

The development of *Chrysanthemum indicum* as a brain nutraceutical

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Abstract

Chrysanthemum indicum L. is a medicinal plant that has been widely used in society due to its high antioxidant activity. *Chrysanthemum* flowers are now being considered as a candidate neuroenhancer to help improve brain cognitive function, from focus to learning ability. Studies have shown that *chrysanthemum* flowers are known to have the potential to be used as a nootropic, antidepressant, and anxiolytic related to their antioxidant effects. Traditional and modern dosage form development options, such as capsules, functional foods, tea, or aromatherapy, are beginning to be used in accordance with consumption convenience and opportunities to increase user acceptance. This review presents a summary of the potential effectiveness and relevance of *C. indicum* for brain health, with evidence related to nootropic, antidepressant, and anxiolytic effects, along with supporting research and implications for dosage form development.

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1. Introduction

The health consequences of cognitive impairment and memory loss are no longer limited to the traditional diagnoses of neurodegenerative diseases. This understanding has extended beyond the medical community to how these conditions affect an individual's ability to live their daily life, their ability to provide for themselves and support their families, and how much they contribute to the healthcare system. In 2021, worldwide dementia was estimated to have affected at least 57 million people and is currently increasing by approximately 10 million new cases annually (WHO, 2025). The most recent report emphasizes that most cases of dementia could be prevented or delayed by controlling modifiable risk factors, such as those related to a person's habits, to strengthen brain health and cognitive function. This action is an important agenda item in long-term prevention and management (Livingston *et al.*, 2024).

Growing concern about cognitive performance has intensified interest in neuroenhancing agents, including nootropics that aim to support thinking, learning, and memory, both before and after functions begin to weaken (Malik and Tlustoš, 2022). However, the field still faces

two recurring barriers because promising candidates rarely act through a single mechanism, and cognition depends on several interacting pathways that must be addressed together. Supporting evidence must also be carried through into products that remain credible for safety and benefit. Natural compounds are attractive for research not only because of their traditional use but also because they provide a spectrum of bioactive molecules that can act on multiple targets.

Chrysanthemum indicum L. is a prime candidate due to its long history of use in traditional medicine and a relatively rich phytochemical database that may contribute to neuroprotective and neuroenhancing activities (Shao *et al.*, 2020). Preclinically, *C. indicum* extracts have been reported to protect neurons from oxidative stress through modulation of the TrkB/Akt/CREB/BDNF pathway, which is closely associated with neuronal resilience and synaptic plasticity (Jeong *et al.*, 2021). In addition to the oral route, the volatile fraction of *C. indicum* has also been studied through essential oil inhalation and has been associated with changes in physiological parameters and EEG activity consistent with relaxation responses, opening opportunities for aromatherapy applications as part of a more convenient

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and popular dosage form (Kim *et al.*, 2018).

C. indicum deserves attention because it has a strong track record of traditional use, especially in Asia, and has been consumed daily. However, discussions about *C. indicum* are often divided between the bioactivity literature and the product development literature. On the one hand, literature frequently positions the chrysanthemum as a plant with promising neuroenhancement potential, while on the other hand, product development is carried out separately. Based on this need, this article aims to summarize *C. indicum* as a neuroenhancer candidate with a focus on formulation development and potential pharmaceutical applications, while highlighting the most realistic forms of utilization for adoption in society.

2. Chrysanthemum overview

C. indicum, commonly known as chrysanthemum, is a plant that grows to a height of 0.25–1 m, with rhizomes varying in size from long to short, erect or spreading stems, branches, rarely stacked, cut bases, and at first glance appear heart-shaped or broadly pointed. The leaves on the middle stem of this plant are oval or elongated oval with a pale green or olive-green surface. The flowers on chrysanthemum plants are classified as compound flowers, have loose tips, varying numbers of capitula, and five rows of phyllaries (Flora of China Editorial Committee, 2011). In natural populations, chrysanthemum flowers have been identified as diploid or tetraploid cytotypes (Li *et al.*, 2013). This chrysanthemum can grow in grasslands on mountain slopes, shrubbery, wet areas along riverbanks, fields, roadsides, coastal areas, or other places at an altitude of 100-2,900 meters above sea level. This plant prefers moist areas and thrives in fertile alluvial soil or sandy loam with good drainage. Chrysanthemums grow well in places with temperatures of 15°C to 30°C and average annual rainfall of 1,000 to 2,000 mm (Lim, 2014). This flower is considered native to China and Japan and is widely cultivated in Indian gardens for its colorful ornamental flowers. *C. indicum* has been used for more than 2000 years to treat various diseases. In traditional Chinese and Ayurvedic medicine, dried chrysanthemum flowers are often used to treat colds, fever, migraines, conjunctivitis, eye irritation, hypertension, inflammation, ulcerative colitis, vertigo, and skin infections (Prakash *et al.*, 2014). Several other studies also mention that *C. indicum* has other biological benefits, such as anticancer, hepatoprotective, and antioxidant properties (Shao *et al.*, 2020).

2.1 Active compounds in chrysanthemum flowers

Chrysanthemum flowers have been shown to contain many active compounds. Shao *et al.* (2020) reported in their publication that chrysanthemum flowers contain

191 identifiable natural compounds, including 42 flavonoids, 96 terpenoids, 21 phenylpropanoids and phenolic acids, 12 spiro ketones, and 20 other compounds. However, the most important compounds in determining their activity are flavonoids and terpenoids (Sulaeman *et al.*, 2022). The compounds identified in chrysanthemums are myricetin and quercetin (Wu *et al.*, 2010).

