist.org, www.biorender.com)

glycosides (Xiao et al. 2016). Extensive research has been conducted on the production of flavonoids in plants derived from the phenylpropanoid metabolic pathway, which contains eight branches: stilbene, aurone, flavone, isoflavone, flavonol, phlobaphene, proanthocyanidin, and anthocyanin (Liu et al. 2021). A common precursor for various flavonoids are chalcones, with CHS as the first committed enzyme in the biosynthesis of flavonoids (Mouradov and Spangenberg 2014). Naringenin plays a key role in the production of flavonoids and serves as a precursor for various polyphenols (Alam et al. 2014), and is involved in the production of spinosin (Tian et al. 2023).

Specifically, the key enzymes for the biosynthesis of spinosin were phenylalanine ammonia-lyase (PAL), cinnamate 4 hydroxylase (C4H), 4-coumarate-CoA ligase (4CL), chalcone synthase (CHS), chalcone isomerase (CHI), flavonol synthase (FLS), flavanone synthase (FNS), etc. (Shen et al. 2022; Wen et al. 2021). A study integrated metabolome and transcriptome sequencing to investigate three distinct growth and developmental stages of the *Ziziphi*

Spinosae seed (Tian et al. 2023). Studies annotated 13,232 differentially expressed genes and 83 flavonoid metabolites (Tian et al. 2023). Additionally, 53 genes encoding 15 enzymes were pinpointed as candidate genes implicated in the biosynthesis of flavonoids in *Z. Spinosae* seed. Among the involved genes, PAL, C4H, 4CL, CHS, CHI, and FNS genes were involved in spinosin biosynthesis (Fig. 3) (Tian et al. 2023). The first step in phenylpropanoids is preceded by the action of PAL catalyzing phenylalanine to cinnamic acid (Nabavi et al. 2020), and further p-coumaric acid under the catalytic effect of C4H. The catalytic effect of 4CL transforms p-coumaric acid into p-coumaroyl-CoA, this compound is then catalyzed by CHS and cofactor malonyl CoA to yield naringenin chalcone (Chen et al. 2006). CHI further catalyzes this compound to produce naringenin, which is then converted into apigenin by FNS, a precursor compound of spinosin. Apigenin gets converted to isovitexin, which is biotransformed into isovitexin 7-O-glucoside by isovitexin- β -glycosyltransferase (UDPG), and finally the synthesis of spinosin is

