A Review on: Alzheimer's disease and mechanistic insights of bioactive compounds in its treatment

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Abstract

Alzheimer's disease is a most common neurological disorder, associated with cognitive disorder. Pathologically, Alzheimer's disease is characterized via the presence of β-amyloid (Aβ) plaques, hyper-phosphorylated tau proteins, and neurofibrillary tangles, but persistence oxidative-nitrative stress, endoplasmic reticulum pressure, mitochondrial disorder, inflammatory cytokines, pro-apoptotic proteins in conjunction with altered neurotransmitters degree are common etiological attributes in its pathogenesis. With the modern state of affairs, the variety of published proofs shows the neuroprotective capability of evidently occurring bioactive molecule via their anti-oxidant, ant apoptotic and neutransmitter modulatory residences. Many researchers have counselled that change of life style, proper diet, can delay or prevent the onset of this ailment. Diet is presently considered to be an important component in controlling fitness and protecting oneself towards oxidative strain and persistent inflammation, and hence towards chronic degenerative illnesses. A wide variety of bioactive food compounds may impact the pathological mechanisms underlying AD. Among them, phenolic compounds, omega-three fatty acids, fats-soluble vitamins, isothiocyanates, seem like the best in stopping neurodegeneration. The present review gathers proof that helps the neuroprotective impact of bioactive materials.

Keywords: *Alzheimer's disease, neurodegeneration, amyloid cascade, tau protein, tau hypothesis, nitric oxide.*

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder manifested by cognitive and functional decline and the emergence of mental health symptoms. The underlying biological mechanism includes formation of insoluble amyloid plaques, hyperphosphorylation and the accumulation of amyloid dyes[1.] Alois Alzheimer, the German psychiatrist and pathologist who first described AD in 1906, is credited with the disease's name[2]. As an epidemic neurodegenerative disease that affects around 40 million people worldwide elderly it is associated with both genetics and environment[3]. Symptoms of mild AD include a decline in memory, a change in personality, impaired reasoning, poor judgement, and difficulty performing daily task. In 2010, the global health care costs exceeded $604 billion. AD is not only one of the biggest threats to healthy aging, but it is also one that is going to overwhelm our future health care system. Finding an effective solution is crucial[4]. Many AD cases are sporadic and are caused by environmental factors with few genetic elements. Evidence of an epsilon 4 allele of Apo lipoprotein E4 (apoe4) in the DNA of AD cases has been found through detailed genome-wide associated studies (GWAS) [5]. The present available treatments of AD are not effective to reverse or stop the disease and therefore a lot research focus on preventing it. Nutrition is one of the primary lifestyle factors that influence the risk of AD, and previous research has indicated that its prevention may be effective.
In several studies, healthy nutrition is suggested to be one of the primary lifestyle factors that reduce the risk of AD. A well-balanced diet can provide neuroprotection, so it is possible that bioactive compounds can affects the underlying pathological mechanism[6].

2. Alzheimer's disease etiology and pathophysiology

Although ongoing research has attempted to explain the etiopathogenesis of this disorder, it still remains uncertain. However, some characteristic mechanisms have been identified at the cell level. Despite significant progress in AD research over the last few decades, the exact cause and pathogenesis of the disease remain unknown, and there is currently no effective treatment for the disease[7].

