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Apigenin and Quercetin: Potential Therapeutic Challenging Effective Against in Alzheimer's Disease

Manmohan S. Jangdey[1]*, Anshita Gupta[1] Khomendra Sarwa[2]

[1]University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur (C. G.) 492001, India
[2]Girls Polytechnic college Baran bazar, Raipur (C. G.) 492001, India

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Corresponding Author:
E-mail : manuiopresearch@gmail.com
Mob.: +919179988727

Abstract

Alzheimer's disease (AD) is an accelerating neurodegenerative disorder, dementia in the world. Current treatments for Alzheimer's disease primarily focus on enhancement of cholinergic transmission & leading to neuronal dysfunction and loss in the brain. Flavonoid bioactive compounds are the major role for the designer of a new generation of therapeutic agents that are clinically effective in treating neurodegenerative diseases. Apigenin & quercetin are attractive biomarkers in this regards which has been epidemiological studies height a Neuroprotective and related to a lower risk of developing dementia or gradual decline its progressive. The continuing investigation of the potential preventive activity of quercetin and apigenin should be evaluated in long-term exposure clinical trials, using preparations with high bioavailability and promising to yield a possible remedy for this pervasive disease. Thus, the aim of the review, we analyzed the enhancing effects of apigenin and quercetin and discuss the potential of these compounds for Alzheimer's disease prevention and treatment.

1 Introduction

Alzheimer's disease (AD) is one of the greatest widespread heterogeneous progressive neurodegenerative disorders of the central nervous system, dementia in the worldwide. Its pathological distinguishing attribute include synaptic degeneration, deposition of Aβ-containing senile plaques and phosphotau-containing tangles in brain. , which ultimately lead to neuronal dysfunction and loss in the brain[1, 2]. Dementia is a multifactorial syndrome that affects memory, thinking, language, behaviour and ability to perform everyday activities. According to the WHO Alzheimer Report today[3, 4]. dementia affects over 46 million people worldwide and this number is estimated to increase to 131.5 million by 2050 due to increased expectation of life and an aging population[5] .The most common form of dementia is Alzheimer disease (AD) that possibly contributes to 60%–70% of cases, with a greater proportion in the higher age ranges[6]. AD is a multifactorial disease with genetic (70%) and environmental (30%) causes. The familial early-onset form of AD is caused by mutations in genes APP (amyloid precursor protein), PSEN1 (Presenilin 1) and PSEN2 (Presenilin 2). The main factors of neurodegeneration are several cellular and molecular events such as oxidative stress, impaired mitochondrial function, and deposition of aggregated proteins, neuroinflammation, and activation of apoptotic factors[7, 8]. Flavonoids are bioactive markers components that are derived from vegetables plants and fruits. Since ancient times, apigenin- and quercetin rich nutraceuticals have been used as food supplements in improving cognitive function and in prevention of neurodegenerative diseases in humans[9]. Apigenin and quercetin rich flavonoids may be able to target multiple sites in the brain and prevent neurodegenerative diseases (Fig 1). Better animal models and good biomarkers for patient sub grouping will be also instrumental for quick advancement in the field[10]. The review revises all these aspects with the objective to generate debate among scientists. In this review, we emphasize the protective and preventive functions of apigenin and quercetin in neurodegenerative diseases by modulation of neurosignaling pathways[11, 12]. In general, the neuroprotective role of activated microglia cells are facilitated by removing

damaged neurons and infectious agents by phagocytosis. However, their chronic activation exacerbates neuronal damage through excessive release of proinflammatory cytokines, and other inflammatory mediators which contribute to neuroinflammation and subsequent neurodegeneration in the CNS. Considering the possible role of neuroinflammation in the pathogenesis of neurodegenerative disorders, an intervention that targets this mechanism may have therapeutic potential. Epidemiological and genetic linkage data indicates strong support of neuroinflammation as drug discovery target for neurodegenerative disorders. Preclinical and animal model studies embody most of the research done and indicate the need for larger in-depth examinations[13,14].