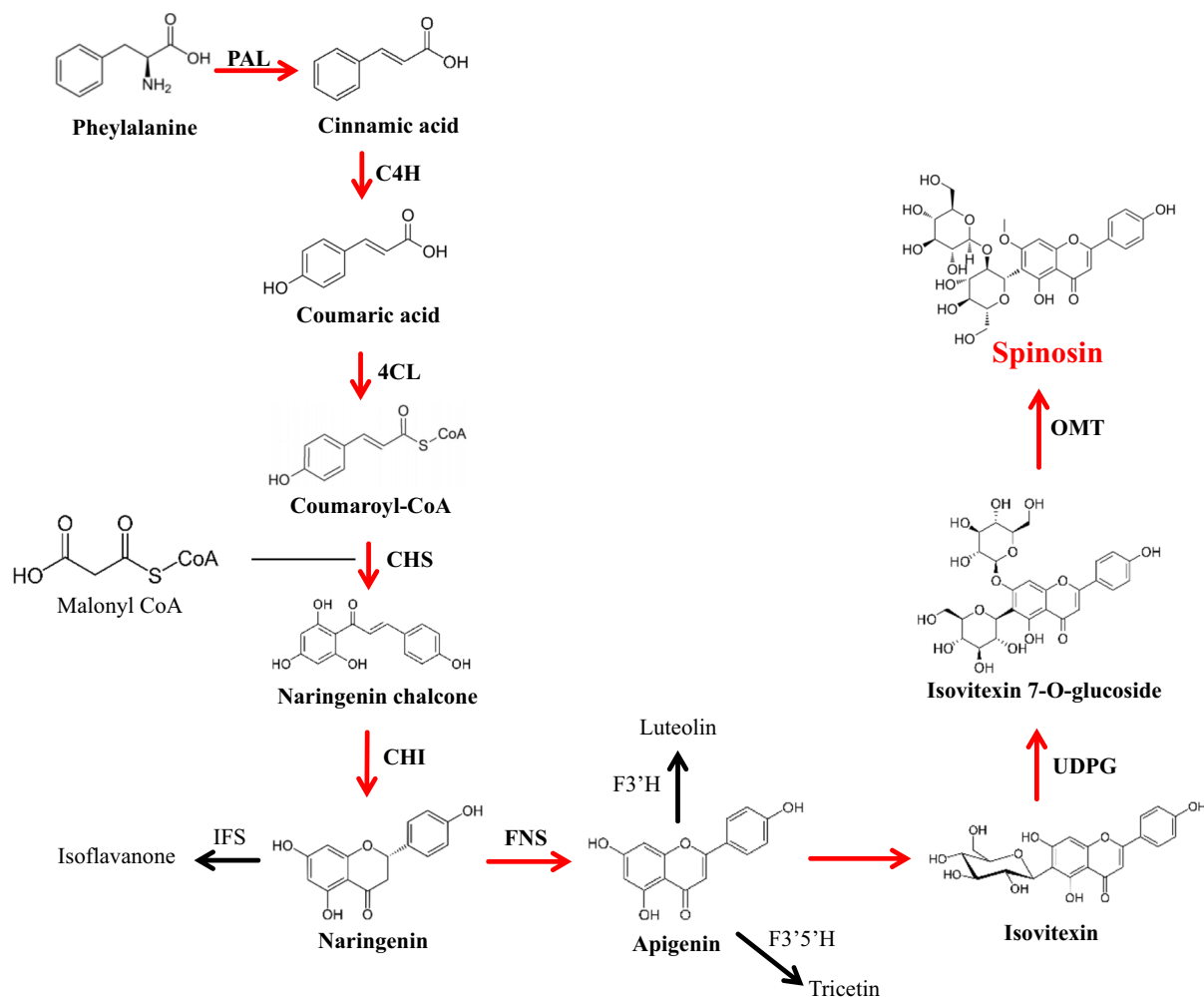


Fig. 3 Biosynthetic pathway of spinosin in *Semen Ziziphi Spinosae* (Tian et al. 2023)

catalyzed by flavonoid-*O*-methyltransferase (OMT) (Obmann et al. 2011; Wen et al. 2021).

Further research is necessary to identify the regulation of spinosin biosynthesis for future biotechnology efforts to produce it in other alternative plants and or enhance its production levels, given its significant potential nutraceutical uses.

Physicochemical properties

Spinosin is a white to yellow powder at room temperature, with molecular formula $C_{28}H_{32}O_{15}$, molecular weight 608.54 g/mol, melting point 149 °C, and boiling point 901.4 ± 65.0 °C (Zhao et al. 2014). Spinosin is a flavone *C*-glycoside that is

flavone substituted by hydroxy groups at positions 5 and 4', a methoxy group at position 7, and a 2-*O*-β-D-glucopyranosyl-β-D-glucopyranosyl residue at position 6 connected via a *C*-glycosidic linkage. The isosbestic point of spinosin occurs at 259 nm, where the absorbance is not affected by pH, and three strong absorption wavelengths, 215, 272, and 334 nm. Assays on spinosin were typically conducted at 334 nm to avoid interference with the detectable wavelength of others, which is different from spinosin's isosbestic point. Moreover, spinosin has higher stability at pH 6 and 7 which may be due to susceptibility of glycosidic bond hydrolysis (Sobhani et al. 2019).

Absorption, metabolism, and excretion

The liver is the major organ for drug metabolism, and one study has characterized the structure of spinosin metabolites by co-incubating spinosin with human liver microsomes (Merrell & Cherrington 2011). Another study has identified 8 spinosin biotransformed metabolites in samples of human liver microsomes (Q. Y. Zhang et al. 2020b). Regarding the site-specific pharmacokinetics of spinosin in vivo has also been reported, Ma et al. have investigated the pharmacokinetics of spinosin in blood, bile, and brain dialysate after administration to rats, with an area under the curve (AUC) of spinosin in blood, bile and brain at 205.70 ± 80.79 mg min/L, $7.77 \times 10^4 \pm 2.13 \times 10^4$ mg min/L, and 2.09 ± 0.03 mg min/L, respectively (Ma et al. 2012). This study suggested that spinosin may be actively excreted into bile, as spinosin levels in bile varied significantly more with concentration gradient than in blood and brain, as estimated by AUC and $T_{1/2}$. The clearance (CL) of spinosin in the brain was significantly higher than that in blood and bile, with its readily penetration inside the brain within 10 min until 50 min after administration inferring that spinosin penetrates the blood–brain barrier efficiently and rapidly, to account for its potential CNS effects. This finding supports the notion that spinosin has pharmacodynamic effect on the CNS.

Administration of rats with oral Suan-Zao-Ren (SZR) decoction enriched in spinosin, mangiferin, and ferulic acid, detected spinosin, mangiferin, and ferulic acid at 1, 6 and 1 ng/mL in plasma, respectively. It should be noted that both spinosin and mangiferin were poorly absorbed in plasma and eliminated more slowly in the insomnia group compared to the normal group, which is likely mediated via insomnia leading to a decrease in enzyme activity (He et al. 2012). This pharmacokinetic study provided a reference for the treatment of insomnia with spinosin. A similar study was conducted by administering *Z. spinosae* seed to rats and then characterizing the metabolic profiles of the 4 representative compounds in *Z. spinosae*: spinosin, isovitexin, jujuboside B, and betulinic acid (Li et al. 2021). This study on spinosin metabolism in rats revealed that spinosin primarily undergoes sulfation, glycosidation, deglycosylation, hydrogenation, hydroxylation, demethylation, methylation, and glucuronidation reactions. Hydrogenation is highlighted as a significant metabolic process for spinosin, with a

total of 18 hydrogenation products associated with spinosin (Li et al. 2021). In contrast, oxidized products of spinosin were predominantly present in rat feces. Overall, this study provided important data for the absorption and metabolism of spinosin in vivo.

