Herbal medicines as promising inhibitors of NF-kB for the therapy of Alzheimer's Disease

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Abstract

The most common cause of dementia is Alzheimer's Disease (AD). It is a brain condition that progressively impairs memory and cognitive functioning as people age. This disease's cause is not yet known. Further research and effective therapies are required since the effects of the available medications for Alzheimer's disease are unclear. Neuronal loss brought on by oxidative stress and neuroinflammation in the brain are associated with AD. A good candidate for AD treatment is the nuclear factor of activated B-cells (NF-κB), which plays a substantial role in inflammatory processes. Phytochemicals may obstruct the NF-κB pathway. They stop the phosphorylation of signalling molecules, hence stopping the deterioration of Interleukin 1 beta. NF-B is prevented from accessing the nucleus and from causing the production of inflammatory cytokines by phytochemicals. Natural agents may inhibit NF-kB transcriptional activity by reducing NF-interaction kB's with target DNA. Strong NF-kB inhibitors for Alzheimer's Disease therapy include genistein, curcumin, gallic acid, macranthoin G, punicalagin, salidroside, resveratrol, lycopene, obovatol, and pterostilbene. A number of alkaloids, including tetrandrine, galantamine, anatabine, glaucocalyxin B, oridonin, and berberine have also been demonstrated to have antiinflammatory activities in Alzheimer's Disease models In vivo and In vitro. Artemisinin, Vitamins, xanthoceraside, tanshinone IIA, dihydroasparagine, geniposide, l-theranine, paeoniflorin, and 1,8-cineole are examples of NF-kB inhibitors. In general, natural substances produced from plants are exciting potential treatments for Alzheimer's disease. They could be good candidates for the creation of compounds with enhanced pharmacological characteristics.

Keywords- *Phytochemicals, NF-kB, neuroinflammation, Alzheimer disease*

Introduction

Alzheimer is a degenerative neurological condition leads to brain cell death, that impairs memory, reasoning, and even basic task-performability. Mid-60s is the average age of individuals with late-onset symptoms(1). It is uncommon for adults from the age of 30 to 60 to have Alzheimer. AD is most frequent cause of dementia among older people. Dr. Alois Alzheimer first used the term "Alzheimer's disease" after discovering irregularities in the brain of a lady who kicked the bucket in 1906 due to a rare mental disorder. Her signs were unpredictable behaviour, memory loss, and communication problems. After she passed out, they discovered numerous abnormal clumps (amyloid plaques), twisted fiber bundles (neurofibrillary, tau, tangles) etc in her brain. The two most visible signs of Alzheimer's Disease are still regarded to be plaques and tangles in the brain. The brain's nerve cells (neurons) losing their connections is another indication. Information is sent by neurons between various brain regions, between the brain and various organs and muscles throughout the body. It is considered that the genesis of Alzheimer's disease involves a plethora of other complicated brain disorders. It indicates that the damage is coming from the hippocampus, which is important for the development of memories. Other areas of the brain are impacted as neurons die. In conclusion, there is significant brain tissue loss due to Alzheimer. The patients having Alzheimer’s have high levels of NF-κB, which is implicated in inflammatory responses. In aged neurons, calcium accumulation leads to increased NF-κB activation. NF-κB and activator protein-1 synthesis is influenced by the binding of adaptor proteins by activated toll-like receptors (TLRs). In animal models, increased inflammation and apoptosis were associated with the activation of TNF, caspase-3, IL-1B, and NF-κB p65. The hippocampus showed a comparable decline in Bcl-2/Bax ratios. TLR2 and TLR4 expression is increased in Alzheimer's patients. Localized neuro-inflammation, oxidative stress, and the etiology of Alzheimer's Disease are all correlated with ROS (reactive oxygen species) and electrophilic or oxidative damage. The genesis of Alzheimer's Disease is heavily influenced by inflammation as well as microglia's increased production of pro-inflammatory cytokines. Macrophages in the CNS (Central Nervous System) cause neuronal death and build-up in the brain of patients with Alzheimer. ROS causes nuclear translocation of NF-κB and the activation of proinflammatory genes by triggering downstream signalling molecules including PKC and MAPKs (mitogen-activated protein kinases). Microglia and astrocytes that have been stimulated by A create reactive oxygen species (ROS). This crucial physiological process guards against bacterial infection and neuronal degeneration. The main cause of neurodegenerative diseases like Alzheimer's and Parkinson's is an imbalance in ROS production. The RAGE-mediated signalling pathway is connected to the pathogenic responses to A that are generated in neurons, microglia, and the blood-brain barrier. The cdc42/Rac, MAPK cascade, NF-kB, and NFAT1 are only a few of the signalling pathways that are activated when A interacts with RAGE. Although there is currently a lack of in vivo data, the p53 MAPK pathway has been investigated as a possible treatment for Alzheimer's Disease.