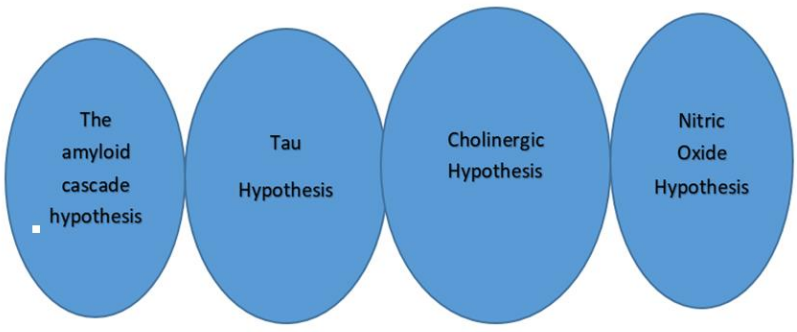

Fig. 1: Pathogenesis of Alzheimer's disease

2.1. The amyloid cascade hypothesis

A protein makes up the majority of the cortical plaques in brain of Alzheimer's disease patients. The mutation in parent protein APP (amyloid precursor protein) found on chromosome responsible for changes in genes and leads to this disease. Specific physiologic roles of APP are unknown, however it is thought to contribute to appropriate neuronal activity and possibly cerebral development in general.[8] Since its inception, the amyloid cascade theory (Fig. 1) has undergone significant changes, while it was originally proposed that a sequestration in plaques but according current version of the concept sequestration of the plaque is not the cause of the disease[9].

Amyloid beta (Aβ) is a 4200-dalton peptide isolated from more parenchymal meningeal vessels, neuritic plaques and neurofibrillary tangles has been discovered as an essential pathological factor in the neural machine. A research on amyloid deposition in the mind and different organs in 105 consecutive autopsy instances on people over the age 59 to 100 years had established a close dating between Aβ and advert. The APP gene is positioned on chromosome 21 in human beings with three major isoforms bobbing up from alternative splicing. These are APP695, APP751 and APP770 (containing 695, 751, and 770 amino acids, respectively). APP695 is predominantly expressed in neurons and lacks the KPI area reports advocate that the protein and mma tiers of KPI containing APP isoforms are multiplied in advert mind related to accelerated Aβ deposition. These findings may suggest that a deregulated splicing of APP RNA contributes to disease pathogenesis[10].

2.2. Tau Hypothesis

Hyper phosphorylated tau-caused disruption of microtubule community effects in each axonal and dendritic neurodegeneration[11]. It's far recognized that the state of tau phosphorylation is particularly regulated through preserving the stability between tau phosphatise and tau kinase activity. Many studies have proven that hyper phosphorylation of tau within the mind of advert might be due to lower of tau phosphatase interest and the enzyme can be used as target of Alzheimer's remedies[12].

2.3. Cholinergic Hypothesis

The cholinergic hypothesis postulated that the synthesis of acetylcholine turned low within the neocortex of the mind with Alzheimer's[13]. It's been said that the extent of choline transferase changed into down regulated within the hippocampus and frontal cortex ensuing in low cholinergic neuron counts inside the nucleus basalis. Primarily based in this speculation a few pills have been put underneath investigation that typically growth the cerebral level of acetylcholine[14].

2.4. Nitric oxide hypothesis

Nitric oxide (NO) theory is some other hypothesis molecular etiology of Alzheimer's[15]. NO and reactive oxygen species seems to play an important role inside the brain. Those consist of physiological tactics together with neuromodulator, neurotransmission synaptic plasticity and pathological strategies which include neurodegeneration and neuroinflammation[16]. NO is synthesized via the nitric oxide synthase (NOS) that is gift in the mammalian mind in three extraordinary isoforms i.e. constitutive enzymes [i.e. neuronal

(nNOS) and endothelial (eNOS)] and one inducible enzyme (iNOS) leading to oxidative strain and activation of intracellular signalling mechanisms[17]. In advert cases, aberrant expression of enos (NOS-3) in cortical pyramidal cells became fairly co-localized with nitro tyrosine. Moreover, iNOS (NOS-2) and eNOS were noticeably expressed astrocytes in Alzheimer's [18]. Over expression eNOS (NOS-3) can bring about apoptosis accompanied via multiple level of p53, p21/Waf1, Bax and CD95[19]. However, iNOS has been observed to be a chief contributor to initiation/ exacerbation of the central apprehensive device (CNS) inflammatory/ degenerative situations through the production of excessive NO which generates reactive oxygen species (mss) [20].