Predictably, it is also important to investigate the interactions between spinosin and gut microbiota considering its poor bioavailability and likely to reach colon at high levels. One report examined the degradation dynamics of spinosin by rat intestinal flora using batch culture revealing that spinosin can be rapidly deglycosylated by rat intestinal microorganisms to swertisin, a metabolite derived from the loss of one glucose-based unit (162 Da) of spinosin (Zhang et al. 2013). Hydrolysis of spinosin by intestinal microorganisms may lead to a decrease in its absolute bioavailability in vivo, highlighting the need to create delivery forms that can improve its bioavailability.

In vitro bioactivities of spinosin

Anti-inflammatory activity

Inflammation is a crucial immune response triggered by external stimuli or injury to biological tissues, involving immune cells, blood vessels, and molecular mediators (Chung et al. 2017). While acute inflammation is an important defense mechanism for the immune system and aids in wound repair and healing, chronic inflammation has been linked to a variety of diseases, including cancer (Buckley et al. 2014; Leuti et al. 2020). Flavonoids and their preparations have a long history of use as anti-inflammatory agents (Ginwala et al. 2019). Treatment with spinosin has been reported to attenuate doxorubicin-induced overexpression of cardiomyocyte inflammatory markers tumour necrosis factor α (TNF- α), interleucina-6 (IL-6), cyclooxygenase-2 (COX-2), and nuclear factor kappa B (NF- κ B), and there was a dose-dependent effect of spinosin treatment (Ismail 2023). Another study reported that spinosin exerted a strong binding affinity to NF- κ B and inhibitor of κ B kinase (I- κ K), with binding energies comparable to MG-132, as determined by molecular docking (Kadioglu et al. 2016). In addition, spinosin exhibited inhibitory effects on nuclear p65 protein levels as observed through electromobility shift assay (EMSA) and western blot assays. Nevertheless, reports on the

in vitro anti-inflammatory activity and action mechanism of spinosin are still scarce. The in vitro bioactivities of spinosin are summarized in Fig. 4 and Table 1, respectively.

Hypoglycaemic activity

Hyperglycemia is the main characteristic disease of diabetes (Bakker et al. 2009). Hyperglycemia damages multiple organs, weakens the immune system, affects the cardiovascular system, and initiates blood clots (Mazeraud et al. 2014). In vitro hypoglycemic activity of spinosin was specifically found to significantly enhance glucose consumption in insulin

resistant HepG2 cells and showed a better effect on elevating the insulin resistance symptom of HepG2 cells (Li et al. 2023). Results indicated that spinosin can improve insulin resistance symptoms by enhancing the energy metabolic level and increasing the glycogen synthase activity of HepG2 cells. In addition, the study also found that saponins of dried *Z. jujuba* Mill. kernel can promote the antioxidant capacity of insulin resistance HepG2 and increase the expression of phosphorylated adenosine 5'-monophosphate (AMP)-activated protein kinase α (p-AMPK), phosphoinositide 3-kinase p110 α (PI3K-p110 α), and phosphorylated glycogen synthase kinase-3 β (p-GSK3 β). Researchers identified spinosin as one

