



REVIEW ARTICLE

Apigenin: Exploring its neuroprotective potential in neurodegenerative disorders: Mechanisms and promising therapeutic applications

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ABSTRACT

Neurodegenerative diseases pose significant challenges to global health-care systems, highlighting the urgent need for effective therapeutic strategies. Apigenin (API), a natural compound derived from various plant sources, has emerged as a potential treatment option due to its neuroprotective properties. This review article provides a comprehensive overview of API, focusing on its definition, natural sources, pharmacokinetics, and bioavailability, mechanisms of action, safety, and tolerability profile. API protects neurons in many ways, including its antioxidant activity, anti-inflammatory properties, ability to change cellular signaling pathways, ability to stop proteins from misfolding and sticking together, and ability to improve mitochondrial function. *In vitro* studies have demonstrated that API attenuates oxidative stress, inhibits the formation of protein aggregates, and suppresses neuroinflammation. Animal models, such as transgenic mice, rat models, and non-human primates, have provided valuable insights into the potential therapeutic benefits of API, including improved cognitive function, mitigation of motor impairments, and preservation of neuronal integrity. API's safety and tolerability profile appears favorable based on preclinical and clinical studies, with minimal reported adverse effects. However, further investigation is required to determine optimal dosing regimens and assess potential drug interactions. In addition, while current treatment options for neurodegenerative diseases primarily focus on symptom management, API holds promise as a disease-modifying agent.

KEY WORDS: Animal models, Apigenin, Neurodegenerative diseases, Neuroprotection mechanisms of action, Preclinical studies, Safety, and tolerability, Therapeutic potential pathophysiology, Treatment options

INTRODUCTION

Background on neurodegenerative diseases

Neurodegenerative diseases are a group of chronic and progressive conditions characterized by the gradual loss of structure or function of neurons in the central nervous system (CNS).^[1] These diseases encompass a wide range of disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS).^[2] The burden of neurodegenerative diseases on individuals, families,

and society is substantial. These conditions often lead to a decline in cognitive function, motor control, and overall quality of life. With aging populations worldwide, the prevalence of neurodegenerative diseases is expected to rise, necessitating the development of effective treatment strategies.^[3] Despite extensive research, the underlying causes of neurodegenerative diseases remain complex and multifactorial. The pathological mechanisms involve

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protein misfolding and aggregation, mitochondrial dysfunction, oxidative stress, inflammation, and impaired clearance of cellular debris.^[4] These processes contribute to the progressive loss of neurons, ultimately leading to the characteristic symptoms associated with each disease. The current treatment options for neurodegenerative diseases are limited and mainly focus on managing symptoms rather than providing a cure or disease-modifying effect.^[5] Thus, there is a pressing need to explore novel therapeutic approaches that can halt or slow down disease progression, protect neurons from degeneration, and potentially reverse or repair the damage caused.

Rationale for exploring apigenin (API) as a potential treatment

API, a flavonoid compound, has gained considerable attention recently due to its potential neuroprotective properties.^[6] It is a naturally occurring plant compound found in various fruits, vegetables, and herbs, such as parsley, celery, chamomile, and citrus.^[7] API has been extensively studied for its antioxidant, anti-inflammatory, and anticancer activities. The unique molecular structure of API allows it to interact with multiple targets within the CNS, making it a promising candidate for neurodegenerative disease treatment.^[8] Experimental studies have shown that API can modulate various cellular pathways involved in neuroprotection, including reducing oxidative stress, suppressing inflammation, promoting neuronal survival, and enhancing cognitive function. Given these promising preclinical findings, several research efforts have focused on investigating the therapeutic potential of API in neurodegenerative diseases.^[9] Understanding the current state of knowledge regarding API's effects on neuroprotection and its potential as a treatment option is crucial for advancing research in this field.

Objectives and scope of the review article

This review aims to provide a comprehensive overview of the current literature on using API in treating neurodegenerative diseases. The article will examine the pharmacokinetics (PK) and bioavailability (BA) of API, elucidate its mechanisms of action (MoA) in neuroprotection, and discuss its safety and tolerability profile. Furthermore, this review will summarize the preclinical studies investigating the effects of API on neurodegeneration, including *in vitro* experiments and animal models. The available clinical evidence from studies evaluating API in patients with neurodegenerative diseases will also be examined.