NF-κB inhibitors are involved in Alzheimer's Disease

Neuronal degeneration has been linked to NF-kB activation in Alzheimer's patients' brains. NF-kB, a heterodimer made up of the various subunits (p50, p65), is the main regulator of the synthesis of inflammatory cytokines. The active transcription factor complex enters the nucleus after being phosphorylated and released by the complex's cytoplasmic inhibitory protein, the inhibitor of B (IB). Alzheimer's patients' glial cells produce more pro-inflammatory cytokines when NF-κB is activated. NF-κB activation is visible in glial cells in the A-plaque zones. TLR activation activates NF-kB via phosphorylation of interleukin-1B. NF-κB is a crucial downstream transcription factor in the TLR signalling pathway. When it binds to TLR-4, NF-κB p65 is moved into the nucleus and proinflammatory mediators like IL-1 and TNF are produced more actively. Interleukins, COX2, the pro-oxidant enzyme superoxide, and NAPDH oxidase dismutase are all controlled by NF-κB activation (SOD). The activity of NF-kB controls the expression of BACE1, nucleotide binding oligomerization domain-like receptor (NALP) 3 inflammasome. BACE1 and NF-κB are likely both involved in the regulation of inflammatory responses since they share a binding site. By activating MAPKs like C-Jun N-terminal kinase (JNK), and p38 through NF-κB signalling, pro-inflammatory mediator genes' downstream transcription is triggered. In numerous studies, the A/ROS/NF-B pathway has been related to the onset of Alzheimer's Disease.

Alzheimer's Disease drug development

Although chemicals that alleviate the symptoms of AD have been found effective therapeutics but yet to be established due to a lack of safe and reliable medications(2). In clinic, AChE inhibitors like galantamine, donepezil and rivastigmine are used for treating AD symptoms. By lowering the acetylcholine (ACh) deficit brought on by impaired cholinergic pathway in the Cerebral cortex and basal forebrain, they boost cognitive performance(3). N-Methyl D-aspartic acid (NMDA) antagonists reduced NMDA receptor overactivity. The decrease of mitochondrial membrane potential which leads to cell death and is a primary cause of Alzheimer disease is reduced(4). The effectiveness of NMDA antagonists on the other hand is a hotly debated topic. NSAIDs (nonsteroidal anti-inflammatory medicines) slow or even stop the progression of alzheimer disease(5). This emphasizes the involvement of inflammation in this condition as a path mechanism. The use of NSAIDS is limited due to cardiac concerns and the danger of gastrointestinal bleeding(6). Quetiapine also inhibited the NF-kB signaling pathway which had anti-inflammatory effects in mice. APPswe/PS1E9 transgenic mice were given valproic acid and showed similar outcomes(7). Because of its action on redox-sensitive proteins, very low dose sodium arsenate was found to be cytoprotective. It improved DNA base excision repair in epithelial fibroblasts indicating that it could be used to treat dementia(8). However, because arsenic acid is a neurotoxic heavy metal that affects behavioral characteristics and disrupts learning capacities this effect is dose-dependent. In high dosages sodium arsenate enhanced the formation of ROS which caused DNA or protein damage, resulting in co-carcinogenic and tumor-promoting properties(9). Synthesized medications have a lot of unfavorable side effects and low response rates. AChE inhibitors are the most popular therapies for Alzheimer. However the effects of AChE inhibitors on AD have yet to be properly studied(3). Following memantine