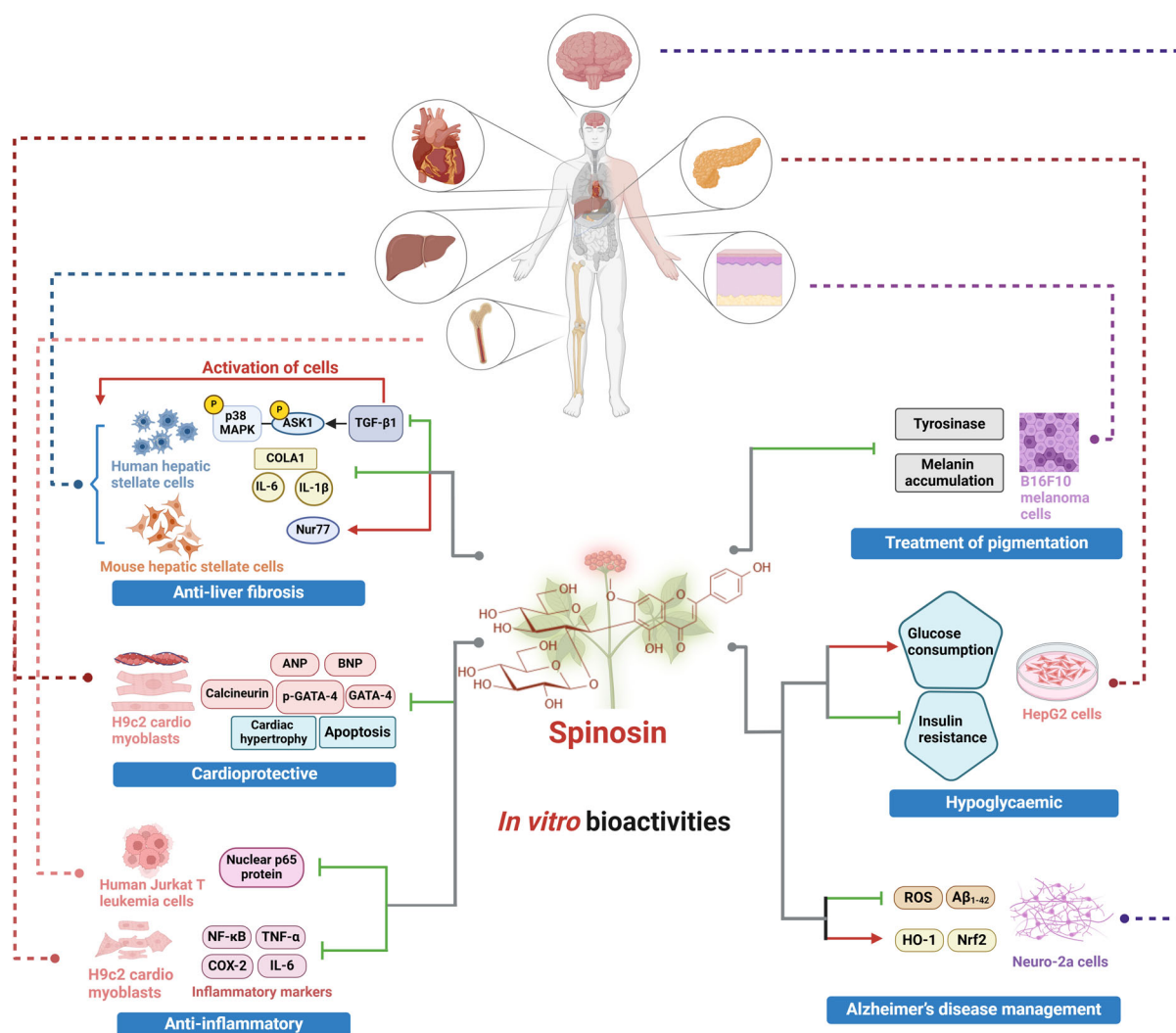


Fig. 4 Overview of spinosin's bioactivities in vitro. The picture materials are from Biorender (www.biorender.com)

Table 1 List of biological activities and molecular action mechanisms of spinosin in vitro

Biological activities	Objectives	Dosage and duration	Alterations	Molecular mechanisms	References
Anti-inflammatory	Human Jurkat T leukemia cells	10 μ M	↓Nuclear p65 protein	Strongly bound to NF- κ B and I- κ K with comparable binding energies and similar docking poses as MG-132	(Kadioglu et al. 2016)
	H9c2 cardio myoblasts	100 mM for 2 h	↓inflammatory markers TNF- α , IL-6, COX-2 and NF- κ B	Protecting against oxidative stress and inflammation	(Ismail 2023)
Hypoglycaemic	HepG2 cells	400 μ g/mL	↑the glucose consumption ability ↓the insulin resistance symptom of HepG2 cells	Improving the insulin resistance symptoms by improving the energy metabolic level and increasing the glycogen synthase activity of HepG2 cells	(Li et al. 2023)
Alzheimer's disease therapeutic	Wild type mouse Neuro-2a cells, N2a cells stably expressing human APP695	6.25, 12.5, 25 μ M for 24 h	↓ROS ↑Nrf2 and HO-1 ↓the level of A β ₁₋₄₂ ↓the aggregation of A β ₁₋₄₂	Reducing A β ₁₋₄₂ production by activating the Nrf2/HO-1 pathway in N2a/WT and N2a/APP695 cells	(X. Y. Zhang et al. 2020c)
Cardioprotective	H9c2 cardio myoblasts	100 mM for 2 h	↓ANP and BNP ↓calcineurin, p-GATA-4, and GATA-4 ↓cardiac hypertrophy in H9c2 cells ↓apoptosis in H9c2 cells	Protecting against cardiomyopathies induced by oxidative stress and inflammation	(Ismail 2023)
Pigmentation treatment	B16F10 melanoma cells	2, 5, 10, 20 μ M for 48 h	↓tyrosinase activity ↓melanin accumulation in B16F10 cells	Binding to and suppressing tyrosinase activity by forming multiple hydrogen bonds and hydrophobic interactions with the binding pocket of tyrosinase	(Moon et al. 2019)
Anti-liver fibrosis	Human hepatic stellate cells (LX-2), mouse hepatic stellate cells (HSC-T6), normal mouse hepatocytes (AML-12)	5, 10, 20, 40, 80 μ M	↓TGF- β 1-mediated activation of both LX2 and HSC-T6 cells ↑Nur77 ↓TGF- β 1-mediated phosphorylation levels of ASK1 and p38 MAPK ↓collagen deposition (COLA1) and inflammatory cytokines (IL-6 and IL-1 β)	Treating liver fibrosis by targeting Nur77 and blocking the ASK1/p38 MAPK signaling pathway	(Lin. et al. 2024)

TNF- α Tumour necrosis factor α , *IL-6* Interleucina-6, *COX-2* Cyclooxygenase-2, *NF- κ B* Nuclear factor kappa B, *I- κ K* Inhibitor of κ B kinase, *ROS* Reactive oxygen species, *Nrf2* Nuclear factor erythroid 2-related factor 2, *HO-1* Heme oxygenase-1, *A β ₁₋₄₂* Amyloid β -protein (1–42), *ANP* Atrial natriuretic peptide, *BNP* B-type natriuretic peptide, *GATA-4* GATA binding protein 4, *TGF- β 1* Transforming growth factor beta 1, *Nur77* Orphan nuclear receptor 77, *ASK1* Apoptosis signal-regulated kinase 1, *MAPK* Mitogen-activated protein kinases

of the major components of saponins in *Z. jujuba* Mill. kernel (Li et al. 2023). Therefore, in conjunction with previous studies, the biological activity of saponins in improving insulin resistance may be mainly derived from spinosin.

