IBRO Neuroscience Reports 18 (2025) 50–56

Contents lists available at ScienceDirect

IBRO Neuroscience Reports

journal homepage: www.sciencedirect.com/journal/IBRO-Neuroscience-Reports

A comprehensive review of the neurological effects of anethole

Ramina Khodadadian, Shima Balali- Dehkordi *

Department of Basic Sciences, Faculty of Veterinary Medicine, Shahrekord University, Shahrekord, Iran

ARTICLE INFO

Keywords:
Anethole
Anti-oxidant properties
Anti-inflammatory effects
Nervous system
Therapeutic use

ABSTRACT

Since ancient times many countries have employed medicinal plants as part of traditional medicine. Anethole is a substance found in various plants and has two isomers, cis-anethole (CA) and trans-anethole (TA). Currently, the food industry extensively use anethole as an aromatic and flavoring component. Extensive scientific research are warranted to provide scientific proof for the usage of anethole, given its widespread use and affordable price. Preclinical studies have suggested several pharmacological effects for anethole including neuroprotective properties. It has been determined that anethole through modulation of monoamines, gamma-aminobutyric acid (GABA)ergic and glutamatergic neurotransmissions as well as its possible anti-inflammatory and antioxidative stress properties affected central nervous system (CNS). In this concept previous studies have demonstrated anxiolytic, antidepressant, antinociceptive, anticonvulsant, and memory improvement effects for anethole. To fully understand its therapeutic potentials, more research are required to elucidate the precise mechanisms by which TA and CA affected CNS. This review summarizes the current knowledge on pharmacological activities of the anethole concentrating its neurological properties, and the possible mechanisms underlying these effects. Various pharmacological effects which have been reported suggesting that anethole could be considered as a potential agent for management of neurological disorders.

1. Introduction

Medicinal herbs have been used to treat illnesses since ancient times (Jamshidi-Kia et al., 2017; Anand et al., 2022; Adhikari et al., 2021). Herbal medicines and natural therapies are a safe and cost-effective approaches to manage illnesses (Shaito et al., 2020; Zahra et al., 2020). Traditional medicines have major role in the healthcare systems of many nations. Despite development of chemical drugs, medicinal plants and their active compounds are being considered by researchers (Costa Font and Sato, 2024). Herbal medicine is more affordable for patients and has fewer adverse effects than synthetic drugs (Jamshidi-Kia et al., 2017; Barkat et al., 2021).

Fennel (*Foeniculum vulgare Mill*), a commonly used herbal remedy, has been shown that exerted variety of pharmacological effects. It is extensively used in traditional medicine for digestive, endocrine, reproductive, and respiratory problems, and is especially valued for its diuretic effects (Saddiqi and Iqbal, 2011). This plant is rich from several useful chemicals, including volatile compounds, flavonoids, and phenolic compounds, which contribute to its pharmacological properties (adgujar SB et al., 2014). Anethole is one of the most common chemicals found in the *fennel*. Anethole has two isomers including cis-anethole (CA) and trans-anethole (TA) (Fig. 1).

Anethole is an aromatic molecule found in many essential oils. It is responsible for unique flavors of many other plants, including *camphor*, *magnolia blossoms*, *star anise (Illiciaceae), licorice (Fabaceae), anise myrtle (Myrtaceae),* and *fennel* (both in the botanical family Apiaceae). Essential oils in plants have two roles: protection and communication. It protects host plants from harmful bacteria and prevents herbivorous animals from eating the plant (Marinov and Valcheva Kuzmanova, 2015). Anethole is a clear, colorless amber liquid with a *sweet anise*-like flavor (Marinov and Valcheva Kuzmanova, 2015). Because anethole can conceal unpleasant odors, it is frequently used as a masking agent in toilet soap, toothpaste, and mouthwash. It is used as a flavoring and scenting addition in the food industry (Marinov and Valcheva Kuzmanova, 2015). Anethole has anti-inflammatory, antispasmodic, antiseptic, carminative, diuretic, and analgesic effects because of its antioxidant properties, and it is used to treat neurological disorders (Delaram et al., 2011; Birdane et al., 2007). Although trans-anethole is the dominant isomer in nature, most studies on anethole's effects do not explicitly differentiate between its isomers. The current study set out to assess anethole's effects on the neurological system in accordance with its significance as a natural component. Various pharmacological effects

* Corresponding author.
E-mail address: shima.balali@sku.ac.ir (S. Balali- Dehkordi).

https://doi.org/10.1016/j.ibneur.2024.12.012
Received 10 October 2024; Received in revised form 17 December 2024; Accepted 24 December 2024
Available online 24 December 2024

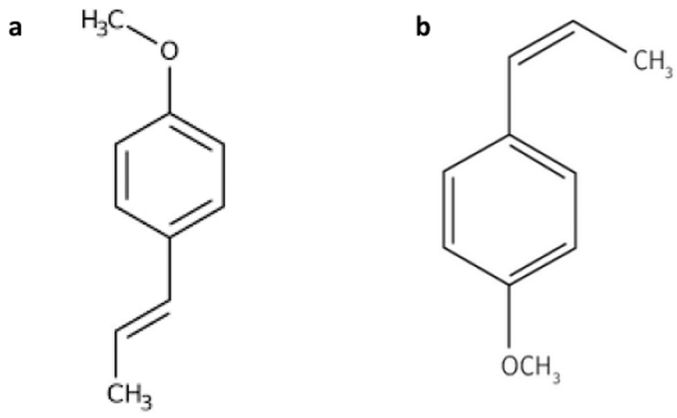

Fig. 1. chemical structure of (a) TA and (b) CA.

which have been reported suggesting that anethole could be considered as a potential agent for management of neurological disorders. Table 1 presents experimental studies investigating the properties of anethole.

2. Methods

Up until April 1, 2024, comprehensive search were undertaken in reputable academic databases such as ScienceDirect, Scopus, EBSCO, Medline, PubMed, Embase, SID, and Iran Medex to investigate anethole, its neurological effects, and its pharmacological effects. In this literature review we conducted search using specific keywords including anethole, trans-anethole, cis-anethole, neurological disorders, neuroprotective, neuroinflammation, oxidative stress, anticonvulsant, seizure, pain, nociception, anxiety, depression, brain, behavior and memory.