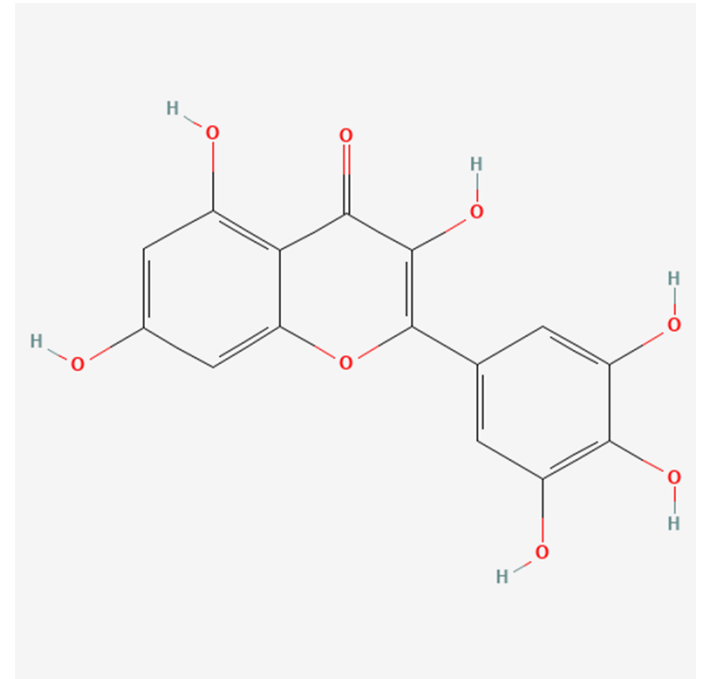


Figure 1. Structure of myricetin (Source: NCBI, 2025a).

Myricetin (3,3',4',5,5',7-hexahydroxyflavone) is a light yellow flavonol derived from the parent compound taxifolin, which is converted to the intermediate compound (+)-dihydromyricetin and can be further chemically modified to produce laricitrin and then syringetin, both of which are molecules in the flavonol class of flavonoids (Ong and Khoo, 1997; Semwal *et al.*, 2016). The phenolic structure of myricetin is also similar to those of other well-known flavonoids, such as quercetin, morin, kaempferol, and fisetin. As such, myricetin is often referred to as hydroxyquercetin (NCBI, 2025a). Myricetin is a flavonol compound that has a pyrogallol based B ring. A multitude of hydroxyl groups are present on the B ring, as can be seen in Figure 1. Because of its hydroxylation pattern, myricetin has a higher degree of lipophilic properties than the other conjugated flavonoids and allows for increased interaction of myricetin with biomembranes. The presence of hydroxyl groups in myricetin, in turn, increases the opportunity for hydrogen-bonding. As a result, this hydrogen-bonding capacity can influence the overall solubility of myricetin and how myricetin interacts with transport proteins in the body (Gupta *et al.*, 2020; Goyal *et al.*, 2024). Myricetin is known to have a log P value of 2.94. Myricetin tends to be less soluble in water but is readily soluble in organic solvents. With a

pKa of 6.63, myricetin tends to be in a non-ionic form at physiological pH (Yao *et al.*, 2014). This allows myricetin to penetrate cell membranes, including the blood-brain barrier.

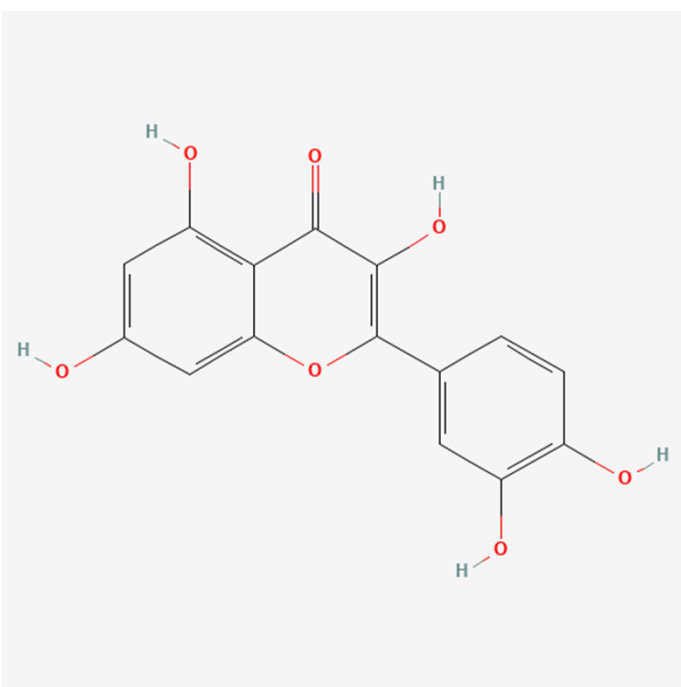


Figure 2. Structure of quercetin (Source: NCBI, 2025b).