Alzheimer's disease management

Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder, characterized by irreversible brain function damage throughout the brain, such as neuronal cell damage and abnormal deposition of beta-amyloid and tau proteins (DeTure & Dickson 2019). Spinosin was believed to potentially improve and treat AD attributed for its sedative effect (Kuang et al. 2022). Wild-type mouse Neuro2a cells (N2a/WT) and N2a stably expressing human APP695 cells (N2a/APP695) are commonly used as a cell model to study the pathogenesis of AD (Wang et al. 2004). Research demonstrated that spinosin down-regulated the level of amyloid β -protein (1-42) ($A\beta$ 1-42) and inhibited the oligomerization of $A\beta$ 1-42 in N2a/WT and N2a/APP695 cells, activating the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway to mediate the expression of beta-secretase 1 (BACE1), and metalloproteinase domain-containing protein 10 (ADAM10) differentially, inhibiting reactive oxygen species (ROS) production (X. Y. Zhang et al. 2020c). The above findings reveal the potential of spinosin as a therapeutic agent for treating AD. Whether spinosin can augment classical anti Alzheimer drugs effect has yet to be revealed.

Cardioprotective effect

Heart diseases, including hypertensive heart disease, coronary heart disease, myocarditis, etc., are highly prevalent in middle-aged and elderly people over 50 years of age, and there has been a trend of rejuvenation in the past decade (Andersson & Vasan 2018; Tang et al. 2017). Doxorubicin is commonly used in the treatment of cancer, has albeit to exert a severe cardiotoxic effect, and can therefore be used to induce cardiotoxicity models (Kong et al. 2022). H9c2 cells are often used as a cellular model for cardiovascular disease in in vitro studies (Zhao et al. 2018). It has been discovered that spinosin reversed doxorubicin-induced cardiomyopathy via multiple mechanisms including reduced cardiomyocyte enlargement,

suppressed expression of hypertrophic and inflammatory markers, attenuated expression of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), reduced expression of calcineurin, GATA binding protein 4 (GATA-4) and p-GATA-4, as well as anti-oxidative and anti-inflammation effects (Ismail 2023). Spinosin showed promise as a potential medication for treating cardiac disease which has yet to be tested clinically.

Pigmentation treatment activity

Tyrosinase, a copper-containing oxidase enzyme, is involved in regulating the process of melanin synthesis and plays a key role in the formation of melanin (Pillaiyar et al. 2017). Studies searching for tyrosinase inhibitors as a treatment for skin hyperpigmentation problems (Wang et al. 2014) revealed that spinosin, one of the 8 major compounds in *Z. jujuba* seeds, showed the strongest ability to inhibit tyrosinase (Moon et al. 2019). This inhibition was primarily due to its ability to prevent α -melanocyte-stimulating hormone (α -MSH) or ultraviolet B (UVB)-induced melanin production in B16F10 cells, without causing harm to the cells. Moon et al. also revealed that spinosin exhibited antimelanogenic effects in experiments on human skin models, and studies further indicated that spinosin acts as a competitive inhibitor of tyrosinase. The protein docking simulation revealed that spinosin possibly inhibits tyrosinase activity by forming multiple hydrogen bonds and hydrophobic interactions with tyrosinase's binding pocket. This evidence supported the potential development of spinosin for treating hyperpigmentation or as an ingredient in whitening cosmetics.

Anti-liver fibrosis effect

Liver fibrosis is a pathophysiologic process, a repair response to diffuse over deposition and abnormal distribution of extracellular matrix in the liver after various types of injury (Pellicoro et al. 2014). If not treated, it may progress to irreversible cirrhosis and eventually to hepatocellular carcinoma (HCC) (Hammerich & Tacke 2023). Recent studies have demonstrated that spinosin can effectively inhibit transforming growth factor beta (TGF- β 1)-mediated activation of human hepatic stellate cells (LX-2) and mice hepatic stellate cells (HSC-T6), enhanced orphan

nuclear receptor 77 (Nur77) expression, decreased TGF- β 1-mediated phosphorylation of apoptosis signal-regulated kinase 1 (ASK1) and p38 mitogen-activated protein kinases (p38 MAPK), strongly suppressed the expression of inflammatory cytokines (Lin. et al. 2024). Molecular docking demonstrated action mechanisms by which spinosin can bind directly to Nur77-LBD and inhibit pro-inflammatory and pro-fibrotic responses via the ASK1/p38 MAPK signaling cascade. These effects significantly hinder the advancement of liver fibrosis and enhance liver function, which provides a guide to the development of therapeutic agents for liver fibrosis.