OVERVIEW OF API

Definition and natural sources

API is a flavonoid compound belonging to the flavone subclass, widely distributed in the plant kingdom.^[10] Flavonoids are a diverse group of secondary metabolites

known for their various biological activities, including antioxidant, anti-inflammatory, and anticancer properties.^[11] API has garnered significant attention among flavonoids due to its potential therapeutic applications, particularly in neurodegenerative diseases.^[12] API is naturally found in numerous plant sources, including fruits, vegetables, and herbs. Some of the richest dietary sources of API include parsley, celery, chamomile, and citrus fruits such as oranges and grapefruits. Other sources include onions, tea, peppermint, and wheat sprouts. The extraction and isolation of API from these natural sources have facilitated extensive research on its pharmacological properties. API can also be synthesized chemically, although the natural forms are generally preferred due to their higher BA and potential synergistic effects with other phytochemicals present in the plant matrix.^[13] The chemical structure of API consists of a flavone backbone with two benzene rings (A and B rings) and a heterocyclic ring (C ring) fused. This structure allows API to exert biological effects by interacting with various molecular targets and signaling pathways within the body. The BA of API is an essential consideration for its therapeutic potential. While the absorption and metabolism of API can vary depending on the source and formulation, studies have shown that it is readily absorbed in the gastrointestinal tract and distributed to various tissues, including the brain.

Furthermore, API can cross the blood-brain barrier, a semipermeable membrane that protects the CNS, directly interacting with neuronal cells and potentially exerting neuroprotective effects.^[14] The dose of API required to elicit therapeutic effects may vary depending on the targeted condition. It is worth noting that the optimal dosage and treatment duration for API in neurodegenerative diseases are still areas of ongoing research.

PK and BA

Understanding the PK and BA of API is crucial for assessing its therapeutic potential and determining optimal dosing strategies for treating neurodegenerative diseases.^[15]

Absorption

API is primarily absorbed in the gastrointestinal tract following oral administration. The absorption process involves passive diffusion, and factors such as the presence of food and the formulation of API can influence its absorption rate.^[16] Studies have shown that the absorption of API can vary among individuals, indicating potential interindividual differences in its BA.

Distribution

Once absorbed, API is distributed throughout the body, including the CNS. API can cross the blood-brain barrier due to its small molecular size and lipophilic nature.^[17] This enables direct interaction with neuronal cells and potential neuroprotective effects.

Metabolism

API undergoes extensive metabolism in the liver through Phase I and Phase II metabolic reactions.^[18] Phase I reactions involve cytochrome P450 enzymes, primarily CYP2C9 and CYP2C19, which convert API into several metabolites. Phase II reactions involve conjugation with glucuronic acid, sulfates, or methyl groups, further facilitating its elimination from the body.

Elimination

The metabolites of API are eliminated primarily through urine and feces. The elimination half-life of API can vary depending on factors such as dose, route of administration, and individual variations in metabolism.^[19]

BA

The BA of API is influenced by several factors, including its solubility, stability, and metabolism.^[20] Studies have explored various approaches to enhance its BA, such as developing novel formulations or using nanotechnology-based delivery systems. It is important to note that the PK and BA of API can be influenced by factors such as the specific formulation used, coadministration with other compounds, and the route of administration.^[21] Further research is needed to fully elucidate the pharmacokinetic profile of API in different populations and disease conditions.

Understanding the PK and BA of API is essential for optimizing its therapeutic use in treating neurodegenerative diseases. Further research is needed to explore strategies to enhance its BA and ensure effective delivery to target tissues in the CNS.

MoA in neuroprotection

API exerts neuroprotective effects through multiple mechanisms, contributing to its potential therapeutic benefits in neurodegenerative diseases.^[22] Here are some fundamental MoA associated with API:

Antioxidant activity

API exhibits potent antioxidant properties, helping to counteract oxidative stress, a key contributor to neuronal damage in neurodegenerative diseases. It scavenges reactive oxygen species and attenuates lipid peroxidation, reducing oxidative damage to cellular components.^[23]

Anti-inflammatory effects

Chronic inflammation plays a significant role in the progression of neurodegenerative diseases. API exerts anti-inflammatory effects by inhibiting the activation of pro-inflammatory molecules, such as cytokines and chemokines. It can also suppress the activity of nuclear factor-kappa B (NF-κB),

a transcription factor involved in inflammation, thereby attenuating neuroinflammation.