3. Various therapeutic strategies for AD

According to current researches on AD there is not a single pathologic mechanism that would be effective for the treatment of manifestation[21]. Till a cure is determined, the intention of treatment includes development in cognition and reminiscence, useful repute and behavioural signs. Additionally, management of underlying or co-morbid situations which includes coronary heart disease, vascular disease, diabetes, coronary obstructive pulmonary disease, hypertension, osteoarthritis ought to be initiated or endured [22]. Research suggests that pharmacological measures specifically focused at improving memory and slowing symptom development are more effective whilst initiated early in the ailment system[23]. Presently, handiest four tablets had been approved with the aid of the FDA for the treatment of Alzheimer's. Those tablets encompass three cholinesterase inhibitors inclusive of donepezil, rivastigmine, and galantamine. Memantine is the fourth drug that is labelled as an N-methyl D-aspartate antagonist (NMDA) that inhibits the manufacturing of glutamate.

Extra glutamate manufacturing ends in activation of NMDA receptors, neuroexcitation and contributes to the inflammatory procedure resulting in neuronal cellular dying[24]. Emerging research helps the hypothesis that irritation performs a tremendous role in cognitive decline and AD. The point of interest on infection presents researchers with modifiable objectives for changing the natural path of Alzheimer's[25]. Drugs used to deal with infection which includes ibuprofen and indomethacin may additionally offer a protective role towords AD through lowering the protein fragment that collect in the mind. Some advanced researches recommended that antioxidant rich diet with different vitamins like (vitamin E, vitamin C) and proper body weight may help to lessen the threat of Alzheimer's disease [26]. Antioxidant acts by clearing the reactive oxygen species molecule (ROS) and free radicals that increases throughout everyday residing and which can harm cells in the course of the frame along with the brain. They could gradual or prevent mind deterioration that occurs in Alzheimer's ailment[27].

3.1 Role of Bioactive Compounds

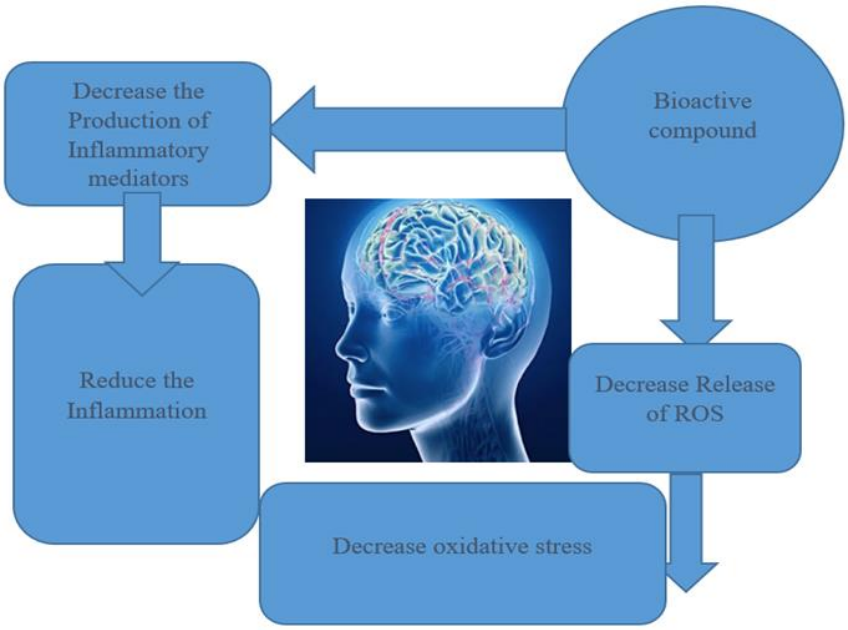

Fig. 2: Role of bioactive compounds in Alzheimer's disease

3.1.1. Flavonoids

The flavonoids are class of secondary metabolites that includes C6-C3-C6 carbon network particularly a phenylbenzopyran functionality relying on the position of the linkage of the fragment ring to the benzopyrano (chromano) moiety, this type of natural product may be divided into three classes i.e. the flavonoids (2-phenylbenzopyrans), isoflavonoids (three-benzopyrans) and the neoflavonoids (four-benzopyrans) [28]. Flavonoids and their analogues are biologically and structurally similar and form big class of plant secondary metabolites. They are found in plant tissues, where they are present in cells or surfaces of the plant tissues[29]. The chemical structure of these compounds are based totally on a C6-C3-C6 skeleton. They differ in the saturation of the heterotopic ring C within the placement of the fragrant ring B at the positions of ring C and in the average hydroxylation styles[30].