Pharmacological actions in animals

Antidiabetic bioactivity

One of the core pathological mechanisms of diabetes, especially type 2 diabetes (T2D), is the development of insulin resistance, and patients with T2D usually show symptoms of insulin resistance before the onset of hyperglycemia (Laakso & Kuusisto 2014). Insulin resistance, also known as decreased insulin sensitivity, refers to the insufficient effect of insulin to carry out its normal physiological role, is a phenomenon in which adipocytes, muscle cells, and hepatocytes do not respond adequately to normal concentrations of insulin (Petersen & Shulman 2006; Yari beygi et al. 2019).

The role of flavonoids in treating insulin resistance and diabetes has been extensively studied (Al-Ishaq et al. 2019; Sun et al. 2020). Researchers discovered that administering 20 mg/kg of spinosin reduced various insulin resistance phenotypes such as body weight, fasting glucose levels, oral glucose tolerance, and insulin resistance index in high-fat-diet (HFD) mice (Ge et al. 2022). This treatment also inhibited ROS production and subsequent inflammation, restored insulin receptor substrate 1 (IRS-1) to activate phosphoinositide 3-kinases (PI3K)/protein kinase B (Akt)/endothelial nitric oxide synthase (eNOS) signaling, and upregulated insulin-mediated NO production in endothelial cells. This mechanism is similar to the in vitro study in which spinosin improved insulin resistance in HepG2 cells. Overall, spinosin exerted anti-hyperglycemic and insulin-sensitizing effects through multiple mechanisms, including promoting

glucose uptake, modulating energy metabolism, reducing oxidative stress, and enhancing insulin signaling pathways. The convergence of in vitro and in vivo results suggests that spinosin may serve as a promising therapeutic candidate for managing insulin resistance and diabetes-related complications. Further clinical research is needed to validate its efficacy and molecular mechanisms in human subjects. The in vivo bioactivity of spinosin is depicted in Fig. 5 in detail.

Therapeutic effects of sedation and insomnia

Long-term reduction in the quality of sleep and insomnia can cause mental state, cognitive and memory decline, and in severe cases will lead to suffering from anxiety or depression, and even jeopardize the body's immune system, cardiovascular and metabolic system to cause damage, triggering a variety of diseases (Palagini et al. 2022; Wang et al. 2019). *Z. Spinosae* seed is a traditional sedative and hypnotic drug, with spinosin as the main active component to account for such an effect (Fan et al. 2022).

There is more than one action mechanism mediating for spinosin hypnotic action. One report found that spinosin has anxiolytic-like effects, mainly on flumazenil-induced anxious mice in the elevated cross maze, light and dark box test, and open field test, and that its mechanism of action appears to be modulated by gamma-aminobutyric acid-A (GABA_A) and 5-hydroxytryptamine-1A (5-HT_{1A}) receptors (Liu et al. 2015). Other studies reported that spinosin significantly enhanced the quality of pentobarbital-induced sleep in rats, as evidenced by the shortening of sleep latency and an increase in the total sleep time, as well as the duration of non-rapid eye movement (NREM) sleep, and the duration of REM sleep, in terms of NREM sleep duration, spinosin primarily increased slow-wave sleep (SWS) (Wang et al. 2010). This hypnotic effect of spinosin may be related to the post-synaptic 5-HT_{1A} receptor. In addition, Wang et al. believed that the enhanced hypnotic effects of pentobarbital as a result of spinosin treatment may not be related to the dopaminergic system, but rather to serotonergic mechanisms (Wang et al. 2008). Spinosin can also lead to a restricted pattern of c-Fos expression within the lateral hypothalamic area orexin neurons and locus coeruleus, and this particular neuronal inactivation contributed to sedation as well as