treatment, there was a decrease in Alzheimer symptoms and an enhancement in cognitive skills. Nonetheless these consequences are still debatable(10). NF-kB inhibitors take a more casual approach, lowering neuronal oxidative stress and consequently neuronal damage leading to a reduction in AD symptoms(11). There are no doubt that new and effective medications are desperately needed. This opens the door for natural chemicals to be used as a pharmaceutical lead in the creation of better medications to prevent or postpone the course of Alzheimer disease(12).

Table 1: Natural substances that suppress the NF-kB pathway

Natural compound	Origin	References
xanthoceraside	Xanthoceras sorbifolia	Shrinivasaan et al.(13)
Vitamin D3	Cholecalciferol	Banerjee anindita et al.(14)
L- Theanine	Camellia sinensis	Kin et al.(15)
Tetrandrine	Stephania tetrandra	Seo jeong-ean et al.(16)
Tanshinone IIA	Slavia milriorrhiza	Ding bo et al.(17)
Salidroside	Rhodiola rosea	Singh shareen et.al.(18)
Vitamin A	Retinoic acid	Lukiw walter et al.(19)
Punicalagin	Punica granatum	Feng xinzhe et al.(20)
Pterostilbene	Prunus dulcis and vaccinium	Liu haixiao et al.(21)
Paeoniflorin	Paeonia lacriflora pall	Cho ju eun et al.(22)
Oridonin	Rabdosia rubescens	Wang sulei et al.(23)
4-O-methylhonokiol	Magnolia virginiana	Lee jung young et al.(24)
Macranthoin G	Eucommia ulmoides	Hu weichung et al.(25)
Lycopene	Solanum lycopersicum	Hwang sinwoo et al.(26)
Glaucocalyxin B	Rabdosia japonica	Jones vaan simon et al.(27)
Ginsenoside Re	Panax ginseng	Razgonova et al.(28)
Ginsenoside Re2	Panax ginseng	Li jing et al.(29)
Genistein	Glycine max	Uddin shahab et al.(30)
Geniposide	Gardenia jasminoides Ellis	Joseph et al.(29)
Galantamine	Galanthus and Amaryllidaceae	Joseph et al.(29)
Gallic acid	Camellia sinensis and Quercus	Hajipour et al.(30)
Dihydroasparagusic acid	Asparagus	Chen h et al.(31)
Curcumin	Curcuma longa	Reddy H et al.(32)
1,8-Cineole	Eucolyptus globules	Khan andleeb et al.(33)
Berberine	coptis chinensis and Hydrastis Canadensis	Cai et al.(34)
Anatabine	Solanaceae	Paris danials et al.(35)

Resveratrol	Arachis hypogaea	Renge D et al.(36)
Alpha-tocopherol	Fagus and Castanea	Jhaa k neeraj et al.(37)