3. Anti-oxidant activity of Anethole

Oxidative stress is a risk element that raises the oxidation of lipids in the central nervous system (CNS), ultimately resulting in tissue damage (Al Rouq and El Eter, 2014). Anti-oxidants act as radical scavengers, inhibit lipid peroxidation and other free radical-mediated harmful processes, and may protect the body from oxidative injury (Abeed et al., 2023a, 2023b). Due to their perceived carcinogenic potential and safety issues, the use of synthetic anti-oxidants in foods should be discouraged (Felter et al., 2021). On the other hand, plant-based anti-oxidants are apparently safer than synthetic ones (Noreen et al., 2024). They have been shown to reduce the risk of oxidative damage in the brain, thereby reduce the likelihood of developing neurological disorders (Ghaemi et al., 2004).

There are several approaches to evaluating TA's anti-oxidant activity. It should be noted that there is no accurate and reliable measurement method to measure the antioxidant capacity of extracts. Anti-oxidant properties of TA has been assessed using the 1,1-diphenyl-2-picrylhydrazil (DPPH) radical scavenging assay, focusing on its ability to donate hydrogen and neutralize free radicals (Freire et al., 2005). Another study used 2-thiobarbituric acid reactive substances (TBARS) as an indicator to determine how well essential oil including anethole reduces lipid peroxidation (Nagababu and Lakshmaiah, 1994). The metal chelating assay was used to determine how well some commercial essential oils can chelate metal ions to prevent metal-accelerated oxidation processes (Lal et al., 2022). The free radical method depends mainly on assessing anethole's ability to neutralize free radicals created by various chemical reactions. In this regards, numerous articles have shown anti-oxidant capacity of *star anise*, *anise myrtle*, *camphor*, *fennel*, *guarana*, *licorice*, and *magnolia blossoms* which are rich from anethole *(*Koçak, 2024*)*. Similarly, Noreen et al., using the ABTS assay have demonstrated that *flaxseed* and *fennel* seeds, both containing TA and very low CA, have good anti-oxidant activities (Noreen et al., 2024). It has been determined that *Illicium verum* essential oil which contain high quantities of TA, has considerable anti-oxidant activity (Luís et al., 2017). Dinesha et al., have discovered that an aqueous extract of powdered *Illicium verum* has considerable anti-oxidant activity against H2O2 and DNA damage (Dinesha et al., 2014).

Rostami-Faradonbeh et al., have found that TA significantly increased hippocampus anti-oxidant capacity and decreased hippocampal malondialdehyde (MDA) levels in the maternal separation-induced depressive-like behaviors in mice (Rostami-Faradonbeh et al., 2024). It has been discovered that TA has neuroprotective characteristics, preventing neuronal cell death owing to oxygen deprivation through its anti-oxidant and anti-stimulant actions as well as its mitochondrial protection effects (Ryu et al., 2014). Previous studies have clarified that TA considerably improved skin wound healing due to its anti-oxidant capabilities (Cavalcanti et al., 2012). Furthermore, a study on albino mice with pancreatic cancer revealed that anethole enhanced survival time, lowered weight and tumor volume, decreased MDA levels, and raised glutathione, indicating its free radical scavenging and suppression of lipid peroxidation (Al-Harbi et al., 1995). Anethole's principal anti-oxidant abilities are due to three mechanisms: increased antioxidant enzyme activity, free radical scavenging, and metal ion chelation (Freire et al., 2005; Shahat et al., 2011). Aforementioned studies have declared considerable anti-oxidant activity of anethole, suggesting that anethole can be considered as a potential agents for targeting oxidative stress- related disorders including neurological diseases.

4. Anti-inflammatory properties of Anethole

Neuroinflammation negatively affects CNS leading to behavioral and neurological disorders. In some cases, chronic systemic inflammation may contribute to the development of neurodegenerative diseases (DiSabato et al., 2016). Anethole's anti-inflammatory qualities have been extensively studied, lending credence to the substance's potential for treating inflammation-related disorders. Domiciano et al., have found that anethole reduced pleural exudate volume, leukocyte migration, and nitric oxide (NO) and prostaglandin levels in rat model of non-immune acute inflammation (Domiciano et al., 2013). It has been determined that TA decreased inflammatory edema by reducing the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukine (IL)-1β, and IL-6 (Haddadi and Rashtiani, 2020). Furthermore, TA has been demonstrated to have anti-inflammatory capabilities by reducing the activity of cyclooxygenase-2 (COX-2), an enzyme involved in the creation of prostaglandins (Freire et al., 2005).

In a mouse model of chronic obstructive pulmonary disease (COPD), anethole has been declared that decreased pro-inflammatory cytokines and improved lung inflammation (Kim et al., 2017). TA has been displayed anti-inflammatory and anti-apoptotic effects in rat model of cerebral ischemia-reperfusion injury, preventing brain damage (Saila and Thakur, 2022). TA improved myocardial ischemia-reperfusion damage by altering gene expression and lowering TNF-α levels (Matboli et al., 2022). Additionally, TA showed promise in treating nonalcoholic steatohepatitis (NASH), lowering hepatic steatosis, inflammation, and fibrosis in diet-induced NASH in mice (Zhang et al., 2021). Several studied have reported anti-neuroinflammatory effects for TA in animal models of neurological disorders (Moradi Vastegani et al., 2023a; Yan et al., 2022).TA has been found to protect against cerebral ischemia, improve motor coordination, lower brain water content, and attenuate excitatory mediators. It also significantly downregulated TNF- α, caspase 3, BCL2 Associated X (BAX), and mitogen-activated protein kinase (MAPK) expressions, thereby preventing cerebral ischemia-reperfusion injury (Saila and Thakur, 2022). Although some studies revealed that essential oils consisting cis-anethole (CA) have significant anti-inflammatory effects, only one study particularly worked on CA and has reported that cis-anethole and ibuprofen have a synergistic anti-inflammatory effect (Wisniewski-Rebecca et al., 2015). All of these

Table 1
Experimental studies investigating the properties of Anethole.