Neuroinflammation is also involved in the complex cascade leading to AD pathology and symptoms. It has been shown that AD is associated with increased levels of cyclooxygenase 1 and 2 and of prostaglandins, release of cytokines and chemokines, acute phase reaction, astrocytosis and microgliosis[15, 16]. These pro-inflammatory factors may induce degeneration of normal neurons through up regulation of nuclear factor-κB, mitogen-activated protein kinase, and c-Jun N-terminal kinase[17]. Finally, in patients with AD epigenetic alterations such as changes in DNA methylation, histone modifications, or changes in miRNA expression have been reported. Histone acetyltransferases HATs) and histone deacetylases (HDACs) promote histone post-translational modifications, which lead to an epigenetic alteration in gene expression. Aberrant regulation of HATs and HDACs in neuronal cells results in pathological consequences such as neurodegeneration[18 19] .

Alzheimer's appears to be a complex and multifactorial disorder in which extracellular Aβ and intraneuronal hyperphosphorylated tau protein are the hallmark neuropathological features, along with oxidative stress and inflammation. Actually, no current effective disease-modifying treatments are available[20]. Moreover, as Aβ-induced changes are believed to occur a long time before the impairment of cognitive function appears, so strategies to stop or to slow the progression of the disease are of greater importance as is an early diagnosis. Owing to the particular multifactorial nature of the disease, a novel approach consists in evaluating substances having multi-target mechanisms, such as flavonoids, apigenin and quercetin are naturally occurring flavonoids of emerging interest are shown in Table 1 and Fig 2.

2 Pharmacokinetics and Multimodal drug therapy of Alzheimer's

The majority of studies on potential anti-AD therapies are per-formed on transgenic models to which the assayed substance(s) is administered. In a high percentage of these studies (i) the actual concentration that reaches the CNS, (ii) the plasma/brain ratio, and (iii) the half-life of the compound in blood or brain are undetermined.

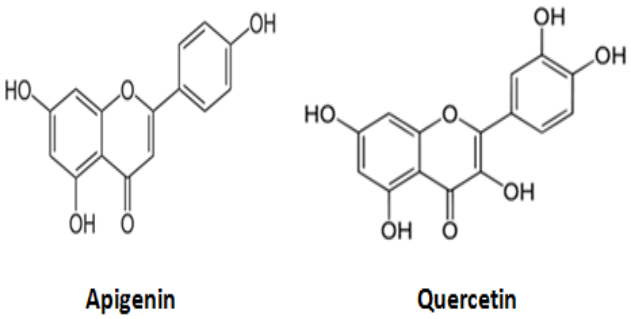

Fig 1: Chemical structure of (A) Apigenin, (B) Quercetin

These parameters are important to understand where, when, and how a given drug is acting. It may also occur that a given drug is acting on quite diverse targets whose distribution in the (rodent or human) body is uneven. For example, Okun et al. (2010)[24], reported a very informative study on dimebon, originally developed as an anti-histamine drug. Dimebon seems to be a multimodal drug with many different targets including g serotonergic, α-adrenergic, anddopaminergic receptors. The results indicate something that should be consid ered in drug discovery, namely that a drug with multiple targets may result in greater benefits than a "clean" drug acting only on a given target . Furthermore, Okun et al. (2010) suggest that it is necessary to understand the role of different pathways in AD and in any other disease with complex etiologies. Such knowledge would surely help in developing multitarget drugs [25].

3 Source, Pharmacokinetics and Mechanism of Neuroprotective Action of Apigenin and Quercetin

Apigenin is a polyphenol, nontoxic, nonmutagenic bioactive flavone (4, 5, 7-Trihydroxyflavone) found in a wide variety of fruits, plants, and vegetables in high level in cherries, onion, apples, grapes, celery and parsley has been reported to have numerous pharmacological properties and anticarcinogenic effects, anti-inflammatory and antioxidant [26, 27, 28]. The cancer chemopreventive properties of apigenin were first demonstrated by Birt et al.2001 who described the antimutagenic and anti-promotion properties of apigenin through inhibition of TPA-induced ornithine decarboxylase activity in mouse skin. These initial studies with apigenin generated further interest in the development of apigenin as a chemopreventive and chemotherapeutic agent [29, 30]. Apigenin has also been shown to suppress protein kinase cell activity and Prevents UVB-induced skin carcinogenesis. Recently, apigenin has been reported to alleviate learning and memory deficits and express the neurovascular protection by decreasing oxidative damage, improving cholinergic neuronal transmission, and preserving the blood-brain barrier integrity in Aβ25–35 intracerebroventricularly injected mice[31]. The inhibition of the influx of extracellular Ca2+ and release of intracellular Ca^{2+} in the rat thoracic aorta[32]. And the antagonism of NMDA and γ-aminobutyric acid (GABA) receptor channels in neurons might be part of the protective mechanisms.