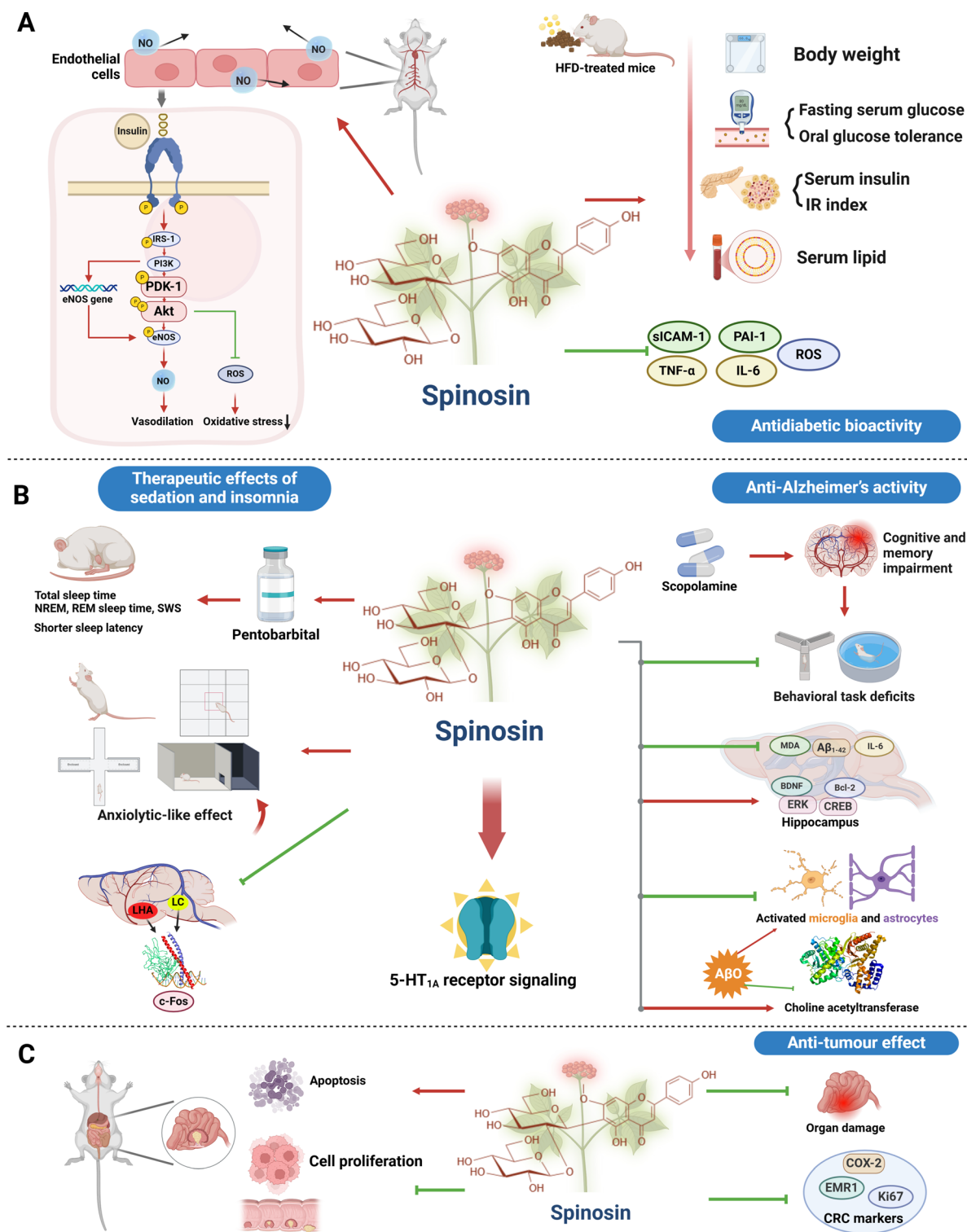


Fig. 5 Summary of spinosin's bioactivities in vivo. **a** Antidiabetic bioactivity. **b** Therapeutic effects of sedation and insomnia, anti-Alzheimer's activity. **c** Anti-tumor. The picture materials are from Biorender (www.biorender.com)

hypnosis (J. P. Zhang et al. 2020a). In summary, spinosin exhibits strong sedative properties, making it a promising candidate for managing mental disorders such as anxiety and agitation, as well as improving sleep disorders. Its potential as a dietary supplement or an adjunct therapy alongside medications like pentobarbital is further explored. Additionally, natural sources of spinosin may be able to play a good role in improving the efficacy of the drug while mitigating its side effects.

Anti-Alzheimer's activity

AD is the most common type of cognitive impairment disorder with an insidious onset and difficult early diagnosis. Mild cognitive impairment and memory problems are early signs of AD (Roy et al. 2016). Cognition is defined as the ability to process information through perception, encompassing various cognitive processes, learning, attention, and memory abilities (Voytek & Knight 2015). Therefore, the search for drugs to intervene as well as to treat cognitive impairment and memory disorders seems warranted (Xia et al. 2023), especially in the context of extending the life expectancy of patients with AD.

The classic sedative and hypnotic effects of spinosin were mentioned earlier, with the role of spinosin in improving memory and cognitive function being previously reported. It has been found that spinosin can improve learning and memory abilities in mice with scopolamine-induced memory impairment by decreasing the aggregation and production of amyloid- β (A β) (Zheng et al. 2022). In addition, spinosin was able to improve scopolamine-induced memory deficits for behavioral tasks in mice, such as a higher rate of spontaneous alternation in the Y-maze task and an extended swimming duration in the target quadrant in the Morris water maze task. These improvements were mediated by the serotonin neurotransmitter cascade, especially 5-HT_{1A} receptor signaling (Jung et al. 2014). Spinosin also elevated the levels of phosphorylated extracellular signal-regulated kinase (ERK) and cAMP response element-binding protein (CREB) in the hippocampus. For A β 1-42 oligomer (A β O) induced cognitive deficits in AD model mice, studies reported that after 7 days of intracerebroventricular (ICV) administration of spinosin, cognitive deficits were significantly attenuated, and the number of activated microglia and astrocytes

were reduced (Ko et al. 2015; Xu et al. 2019). Additionally, levels of malondialdehyde (MDA) and A β 1-42 accumulation in the hippocampus were effectively reduced, concurrent with expression of brain-derived neurotrophic factor (BDNF) and B-cell lymphoma-2 (Bcl-2).