Quercetin is a type of a flavanol with C6-C3-C6. This compound consists of two phenyl rings and one heterocyclic ring. Based on Figure 2, this molecule has a backbone structure with hydroxyl groups at specific positions, which play an important role in determining its biological activity. The hydroxyl groups of quercetin are located at positions 3, 5, 7, and 4 on the phenyl ring. The quercetin molecule also adopts a largely planar structure that plays an important role in its interaction with biological membranes and proteins (Protsenko *et al.*, 2010). Quercetin's capacity to cross the blood-brain barrier (BBB) is principally attributed to its lipophilic nature. Being lipophilic in nature, quercetin can effortlessly diffuse through the double lipid layer of the endothelial cells that form the BBB, thus getting into the brain. Moreover, the permeability of quercetin to the BBB is impacted by the involvement of membrane transporters, especially the ABC (ATP-binding cassette) transporters. Based on research conducted by Li *et al.* (2024) and Huang *et al.* (2024), quercetin can interact with P-glycoprotein (P-gp), the main transporter for the efflux of compounds in the BBB.

2.2 Neuroenhancement potential of chrysanthemum flowers

Chrysanthemum flower extract was reported to have an IC_{50} value of 67.80 ± 2.37 mg/mL (Rahmasari *et al.*, 2024). In another study conducted by Fatimawali *et al.* (2025), the IC_{50} value of the chrysanthemum flower ethanol extract was found to be 1.35 μ g/mL as well as

the IC_{50} values for water and n-hexane fractions of chrysanthemum flower extracts being found as 1.11 and 7.59 μ g/mL, respectively (Dolongtelide *et al.*, 2023). These studies concluded that the antioxidant activity was classified as very strong. Antioxidants are compounds that are essential in the mechanism of neutralizing damage caused by free radicals. These compounds work by inhibiting the formation of free radicals, thereby reducing the risk and eliminating oxidative stress (Jeon *et al.*, 2021). Given the fact that antioxidant potential has the flower extract of asteraceae family, chrysanthemum could be an excellent neuroprotective aid and memory enhancer.

2.2.1 Nootropics

Nootropics, sometimes called "smart drugs," are defined as compounds that can help improve learning and memory skills. Nootropics generally affect nerve cell function through modification of existing signaling pathways. While nootropics can be effective in addressing many types of cognitive disorders, they are most commonly used to treat disorders associated with cognitive dysfunction (Malik and Tlustoš, 2022). Nootropics are usually well-tolerated. Treatment with nootropics should be continued for at least 2-3 weeks after being prescribed (Giurgea, 1973).

C. indicum has shown promise as a potential treatment for neurodegenerative diseases through several different mechanisms. For example, 3,5-Diarylpyrazole derivatives isolated from chrysanthemum flowers have been shown to inhibit A β aggregation, one of the defining characteristics of AD. These derivative compounds are known to exhibit strong activity against A β aggregation with EC_{50} values ranging from 1.3 to 15.8 μ M (Wu *et al.*, 2015). In an analysis of neuroprotective effects using SH-SY5Y cell lines, the compounds myricetin, quercetin, and 3,5-diarylpyrazole derivatives in chrysanthemum flowers showed significant neuroprotective activity against A β -induced cytotoxicity in nerve cell lines. Specifically, the compound myricetin in chrysanthemum flowers is known to prevent A β aggregation through modulation of A β conformational changes that reduce its neurotoxicity (Shimmyo *et al.*, 2008). Myricetin can also bind metal ions such as Cu and Zn which are known to promote amyloidogenic processes and this interaction plausibly strengthens the anti amyloidogenic profile associated with chrysanthemum derived constituents (DeToma *et al.*, 2011). Beyond A β centered effects, *C. indicum* may also relate to mitochondrial protection because in damaged N2a SW cell models myricetin was

reported to improve mitochondrial membrane potential and support mitochondrial stability which can make cells more resilient even under A β challenge (Yao *et al.*, 2022). This causes cells to become more stable and unaffected even when induced by A β .

In Alzheimer's disease, nootropic effects include the modification of various molecular pathways that play an important role in the pathogenesis of this disease. Research shows that chrysanthemum flower extract plays a role in inhibiting acetylcholinesterase (AChE) activity and activating the TrkB/Akt signaling pathway. In inhibiting acetylcholinesterase (AChE) activity, studies in Alzheimer's mice involving the administration of chrysanthemum flower extract, either mixed into drinks or given at a dose of 0.1 mg/gBW, have been shown to improve long-term memory and reduce AChE activity in the brain. The ethanol extract of chrysanthemum flowers contains active compounds, such as acacin and acacetin-7-O- β -D-galactopyranoside, which have been shown to significantly inhibit the activity of acetylcholinesterase (AChE) in vitro (Jeung *et al.*, 2007). A decrease in AChE activity in the brain results in an increase in the amount of acetylcholine available for neurotransmission, which may have the potential to enhance cognitive function in AD patients. Additionally, chrysanthemum flower extracts have also been shown to activate the TrkB/Akt signaling pathway. *Sophora japonica* flower extract has been reported to increase phosphorylation of the TrkB, Akt, and their downstream effectors, resulting in increased antioxidant defense and decreased apoptosis in hippocampal neurons (Jeong *et al.*, 2021). These studies are sufficient to illustrate the potential of chrysanthemum flowers in the treatment of Alzheimer's disease.