Further, we demonstrated that apigenin exerted neuroprotection against Aβ-mediated toxicity mainly through the mechanisms of regulating redox imbalance, preserving mitochondrial function, inhibiting p38 MAPK-MAPKAP kinase-2 (MK2)-heat shock protein 27 (HSP27) and stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK)-c-Jun pathways, and depressing apoptosis [33]. Several groups have reported the anti-inflammatory action of apigenin in a number of human and animal inflammatory cell lines and animal models. Furthermore, analysis of the neuroprotective potential of apigenin in a double transgenic mouse model of AD (APP/PS1) indicated that apigenin could ameliorate AD-associated memory impairment, reduce the Aβ plaque burden and inhibit oxidative stress23. Several groups have reported anti-apoptotic effects of apigenin in murine HT2224 and human SH-SH5Y cell lines 25 and shown that apigenin can reduce glutamate-induced Ca^{2+} signalling in murine cortical neurons. Collectively, these results indicate that apigenin may have potent neuroprotective properties. However its contribution to neuroprotective mechanisms in human AD neurons is currently unknown [34,35].

Table 1: Flavonoid compounds, their representative biomarker and naturally occurring source[21, 22, 23]

Flavonoids	biomarkers	Natural source
Flavones	Apigenin, Luteolin	Cherries, onions, grapes, apples, Parsley, celery
Flavonols	Quercetin, Rutin, Myricetin, Kaempherol	Leeks, onions, broccoli, kale, apples,cherries, berries, tea, red wine
Isoflavones	Genistein ,Glycetin, Daidzein, Formanantine	Legumes, soybeans, Daidzein soy products
Flavanols	Epigallocatechin, Catechin, epigallocatechin gallate, Epicatechin	chocolate, apples, Green tea, red wine,
Flavanones	Naringenin, Taxifolin, Isoxanthohumol	Citrus fruits, tomatoes
Anthocyanidins	Pelargonidin, Malvidin, Delphinidin, Cyanidin	cherries, grapes , Red wine, berry fruits,

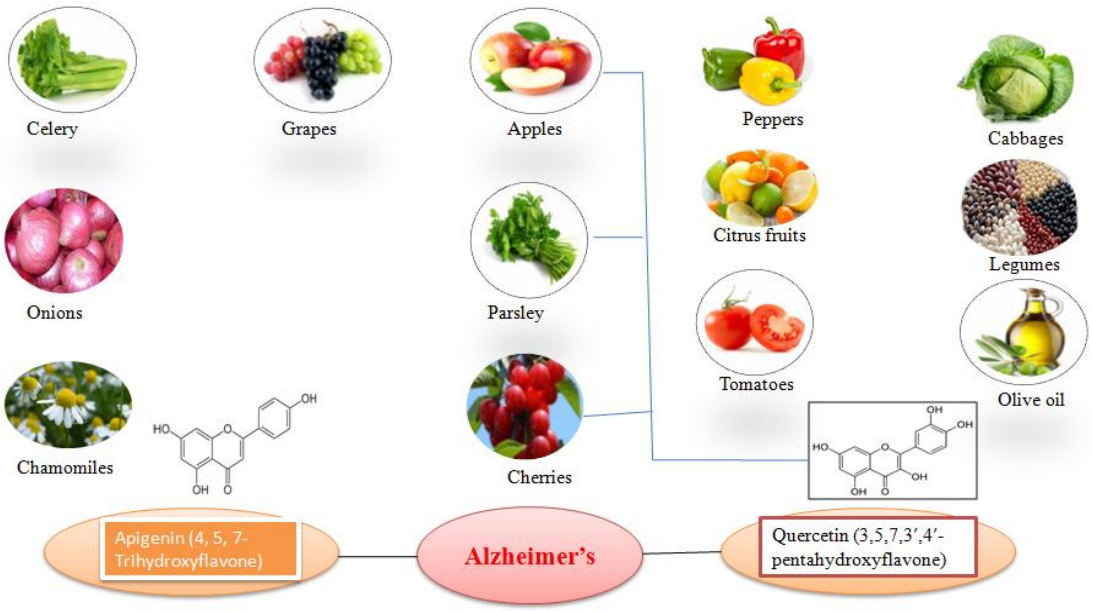

Fig 2: Natural sources of biomarkers used in neurodegenerative Alzheimer's disease

Pharmacokinetics studies of Apigenin crosses the brain-blood-barrier, and concentrations in rats reached 1.2 μM after daily intraperitoneal administration of 20 mg/kg of apigenin potassium salt (which was solubilized in water and stored frozen until use) for 1 week (Popovic et al., 2014).