Authors	properties	year	Findings	Ref.No
Freire RS, et al.	Antioxidant activity	2005	Scavengered and neutralized free radicals	20
Nagababu E, et al.		1994	Reduced lipid peroxidation	21
Lal M, et al.		2022	Chelated metal ions to prevent metal-accelerated oxidation processes	22
Rostami-Faradonbeh N, et al.		2014	Decreased hippocampal malondialdehyde (MDA) levels	26
		2014	Protected mitochondria against oxygen deprivation	27
Ryu S, et al.		1995	Decreased MDA levels and raised glutathione	29
Al-Harbi MM, et al.				
Domiciano TP, et al.	Anti-inflammatory	2013	Reduced pleural exudate volume, leukocyte migration, nitric oxide (NO) and prostaglandin	32
Haddadi R, et al.	properties	2020	levels	33
Freire RS, et al.		2005	Decreased inflammatory edema by reducing the production of pro-inflammatory cytokines	20
Kim KY, et al.		2017	such as tumor necrosis factor (TNF)-α, interleukine (IL)−1β, and IL−6	34
Saila HM, et al.		2022	Reduced the activity of cyclooxygenase−2 (COX−2)	35
Matboli M, et al.		2022	Decreased pro-inflammatory cytokines and improved lung inflammation	36
Zhang C, et al.		2021	Prevented brain damage by anti-inflammatory and anti-apoptotic effects	37
Saila HM, et al.		2022	Improved myocardial ischemia-reperfusion damage by altering gene expression and lowering TNF-α levels Lowered hepatic steatosis, inflammation, and fibrosis in diet-induced nonalcoholic steatohepatitis (NASH) in mice Protected against cerebral ischemia via downregulating TNF- α, caspase 3, BCL2 Associated X (BAX), and mitogen-activated protein kinase (MAPK) expressions	35
Dinesh D	Antidepressant effects	2019,	Inhibited brain monoamine oxidase-A (MAO-A), reduced oxidative stress, and reverse	41,
Dhingra D, et al.		2022	stress-induced increase in corticosterone levels	42,43
Hassanzadeh SA,et al.		2024	Modulated oxidative stress and nitrite imbalance in the hippocampus	26
Rostami-Faradonbeh N, et al.				
Ryu S, et al.	Neuroprotective effects	2014	Inhibited excitotoxicity, oxidative stress, mitochondrial dysfunction and prevented ischemic	27
Moradi Vastegani S, et al.		2023	neuronal damage	44
Younis NS, et al.		2023	Modulated neuronal firing rate, improved blood-brain barrier (BBB) function in rotenone-	45
Chang W, et al.		2022	induced Parkinson's disease in rats	46
Naseri Z, et al.		2023	Modulated c-Jun N-terminal Kinase (JNK), p38, matrix metalloproteinase (MMP)−2, and	47
Saila HM, et al.		2022	MMP−9, boosted BBB integrity, and reduced oxidative stress, neuroinflammation, and	35
Vastegani SM, et al.		2022	apoptosis against cerebral ischemia/reperfusion-induced brain damage and BBB permeability leakage Improved both N-methyl-D-aspartate (NMDA) receptor-dependent and -independent long-term potentiation (LTP) in the hippocampus and reduced trimethyltin-induced LTP impairment Enhanced motor recovery and nerve regeneration in a rat model of sciatic nerve damage Prevented brain ischemia-reperfusion injury by decreasing inflammation and apoptosis Improved cognitive performance, raised pain threshold, and lowered oxidative stress in the hippocampus In a Parkinson's disease model	48
Alvarado-García PAA et al.	Anxiolytic effects	2022, 2014	Alleviated anxiety-related behaviors in rodents	52,53,54
Miyagawa M, et al.				
Mesfin M, et al.				
Joshi H, et al. Raman S, et al.	Memory improvement effects	2006, 2020, 2013	Improved memory in animal models	55,56,57
Koppula S, et al.				
Ghasemi Z, et al.	Anticonvulsant	2011	Influenced the activity of Ca^{2+} channels and K^{+}-activated Ca^{2+} channels, changed cell	64
Salimian S, et al.	properties	2022	membrane potential and neurotransmission in brain Reduced oxidative stress	65
Moreira-Junior L, et al.	Anti- neurodegenerative	2024	Decreased neuronal activity by blocking voltage-gated Na+ channels (VGSCs) in a state-	66
Joshi H, et al.	diseases	2006	dependent way	55
Chang W, et al.		2022	Suppressed acetylcholinesterase activity in the Alzheimer disease	46
Rajan PD, et al.		2020	Improved long-term potentiation and reduced trimethyltin-induced synaptic plasticity	67
Vastegani SM, et al.		2023	deficits in Alzheimer disease	48
Moradi Vastegani S, et al.		2023	Displayed protective efficacy against 3-nitro propionic acid-induced neurotoxicity in	68
Yadollahi-Farsani Y, et al.		2024	Huntington's disease Lowered oxidative stress and neuronal death in the hippocampus and attenuated rotenone-induced non-motor impairments in Parkinson's disease Reduced α-synuclein expression and oxidative stress, improved motor function, striatal neuronal activity, and BBB integrity in rotenone-induced Parkinson's disease Boosted the expression of phosphoinositide 3-kinases (PI3K), protein kinase B (PKB), also known as Akt, and the mammalian target of rapamycin (mTOR) genes in the hippocampus thus reduced autistic-like behavior in mice	69
Vastegani SM, et al.	Antinociceptive	2023	Increased thermal pain threshold, increased superoxide dismutase (SOD) and glutathione	48
Ritter AMV, et al.		2014	peroxidase (GPx) activities, decreased MDA levels, and increased brain-derived	70
Wang B, et al.		2018	neurotrophic factor (BDNF) expression in the hippocampus	71
Ritter AM, et al.		2013	Decreased the generation or release of inflammatory mediators in writhing model caused by acetic acid as well as in the second phase of the formalin test and exerted antinociceptive effect Alleviated hyperalgesia, allodynia, and abnormal sciatic nerve conduction in mice. Suppressed glial cell activation, down-regulated pro-inflammatory cytokines, and up-regulated anti-inflammatory cytokines in chronic constriction injury (CCI)-induced neuropathic pain Possessed anti-inflammatory and analgesic properties in acute and chronic inflammation pain	72

findings indicated anethole's promising anti-(neuro) inflammatory properties and highlight its potential in targeting inflammatory reactions as well as CNS-related neuroinflammatory disorders.