Phytomedicine's mechanism of action via the Nf-kB pathway

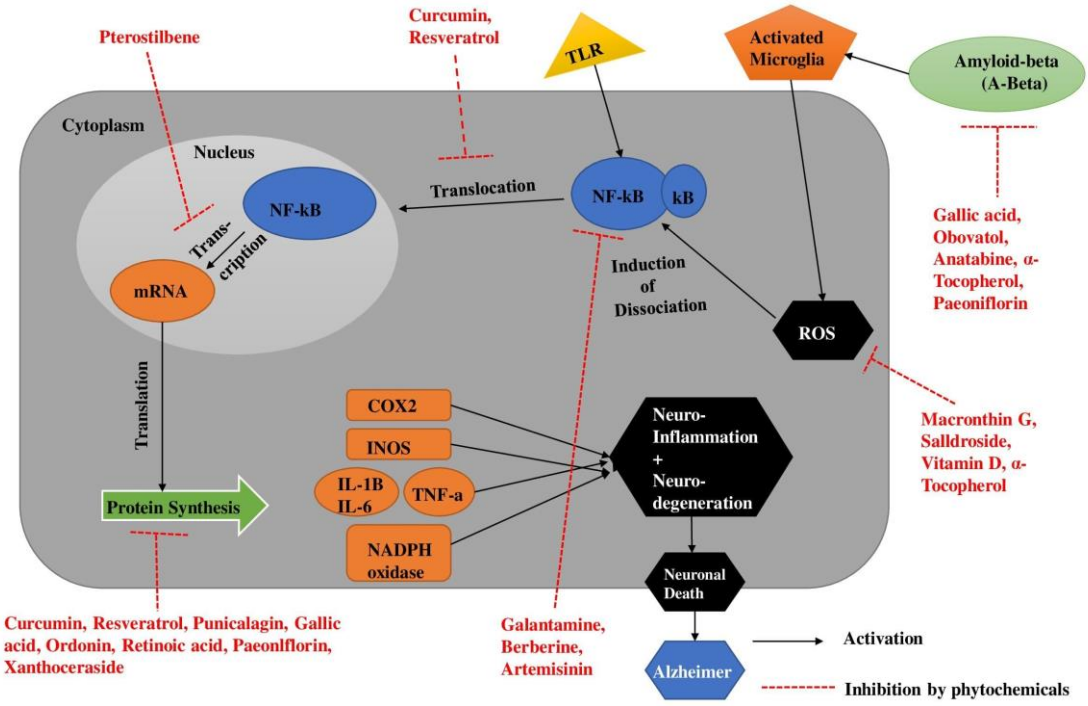

Fig.2 Activation of NF-kB Pathway and downstream of pro-inflammatory cascade along with their inhibitors

Anti-NF-kB properties of phytochemical

The origins of the phytochemicals studied are listed in Table 1, and Fig. 2 demonstrates activation and inhibition of NF-kB by phytochemicals.

Curcumin

This substance is found in the curcuma longa (Zingiberaceae) roots. It is a water-hating polyphenol having anticancer effects. It was discovered that curcumin has a range of anti-inflammatory properties. It has anti-inflammatory and cytokine inhibitory properties and reduces the production of COX-2, LOX, and iNOS. In lipopolysaccharide-stimulated monocytes and alveolar macrophages, curcumin decreased the synthesis of neurotoxic compounds as well as pro-inflammatory cytokines, such as TNF-,IL-1,2,6 and 8. The anti-inflammatory compound curcumin suppresses the NF-kB pathway. IB's phosphorylation, degradation, and translocation of NF-κB p65 to the nucleus were all blocked by curcumin. Improvements in memory issues brought on by AD have been associated with activation of the PRAR (Peroxisomes Proliferation Activated Receptor) pathway, which suppresses the nf-kb signalling pathway and so decrease the neuro-inflammatory responses.

Wine grapes

Antioxidant, antiinflammatory, neuroprotective, and antiaging effects are all found in wine grape polyphenols. Through increased anti-oxidant activity, resveratrol improved spatial memory in Alzheimer's disease mice. Resveratrol penetrated the blood-brain barrier (BBB) and suppressed many inflammatory indicators, including TNF-, COX2, and interleukins(36). Furthermore, it suppressed the activity of NF-κB by decreasing the phosphorylation of IKK and IB in response to LPS stimulation. Resveratrol phosphorylated STAT3 and STAT1, two transcription factor signal transducers and activators(38). Resveratrol stopped TLR4 from oligomerizing after it was activated. In A-activated glial cells, NO and iNOS production, as well as PGE2 and COX2 production, were all reduced. Reduced nuclear NF-kB translocation was responsible for all of these adverse effects(39).