Quercetin (3,5,7,3′,4′-pentahydroxyflavone), the major flavonoid in the human diet, is widely found in fruits and vegetables, such as onions and apples, and red wine, has potential nutraceuticals and pharmaceutical uses [36]. These potential uses may be due to its high oxygen radical scavenging activity or its ability to inhibit xanthine oxidase and lipid peroxidation in vitro. Furthermore, quercetin reliably exerts neuroprotective effects against agent induced toxicity and increases the resistance of

neurons to oxidative stress and excitotoxicity by modulating the mechanisms of cell death[38,39]. There has been increasing interest in quercetin in the sports science and athletic communities because research has shown that its antioxidant, anti-inflammatory, psycho-stimulant and other properties are likely to improve mental and physical performance. Human clinical trials have confirmed that quercetin enhances endurance and performance. Also, emerging research suggests quercetin may reduce infection risk during intense physical exercise. In addition, quercetin has demonstrated the ability to stimulate mitochondrial biogenesis in vivo (mice)[40].

4 Molecular mechanisms of neuroprotection by apigenin and quercetin

Apigenin and quercetin are known to provide neuroprotective effects by interacting with brain tissue at multiple sites. The neuroprotective action of dietary flavonoids includes their potential to protect neurons against oxidative stress and neuronal injury via their potential as antioxidants, an ability to suppress neuroinflammation, and the potential to modulate cell signaling pathways. Apigenin and quercetin are well-known antioxidants, and they may protect cell constituents against oxidative stress and therefore reduce the risk of neurodegenerative disease associated with oxidative stress. Apigenin and quercetin also protect neurons against some neurotoxic drugs whose toxicity is linked to the stimulation of oxidative stress. In addition, MPTP-induced neurotoxicity is also decreased by EGCG and quercetin[41]. Flavonoids interact not only through their antioxidant potential in protecting neurons but they also modulate various cell signaling pathways. It has become evident that flavonoids interact with critical neuronal intracellular signaling pathways and are able to exert neuroprotective actions[42].

5 Discussions

The current study further clarified the beneficial effects of apigenin on AD-associated pathology. Our findings indicate a clear rescue of learning and memory deficits in apigenin-treated APP/presenilin-1 (PS1) double-transgenic mice. Apigenin also showed effects on affecting APP processing and preventing Aβ burden involving the decrease of BACE1 and β-CTF levels, the relief of Aβ deposition, and the reduction of insoluble Aβ levels. Alzheimer's is a multifactorial disorder that requires drugs capable of operating on multiple brain targets. Flavonoids, mainly Apigenin and quercetin, having neuroprotective effects appear to be ideal candidates to prevent or treat neurodegenerative disorders however, their clinical efficacy and utility is still an open question. Better animal models and good biomarkers for patient sub grouping will be also instrumental for quick advancement in the field. The review revises all these aspects with the objective to generate debate among scientists.

6 Conclusion

Apigenin and quercetin has been demonstrated to have therapeutic potential for various chronic Neuroinflammation diseases, essentially due to its anti-inflammatory and anti-oxidative properties against a vast array of molecular targets. A large body of investigation has provided important insights into the anti-inflammation effects of Apigenin and quercetin which will constitute the basis for the further design and clinical application of extraordinarily potent drugs with potential therapeutic significance. Alzheimer's is a multifactorial disorder that requires drugs capable of operating on multiple brain targets. Flavonoids, mainly Apigenin and quercetin, having neuroprotective effects appear to be ideal candidates to prevent or treat neurodegenerative disorders however, their clinical efficacy and utility is still an open question.

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8 Conflict of interest

The authors have declared no conflict of interest.

7 Author's contributions

MSJ, AG and KS collected the data from different sources. MSJ has drafted the manuscript.

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