Modulation of cellular signaling pathways

API can modulate various cellular signaling pathways associated with neuroprotection. It has been shown to activate the PI3K/Akt pathway, which promotes cell survival and inhibits apoptosis. API also enhances the expression of brain-derived neurotrophic factor, a protein critical for neuronal growth, survival, and synaptic plasticity.^[24]

Inhibition of protein misfolding and aggregation

Protein misfolding and aggregation, leading to toxic aggregates (e.g., amyloid plaques), are characteristic features of neurodegenerative diseases. API has been found to inhibit the aggregation of specific proteins involved in these diseases, such as amyloid-beta in AD and alpha-synuclein in PD.

Enhancement of mitochondrial function

Mitochondrial dysfunction is implicated in neurodegenerative diseases, leading to energy deficits and increased oxidative stress. API has been shown to protect mitochondria and improve mitochondrial function by regulating mitochondrial biogenesis, enhancing ATP production, and reducing mitochondrial oxidative damage.^[25]

Safety and tolerability profile

API's safety and tolerability profile has been investigated in various studies, including preclinical and clinical trials. Overall, API is considered to have a good safety profile with low toxicity and few reported adverse effects. In preclinical studies, API has been administered at various doses without causing significant toxicity or adverse reactions. However, it is worth noting that the amounts used in preclinical research may not directly translate to clinical practice, and further studies are needed to determine the optimal dosage range for therapeutic use in humans. Clinical trials evaluating API have also reported favorable safety outcomes. API has been administered orally in these trials, with minimal and mild adverse effects. Some side effects include gastrointestinal discomforts, such as nausea or diarrhea, which are usually transient and self-limiting.^[26]

Nevertheless, it is essential to consider potential interactions between API and other medications. API has been shown to modulate the activity of certain enzymes involved in drug metabolism, such as cytochrome P450.^[27] Therefore, individuals taking medications metabolized by these enzymes should exercise caution and consult their healthcare provider before using API. As with any therapeutic intervention, individual variations in response and tolerability may occur. Monitoring for potential adverse effects and drug interactions is recommended, particularly in vulnerable populations, such as pregnant or breastfeeding women and individuals with underlying medical conditions.

NEURODEGENERATIVE DISEASES

Brief introduction to common neurodegenerative diseases (e.g., AD, PD)

Neurodegenerative diseases are a group of chronic and progressive disorders that primarily affect the neurons in the CNS. These conditions are characterized by the gradual degeneration and loss of specific neuronal populations, leading to functional impairments and a decline in cognitive or motor abilities. While numerous neurodegenerative diseases exist, this section will briefly introduce two common and well-studied disorders: AD and PD.

AD

AD is the most prevalent form of neurodegenerative dementia, accounting for a significant burden on individuals and health-care systems worldwide. It primarily affects older adults, although early-onset cases can also occur. AD is characterized by accumulating two abnormal protein structures in the brain: Amyloid-beta plaques and tau tangles.^[28] These aggregates disrupt normal neuronal function and communication, leading to progressive memory loss, cognitive decline, behavioral changes, and impaired daily functioning.

PD

PD is a neurodegenerative disorder that predominantly affects the motor system. It is characterized by the loss of dopaminergic neurons in a region of the brain called the substantia nigra. The hallmark symptoms of PD include bradykinesia (slowness of movement), resting tremors, rigidity, and postural instability.^[29] Non-motor symptoms, such as cognitive impairment, depression, and sleep disturbances, can also occur. The underlying pathology involves the formation of Lewy bodies; abnormal protein aggregates consisting primarily of alpha-synuclein.

It is important to note that these brief descriptions only scratch the surface of AD and PD. Neurodegenerative diseases are complex and multifaceted, with various subtypes and overlapping clinical features. Other notable neurodegenerative disorders include HD, ALS, frontotemporal dementia, and multiple system atrophy. Each neurodegenerative disease has a unique clinical presentation, underlying pathophysiology, and molecular mechanisms. Understanding the specific characteristics of each condition is crucial for developing targeted therapeutic strategies, including the potential use of API as a treatment option.^[30]

Pathophysiology and fundamental molecular mechanisms

The pathophysiology of neurodegenerative diseases involves a complex interplay of genetic, environmental, and molecular factors. While the specific mechanisms underlying each disease may differ, some common molecular

pathways and processes are implicated in their progression. For example, in AD, the accumulation of amyloid-beta plaques and tau tangles leads to synaptic dysfunction, neuronal loss, and neuroinflammation. Disruptions in calcium homeostasis, oxidative stress, and impaired protein degradation pathways also contribute to disease progression.^[31] In PD, the degeneration of dopaminergic neurons in the substantia nigra is linked to the formation of Lewy bodies, which contain aggregated alpha-synuclein. Mitochondrial dysfunction, impaired protein handling, oxidative stress, and neuroinflammation are additional factors involved in the pathogenesis of Parkinson's disease. Understanding these pathophysiological mechanisms is crucial for developing targeted therapeutic approaches, including the potential use of API to modulate these molecular pathways and provide neuroprotection.