Chrysanthemum flowers have also attracted attention for their potential in treating Parkinson's disease (PD). The mechanism explaining this potential is related to the ability of the compounds myricetin and quercetin to modulate cellular signaling pathways. Myricetin has been tested in various preclinical models of PD. In the case of the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model, myricetin beat the mice model and motor function was improved. Moreover, myricetin resulted in even more significant dopamine levels while protecting the neurons active in dopamine production (e.g. tyrosine hydroxylase-positive ones) from dying in the case of rotenone-induced *Drosophila* model (Dhanraj *et al.*, 2018). Furthermore, myricetin and quercetin were also

shown to ameliorate the striatum of the mouse against the downfall of not only dopamine but also its metabolite (3,4-dihydroxyphenylacetate) in a case where the mouse model was 6-hydroxydopamine (6-OHDA) treated (Ma *et al.*, 2007; Wang *et al.*, 2021). The potential of myricetin compounds in chrysanthemum flowers is also mediated by other molecular pathways, such as Nrf2. Myricetin was found to trigger the nuclear factor E2-related factor (Nrf2), which leads to higher expression of antioxidant enzymes, for instance, NQO-1 and HO-1. In a newborn mouse model with hypoxic-ischemic brain damage, myricetin reduced brain infarct volume and oxidative stress markers through Nrf2 signaling (Chen *et al.*, 2023). By a similar mechanism, the compound quercetin is known to activate sirtuin (SIRT1), autophagy, paraoxonase 2 (PON2), and Nrf2-ARE, which play a role in cellular defense mechanisms (Wang *et al.*, 2021).

Recent research on the potential of chrysanthemum flowers has begun to highlight the potential benefits of their use in stroke therapy, Chrysanthemum extract protects ischemic stroke patients by improving neuronal health and lessening the severity of the stroke. In one clinical trial, patients receiving chrysanthemum extract had a more significant decrease in NIHSS score, serum levels of neuron-specific enolase (NSE), S100, and malondialdehyde (MDA) than those treated with placebo, as well as an increase in brain-derived neurotrophic factor (BDNF), superoxide dismutase (SOD), and total antioxidant capacity (TAC) levels after four days of use (Healthcare Engineering, 2023). A study of gerbil CA1 hippocampal cells found that the immunoreactivity of antioxidant enzymes such as SOD1, CAT, and GPX was significantly higher in gerbil CA1 pyramidal cells treated with *C. indicum* extract compared to those that experienced ischemia without chrysanthemum extract administration (Kim *et al.*, 2017). In addition, CAT and GPX immunoreactivity was significantly greater in the *C. indicum* group than in the ischemic group without treatment. Chrysanthemum treatment helped to increase the number of NeuN-positive neurons in the CA1 region of the hippocampus. In the *C. indicum* group, 68% of the neurons were protected compared to only 9% in the untreated control group. This indicates that chrysanthemum treatment keeps enzyme levels higher and provides a protective effect against oxidative damage. Chrysanthemum water extracts were also tested against an in vitro model of cerebral ischemia. This model involved exposing SK-N-SH neuroblastoma cells to oxygen and glucose deprivation, mimicking

stroke conditions. Based on the results, chrysanthemum flower extract increased cell viability by approximately 20-27% compared to untreated ischemic cells (Chun *et al.*, 2008).

2.2.2 Antidepressant

A 10-day animal study performed on Swiss albino mice demonstrated a reduction in the immobile time of mice during the despair swimming test (DST) and tail suspension test (TST), which confirmed the antidepressant effect of chrysanthemum flowers. When *C. indicum* was given, the TST results showed reduced immobile time for the mice that were in the TST. In the research, extracts at doses of 250 mg/kg (161.7 ± 3.159) and 500 mg/kg (136.3 ± 2.140) produced significant antidepressant effects, and their effectiveness was found to be comparable to the standard drug Imipramine (114.5 ± 1.688) (Shewale *et al.*, 2020). The study concluded that EECI at a dose of 500 mg/kg showed more significant antidepressant activity than the 250 mg/kg dose, indicating a dose-dependent effect. Another study observing the effects of administering supercritical carbon dioxide liquid extract from *C. indicum* (SEC) to rats experiencing chronic unexpected mild stress (CUMS) found that SEC could restore weight loss due to CUMS in rats, demonstrating its potential as an antidepressant (Shewale *et al.*, 2020). Moreover, it was shown that the SEC administration led to a decrease in the depressive behavior of the mice. The criteria for this were the increased consumption of the sweet solution in the respective test, enhanced movement in the open field test (OFT), and the decreased immobility in the forced swim test (FST) and tail suspension test (TST).

One of the main components in chrysanthemum flowers, which is also one of the identity compounds, is myricetin. It has been found that the anti-depressive effect of myricetin is through the reduction of depression-like behavior as indicated by the decrease of immobility time in the forced swim test (FST) of the rats with PTSD. The histological and behavioral changes brought about by the antidepressant treatment correlates with the suppression of the hypothalamic-pituitary-adrenal axis as seen in the reductions of plasma levels of corticosterone (CORT) and adrenocorticotrophic hormone (ACTH), which are indicators of stress response, also decreased with myricetin administration. Treatment with myricetin restored neurotransmitter balance by increasing serotonin (5-HT) levels and decreasing norepinephrine levels in brain regions associated with fear and stress, such as the prefrontal cortex and hippocampus (Sur and Lee,

2022). Additionally, intraperitoneal administration of 10 mg/kg myricetin for 14 days reversed depression-like behavior and reduced IL-6 levels in the hippocampus in a chronic mild stress (CMS) model (Pereira *et al.*, 2022). The reduction in IL-6 levels has been widely reported due to its association with decreased neuroinflammation, which is one of the causes of depression.