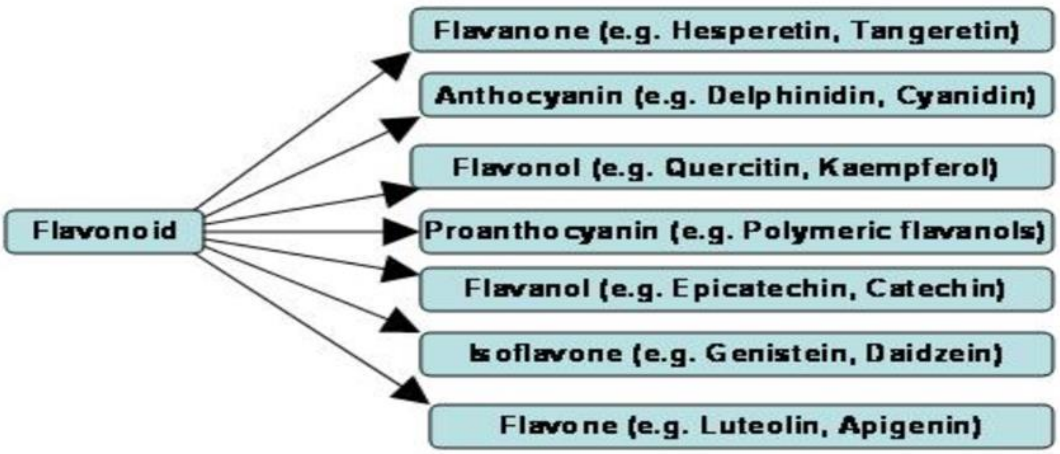

Fig. 3: Types of Flavonoids

Right vitamins are key nutrients of a healthful lifestyle, and it appears to play an essential role within the prevention of neurodegenerative illnesses, along with AD. A balanced diet wealthy in bioactive compounds can lessen the chances of dimentia[31]. Given the scarcity of human interventions it stays uncertain whether these materials exert all the neuroprotective results observed in in-vitro, animal model and in human physiological conditions. There's additionally a lack of knowledge how the quantities and chemical of these in meals cause them to sufficiently bioavailable. However, their high quality consequences are in large part supported by observational epidemiological cohort studies and experimental research that explains the molecular mechanism of promising bioactive compounds in the prevention of Alzheimer's symptoms. Many of those compounds belong to one of the following chemical classes: phenolic compounds, fat soluble nutrients and critical omega three fatty acids, isothiocyanates or carotenoides[32].

3.1.2. Phenolic Compounds

Phenolic compounds are determined in commonplace in edible plant source, and one of their most crucial resources is olive oil, which contains oleuropein, hydroxytyrosol, and oleocanthal. Oleuropein is a glycosylated seco-iridoid with many beneficial residences; it has a robust antioxidant capability and protects nerve cells from neurotoxin-induced apoptosis. It may additionally decrease Aβ level and save its aggregation, concurrently decreasing the expression of glutaminyl cyclise, an enzyme in Aβ synthesis[33]. It may additionally decrease Aβ levels and its aggregation, concurrently decreasing the expression of glutaminyl cyclise, an enzyme involved in Aβ synthesis[33]. An in vitro experimentation, demonstrated that oleuropein avoided the accumulation of a mutated, rapidly aggregating tau protein through 67% relative to the control organization. These consequences advise that oleuropein can prevent the formation of poisonous tau aggregates, likely because of the presence of aldehyde corporations within the tautomeric types of its aglycone metabolite[34]. The authors counselled that hydroxytyrosol acts as an anti-inflammatory agent and reduce the pastime nuclear factor kappa B (NF-κb) that triggers some of the neurotoxic reactions caused by amyloid plaques[35]. Some other phenolic compound is oleocanthal, a substance answerable for olive oil's bitter flavour. It reduces infection via inhibiting the cyclooxygenase enzyme (COX), which participates in the synthesis of anti-inflammatory prostaglandins. Confirmed its capability to reduce Aβ aggregation and modulate its clearance from the brain[36].