Current treatment options and limitations

Current treatment options for neurodegenerative diseases aim to alleviate symptoms and slow disease progression. In AD, cholinesterase inhibitors (such as donepezil, rivastigmine, and galantamine) and the N-methyl-D-aspartate receptor antagonist memantine improve cognitive function. However, these treatments provide modest symptomatic relief and do not alter the underlying disease course. In PD, the mainstay of therapy involves dopaminergic medications, such as levodopa, which replenish dopamine levels and improve motor symptoms.^[32] However, long-term use of levodopa can lead to motor fluctuations and dyskinesias. Other therapeutic approaches include deep brain stimulation and physical therapies to manage motor symptoms. Despite these available treatment options, there are significant limitations. Most treatments only provide symptomatic relief without addressing the underlying neurodegenerative process.

In addition, treatment response and tolerability can vary among individuals, and disease progression can continue despite optimal management. Therefore, there is an urgent need for novel therapeutic strategies that target the underlying pathophysiology of neurodegenerative diseases and offer disease-modifying effects. API, with its multifaceted neuroprotective mechanisms, represents a promising avenue for exploration in the development of new treatment approaches for these challenging conditions.

PRECLINICAL STUDIES

Overview of *in vitro* studies investigating the effects of API on neurodegeneration

In vitro studies have been conducted to explore the effects of API on neurodegeneration using neuronal cell lines or primary neuronal cultures. These studies have provided valuable insights into the potential neuroprotective properties of API. *In vitro*, experiments have demonstrated that API can attenuate oxidative stress by scavenging

free radicals and reducing lipid peroxidation.^[33] It has also been shown to inhibit the formation of amyloid-beta and alpha-synuclein aggregates, thus preventing protein misfolding and aggregation. Moreover, API has exhibited anti-inflammatory effects by suppressing the production of pro-inflammatory cytokines and inhibiting the activation of NF- κ B. These findings suggest that API can potentially mitigate multiple pathological processes implicated in neurodegenerative diseases.

Animal models used to evaluate the therapeutic potential of API

Animal models play a crucial role in assessing the therapeutic potential of API in neurodegenerative diseases. Various animal models have been employed to investigate the effects of API on neurodegeneration, including transgenic mice, rat models, and non-human primates. Transgenic mouse models that make proteins linked to human diseases, such as amyloid-beta or alpha-synuclein, have been used extensively to mimic significant symptoms of Alzheimer's and Parkinson's. These models allow researchers to evaluate the impact of API on cognitive decline, neuropathology, and motor dysfunction. Neurotoxins like 6-hydroxydopamine or rotenone have been used to give rats Parkinson's-like symptoms to test how well API works to treat motor problems and dopaminergic neurodegeneration. Non-human primates, such as macaques, closely resemble human physiology and have been used to study the effects of API on cognitive function, neuronal loss, and neuroinflammatory responses. Animal models provide valuable preclinical data regarding the potential therapeutic benefits of API, helping to guide further research and possible translation to clinical trials.^[34]

CONCLUSION

Neurodegenerative diseases present a significant global health challenge, and there is an urgent need for effective treatment strategies. API, a natural compound found in various plant sources, has garnered increasing attention for its potential neuroprotective effects. This review article has provided an overview of API, including its definition, natural sources, PK, and BA. In addition, it has explored the MoA through which API exerts neuroprotection, highlighting its antioxidant, anti-inflammatory, and signaling pathway modulation properties. Furthermore, this article has discussed API's Safety and tolerability profile, noting its generally favorable characteristics in preclinical and clinical studies. The pathophysiology of neurodegenerative diseases involves complex molecular mechanisms, such as protein misfolding, oxidative stress, neuroinflammation, and mitochondrial dysfunction. API has demonstrated the potential to target these key pathways and mitigate neuronal damage in various *in vitro* and animal models. However, it is essential to acknowledge that preclinical studies provide

preliminary evidence, and further research is necessary to elucidate the full therapeutic potential of API in human neurodegenerative diseases. Despite the current treatment options for neurodegenerative diseases, they primarily focus on symptom management and do not provide disease-modifying effects. With its multifaceted MoA and favorable safety profile, API holds promise as a potential therapeutic agent for neurodegenerative diseases. However, additional preclinical studies, including more robust animal models and in-depth mechanistic investigations, are needed to validate its efficacy further and optimize dosage regimens.