5. Antidepressant effects of Anethole

Numerous research have examined the plausible antidepressant properties of anethole, elucidating its therapeutic potential for managing of depression. TA's antidepressant impact in animal models is due to its capacity to inhibit brain monoamine oxidase-A (MAO-A), an enzyme metabolizing monoamines, reduce oxidative stress, and reverse stress-induced increase in corticosterone levels (Dinesh and Sudha, 2019). Evidences have revealed that TA had strong antidepressant-like effects in both unstressed and stressed animals, potentially by inhibiting brain MAO-A activity and the reduction of oxidative stress (Dhingra and Sudha, 2019). Hassanzadeh et al., have studied the anti-depressant efficacy of TA and its potential mechanism in mice. According to their findings, the monoaminergic system is involved in TA's anti-depressive action (Hassanzadeh et al., 2022). Rostami-Faradonbeh et al., have reported an antidepressant-like effect for anethole, they concluded that anethole via modulating oxidative stress and nitrite imbalance in the hippocampus exerted antidepressant-like effects in mouse model of maternal separation stress (Rostami-Faradonbeh et al., 2024). Further investigations are needed to determine full and exact mechanisms involved in antidepressant properties of TA and CA. However, aforementioned studies have opened a way for future researches to evaluate neuroprotective effects of TA focusing on its antidepressant effects.

6. Neuroprotective effects of Anethole

Anethole has neuroprotective characteristics. It prevents neuronal injury and supports brain health by lowering neuroinflammation and oxidative stress, which critically are involved in development of neurological disorders. A study on TA's neuroprotection against oxygen-glucose deprivation/reoxygenation-induced cortical neuronal cell injury suggested that it via inhibition of excitotoxicity, oxidative stress, and mitochondrial dysfunction possessed neuroprotective effect and thus prevented ischemic neuronal damage (Ryu et al., 2014). It has been demonstrated that anethole through modulating of neuronal firing rate, improvement of blood-brain barrier (BBB) function as well as attenuation of oxidative stress exerted neuroprotective effects in rotenone-induced Parkinson's disease in rats (Moradi Vastegani et al., 2023a). Younis et al., have studied anethole's neuroprotective effects against cerebral ischemia/reperfusion-induced brain damage and BBB permeability leakage. They concluded that TA modulated c-Jun N-terminal Kinase (JNK), p38, matrix metalloproteinase (MMP)-2, and MMP-9, boosted BBB integrity and reduced oxidative stress, neuroinflammation, and apoptosis (Younis and Mohamed, 2023).

TA has reported that improved both N-methyl-D-aspartate (NMDA) receptor-dependent and -independent long-term potentiation (LTP) in the hippocampus and reduced trimethyltin-induced LTP impairment (Chang et al., 2022a). In a rat model of sciatic nerve damage, TA enhanced motor recovery and nerve regeneration (Naseri et al., 2023). Evidences have declared that anethole prevented brain ischemia-reperfusion injury by decreasing inflammation and apoptosis in the brain (Saila and Thakur, 2022). In a Parkinson's disease model, anethole improved cognitive performance, raised pain threshold, and lowered oxidative stress in the hippocampus (Vastegani et al., 2023). These aforementioned studies collectively indicated neuroprotective benefits of anethole. The anethole's capacity to control synaptic plasticity and preserve neurons suggests that it could be used to treat a variety of neurodegenerative disorders and nerve injuries.

7. Anethole's Interaction with gamma-aminobutyric acid (GABA)

GABA is the CNS's major inhibitory neurotransmitter. It controls neuronal activity, mood, and anxiety. It has been proposed that TA interacted with the GABAergic system, thereby altering its activity. Xu et al., have determined effects of TA on trimethyltin chloride-induced impairments in long-term potentiation (LTP). Their findings indicated that TA may have neuroprotective benefits via altering GABAergic signaling pathway (Chang et al., 2022b). Sahraei et al., have declared that the essential oil of *P. anisum* attenuated the effects of morphine through a GABAergic mechanism (Sahraei et al., 2002). An additional investigation by Guedes et al., has looked into the mechanisms behind TA's anticonvulsant action. The study implied that TA interacted with the GABAergic pathway (Da Guedes et al., 2022). Further researches are needed to elucidate the effects of anethole on GABAergic neurotransmission.

8. Anxiolytic effects of Anethole

Anxiety disorders are debilitating conditions marked by excessive concern and fear. Given anxiety interaction with the GABAergic system, anethole is being studied for its anxiolytic effects. Alvarado-García et al., have studied the anxiolytic effects of *Foeniculum vulgare* essential oil, an TA-rich oil. They concluded that anethole alleviates anxiety-related behaviors (Alvarado-García et al., 2022). Previous findings have demonstrated that anxiety -like behaviors significantly attenuated following treatment with TA in mice (Miyagawa et al., 2014). Mesfin et al., have examined the anxiolytic efficacy of essential oil of the aerial part of *Foeniculum vulgare Miller* in adult mice. They concluded that anethole mediated anxiolytic-like effects of this oil (Mesfin et al., 2014). Miyagawa et al., have reported their findings, looking into the anxiolytic-like effects of TA in mice. The investigation confirmed that TA has anxiolytic characteristics (Miyagawa et al., 2014).

9. Memory improvement effects of Anethole

The effect of *fennel* has been studies on memory function in rodents. In this regards, various studies have determined that this plant, which is rich in anethole, improved memory (Joshi and Parle, 2006; Raman et al., 2020). Koppula et al., have examined the effects of *fennel* extract on memory function in rats. This study indicated that this herb reduced stress and stress-related disorders like memory dysfunction (Koppula and Kumar, 2013).

10. Anticonvulsant properties of Anethole

Epilepsy is a chronic neurological disorder defined by spontaneous repeated seizures with transient symptoms caused by aberrant, excessive, or synchronized brain neuronal activity (Lowenstein, 2015; Falco-Walter et al., 2018). The occurrence of epilepsy is linked to a complex of neurotransmitter dysregulation involving glutamate, acetylcholine, and GABA (Werner and Coveñas, 2017; Patel et al., 2019). Although the pathophysiology of seizures is not well understood, a widely accepted premise is that glutamate, the primary excitatory neurotransmitter, is overly produced and binds to its receptors, particularly NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), resulting in seizures. In contrast, inhibitory interneurons GABAergic slightly released inhibitory transmitter GABA (Mansour and Ibrahim, 2015).

A study reveals that both TA and CA influenced brain excitatory/inhibitory pathways (Boissier et al., 1967). Following these findings, it has been proven that anethole can influence the activity of Ca2 + channels and K+ -activated Ca2 + channels, which may be related to changes in brain cell membrane potential and the subsequent neurotransmission (Ghasemi et al., 2011). Salimian et al., have explored

anethole's anticonvulsant effects in the PTZ-induced seizure model in male mice. The study results revealed that anethole's anticonvulsant effects could be mediated by reducing oxidative stress (Salimian et al., 2022). However, additional extensive pharmacological investigations are required to better understand the many pathways involved in anticonvulsant properties of TA and CA.