In addition to myricetin, quercetin has also been tested in various validated mouse models for depression and has consistently demonstrated the ability to reduce depressive behavior in animals through changes in biochemical indices related to oxidative stress, inflammation, and neuroplasticity. The reported doses range from tens to hundreds of mg/kg in systemic paradigms and high-dose experimental regimens in metabolic/protective studies. Administration of 25 mg/kg quercetin for 4 weeks in a model of mild unexpected chronic stress depression (UCMS) showed an increase in swimming and escape attempts in the tail suspension test (TST) and modified forced swimming test (MFST) (Khan *et al.*, 2019). Administration of 50 mg/kg quercetin for 21 days in the same model demonstrated that treatment with quercetin reduced apoptosis in the hippocampus and prefrontal cortex. Additionally, there was a decrease in Nrf2 protein expression, ERK phosphorylation, and CREB activity in the test animals (Ge *et al.*, 2024). In a study, administration of quercetin and imipramine reduced IL-6 levels and increased BDNF levels in a male rat model of depression induced by monosodium glutamate (MSG) (Sriram and Ravichandra, 2019). Quercetin has also been shown to have good antidepressant effects by inhibiting NMDAR1 expression through disruption of the interaction between $\alpha 2\delta$ -1 and NMDAR, as well as reducing HPA axis excitability in the CUMS mouse model (Wang *et al.*, 2024). In terms of dosage form, intranasal administration of a nanotransferosomal gel targeting the brain at a dose of 10 mg/kg was able to improve behavioral parameters and reduce neuronal activation markers (c-fos) compared to non-targeted formulations in experimental rats (Elkomy *et al.*, 2023). Based on research by Li *et al.* (2024), When a dosage of 50 milligrams of Quercetin per kilogram (mg/kg) was given using the gastrointestinal (GI) route, alterations occurred in the make-up of the gut flora, as well as changes in the pattern of brain metabolism in the glycolysis, Sphingo-lipid and pentose phosphate pathway to improve behaviour. This shows that quercetin is a possible candidate for the development of anti-depressant therapies from plant sources.

2.2.3 Anxiolytic

In a study conducted by Hong *et al.* (2012), chrysanthemum flower water extract was shown to significantly increase the time spent on the EPM test compared to the control group. In this study, it was also evident that the anxiolytic effects of chrysanthemum water extract (CWE) given at 500 mg/kg was blocked by a GABAA receptor antagonist named Bicuculline as well as a selective serotonin receptor antagonist called WAY100635. This suggests that the anxiolytic effects of the flower may be due to the action of GABAA and/or 5-HT_{1A} receptors. Moreover, both the ethanol and chloroform extracts of the *C. indicum* flower demonstrated anxiolytic activity at a dosage of 500 mg/kg, based on increased time spent, and increased number of entries, into the open arms in elevated plus maze (EPM) testing, as well as an increase in the time spent in the center and a decrease in grooming time in the open field test (OFT) in test animals (Sheela *et al.*, 2017). Complementing these findings, fractionation studies showed that the HP20 and water fractions had potent anxiolytic effects at much lower doses (3–15 mg/kg), resulting in improvements in the EPM, OFT, in addition to this, both the light-dark box tests demonstrated similar efficacy to Buspirone (Jang, 2013).

However, the crude water extract needed higher doses to yield significant evidence, which suggests that the majority of the pharmacologically active constituents for anxiety relief are contained in the HP20 and water fractions. Myricetin and quercetin are also included in the findings related to mood as studied through trying to falsify mood related outcome measures. Quercetin produced anxiolytic-like effects in animal behavior tests at a level reported as comparable to diazepam. The proposed mechanism involves its interaction with the GABA_A receptor α_2 , which creates benzodiazepine-like effects (Islam *et al.*, 2022). Jung and Lee (2014) reported anxiolytic effects of quercetin without sedation or myorelaxation that suggested involvement of GABAergic signaling, highlighting its potential as a non-benzodiazepine modulation therapy. Myricetin also shows consistent anxiolytic effects that are linked to the stress axis and neurotrophic signaling. A study on PTSD-like rodents reported that myricetin can reduce anxiety-like symptoms associated with HPA axis regulation and BDNF/ERK signaling activation (Sur and Lee, 2022). A possible pathway proposed was the reduction of anxiety by dampening the stress endocrine load while supporting the brain's plasticity.

2.3 Development of chrysanthemum in dosage forms

2.3.1 Hard candy

Hard candy is a concentrated sugar system, cooked to a low water content, and rapidly cooled into an amorphous or glassy matrix (Ozel *et al.*, 2024). The stability of this formulation is highly dependent on the type of sweetener, cooking temperature, and water content (Hartel and Nowakowski, 2017). Along with the shift in trends towards healthy foods, the candy industry has also significantly shifted to sugar-free formats. Sugar-free variants that replace sucrose with polyols (maltitol, isomalt, xylitol, sorbitol) require adjustments to the cooking endpoint and cooling regimen to achieve transparency and hardness, as well as to avoid graining or stickiness. In formulation, ingredients such as hygroscopic additives (e.g., some polyols, acids) can soften the matrix and lower the glass transition temperature (T_g), while flavors, acids, pigments, and plant extracts should be added after cooking or during cooling to preserve volatile compounds and manage pH-dependent interactions with the sugar matrix (Ozel *et al.*, 2024; Sarkar *et al.*, 2024).

From a consumer and sensory perspective, acceptance is driven by the maintenance of core candy attributes, such as sweetness, familiar flavor, and hard, transparent, non-sticky texture (Jeon *et al.*, 2021; Khemacheevakul *et al.*, 2021). In addition to its pleasant taste, hard candy has great practical advantages for the delivery of nutraceuticals because it can be used as a combined delivery system and it can also be a solution for patient discomfort and non-compliance with conventional preparations (Sangle and Tathe, 2023). Hard candy is a traditional oral dosage form as well. The well-known candy formulations, such as lozenges and medicinal lollipops, can provide local or systemic effects and may partially avoid first-pass loss while enhancing functional efficacy through prolonged residence in the mouth (Rathod *et al.*, 2018).

