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Role of Phytochemicals, Proteins and Associated Receptors in Alzheimer's Disease

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Abstract: ***Alzheimer's disease (AD) is characterized by progressive dementia along with increasing age. Degenerative disease has 60-80% cases in dementia. Alzheimer's disease (AD) is considered about 3 types according to their genetic change in the brain such as late-onset type, early-onset type, and familial type. The proteins may build-up up into the brain manifests through two types: plaques and Tangles. It was noticed that according to age, the brain changes the rest of the body cells by facing difficulties through losing the brain capacity of remembering and thinking things. Phytochemicals are responsible to mediate their protection and communication of the plant. These compounds are categories into three types; Alkaloids, Terpenes, and Phenolic. Phytochemicals plants overlap and appear with a particular function. Ginko biloba leaf extracts may contain several bioactive components, like diterpenes, ginkgolides A, B, C, J & M, and their sesquiterpene bilobalide with a range of flavonoids. Ginseng comprises forty or more than forty bioactive Saponins called ginsenosides. Melissa is a type of terpene with a long history of treating disorders or diseases including their memory and mood enhancer. Sage is come from ancient Greeks where it is used it as a cognitive enhancer in their history and stretching back to prevent age-related decline wisdom. More than 10,000 compounds are described as polyphenols and they comprise a larger class in both flavonoid and non-flavonoid forms in AD. Resveratrol is significantly able to exert its anti-inflammatory effects with directly interact in cell signaling and linked cardiovascular health respectively. The human apolipoprotein E (apoE) protein has 299 types of amino acid glycoprotein with their variable posttranslational sialyation levels by threonine 194 residue with O-linked glycosylation. Cathepsin D may also break down the intracellular protein, which plays an important role in APP processing. Glypican-1 is a protein, which encoded by the GPC1 gene in humans. Chromosome 19 cluster has fifteen located kallikrein-6 subfamily members. Thus, the reduction of drebrin has not restricted the activity of the hippocampus, which is obtained throughout the cerebral cortex.***
Keywords: Phytochemicals, Terpenes, Phenolic, APOE and Cathepsin D.

I. INTRODUCTION

In 1907, Alois Alzheimer was identified on account of a 51-year-old female patient, Auguste D that was suffering from a lot of jealously towards her husband [1], which increased their memory impairment, hallucinations, disorientation, and loud aggressive behaviour. After four and half years she suffered from mental illness [3]. She has the combination of progressive presenile dementia with neurofibrillary tangles and senile plaques in the brain, which was known as Alzheimer's disease [2]. Nowadays, degenerative disease has 60-80% cases in dementia [4]. We can say that AD is a major type of normal aging [5]. AD is considered about 3 types according to their genetic change in the brain such as late-onset type, early-onset type, and familial type. Late-Onset Type is initial stages, the memory loss is mild, but over time or years in the late stage, AD patients completely lose their aptitude to convey any message or reply to the surroundings [6]. Symptoms were firstly approved in their mid-60s. Early Onset Type may occur between a person's 30s and mid-60s in rare cases. It is the most common cause of dementia among older adults with AD. According to Mayo Clinic, there are several types of genetic genes are found within chromosome 14 as APP, PSEN 1, or the PSEN2 genes in the early stage [7].Familial Type is based on an early-onset form in AD. This is based upon genetic fault on chromosomes 1, 14, or 21 with 50% of next-generation offspring [7]. It is difficult to interact with the patient for extremely challenging [8].

Causes occur approximately 70-75% of reasons for Alzheimer's are genetic [9] and several factors raise their risk for developing their conditions such as Family history, untreated depression, and lifestyle-related factors, which are linked with cardiovascular events [10].

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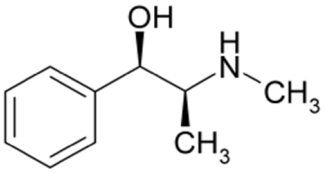
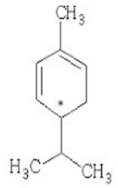
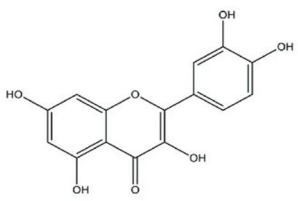
The proteins may build-up up into the brain manifests through two types [11]. Plaques- Different types of proteins are deposited in "beta-amyloid" which accumulates in their spaces between the nerve cells. Tangles- Proteins can deposit in the form of "tau" which can accumulate inside their nerve cells. Symptoms has been generally noticed that, according to age, the brain changes the rest of the body cells by facing difficulties through losing the brain capacity of remembering and thinking things. In advance stages, brain occurs changes and cause generation of progressively awful symptoms, which including in disorientation, behaviour and mood changes and baseless doubts about family, friends, and professional caregivers, and deepening skepticism about events, location and time, and serious loss of their memory and difficulties in everyday jobs like walking, speaking, swallowing, etc. [12]. Several people have numerous threatening signs and symptoms to a diverse degree:-