11. Beneficial effects of Anethole in neurodegenerative diseases

According to several studies, anethole may have therapeutic promise in neurodegenerative illnesses. Moreira-Junior et al., have demonstrated that anethole decreases neuronal activity by blocking voltage-gated Na^+ channels (VGSCs) in a state-dependent way, with potential benefits in neurodegenerative disorders (Moreira-Junior et al., 2024). Neurodegenerative illnesses, such as Alzheimer and Parkinson, are distinguished by gradual neuronal death. Joshi et al., have studied the effect of *fennel* extract on acetylcholinesterase and neurotropic factors in mice. The results of their investigation revealed that *fennel* extract strongly suppressed acetylcholinesterase. This study suggests that *fennel* could be utilized to treat cognitive illnesses including dementia and Alzheimer disease (Joshi and Parle, 2006).

In Alzheimer disease models, TA has been shown that improved long-term potentiation and reduces trimethyltin-induced synaptic plasticity deficits (Chang et al., 2022a). In Huntington's disease, TA has been displayed protective efficacy against 3-nitro propionic acid-induced neurotoxicity (Rajan et al., 2020). In Parkinson's disease models, anethole has been confirmed that attenuated rotenone-induced non-motor impairments such as cognitive impairment and pain sensitivity, while lowering oxidative stress and neuronal death in the hippocampus (Vastegani et al., 2023). In rotenone-induced Parkinson's disease, anethole reduced α-synuclein expression and oxidative stress, improving motor function, striatal neuronal activity, and BBB integrity (Moradi Vastegani et al., 2023b). Yadollahi-Farsani et al., have found that anethole reduced autistic-like behavior in mice. They discovered that anethole boosted the expression of phosphoinositide 3-kinases (PI3K), protein kinase B (PKB), also known as AKT, and the mammalian target of rapamycin (mTOR) genes in the hippocampus. The study concluded that anethole, through an increase in the gene expression of PI3K/AKT/mTOR, reduced autistic-like symptoms induced by maternal separation in mice (Yadollahi-Farsani et al., 2024).

12. Beneficial effects of Anethole in pain management

Anethole has been reported that exert analgesic characteristics. Pain is a complicated sensory experience that is frequently connected with nervous system dysfunction. A study by Vastegani and colleagues has declared that chronic rotenone administration caused cognitive deficits, reduced thermal pain threshold, decreased superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities, increased MDA levels, and reduced brain-derived neurotrophic factor (BDNF) expression in the hippocampus. They have determined that treatment with anethole improved cognitive function and increased pain threshold, but decreased MDA levels and increased surviving neurons in the hippocampus (Vastegani et al., 2023). Ritter et al., have discovered that anethole has an antinociceptive effect in the writhing model caused by acetic acid as well as in the second phase of the formalin test. This impact could be attributed to a decrease in the generation or release of inflammatory mediators (Ritter et al., 2014). Wang et al., have found that anethole treatment significantly alleviated hyperalgesia, allodynia, and abnormal sciatic nerve conduction in mice. They proposed that suppressed glial cell activation, down-regulated pro-inflammatory cytokines, and up-regulated anti-inflammatory cytokines are involved in the antinociceptive effect of anethole in chronic constriction injury (CCI)-induced neuropathic pain (Wang et al., 2018). Ritter et al., have investigated the effects of anethole on two inflammatory pain models: acute and chronic inflammation pain. Their study's results demonstrated that anethole had anti-inflammatory and analgesic properties (Ritter et al., 2013).

13. Other pharmacological effects of Anethole

Anethole's pharmacological characteristics are broad, highlighting its potential for medicinal uses. While this review concentrates on the compound's neurological effects, its broader pharmacological activities, such as antimicrobial, antitumor, and metabolic properties, serve as a framework for understanding how it affects the nervous system. Studies have shown that it is effective against bacteria such as Staphylococcus aureus and fungus like Candida albicans (Kwiatkowski et al., 2020; Dąbrowska et al., 2021; Fujita et al., 2017). Furthermore, previous studies have reported anticancer activity for anethole. It affects pathways such as NF-κB and caspase cascades affecting cell survival and apoptosis (Chen et al., 2009; Choo et al., 2011; Jana et al., 2015). It has been demonstrated that anethole has ability to improve metabolic parameters such as insulin sensitivity and reduce lipid metabolism (Torghabeh et al., 2024; Song et al., 2020).

14. Conclusion

Anethole, a common component found in many herbs, has exerted potential beneficial effects on the CNS disorders. Preclinical investigations have indicated that anethole has neuroprotective effects. Evidences have determined that anethole through modulation of monoamines, GABAergic and glutamatergic neurotransmissions as well as its possible anti-neuroinflammatory and antioxidative stress properties possessed neuroprotective effects against neurological disorders. In this concept previous studies have demonstrated anxiolytic, antidepressant, antinociceptive, anticonvulsant, and memory improvement effects. This study evaluates anethole's neurobiological properties without isolating the contributions of its isomers. While TA dominates in natural sources and literature, future research should explore the distinct properties of CA to clarify its potential contributions.

Consent to Publish

All authors reviewed and approved the manuscript.

CRediT authorship contribution statement

Ramina Khodadadian: Writing – review & editing, Writing – original draft. **Shima Balali- Dehkordi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors have no conflicts of interest to declare regarding the study described in this article and preparation of the article.

References

A beed, A.H., Al-Huqail, A.A., Albalawi, S., Alghamdi, S.A., Ali, B., Alghanem, S.M., El-Mahdy, M.T., 2023a. Calcium nanoparticles mitigate severe salt stress in Solanum lycopersicon by instigating the antioxidant defense system and renovating the protein profile. S. Afr. J. Bot. 161, 36–52.

adgujar SB, Patel, V.V., Bandivdekar, A.H., 2014. Foeniculum vulgare Mill: a review of its botany, phytochemistry, pharmacology, contemporary application, and toxicology. Biomed. Res. Int. 2014 (1).

Adhikari, B., Marasini, B.P., Rayamajhee, B., Bhattarai, B.R., Lamichhane, G., Khadayat, K., et al., 2021. Potential roles of medicinal plants for the treatment of viral diseases focusing on COVID-19: A review. Phytother. Res. 35 (3), 1298–1312.

Al Rouq, F., El Eter, E., 2014. PPAR-γ activator induces neuroprotection in hypercholesterolemic rats subjected to global cerebral ischemia/reperfusion injury: In vivo and in vitro inhibition of oxidative stress. Exp. Gerontol. 51, 1–7.