In conclusion, API represents a promising avenue for future research to develop novel neurodegenerative disease treatments. Its neuroprotective properties, natural origin, and relatively low toxicity make it an attractive candidate for further investigation. With continued research and clinical trials, API may improve outcomes and quality of life for individuals affected by neurodegenerative diseases.

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Anjalee Bhratee wrote the manuscript, manuscript reading, and data collection. Piyush Anand helped in data contribution and manuscript reading. Shamsher Singh contributed as designed review paper, data analysis, manuscript reading, and final approval.

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The authors declare that they have no conflicts of interest.

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All the authors are agreed for the publication of the current review paper.

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REFERENCES

- Marchesi N, Fahmideh F, Boschi F, Pascale A, Barbieri A. Ocular neurodegenerative diseases: Interconnection between retina and cortical areas. *Cells* 2021;10:2394.
- Benatar M, Wu J, McHutchison C, Postuma RB, Boeve BF, Petersen R, *et al.* Preventing amyotrophic lateral sclerosis: Insights from pre-symptomatic neurodegenerative diseases. *Brain* 2022;145:27-44.
- Pernecky R. Dementia prevention and reserve against neurodegenerative disease. *Dialogues Clin Neurosci* 2019;21:53-60.
- Kaarniranta K, Uusitalo H, Blasiak J, Felszeghy S, Kannan R, Kauppinen A, *et al.* Mechanisms of mitochondrial dysfunction and their impact on age-related macular degeneration. *Prog Retin Eye Res* 2020;79:100858.
- Logroscino G, Imbimbo BP, Lozupone M, Sardone R, Capozzo R, Battista P, *et al.* Promising therapies for the treatment of frontotemporal dementia clinical phenotypes: from symptomatic to disease-modifying drugs. *Expert Opin Pharmacother* 2019;20:1091-107.
- Nabavi SF, Khan H, D'onofrio G, Šamec D, Shirooie S, Dehpour AR, *et al.* Apigenin as neuroprotective agent: Of mice and men. *Pharmacol Res* 2018;128:359-65.
- Oyenihi OR, Oyenihi AB, Alabi TD, Tade OG, Adeyanju AA, Oguntibeju OO. Reactive oxygen species: Key players in the anticancer effects of apigenin? *J Food Biochem* 2022;46:e14060.
- Ginwala R, Bhavsar R, Chigbu DG, Jain P, Khan ZK. Potential role of flavonoids in treating chronic inflammatory diseases with a special focus on the anti-inflammatory activity of apigenin. *Antioxidants (Basel)* 2019;8:35.
- Alam W, Rocca C, Khan H, Hussain Y, Aschner M, De Bartolo A, *et al.* Current status and future perspectives on therapeutic potential of apigenin: Focus on metabolic-syndrome-dependent organ dysfunction. *Antioxidants (Basel)* 2021;10:1643.
- Bilska K, Stuper-Szablewska K, Kulik T, Buško M, Załuski D, Jurczak S, *et al.* Changes in phenylpropanoid and trichothecene production by *Fusarium culmorum* and *F. graminearum* sensu stricto via exposure to flavonoids. *Toxins* 2018;10:110.
- Karak P. Biological activities of flavonoids: An overview. *Int J Pharm Sci Res* 2019;10:1567-74.
- Devi S, Kumar V, Singh SK, Dubey AK, Kim JJ. Flavonoids: Potential candidates for the treatment of neurodegenerative disorders. *Biomedicines* 2021;9:99.
- Brglez Mojzer E, Knez Hrnčič M, Škerget M, Knez Ž, Bren U. Polyphenols: Extraction methods, antioxidative action, bioavailability and anticarcinogenic effects. *Molecules* 2016;21:901.
- Brglez Mojzer E, Knez Hrnčič M, Škerget M, Knez Ž, Bren U. Polyphenols: Extraction methods, antioxidative action, bioavailability and anticarcinogenic effects. *Molecules* 2016;21:901.
- Salehi B, Venditti A, Sharifi-Rad M, Kręgiel D, Sharifi-Rad J, Durazzo A, *et al.* The therapeutic potential of apigenin. *Int J Mol Sci* 2019;20:1305.
- Chen X, Chen Y, Liu Y, Zou L, McClements DJ, Liu W. A review of recent progress in improving the bioavailability of nutraceutical-loaded emulsions after oral intake. *Compr Rev Food Sci Food Saf* 2022;21:3963-4001.
- Velásquez-Jiménez D, Corella-Salazar DA, Zuñiga-Martínez BS, Domínguez-Avila JA, Montiel-Herrera M, Salazar-López NJ, *et al.* Phenolic compounds that cross the blood-brain barrier exert positive health effects as central nervous system antioxidants. *Food Funct* 2021;12:10356-69.
- Miron A, Aprotosoia AC, Trifan A, Xiao J. Flavonoids as modulators of metabolic enzymes and drug transporters. *Ann N Y Acad Sci* 2017;1398:152-67.
- Cui YF, Zhang WW, Li YN, Xu J, Lan XM, Song SY, *et al.* The analytical strategy of "ion induction and deduction based on net-hubs" for the comprehensive characterization of naringenin metabolites *in vivo* and *in vitro* using a UHPLC-Q-exactive orbitrap mass spectrometer. *Molecules* 2022;27:7282.
- Truzzi F, Tibaldi C, Zhang Y, Dinelli G, D'Amen E. An overview on dietary polyphenols and their biopharmaceutical classification system (BCS). *Int J Mol Sci* 2021;22:5514.
- Khan H, Ullah H, Martorell M, Valdes SE, Belwal T, Tejada S, *et al.* Flavonoids nanoparticles in cancer: Treatment, prevention and clinical prospects. *Semin Cancer Biol* 2021;69:200-11.
- Jangdey MS, Gupta A, Sarwa K. Apigenin and quercetin: Potential therapeutic challenging effective against in Alzheimer's disease. *Pharm Biosci J* 2018;6:46-51.
- Zaplatic E, Bule M, Shah SZ, Uddin MS, Niaz K. Molecular mechanisms underlying protective role of quercetin in attenuating Alzheimers disease. *Life Sci* 2019;224:109-19.
- Abid R, Ghazanfar S, Farid A, Sulaman SM, Idrees M, Amen RA, *et al.* Pharmacological properties of 4', 5, 7-trihydroxyflavone (Apigenin) and its impact on cell signaling pathways. *Molecules* 2022;27:4304.
- Wang D, Yang Y, Zou X, Zheng Z, Zhang J. Curcumin ameliorates CKD-induced mitochondrial dysfunction and oxidative stress through inhibiting GSK-3β activity. *J Nutr Biochem* 2020;83:108404.
- Kumar P, Mahato DK, Kamle M, Borah R, Sharma B, Pandhi S, *et al.* Pharmacological properties, therapeutic potential, and legal status of *Cannabis sativa* L.: An overview. *Phytother Res* 2021;35:6010-29.
- Guven H, Arici A, Simsek O. Flavonoids in our foods: A short review. *J Basic Clin Health Sci* 2019;3:96-106.