A. Separation from social events or works.
B. Alteration of personality and mood.
C. Reduction of judgments skill.
D. Forgetting things and reducing the capacity to repeat phases.
E. Difficulty in speaking or writing.
F. Trouble in visualization and spatial dealings.
G. Misperception about their place and time.
H. Trouble in doing routine works at home.
I. Alteration in her planning or problem-solving ability.
J. Memory deficit that was interrupts daily life.

II. POTENTIAL BENEFITS OF PHYTOCHEMICALS AGAINST ALZHEIMER'S DISEASE

Phytochemicals are responsible to mediate their protection and communication of the plant [13]. These compounds are categorized into three types: Alkaloids, Terpenes, and Phenolic. Phytochemicals plants overlap and appear with a particular function.
Terpenes have to play an important role in defense and deterrence the function but their provision may attractive their colors and smells within demonstrates plant and may also attract to facilitate pollination. Finally, the phenolic term is used for safety purposes and their role occurs for appears to be one of protection and expressed when the plant comes under any kind of stress [13].

Function of phytochemicals with their food sources			
Compounds	Structure	Food source	Function (S)
Alkaloids		Coffee seeds, cocoa seeds, tea leaves, tomatoes and potatoes	End products of metabolism or waste products, storage reservoirs of nitrogen, protective agents for the plant against attack by predator, growth regulators and substitutes for minerals in plants such as potassium and calcium
Terpene		Mango, bay leaves, peppermint, lemon grass, rosemary and fruit rinds	Metabolite activity for their growth and development, interaction occur directly in central nervous system (CNS), antimicrobial properties measures and has symbiotic relationship between biotic and abiotic conditions.
Ginkgo Biloba		Fish, flax and nuts	Used for treated sickness, cerebral vascular insufficiency, cognitive disorders, dementia, dizziness/vertigo, intermittent claudication, memory loss SSRI-induced sexual dysfunction and as a vasodilator

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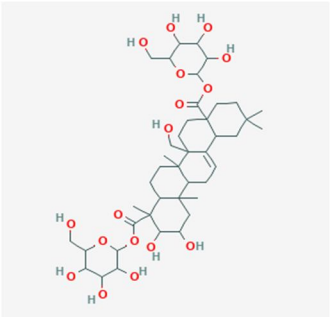
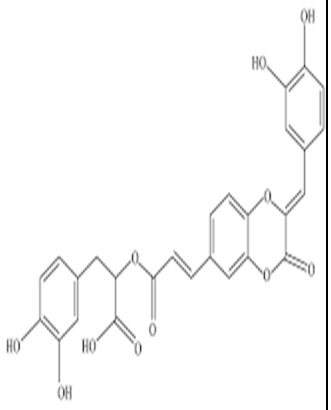
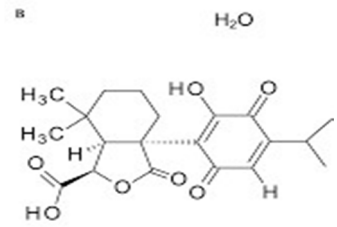
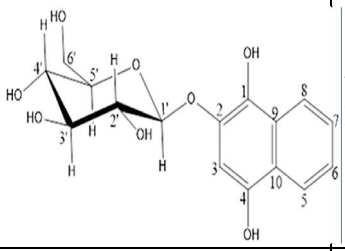
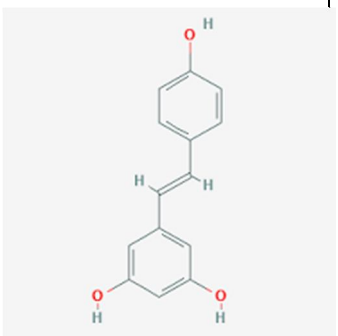
Ginseng		Energy drink, tea, dried herbs, capsules, powder and dietary supplement	Stimulating nitric oxide production, acting an antioxidant, acting on ligand for glucocorticoid or androgen receptors, beneficial antioxidant and anti-inflammatory properties
Melissa Officinalis		Lemon balm, iranian folk medicine, teas, marinate chicken or fish	Involve in beta-amyloid protein called amyloid precursor protein, having antioxidant, anti-inflammatory and immunomodulatory effects, and increase production of reactive oxygen species by autoxidation.
Salvia Lavan Dulaffolia and Salvia Officinalis		Essential oils, sage tea and flavorful butter sauce	Natural cleaning agent, pesticide and spiritual sage burning or smudging, reduced blood sugar levels, support memory and brain health.
Phenolic		Soya, fruits, vegetables like onions and citrus fruits	Inhibition of amyloid β-aggregation, amyloid precursor proteins, presenilin 1 & presenilin 2, increase the brain aggregation and fibrillation of amyloid-β peptide in dementias AD.
Resveratrol		grapes and wines	Used in supplementation, increased life expectancy reduced cognitive impairment by preserving memory and reduced amyloid deposition in the hippocampus and tau protein levels in cortex and hippocampus activated the AMPK and SIRT1 pathways.

