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Protective effect of a hydromethanolic extract from *Fraxinus excelsior* L. bark against a rat model of aluminum chloride-induced Alzheimer's disease: Relevance to its anti-inflammatory and antioxidant effects

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Abstract

Ethnopharmacological relevance

Fraxinus *excelsior* L. (FE), commonly known as the ash, belongs to the Oleaceae family and has shown several pharmacological and biological properties, such as antioxidant, immunomodulatory, neuroprotective, and anti-inflammatory effects. It has also attracted the most attention toward neuroinflammation. Moreover, FE bark and leaves have been used to treat neurological disorders, aging, neuropathic pain, urinary complaints, and articular pain in traditional and ethnomedicine. Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder resulting from the involvement of amyloid-beta, metal-induced oxidative stress, and neuroinflammation.

Aim of the study

The objective of the current study was to assess the neuroprotective effects of hydromethanolic extract from FE bark in an $AlCl_3$-induced rat model of AD.

Materials and methods

The maceration process was utilized to prepare the hydromethanolic extract of FE bark, and characterized by LC-MS/MS. To assess the anti-AD effects of the FE extract, rats were categorized into five different groups, $AlCl_3$; normal control; FE-treated groups at 50, 100, and 200 mg/kg. Passive avoidance learning test, Y-maze, open field, and elevated plus maze behavioral tests were evaluated on days 7 and 14 to analyze the cognitive impairments. Zymography analysis, biochemical tests, and histopathological changes were also followed in different groups.

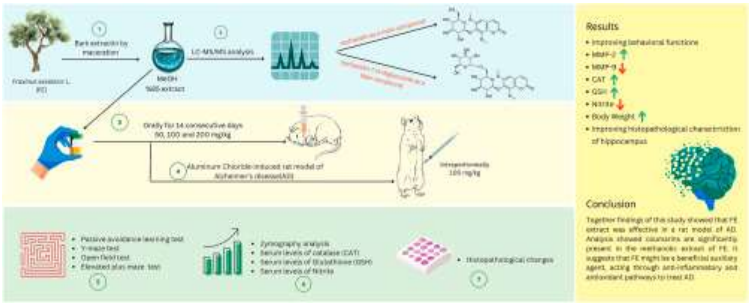
Results

LC-MS/MS analysis indicated the presence of coumarins, including isofraxidin7-O-diglucoside in the methanolic extract of FE as a new isofraxidin derivative in this genus. FE significantly improved memory and cognitive function, maintained weight, prevented neuronal damages, and preserved the hippocampus's histological features, as demonstrated by behavioral tests and histopathological analysis. FE increased anti-inflammatory MMP-2 activity, whereas it decreased that of inflammatory MMP-9. Moreover, FE increased plasma antioxidant capacity by enhancing CAT and GSH while decreasing nitrite levels in the serum of treated groups. In comparison between the treated groups, the rats that received high doses of the FE extract (200 mg/kg) showed the highest therapeutic effect.

Conclusion

FE rich in coumarins could be an effective anti-AD adjunct agent, passing through antioxidant and anti-inflammatory pathways. These results encourage further studies for the development of this extract as a promising agent in preventing, managing, or treating AD and related diseases.

Graphical abstract



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Introduction

As the leading etiology of dementia, Alzheimer's disease (AD) is distinguished with the aberrant extracellular accumulation of amyloid-β (Aβ) plaques and the accumulation of intracellular hyperphosphorylated tau proteins (p-tau) (Fakhri et al., 2021; Knopman et al., 2021).

As a multifactorial neurological condition, AD is affected by a complex interplay between hereditary and environmental factors. Aβ plaques and tau-containing neurofibrillary tangles (NFTs), serve as prominent pathological hallmarks of AD in the brain. Based on these observations, they have been considered the primary culprit in AD. However, growing data showed the insufficiency of the amyloid cascade hypothesis, bringing on alternative explanations (Herrup, 2015). Inflammation, apoptosis, and oxidative stress are the main dysregulated pathways implicated in the progression of AD (Fakhri et al., 2020). Neuroinflammation has been postulated as a vital player in AD pathogenesis and progression, primarily through microglial activation (Heneka et al., 2015). The activation and release of pro-inflammatory mediators like interleukin-6 (IL-6), IL-1β, and tumor necrosis factor-alpha (TNF-α) by the innate immune system lead to synaptic dysfunction, neuronal death, and neurogenesis inhibition (Leng and Edison, 2021). Matrix metalloproteinases (MMPs) are among the proteins whose role in neuroinflammation and neurodegeneration has attracted growing attention (Zipfel et al., 2020). Several MMPs, including MMP-2 and MMP-9, cleave Aβ monomers and oligomers, resulting in neurotoxicity (Ciccone et al., 2021).