Grapes and blue berries

Pterostilbene is a phenol containing molecule found in grapes and blueberries that is similar to resveratrol chemically. It's found in sandalwood and has been shown to help with cognition and neural function(40). Through PPAR modulation NF-κB transcription and JNK phosphorylation, it is even more effective than resveratrol. Pterostilbene's lipophilicity is increased by replacing the 3 and 5 -OH group of resveratrol with -CH_3 group. The protective benefits in the brain were magnified by pterostilbene's higher bioavailability(41).

Rhodiola rosea:

Salidroside, found naturally in Rhodiola rosea L has various pharmacological properties, including anti-aging, anti-fatigue and anti-oxidant properties as well as anticancer and antiinflammatory properties(42). Salidroside reduced cognitive impairment in an Alzheimer rat model by modulating the expression of thioredoxin interacting protein, thioredoxin, and NF-κB pathway proteins such NF-κB p65, IB, IKK, and IKK(43).

Tomatoes:

A pigment contained in tomatoes called lycopene is a potent antioxidant with a significant capacity to quench singlet oxygen. Lycopene is a hypocholesterolemia molecule with potential neuroprotective, antiproliferative and anti-cancer properties(44). In macrophages, lycopene also suppressed the production of proinflammatory chemokines and chemokines. The interruption of NF-kB signalling and the regulation of inflammatory cytokines improved ICV A1-42- triggered spatial learning and memory deficits were alleviated(45).

Soybean:

Isoflavones and genistein are one of the active ingredients of soybean having anti-estrogen, antioxidant, and antiinflammatory characteristics as well as the ability to change signalling pathways(46). A25-35-stimulated NF-κB and TLR4 expression, DNA binding, and NF-κB activity were markedly reduced after pretreatment with genistein(47).

Japanese curcumber:

Obovatol is a biphenolic molecule derived from Magnolia obovate inhibited LPS stimulated microglial activity in vitro and in vivo, as well as demonstrating neuroprotective properties

against neuroinflammation(48). With the treatment of obovatol, ICV infusion impairments by A1-42 were significantly minimized. When mice expressing mutant human APP were given Obovatol (1 mg/kg/day) for three months, cognitive capabilities improved dramatically(49).

Gall nuts:

Gallic acid is a polyphenol found naturally in gallnuts. It showed substantial anti Histone Acetyltransferase (HAT) activity and prevented ReLA acetylation by suppressing HAT enzymes directly, resulting in downregulation of many inflammatory signalling pathways(50). Gallic acid reduced A-activated NF-kB activity and cytokine production in microglial cells via reducing RelA acetylation, which in turn reduced A-activated neurotoxicity(51).

Tea leaves:

Galantamine is derived from Galanthus species, is a new medication for the treatment of weak to moderate Alzheimer's disease. It inhibits AChE in a competitive and reversible manner, resulting in raised ACh concentrations in the brain and hence increased cholinergic activity(52). Galantamine also interacted allosterically with nicotine ACh receptors to boost their agonist activity and amplify the ACh reaction by increasing ACh release. Galantamine protected brain microvascular endothelial cells by upregulating heme oxygenase-1 by activating NF-κB(53).

Vitamin-A metabolites:

A metabolite of vitamin A is retinoic acid. Proliferation, differentiation, survival, and apoptosis are all important biological processes that it is linked to. Retinoic acid inhibited the expression of inflammatory mediators like IL-6, IL-12, TNF and modulated NF-κB signaling resulting in anti-inflammatory properties(54). The most physiologically active form of retinoic acid is all-trans-retinoic acid. It suppressed LPS-induced nuclear translocation of NF-κB and it’s binding to the promoter of BACE1, as well as reducing BACE1 expression. It also prompted the nuclear receptor co-repressor to join the party (NCoR)(55).