C. indicum contains flavonoids, particularly myricetin and quercetin, which can limit its production process. Given the low water solubility and extensive first-pass metabolism of flavonoids, nanoencapsulation, microspheres, liposomes, cyclodextrin inclusion complexes, and other polymer carriers can protect the active compounds, improve dispersion, and enhance intestinal absorption. This need is illustrated by myricetin, which has an absolute oral bioavailability of 9.6% in rats but increases approximately fourfold with a tailored microcell carrier, and quercetin, which shows low

and variable exposure but can be enhanced through cyclodextrin, nanoparticles, liposomes, phospholipid complexes, or prodrug strategies (Ng and Yong, 2023; Nie *et al.*, 2024). Specific stability risks in hard candies, such as granule formation and stickiness caused by moisture migration and mobility near T_g, must be addressed through moisture control, the use of minor sugars or oligosaccharides to slow crystallization, and the careful addition of heat-sensitive active ingredients after the highest cooking step or as dry capsules compatible with low-moisture glass matrices (Leinen and Labuza, 2006; Rahmasari *et al.*, 2024). In addition to solubility and stability issues, the use of *C. indicum* in hard candies can affect taste. The use of flavorings and determination of active ingredient load limits per unit are necessary to maintain consumer acceptance, as consumers demand low-sugar options and accept new formats when sensory quality remains high and functional claims are credible (Ozel *et al.*, 2024).

2.3.2 Gummy candy

Gummy candies are one of the most popular types of candy. These candies have a distinctive gel texture. The advantages of these candies are that they are easy to consume, have an attractive shape, taste sweet, and are suitable for all ages (Nishiyama-Hortense *et al.*, 2022). In general, gummy candy consists of thickening agents, sweeteners, water, acids or flavorings, and optional functional ingredients (Rashmi and Mona, 2023; Ghodsi and Nouri, 2024). Manufacturers typically vary in their use of sweeteners and fillers in their products, and may add fruit and vegetable purees, gum, oils, pigments, and encapsulated powders or microcapsules to add nutrients or active ingredients (Roobab *et al.*, 2020; Ghodsi and Nouri, 2024; Kaewpetch *et al.*, 2024). In production, chrysanthemum extract can be added in the form of dry extract. The chewy texture of this preparation is obtained from the use of a thickening agent called hydrocolloid. Gelatin is widely used for classic gummy candies, while plant-based matrices such as agar, carrageenan, gum Arabic, and pectin are used for vegan gummy candies (Zhang *et al.*, 2018; Gorjanović *et al.*, 2024; Kaewpetch *et al.*, 2024). Water activity, pH, heat and agitation, are all important variables in the process control of gummy candies that have bioactive properties, microbiological safety and target texture (Ozkan *et al.*, 2022; Kaewpetch *et al.*, 2024).

Consumer acceptance of gummy and jelly candies is influenced by appearance, texture, and a balanced sweetness profile. In hedonic testing of

fruit-based gummy candies, results show that bright yet natural colors increase liking, while optimizing sugar levels or sugar substitutes maintains acceptance without compromising texture (Cano-Lamadrid *et al.*, 2020; Gorjanović *et al.*, 2024). When manufacturers produce chrysanthemum gummy candies, they face the challenge of how to deal with the taste of the astringent polyphenols. The polysaccharides used in making the candy need to mask or delay the release of the bitterness caused by the polyphenols, allowing the consumer to enjoy the taste of the candy without experiencing the degradation of the flavour, while also limiting the number of polyphenols that can be consumed in the tasty gummy candy. A related challenge is the loss of chrysanthemum flower active compounds due to temperature exposure during the candy-making process. Manufacturers typically encapsulate products to minimise this degradation (Bobrysheva *et al.*, 2025). Based on research by Abolhasanzadeh *et al.* (2024), encapsulation of active compounds in gummy candies has been shown to maintain activity, increase bioavailability of active compounds, and reduce the unpleasant taste of active compounds. For hydrophobic polyphenols such as quercetin, encapsulation improves dispersion, encapsulation shields compounds from the effects of processing and digestion, and can slow the release of the compound. Examples of other successful carriers used in food matrixes include liposomes, double emulsions, coacervate complexes, polymer particles, and fibre-phenol complexes. These carriers are typically added during the cooling or final mixing stages to ensure that the structure of the carrier remains intact (Buljeta *et al.*, 2022; Abolhasanzadeh *et al.*, 2024; Jiang *et al.*, 2024; Shishir *et al.*, 2024).

2.3.3 Tea

Chrysanthemum flowers have been part of various traditional medicines, ceremonies, and culinary customs throughout East, South, and Southeast Asia, with product forms varying in terms of formula and production methods (Liu *et al.*, 2025; Patil *et al.*, 2025). Chrysanthemum flowers can be made into tea by processing them with or without other ingredients, and the product form is determined by local processing traditions. *C. Indicum* is highly valued in traditional Chinese medicine (TCM) for its ability to cool the body and purify it of toxins (Gu *et al.*, 2022). These flowers are consumed as herbal teas or other functional foods to treat liver inflammation and improve vision (Gu *et al.*, 2022).