Al-Harbi, M.M., Qureshi, S., Raza, M., Ahmed, M.M., Giangreco, A.B., Shah, A.H., 1995. Influence of anethole treatment on the tumour induced by Ehrlich ascites carcinoma cells in paw of Swiss albino mice. Eur. J. Cancer Prev. 4 (4), 307–318.
Alvarado-García, P.A.A., Soto-Vasquez, M.R., Rosales-Cerquin, L.E., Rodrigo-Villanueva, E.M., Jara-Aguilar, D.R., Tuesta-Collantes, L., 2022. Anxiolytic and antidepressant-like effects of Foeniculum vulgare essential oil. Pharmacognosy J. 14 (2).
Anand, Tudu, U., Nandy, C.K., Sunita, S., Tripathi, K., Loake, V., et al., 2022. Ethnodermatological use of medicinal plants in India: From ayurvedic formulations to clinical perspectives–A review. J. Ethnopharmacol. 284, 114744.
B arkat, M.A., Goyal, A., Barkat, H.A., Salauddin, M., Pottoo, F.H., Anwer, E.T., et al., 2021. Herbal medicine: Clinical perspective and regulatory status. CCHTS 24 (10), 1573–1582.
B irdane, F.M., Cemek, M., Birdane, Y.O., Gülçin, İ., Büyükokuroğlu, M.E., 2007. Beneficial effects of Foeniculum vulgare on ethanol-induced acute gastric mucosal injury in rats. WJG 13 (4), 607.
Boissier, J.R., Simon, P., Le Bourhis, B., 1967. Experimental psychotropic action of cis and trans isomers of anethol. Therapie 22 (2), 309–323.
Cavalcanti, J.M., Leal-Cardoso, J.H., Diniz, L.R.L., Portella, V.G., Costa, C.O., Linard, C.F. B.M., et al., 2012. The essential oil of Croton zehntneri and trans-anethole improves cutaneous wound healing. J. Ethnopharmacol. 144 (2), 240–247.
Chang, W., An, J., Seol, G.H., Han, S.H., Yee, J., Min, S.S., 2022a. Trans-anethole alleviates trimethyltin chloride-induced impairments in long-term potentiation. Pharmaceutics 14 (7), 1422.
Chang, W., An, J., Seol, G.H., Han, S.H., Yee, J., Min, S.S., 2022b. Trans-anethole alleviates trimethyltin chloride-induced impairments in long-term potentiation. Pharmaceutics 14 (7).
Chen, C.H., Gasperi, M., Salcedo, R., Cavazos, D.A., Degraffenried, L.A., 2009. Evaluation of the phytochemical anethole as an anti-tumor agent in MCF-7 cells. Cancer Res. 69.
Choo, E.J., Rhee, Y., Jeong, S., Lee, H., Kim, H.S., Ko, H.S., Kim, J., Kwon, T., Jung, J.H., et al., 2011. Anethole exerts antimetatstaic activity via inhibition of matrix metalloproteinase 2/9 and AKT/mitogen-activated kinase/nuclear factor kappa B signaling pathways. Biol. Pharm. Bull. 34 (1), 41–46.
Costa Font, J., Sato, A., 2024. Cultural persistence and the 'herbal medicine paradox': Evidence from European data. J. Health Psychol.
Delaram, M., Kheiri, S., Hodjati, M.R., 2011. Comparing the effects of Echinophora-platyloba, fennel and placebo on pre-menstrual syndrome. JRI 12 (3), 221.
Dhingra, D., Sudha, 2019. Antidepressant-like activity of trans-anethole in unstressed mice and stressed mice. Asian J. Pharm. Clin. Res.
Dinesha, R., Thammannagowda, S.S., Prabhu, M.S.L., Madhu, C.S., Srinivas, L., 2014. The antioxidant and DNA protectant activities of Star Anise (Illicium verum) aqueous extracts. JPP 2 (5), 98–103.
Dinesh, D., Sudha, 2019. antidepressant-like activity of trans-anethole in unstressed mice and stressed mice. Asian J. Pharm. Clin. Res. 12, 121–127.
DiSabato, D.J., Quan, N., Godbout, J.P., 2016. Neuroinflammation: the devil is in the details. J. Neurochem. 139, 136–153.
Domiciano, T.P., Dalalio, M.M.D.O., Silva, E.L., Ritter, A.M.V., Estevão-Silva, C.F., Ramos, F.S., Bersani-Amado, C.A., et al., 2013. Inhibitory effect of anethole in nonimmune acute inflammation. Naunyn Schmiede Arch. Pharmacol. 386 (4), 331–338.
Dąbrowska, M., Zielińska-Bliźniewska, H., Kwiatkowski, P., Łopusiewicz Ł., Pruss, A., Kostek, M., Sienkiewicz, M., 2021. Inhibitory effect of eugenol and trans-anethole alone and in combination with antifungal medicines on Candida albicans clinical isolates. Chem. Biodivers. 18 (5), e2000843.
Falco-Walter, J.J., Scheffer, I.E., Fisher, R.S., 2018. The new definition and classification of seizures and epilepsy. Epilepsy Res. 139, 73–79.
Felter, S.P., Zhang, X., Thompson, C., 2021. Butylated hydroxyanisole: Carcinogenic food additive to be avoided or harmless antioxidant important to protect food supply? Regul. Toxicol. Pharmacol. 121, 104887.
Freire, R.S., Morais, S.M., Catunda Junior, F.E.A., Pinheiro, D.C., 2005. Synthesis and antioxidant, anti-inflammatory and gastroprotector activities of anethole and related compounds. Bioorg. Med. Chem. 13 (13), 4353–4358.
Fujita, K., Ishikura, T., Jono, Y., Yamaguchi, Y., Ogita, A., Kubo, I., Tanaka, T., 2017. Anethole potentiates dodecanol's fungicidal activity by reducing PDR5 expression in budding yeast. Biochim. Et. Biophys. acta. Gen. Subj. 1861 (2), 477–484.
Ghaemi, S.N., Rosenquist, K.J., Ko, J.Y., Baldassano, C.F., Kontos, N.J., Baldessarini, R.J., 2004. Antidepressant treatment in bipolar versus unipolar depression. Am. J. Psychiatry 161 (1), 163–165.
Ghasemi, Z., Hassanpour-Ezatti, Kamalinejad, M., Janahmadi, M., 2011. Functional involvement of Ca2+ and Ca2+ -activated K+ channels in anethol-induced changes in Ca2+ dependent excitability of F1 neurons in Helix aspersa. Fitoterapia 82 (5), 750–756.
Da Guedes, E., Ribeiro, L.R., Carneiro, C.A., Santos, A.M.F., Brito Monteiro, Á., De Andrade, H.H.N., Stiebbe Salvadori, M.G., et al., 2022. Anticonvulsant activity of trans-anethole in mice. Biomed. Res. Int. 2022 (1), 9902905.
Haddadi, R., Rashtiani, R., 2020. Anti-inflammatory and anti-hyperalgesic effects of milnacipran in inflamed rats: involvement of myeloperoxidase activity, cytokines and oxidative/nitrosative stress. Inflammopharmacology 28 (4), 903–913.
Hassanzadeh, S.A., Abbasi-Maleki, S., Mousavi, Z., 2022. Anti-depressive-like effect of monoterpene trans-anethole via monoaminergic pathways. Saudi J. Biol. Sci. 29 (5), 3255–3261.
Jamshidi-Kia, F., Lorigooini, Z., Amini-Khoei, H., 2017. Medicinal plants: Past history and future perspective. J. Herbmed Pharmacol. 7 (1), 1–7.
Jana, S., Patra, K., Mukherjee, G., Bhattacharjee, S., Mandal, D.P., 2015. Antitumor potential of anethole singly and in combination with cyclophosphamide in murine Sarcoma-180 transplantable tumor model. RSC Adv. 5, 56549–56559.