Other neuroprotective phenolic compounds are anthocyanins. They belong to the flavonoid group and are answerable for crimson, violet, and blue coloration of many end result and veggies. Anthocyanins ameliorate oxidative strain through reducing free radical production and lipid peroxidation. In addition they lessen prostaglandin synthesis by way of inhibiting COX. Moreover, anthocyanins increase the activation of the FKBP52 protein, which has an affinity for phosphorylated tau protein and stops its aggregation. They lower the intracellular Ca2+ ion awareness and inhibit caspase-three, which regulates neuronal apoptosis[37].

Curcumin, a natural factor of turmeric, is some other phenolic compound that suggests promising neuroprotective properties. It is strong antioxidant, reduces protein oxidation products, attenuates infection via inhibiting each COX and lipoxygeanse enzymes, and

lowers microglia interest. The chemical shape of curcumin is much like Congo purple, a substance used for staining senile plaques. This function makes it efficient in binding Aβ and stopping its oligomer formation in brain area [38].

Genistein, an isoflavone determined mainly in soy merchandise, is another compound, this is doubtlessly effective in preventing Alzheimer's. It reduces oxidative pressure by using inhibiting the synthesis of oxygen reactive species[39].

3.1.3. Isothiocyanates

The subsequent of bioactive compound useful in Alzheimer's prevention is isothiocyanates. They are derivatives of glucosinolates present broadly speaking in cruciferous vegetables. Due to the sulphur atom of their molecule, isothiocyanates act as antioxidants, specifically those containing an aromatic ring without delay bonded to the thiocyanate group. They are additionally robust COX inhibitors and display anti-inflammatory effects. Moreover, some isothiocynates successfully suppress acetyl cholinesterase hobby, thereby prolonging the half lifestyle of acetylcholine, a neurotransmitter whose awareness is generally decreased in patient with Alzheimer's[40]. Epidemiological studies recommended that isothiocyanates should display neuroprotective effects. The authors discovered that who ate extra cruciferous vegetables consisting of cabbage, cauliflower, broccoli, and Brussels sprouts scored better in cognitive exams [41].

3.1.4. Carotenoids

Carotenoids are plant-derived pigments found in high land areas, which are responsible for their yellow, orange, and pink colour. They can also be produced by means of microalgae, a food supply for marine animals, which makes these algae an additional nutritional source of these compounds. Carotenoids play an auxiliary function in photosynthesis and protect towards photo oxidation. One of the most beneficial carotenoid compounds is astaxanthin. It acts as an unfastened radical scavenger and reduces oxidative strain, lipid peroxidation, and protein peroxidation products. It also will increase the degrees of antioxidant enzymes such as catalase and superoxide dismutase[42].

Lycopene, another carotenoid compound, also has neuroprotective capacity. It is an amazing antioxidant that effectively neutralizes singlet oxygen, lowers lipid oxidation markers, and protects DNA in opposition to oxidative harm[43]. Vitamin D is some other neuroprotective compound. Even though its synthesis is stimulated broadly speaking via ultraviolet radiation, it can also be obtained from dietary assets inclusive of fish [44]. Diet D may be taken into consideration as a dementia-stopping agent because of its anti-inflammatory and anti-amyloid property, which includes better Aβ clearance from the brain through phagocytosis, however additionally has an impact of Aβ production and enzymatic degradation. It inhibits TNF-α and interleukin-6 manufacturing inside the microglia as well as reduces Aβ tiers inside the hippocampus and promotes its phagocytosis by way of macrophages[45].

4. Conclusion

Bioactive compound play a vital role for prevention of Alzheimer's symptoms and can also enhance cognitive capabilities. Their mechanisms of movement are numerous, but the number one beneficial result encompasses the subsequent reduction of reduction of Aβ levels and tau phosphorylation chargeprevention of Aβ and tau aggregation protection towards oxidative stress and inflammation, because of their beneficial outcomes.

5. Author Contributions

All authors have read and agreed to the published version of the manuscript.

6. Conflict of Interest

The authors declare no conflict of interest.

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