In formulation, the most important process is the extraction method. The selection of methods is based

on the desired quality and potential activity. Among the public, the most relevant and frequently applied traditional methods are simple infusion and water decoction. This approach generally produces water-based extracts containing polar components, such as flavonoid glycosides and phenolic acids, which often determine the character of the resulting tea. In another study using hot water extraction, it was found that this method provided the highest total phenolic content and antioxidant activity for the water extract fraction. A preclinical study by Bello (2025), multiple toxicants and chemicals have been used for millennia in the production of traditional fermented beverages. Historically, boiling and drying were used together to create a dry extract that allowed for the eventual standardization of testing activity and formulation development.

In recent years, there are extraction techniques specifically designed to maximize compound yield and target selectivity through the use of a variety of solvent systems and production technologies. One reported innovation is the DES/SHS/H₂O (eutectic solvent/switchable hydrophilic solvent/water) system combined with high-speed homogenization, which is capable of increasing the extraction of phenolic compounds, flavonoids, and essential oil components more efficiently than conventional approaches, as well as producing a better anti-inflammatory profile in reported trials (Liu *et al.*, 2023). Modern approaches such as this provide advantages for standardized extract formulations because they improve the homogeneity of the main active ingredient test and reduce inter-product variation. In other words, water is suitable for highlighting the characteristics of tea, while combination methods can be chosen if the desired effectiveness is a specific function, such as fractionation.

The availability of more effective modern approaches and the trend toward commercialization of chrysanthemum flower products have encouraged the development of ready-to-drink products that require minimal consistency and variation between batches. An optimization study conducted by Li *et al.* (2023) reported that a consumer-acceptable beverage formulation can be achieved by brewing 2 g of chrysanthemum powder at 90°C and adding sugar at a concentration of 14.28%, extraction techniques aimed at achieving a balance of chemical compounds with hedonic acceptance within the beverage matrix are becoming more common as manufacturers look to enhance phenolic absorption at intestinal absorption sites. Brewing conditions also impact the formation of submicron-sized particles

within brewed beverages, which may enhance phenolic absorption at intestinal sites, indicating the role brewing conditions play in determining the absorption potential and extent of various chemical constituents within the beverage (Julianti *et al.*, 2025). Although it is quite rare, some studies also developed *Chrysanthemum indicum* in the form of syrup.

2.3.4 Capsules

In modern practice, there has been a significant shift from herbal preparations to capsules because capsules are mass-produced, easier to use, have a neutral taste, and are more standardized in dosage. Capsule preparations are also available in health product stores, online markets, and some pharmacies in Asia (Feiyan *et al.*, 2013). This shift has been driven by significant industrial activity and patents for capsule formulations, soft gels, slow-release preparations, and multi-component herbal combination products (Cheng *et al.*, 2010; Ruiqin, 2012; Feiyan *et al.*, 2013). In many jurisdictions, chrysanthemum capsules are more realistically categorized as traditional medicines or health supplements, so their function in society often falls within the realm of traditional use and wellness, which is more readily accepted by the public.

The development of chrysanthemum in capsule form is essentially the first step taken to change the traditional decoction practice that has been commonly used by the community (Feiyan *et al.*, 2013). The aim is to transform chrysanthemum into practical, oral preparations are easier to formulate accurately in the form of capsules since all capsules can be used directly from a kit created specifically for the preferred dosages and quality (Ruiqin, 2012). The capsule formulation process starts by obtaining the raw medicinal extracts through extraction via decoction or similar method (soaked) of raw materials into an appropriate ratio of solvent to raw materials. The next step is to reduce contaminants from the capillary cell using cold alcohol and to monitor quality by monitoring the presence of targeted active compounds (Feiyan *et al.*, 2013). The next step is to flavour-adjust the extract, which is usually in a concentrated form, to enhance the palatability of the final product since all concentrated extracts will be freeze dried (lyophilized) to produce the dry powder form of the extract without destroying heat-labile compounds. Freeze-drying processes are also used to help cover up bitter taste to improve compliance when encapsulated into hard capsules. Addition of commonly used excipients is also required to provide effective flow of the

powdered mixture and effective filling of the capsule, such as fillers to increase volume and flow properties, binders to aid in granule formation, and lubricants to prevent sticking during the filling process (Ruiqin, 2012). The choice of capsule shell is also tailored to the characteristics of the extract: hard gelatin capsules are generally used for dry extracts, Hydroxypropyl Methylcellulose (HPMC) is preferred for hydrophilic or hygroscopic extracts, whereas soft capsules are used for concentrated essential oils or emulsified extracts (Feiyan *et al.*, 2013; Yuanfa, 2020). Once the laboratory-scale production is completed and scaled up, the following step typically involves establishing consistency and reliability of the manufacturing methods through the use of orthogonal experimental design principles that focus upon critical extraction conditions, ranging from soaking time, reflux duration, solvent-to-material ratio, to the number of extraction cycles required (Feiyan *et al.*, 2013). Optimization decisions focus not only on yield but also directly on quality indicators, as key markers of quality during the process. Another commonly used method is Quality-by-Design, which can provide consistent results despite variations (Youssef *et al.*, 2020). To strengthen process standardization in the preparation of TCM-based solid oral preparations, the Manufacturing Classification System (MCS) approach is also mentioned as a framework that assists in manufacturing classification and process standardization to improve reproducibility and make scalability more focused (Xiaoqing, 2023).