Joshi, H., Parle, M., 2006. Cholinergic basis of memory-strengthening effect of Foeniculum vulgare Linn. J. Med. Food 9 (3), 413–417.
Kim, K.Y., Lee, H.S., Seol, G.H., 2017. Anti-inflammatory effects of trans-anethole in a mouse model of chronic obstructive pulmonary disease. Biomed. Pharm. 91, 925–930.
Koçak, M.Z., 2024. Phenolic Compounds, Fatty Acid Composition, and Antioxidant Activities of Some Flaxseed (Linum usitatissimum L.) Varieties: A Comprehensive Analysis. Processes 12 (4), 689.
Koppula, S., Kumar, H., 2013. Foeniculum vulgare Mill (Umbelliferae) attenuates stress and improves memory in wister rats. TJPR 12 (4).
Kwiatkowski, Wojciuk, P., Wojciechowska-Koszko, B., Łopusiewicz, I., Grygorcewicz, B., Pruss, A., et al., 2020. Innate immune response against Staphylococcus aureus preincubated with subinhibitory concentration of trans-anethole. Int. J. Mol. Sci. 21 (11), 4178.
Lal, M., Begum, T., Gogoi, R., Sarma, N., Munda, S., Pandey, S.K., Saikia, S., et al., 2022. Anethole rich Clausena heptaphylla (Roxb.) Wight & Arn., essential oil pharmacology and genotoxic efficiencies. Sci. Rep. 12 (1), 9978.
Lowenstein, D.H., 2015. Edging toward breakthroughs in epilepsy diagnostics and care. Nat. Rev. Neurol. 11 (11), 616–617.
Luís, Â., Duarte, A.P., Pereira, L., Domingues, F., 2017. Chemical profiling and evaluation of antioxidant and anti-microbial properties of selected commercial essential oils: A comparative study. Medicines 4 (2), 36.
Mansour, M., Ibrahim, A., 2015. Possible anticonvulsant effect of ivabradine in kainite–induced epilepsy in rats: amelioration of oxidative stress. World J. Pharm. Res. 4, 247–257.
Marinov, V., Valcheva Kuzmanova, S., 2015. Review on the pharmacological activities of anethole. Scr. Sci. Pharm. 2 (2), 14–19.
Matboli, M., Hasanin, A.H., Hamady, S., Khairy, E., Mohamed, R.H., Aboul-Ela, Y.M., Agwa, S.H., et al., 2022. Anti-inflammatory effect of trans-anethol in a rat model of myocardial ischemia-reperfusion injury. Biomed. Pharm. 150, 113070.
Mesfin, M., Asres, K., Shibeshi, W., 2014. Evaluation of anxiolytic activity of the essential oil of the aerial part of Foeniculum vulgare Miller in mice. BMC Complement Alter. Med. 14, 1–7.
Miyagawa, M., Satou, T., Yukimune, C., Ishibashi, A., Seimiya, H., Yamada, H., Koike, K., et al., 2014. Anxiolytic-like effect of Illicium verum fruit oil, trans-anethole and related compounds in mice. Phytother. Res. 28 (11), 1710–1712.
Moradi Vastegani, S., Khoshnam, S.E., Ghafouri, S., Bakhtiari, N., Farbood, Y., Sarkaki, A., 2023a. Anethole attenuates motor dysfunctions, striatal neuronal activity deficiency and blood brain barrier permeability by decreasing striatal α-synuclein and oxidative stress in rotenone-induced Parkinson's disease of male rats. Plos One 18 (11), e0294612.
Moradi Vastegani, S., Khoshnam, S.E., Ghafouri, S., Bakhtiari, N., Farbood, Y., Sarkaki, A., 2023b. Anethole attenuates motor dysfunctions, striatal neuronal activity deficiency and blood brain barrier permeability by decreasing striatal α-synuclein and oxidative stress in rotenone-induced Parkinson's disease of male rats. PLOS ONE 18 (11), e0294612.
Moreira-Junior, L., Leal-Cardoso, J.H., Cassola, A.C., Carvalho-de-Souza, J.L., 2024. State-dependent blockade of dorsal root ganglion voltage-gated Na+ channels by anethole. Int. J. Mol. Sci. 25 (2), 1034.
Nagababu, E., Lakshmaiah, N., 1994. Inhibition of microsomal lipid peroxidation and monooxygenase activities by eugenol. Free Radic. Res. 20 (4), 253–266.
Naseri, Z., Mamoudi, F., Abdolmaleki, A., Soluki, M., 2023. Neuroprotective potential of trans-anethole following crush injury of the sciatic nerve in rats. IrJNS 9.
Noreen, S., Tufail, T., Ain, H., Khalid, W., Hanif, A., Ali, B., Abeed, A., et al., 2024. Assessment of antioxidant activities of flaxseed (Linum usitatisimum L.) and fennel seed (Foeniculum vulgare Mill.) extracts. Pol. J. Environ. Stud. 33 (3).
Patel, D.C., Tewari, B.P., Chaunsali, L., Sontheimer, H., 2019. Neuron–glia interactions in the pathophysiology of epilepsy. Nat. Rev. Neurosci. 20 (5), 282–297.
Rajan, P.D., Sharma, P., Parihar, L., 2020. Protective activity of alpha-pinene and trans-anethole against 3-nitro propionic acid induced neurotoxicity in animal model of Huntington's disease. IRJP 11 (6), 32–38.
Raman, S., Asle-Rousta, M., Rahnema, M., 2020. Protective effect of fennel, and its major component trans-anethole against social isolation induced behavioral deficits in rats. Physiol. Int. 107 (1), 30–39.
Ritter, A.M.V., Ames, F.Q., Otani, F., de Oliveira, R.M.W., Cuman, R.K.N., Bersani-Amado, C.A., 2014. Effects of anethole in nociception experimental models. eCAM 2014 (1), 345829.
Ritter, A.M., Domiciano, T.P., Verri, W.A., Zarpelon, A.C., da Silva, L.G., Barbosa, C.P., Bersani-Amado, C.A., et al., 2013. Antihypernociceptive activity of anethole in experimental inflammatory pain. Inflammopharmacology 21, 187–197.
Rostami-Faradonbeh, N., Amini-Khoei, H., Zarean, E., Bijad, E., Lorigooini, Z., 2024. Anethole as a promising antidepressant for maternal separation stress in mice by modulating oxidative stress and nitrite imbalance. Sci. Rep. 14 (1), 7766.
Ryu, S., Seol, G.H., Park, H., Choi, I.Y., 2014. Trans-anethole protects cortical neuronal cells against oxygen–glucose deprivation/reoxygenation. Neurol. Sci. 35, 1541–1547.
Saddiqi, H.A., Iqbal, Z., 2011. Usage and significance of fennel (Foeniculum vulgare Mill.) seeds in Eastern medicine. in Nuts and seeds in health and disease prevention. Elsevier, pp. 461–467.
Sahraei, H., Ghoshooni, H., Salimi, S.H., Astani, A.M., Shafaghi, B., Falahi, M., Kamalnegad, M., 2002. The effects of fruit essential oil of the Pimpinella anisum on acquisition and expression of morphine induced conditioned place preference in mice. J. Ethnopharmacol. 80 (1), 43–47.
Saila, H.M., Thakur, S., 2022. Transanethole protects against Global Cerebral Ischemia through its anti-inflammatory and anti apoptotic activity. RJPT 15 (4), 1713–1720.