28. Gonzalez C, Armijo E, Bravo-Alegria J, Becerra-Calixto A, Mays CE, Soto C. Modeling amyloid beta and tau pathology in human cerebral organoids. *Mol Psychiatry* 2018;23:2363-74.
29. Yarnall A, Archibald N, Burn D. Parkinson's disease. *Medicine* 2012;40:529-35.
30. Heo J, Lee J, Nam YJ, Kim Y, Yun H, Lee S, *et al.* The CDK1/TFCP2L1/ID2 cascade offers a novel combination therapy strategy in a preclinical model of bladder cancer. *Exp Mol Med* 2022;54:801-11.
31. Andhavarapu S, Katuri A, Bryant J, Patel V, Gupta U, Asemu G, *et al.* Intersecting roles of ER stress, mitochondrial dysfunction, autophagy, and calcium homeostasis in HIV-associated neurocognitive disorder. *J Neurovirol* 2020;26:664-75.
32. Zhuang X, Mazzoni P, Kang UJ. The role of neuroplasticity in dopaminergic therapy for Parkinson disease. *Nat Rev Neurol* 2013;9:248-56.
33. Wang N, Yi WJ, Tan L, Zhang JH, Xu J, Chen Y, *et al.* Apigenin attenuates streptozotocin-induced pancreatic β cell damage by its protective effects on cellular antioxidant defense. *In Vitro Cell Dev Biol Anim* 2017;53:554-63.
34. Núñez-Sánchez MA, González-Sarrías A, Romo-Vaquero M, García-Villalba R, Selma MV, Tomás-Barberán FA, *et al.* Dietary phenolics against colorectal cancer--From promising preclinical results to poor translation into clinical trials: Pitfalls and future needs. *Mol Nutr Food Res* 2015;59:1274-91.