Along with neuroinflammation, Aβ, and tau toxicity, a large body of evidence reveals oxidative stress as a significant contributor to AD pathogenesis and exacerbation (Gella and Durany, 2009). Oxidative stress manifests as a grave disarray in the equilibrium between generating reactive nitrogen species (RNS) and reactive oxygen species (ROS) and antioxidant defenses. The chronic presence of an inflammatory response and the release of toxic products including ROS and nitric oxide (NO) by activated microglia, is associated with neurodegeneration and exacerbating both Aβ and NFTs pathologies (Forman and Zhang, 2021; Kinney et al., 2018). Additionally, it has been demonstrated that ROS accelerates the oxidation of glycated proteins which are potent neurotoxic species (Cassidy et al., 2020).

The complex and multifactorial pathogenesis of neurodegenerative disorders like AD encompasses multiple molecular pathways (Wang et al., 2017). Therefore, drug discovery for AD necessitates multi-target strategies that consider multiple interacting mechanisms (Gong et al., 2018; Iqbal and Grundke-Iqbal, 2010). In addition to selective modifications on tau and Aβ, targeting neuroinflammation and oxidative stress can lead to promising results in controlling AD (Li et al., 2022; Tönnies and Trushina, 2017). For this purpose, natural products with anti-inflammatory and antioxidant characteristics are excellent resources for further investigations in this area.

Fraxinus excelsior L. (FE), commonly known as the common ash, is an anemophilous tree from the Oleaceae family, native to the countries of temperate Asia and Europe (Middleton et al., 2010). FE has been traditionally used for a variety of ailments such as nervous disorders, neuralgia, aging, minor articular pain, rheumatism, neuroinflammation, urinary complaints, gout, and etc. (Cavero and Calvo, 2015; Neves et al., 2009; Qasaymeh et al., 2023; Vitalini et al., 2015). In traditional resources of Persian medicine FE is used for neurological disorders including neurodegeneration, aging and neuralgia (Khorasani, 2001; Tonkaboni, 2007). FE is also used to treat neuralgia in the Trás-os-Montes region, a small region located in northern Portugal (Neves et al., 2009). Recent studies illustrated chronic pain and neuralgia could accelerate AD pathogenesis due to neuronal damages, pro-inflammatory mediators activation, neuroinflammation, and oxidative stress (Cao et al., 2019; Cheng et al., 2022).

The bark of FE stands as an eminent reservoir of phytoconstituents, notably featuring hydroxyl coumarins such as isofraxidin (7-hydroxy-6, 8-dimethoxy coumarin), alongside fraxidin, fraxetin, fraxinol, polyphenols, flavonoids, tannins, alkaloids, and sterols/triterpenes and their glycosylated counterparts (Amamra et al., 2018; Cotrozzi et al., 2018a; Qasaymeh et al., 2023; Qazi et al., 2018). Beyond this, a diverse array of bioactive compounds, including secoiridoids, flavonoids, phenylethanoids, and lignans, meticulously extracted from *Fraxinus* species, bestow upon this botanical entity a rich pharmacological tapestry (Nemesio-Gorriz et al., 2020; Sanz et al., 2012). Among these, isofraxidin emerges as a pivotal player, its multifaceted pharmacological activities warranting thorough exploration.

Isofraxidin takes center stage for its potent anti-inflammatory attributes (Lian et al., 2022; Su et al., 2019). The anti-inflammatory activity of aqueous/alcoholic extract from FE has been illustrated in some research studies (El-Ghazaly et al., 1992; Middleton et al., 2010). The alcoholic extract of FE barks has similar anti-inflammatory activity as diclofenac (Meyer et al., 1995; Von Kruedener et al., 1996). Its nuanced intervention in inflammatory pathways holds promise for mitigating the chronic neuroinflammation inherent in AD, regulating cytokines and inflammatory mediators to foster a neuroprotective microenvironment. Isofraxidin, with its robust antioxidant capacity, assumes the role of a sentinel, guarding against ROS and RNS (Durmaz et al., 2023). This defensive stance may alleviate oxidative stress, thereby preserving neuronal integrity. Isofraxidin exhibits potential interference with Aβ aggregation, presenting a prophylactic measure against the formation of amyloid plaques (Lian et al., 2022; Wu et al., 2022).