Berberis:

Hydrates Canadensis yields berberine, which can be extracted. In mice, the compound suppressed inflammatory responses while also improving colitis. Rats, too. Inflammatory events were reduced by berberine(56). It can be found in a variety of inflammatory illnesses. Berberine also lowered phosphorylation and expression levels. Page 65 Berberine also prevented IB from becoming phosphorylated. Microglial cells stimulated by A Berberine stopped p38 from working. The AB-stimulated ERK and Akt signaling pathways(56).

Ginseng:

Panax ginseng and P. pseudoginseng both contain ginsenosides, which have been shown to boost cognition and memory. Ginsenosides including Rb1, Rg1 and Rg2 have been shown to have antiaging properties, protecting neurons and memory in the brain. The treatment of mice with ginsenosideReRg3Rg1(25 mg/kg) significantly lowered A levels in the brain(57). Ginsenoside Rd demonstrated neuroprotective benefits in rat brains with A40 activation

deficits and improved learning and memory in APP transgenic mice via lowering NF-κB activity. Ginsenoside Rg1 dramatically decreased the expression of TLR3, TLR4, NF-B, and TNF Receptor Associated Factor 6 (TRAF6) protein and mRNA, as well as TNF and IFN-B(58).

Artemisinin:

The herb Artemisia annua, which is used in traditional Chinese medicine, contains artemisinin naturally. It's a common anti-malarial medicine that's also being researched for cancer treatment. Furthermore, inhibiting the activation of NF-B displays promise anti-inflammatory properties(59). In APPswe/PS1E9 transgenic mice, artemisinin reduced the expression of A via inhibiting the activity of the NALP3 inflammasome(60).

Geniposide:

By blocking RAGE-related signaling, Geniposide derived from Gardenia jasminoides Ellis, reduced A1-42-stimulated inflammation(61). In vivo, geniposide significantly reduced RAGE-related signalling, including ERK and IB/NF-B, as well as TNF-, IL-1 production and cerebral A buildup(62).

Conclusion

Due to a lack of understanding of the pathophysiology there are currently no effective or safe medicines for preventing, postponing or treating Alzheimer's disease. As the world's population lives longer more people develop Alzheimer's disease. This necessitates considerably more research in this area. The BBB is a crucial homeostasis control factor, which might make it challenging for drugs to enter the brain. The discovery of anti-inflammatory medications which may not totally cure AD but may slow its growth appears to be the most viable treatment option. Extracellular a deposition in the hippocampus is part of the molecular pathogenesis. Aggregated A^{β} activates microglia and astrocytes causing the release of inflammatory molecules including as NO, prostaglandins, ILs, and TNF, which promote neuronal death. In vivo and in vitro studies indicated that a variety of natural substances can reduce inflammation. Phytochemicals have been found to lower block neurotoxicity, control A^{β}-induced inflammation and down-regulate the expression of ILs and iNOS according to numerous researches. Natural goods are believed to be safe and well accepted when taken with regular medications due to their lengthy history of usage in traditional medicine. Combination therapy permits many targets to be inhibited, potentially increasing the odds of stopping or delaying disease development. If utilized as "first-line" treatments for Alzheimer's disease phytochemicals may offer more cognitive and functional improvements. Indeed, for the treatment of Alzheimer's disease the combination of selegiline and -tocopherol was more effective than either chemical alone. One study looked into the efficacy of treating people with AChE inhibitors and Ginkgo biloba. In comparison to donepezil monotherapy, the adverse effects of Ginkgo biloba and the combination were less. Combination therapy involving phytochemicals and traditional pharmaceutical treatments have yet to be thoroughly researched. We believe, however, that such combination medicines have the potential to significantly improve Alzheimer's disease treatment methods. Phytochemicals are interesting therapeutic options for AD therapy due to their powerful

suppression of NF-B signalling and low side effects. Phytochemicals could act as chemical scaffolding for the development of derivatives with better pharmacological properties.

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