2.3.5 Aromatherapy

Based on the availability of volatile fractions in chrysanthemum flower extracts, formulation development has also largely focused on volatile fractions for use in aromatherapy. These fractions determine the aroma characteristics of the final product. Essential oils in *C. indicum* are reported to have yields and chemical profiles that are highly influenced by the extraction method. Therefore, methods that can preserve the active compounds in accordance with the desired potency and aroma are needed. Methods with low temperatures and relatively fast processing times, such as supercritical CO₂ extraction (SFE) and solvent-free microwave extraction (SFME/SLMHD), tend to be preferred when the primary goal is to preserve heat-sensitive volatile components and maintain aroma retention (Chang *et al.*, 2010; Wei, 2013), while conventional steam distillation risks reducing yields and damaging some heat-sensitive components. More specifically, SFE is reported to be optimal at an extraction temperature of 35°C, a separation temperature of 30°C,

a pressure of 25 MPa, a time of 90 minutes, and a CO₂ flow rate of 30 kg/hour, with yields of up to 9.7% and higher compound diversity compared to steam distillation. On the other hand, the steam distillation method, which involves prolonged heating at boiling temperatures, is reported to produce lower yields than SFE and decompose some heat-sensitive components (Wei, 2013). To improve process efficiency while maintaining aroma profile, SFME/SLMHD methods can help improve yields and achieve similar extraction ratios as conventional hydro distillation, which can potentially take 180 minutes to process, while significantly reducing process duration. Typically, optimization occurs during the pre-extraction stage and typically involves pretreatments that increase oil yield and purity such as freeze/thaw cycling, immersion at 60-70°C, and sonication. Additionally, several patents refer to using ultrasonically assisted solvent-free microwaving as a method for shortening process times whilst increasing extraction ratios. While it is important to maximize yield with extraction methods, literature shows that some extraction methods can significantly impact extracted component composition, thus altering their activity profile, so ideal optimization must consider both profile and yield effects simultaneously (Fan *et al.*, 2018).

In the development of aromatherapy products, chrysanthemum essential oil is generally developed for direct inhalation or fragrance blends for relaxation. Additionally, in addition to yield, the literature indicates extraction methods can have a significant impact on the overall profile and stability of the extracted product. Many commercial products contain ingredients for topical and cosmetic use, including aroma blends for aroma therapy and incense and patents for formulations based upon patented aroma blends, and the establishment of reasonable delivery systems (example O/W microemulsions and Hyaluronic Acid hydrogels) to improve the stability, rheology, and gradual release of volatile constituents (Lee *et al.*, 2015; Fan *et al.*, 2018). Purification steps are also an important part when the main objective is sensory quality. Studies show that purification through adsorption or desorption using macroporous resins removes non-volatile components and residues that can interfere with the desired aroma profile (Lee *et al.*, 2015). The research currently available regarding the stability of chrysanthemum aromatherapy products is limited, therefore, additional investigations into chrysanthemum-aromatherapy process parameters are required. In addition to developing products that

Table 1. Practical dosage form opportunities for *C. indicum*.

Dosage form	Community use	Practical role	Reference
Hard candy	User-friendly dosage form for people who dislike swallowing capsules, convenient for on-the-go intake	Chosen for its palatability and prolonged oral residence, that can improve overall acceptability	Rathod <i>et al.</i> , 2018; Jeon <i>et al.</i> , 2021; Sangle and Tathe, 2023
Gummy candy	Suitable for every age group because of its chewy texture and palatability	Chosen because it is easy to use and sensory appealing, particularly for daily use	Cano-Lamadrid <i>et al.</i> , 2020; Gorjanović <i>et al.</i> , 2024
Tea	Household preparation and common traditional use, usually consumed as a routine morning drink	Chosen because it is familiar, culturally embedded, and easy to prepare at home	Liu <i>et al.</i> , 2025; Patil <i>et al.</i> , 2025
Capsules	Sold through pharmacies, online marketplaces, and wellness stores, usually consumed by adults daily	Chosen because it is portable, able to mask the taste, and offered more measured dosage	Cheng <i>et al.</i> , 2010; Ruiqin, 2012; Feiyan <i>et al.</i> , 2013
Aromatherapy	Used mainly for relaxation purposes and in fragrance-oriented products	Chosen because it is easy to use and non-oral	Chang <i>et al.</i> , 2010; Wei, 2013

are consistent in aroma, quality control systems will need to be developed to assess the volatility and or stability characteristics associated with chrysanthemum-aromatherapy formulations. The development and implementation of such systems will play an important role in the selection of the extraction methods used and the overall sensory acceptance of the finished product.

The wide range of chrysanthemum dosage form developed is evidence that *C. indicum* formulation can be administered via oral or nasal. A summary of the uses of each dosage form can be seen in Table 1.

Conclusion

In conclusion, *C. indicum* has a strong ethnopharmacological basis and is supported by consistent preclinical evidence that its active compounds contribute to antioxidant, anti-inflammatory, neuroprotective, and cognitive function-enhancing activities. Currently, there is a trend toward using new delivery methods for products to replace traditional methods. The most common types of new delivery systems are capsules, candy gels, and aromatherapy. New technologies are also being developed to provide more consistent results through better standardization of raw materials, improved stability of products, and improved sensory characteristics of products. In order for new health claims to be substantiated, there must be complementary clinical studies conducted on humans. In the future, we will see the combination of raw material standardization and advanced delivery systems that provide increased bioavailability of nutrients, and consistent manufacturing design will be key to developing chrysanthemum as an evidence-based product.

Conflict of interest

The authors declare no conflict of interest.

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