Overall, the evidence from both in vitro and in vivo studies highlights the multifaceted effects of spinosin on AD pathology and cognitive function. Spinosin not only reduces A β accumulation and oligomerization but also mitigates oxidative stress and inflammation, modulating key signaling pathways such as Nrf2/HO-1 and ERK/CREB activation. Whether spinosin can augment the effects of classical anti-AD drugs remains to be further explored, but its potential as a complementary therapeutic agent for treating AD-related cognitive impairment is evident.

Anti-tumour effect

Colorectal cancer (CRC) is a type of cancer that impacts the colon or rectum, and it has the third-highest incidence and second-highest mortality rate of all cancers (Wu et al. 2023). Currently, the primary treatment for colorectal cancer remains surgical resection and chemotherapy, which are associated with high side effects (Dekker et al. 2019). Some of the polyphenols with anti-colorectal cancer activity such as EGCG, resveratrol, and curcumin have been recognized (Ding et al. 2020). Spinosin has also been found to exert significant anti-colorectal cancer activity, as evidenced by inhibition of cell proliferation, promotion of apoptosis, and increased chemosensitivity of CRC cells (Shan et al. 2020).

In a mouse model of colitis-associated carcinoma (CAC) induced by AOM/DSS, spinosin effectively reduced the number and volume of CAC polyps in a dose-dependent manner and effectively limited organ damage. Spinosin treatment was also effective in preventing the elevation of early CRC markers such as COX-2, EGF-like module-containing mucin-like hormone receptor-like 1 (EMR1), and antigen Kiel 67 (Ki67) in CAC mice, indicating that spinosin has potential as a natural anti-CRC agent yet to be tested in humans. These studies provided foundational knowledge and evidence based on which it can be hypothesized that spinosin could potentially play a role in early intervention and treatment of different types of cancer. Determination of synergistic effects of

spinosin with other standard chemotherapies to broaden its application in different cancer types and likewise lessen the dose of cytotoxic chemotherapeutics.

Toxicology and safety

A study was conducted to examine the acute toxicity of spinosin in mice by intraperitoneal administration of graded doses ranging from 200 mg/kg to 10 g/kg. The results showed that no mice died in any group at the 10 g/kg dose, indicating that spinosin is physiologically safe and harmless (Shin. et al. 1978).

At the cellular level, spinosin doses ranging from 0–400 μ M did not significantly impact the cell survival of N2a/WT (X. Y. Zhang et al. 2020c). However, cytotoxicity was observed at 200–400 μ M in N2a/APP695. Therefore, spinosin administration in the range of 0–100 μ M was found to be safe for both N2a/WT and N2a/APP695 cells. Furthermore, 20 μ M of spinosin had no cytotoxic effects on a variety of other cell lines, such as B16F10 cells, human keratinocyte-forming cells (HaCat), and human fibroblasts (Hs27) (Moon et al. 2019).

Patents

A patent reportedly pertaining to a pharmaceutical composition comprising spinosin for use in the prevention and treatment of cognitive disorders has been granted. Specifically, this patent describes pharmaceutical compositions comprising spinosin that enhance memory and learning ability, thereby effectively preventing and treating diseases such as AD and amnesia (US9956242B2). Another patent disclosed a preparation method and a quality control method for Suan-Zao-Ren decoction formula granules containing spinosin, which quantifies the content of spinosin in the granules and sets a content standard of not less than 0.25 mg of spinosin per 1 g of granules (CN105535395A).

Furthermore, there are two patents related to skin applications of spinosin. The first patent is for a spinosin containing cream-like product preparation for treating skin abnormalities of the eyes and face induced by helminth mite infection (JP2021532152A). The second patent pertains to a

skin-whitening cosmetic composition of spinosin, in which the inventor conducted a study and found that the composition containing spinosin as an active ingredient had the effect of inhibiting tyrosinase activity and inhibiting melanin formation. Consequently, the patented invention is a topical preparation for preventing or treating skin pigmentation (KR102002627B1).

Conclusion

Spinosin, a flavone C-glycoside with diverse bioactivities, holds significant therapeutic potential across various domains, including neurology, cardiology, oncology, and metabolic disorders. The review highlights its rich plant sources, biosynthetic pathways, promising pharmacological properties, and low toxicity. However, current research primarily focuses on in vitro studies, with limited in vivo and clinical validation of its therapeutic effects. A comprehensive exploration of its absorption, metabolism, and mechanism of action will strengthen its applications in medicine, and biotechnology. Second, pharmacokinetic studies on spinosin are more adequate, but more studies on its catabolism and utilization in the gastrointestinal tract need to be complemented, especially regarding how gut microbiota influences its pharmacokinetics. Third, in terms of biological activities, studies on the neuropathological activities of spinosin, such as sedation and hypnosis, have been more fully investigated, but its anti-inflammatory, immunomodulatory, and anticancer activities are still inadequately reported. Consequently, future research should focus on improving spinosin's biosynthetic and metabolic pathways in vivo while further elucidating the molecular mechanisms underlying its biological activities. This will help maximize its therapeutic potential and identify targeted effects to be tested clinically in humans, particularly for AD and metabolic disorders. The development of innovative drug delivery systems to enhance spinosin's stability, solubility, and targeted delivery for improved therapeutic outcomes should be considered in the future.

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