Salimian, S., Habibian-Dehkordi, S., Kaboutari, J., Amini-Khoei, H., Barkhordari, M.S., 2022. Anethole exerted anticonvulsant effect in pentylenetetrazole-model of seizure in male mice: Possible antioxidant effects. Future Nat. Prod. 8 (1), 2–6.
Shahat, A.A., Ibrahim, A.Y., Hendawy, S.F., Omer, E.A., Hammouda, F.M., Abdel-Rahman, F.H., Saleh, M.A., 2011. Chemical composition, antimicrobial and antioxidant activities of essential oils from organically cultivated fennel cultivars. Molecules 16 (2), 1366–1377.
Shaito, A., Thuan, D.T.B., Phu, H.T., Nguyen, T.H.D., Hasan, H., Halabi, S., 2020. Herbal medicine for cardiovascular diseases: efficacy, mechanisms, and safety. Front. Pharmacol. 11, 422.
Song, A., Park, Y., Kim, B., Lee, S.G., 2020. Modulation of lipid metabolism by trans-anethole in hepatocytes. Molecules 25 (21), 4946.
Torghabeh, F.D., Javadi, B., Sahebkar, A., 2024. Dietary anethole: a systematic review of its protective effects against metabolic syndrome. J. Diabetes Metab. Disord. 23 (1), 619–631.
Vastegani, S.M., Khoshnam, S.E., Mansouri, E., Hajipour, S., Ghafouri, S., Bakhtiari, N., Farbood, Y., et al., 2023. Neuroprotective effect of anethole against rotenone induced non-motor deficits and oxidative stress in rat model of Parkinson's disease. Behav. Brain Res. 437, 114100.
Wang, B., Zhang, G., Yang, M., Liu, N., Li, Y.X., Ma, H., Yu, J., et al., 2018. Neuroprotective effect of anethole against neuropathic pain induced by chronic constriction injury of the sciatic nerve in mice. Neurochem. Res. 43, 2404–2422.
Werner, F.M., Coveñas, R., 2017. Classical neurotransmitters and neuropeptides involved in generalized epilepsy in a multi-neurotransmitter system: How to improve the antiepileptic effect? Epilepsy Behav. 71, 124–129.
Wisniewski-Rebecca, E.S., Rocha, B.A., Wiirzler, L.A., Cuman, R.K., Velázquez-Martínez, C.A., Bersani-Amado, C.A., 2015. Synergistic effects of anethole and ibuprofen in acute inflammatory response. Chem. -Biol. Interact. 242, 247–253.
Yadollahi-Farsani, Y., Vanani, V.R., Lorigooini, Z., Farahzad, A., Amini-Khoei, H., 2024. Anethole via increase in the gene expression of PI3K/AKT/mTOR mitigates the autistic-like behaviors induced by maternal separation stress in mice. IBRO Neurosci. Rep. 16, 1–7.
Yan, X.L., Xu, F.Y., Ji, J.J., Song, P., Pei, Y.Q., He, M.J., Jia, J., et al., 2022. Activation of UCP2 by anethole trithione suppresses neuroinflammation after intracerebral hemorrhage. Acta Pharmacol. Sin. 43 (4), 811–828.
Younis, N.S., Mohamed, M.E., 2023. Anethole pretreatment modulates cerebral Ischemia/Reperfusion: the role of JNK, p38, MMP-2 and MMP-9 pathways. Pharmaceuticals 16 (3), 442.
Zahra, W., Rai, S.N., Birla, H., Singh, S.S., Rathore, A.S., Dilnashin, H., et al., 2020. Economic importance of medicinal plants in Asian countries. Bioeconomy Sustain. Dev. 359–377.
Zhang, C., Zhang, B., Chen, A., Yin, Q., Wang, H., 2021. Trans-anethole attenuates diet-induced nonalcoholic steatohepatitis through suppressing TGF-β-mediated Fibrosis. Clin. Res. Hepatol. Gastroenterol. 46 (4), 101833.