MMPs are implicated in neuroinflammation, and face modulation from isofraxidin, particularly in the form of MMP-2 and MMP-9 (Yamazaki and Tokiwa, 2010; Załuski et al., 2016). This orchestration presents an anti-neuroinflammatory effect, potentially safeguarding against blood–brain barrier (BBB) disruption and neuronal damages.

In this symphony of pharmacological prowess, isofraxidin, along with its botanical companions within FE bark, unveils a promising avenue for comprehensive therapeutic interventions in the realm of AD (Sarfraz et al., 2017).

The current study evaluated the possible neuroprotective properties of the hydromethanolic extract of FE bark in an aluminum chloride ($AlCl_3$)-induced behavioral and biochemical changes in a rat model of AD. This study introduces FE extract as a promising adjuvant therapy in treating AD by addressing neuroinflammatory and oxidative stress pathogeneses of the disease.

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Chemicals

Standard isofraxidin (≥98.0% HPLC) was purchased from Merck Co, (Darmstadt, Germany, CAS number: 486-21-5). $AlCl_3$, methanol, formic acid, acetic acid, 5, 5′-dithiobis-(2-nitrobenzoic acid) (DTNB), ammonium molybdate, sodium nitrite, N-(1-naphthyl) ethylenediamine dihydrochloride (NED), hydrogen peroxide (H_2O_2), acrylamide, sodium dodecyl sulfate

(SDS), Coomassie brilliant blue G-250 and Triton X-100 were obtained from Sigma-Aldrich Co, (MO, USA). Ketamine was procured from Alfasan (Woerden, …

LC-MS/MS analysis of FE

Based on the highest intensity of total ion chromatogram (TIC) obtained by injection of FE into LC-MS/MS in positive mode, molecular ions of 547 m/z, 385 m/z, and 223 m/z were observed (Fig. 1A). On the other hand, the fragmentation results of 547 m/z produced two molecular ions 385 m/z and 223 m/z, which indicate the loss of two sugar molecules (M-2 (162)) from 547 m/z (Fig. 1B). Then 223 m/z was fragmented to produce 209 m/z, 191 m/z, 163 m/z ions (Fig. 1C). Therefore, according to the …

Discussion

Alzheimer's disease (AD) stands as a persistent and progressive degenerative disorder, predominantly afflicting memory and cognitive functions (Scheltens et al., 2021). Despite ongoing research, the precise etiological underpinnings of AD remain elusive, with multifarious factors and processes implicated in its pathogenesis (Breijyeh and Karaman, 2020). The degeneration of neural cells and cognitive decline in AD is thought to be influenced by chronic inflammation in the brain, which is …

Conclusions

In conclusion, our study has thoroughly investigated the benefits of a FE bark extract in countering the effects of $AlCl_3$ AD model. By combining techniques such as LC-MS/MS analyses, behavioral assessments, biochemical analyses, and histopathological examination, we have gained a comprehensive understanding of how this extract works and showed coumarins are significantly present in the methanolic extract of FE. The observed improvements in function well as its antioxidant and anti-inflammatory …

Ethics approval

All phases of working with animals were authorized by the ethics committee for working with animals of Kermanshah University of Medical Sciences, Iran (IR.KUMS.REC.1399.557). …

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CRediT authorship contribution statement

Amin Iranpanah: Investigation, Project administration, Writing – original draft. **Sajad Fakhri:** Methodology, Writing – review & editing. **Gholamreza Bahrami:** Methodology, Validation. **Mohammad Bagher Majnooni:** Methodology, Project administration, Validation. **Mohammad Mehdi Gravandi:** Investigation. **Sara Taghavi:** Investigation, Writing – original draft. **Mehdi Azadi Badrbani:** Writing – original draft. **Roshanak Amirian:** Software. **Mohammad Hosein Farzaei:** Conceptualization, Supervision, Writing – …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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None. …

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