Table 1 – Function of phytochemicals in Alzheimer's disease.

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A. Terpene

It is a large group and has more than 30,000 types of different lipid-soluble compounds by exhibit their toxicity from edible types. They are considered as a wide range of ecological roles, which may have antimicrobial properties to measures a range and also attract the symbiotic activity for measuring the range of seed dispersal, pollination, and secondary protective roles. These complex types of communication ability are required to interact directly through their central nervous system (CNS) with insects and including, hormones and activity of γ aminobutyric acid and cholinergic neurotransmitter systems. These interactions will be translated to the human from CNS in future research and provide results with benefits to AD [13].

B. Ginkgo Biloba

G. biloba has used the part of leaf extracts, which may contain different types of
bioactive components, like diterpenes, ginkgolides A, B, C, J & M [14]. The up-regulation activity is responsible for regulating the vasorelaxatory neurotransmitter in nitric oxide and has shown their result in the form of enhancing cerebral blood flow [15]. The downregulation is the enzymatic deamination regulating system through monoaminergic neurotransmitters with their free radicals scavenging and neuroprotection process, which may reduce by amyloid-β neurotoxicity [16]. This type of interaction is supporting the medical treatment and helps to prescribe the medicines according to their disorder including AD [17].

There benefit effects can show in vitro and in vivo models of animals in AD, which occur attenuation of cognitive decline in AD mouse [18]. It often reported the protection against amyloid-β-induced oxidative stress and also controlled for intervention trials in human subjects, which has positive results [19].

Promising evidence has been reported in 2002, that has the quality to improve the function with associated ginkgo [20], but in 2002, changes this report to one blighted due to unconvincing or inconsistent results [21]. In 2010, nine studies have worked where 2372 patients are comprised with different dementias, which occur in ginkgo attenuated declines in their cognitive function through all dementia tested and improving their activity in daily living AD groups [22]. In at same year, the ginkgo result is significantly improved on ADAS-cog between 6 months of administration [23].

C. Ginseng

In 5000 year-long history, Ginseng comprises forty or more than forty bioactive Saponins called ginsenosides [24], which have the anti-fungal/bacterial/viral/feeding effects within the plant [25]. It is a derivative of nutritional supplements, which many consider their efficacy for interacting with various numerous physiological systems.

This may include their acting as stimulating nitric oxide production, acting as an antioxidant and ligand for glucocorticoid or androgen receptors. They increase the function of the immune system, which enhances the function of CNS and prevents CVD in animal models [26].

The specific neurotransmitter function and neurocognitive interacts have long-term potential for exerting anti-stress, anxiolytic effects, and antidepressants to improve fatigue and memory-impaired rodents [27], [28]. *In vitro* process, the animals have specific benefits to AD-induced cognitive decline and observed inhibitory effects against an amyloid-β protein on cholinergic transmission by ginsenosides in rats [29].

D. Melissa Officinalis (Lemon Balm)

Melissa is a type of terpene with a long history of treating disorders or diseases including their memory and mood enhancer [30]. These bioactive compounds showed the effects including monoterpenes and sesquiterpenes having 1,8cineole [31]. Additionally, the CNS-relevant compounds have effects in antioxidant activity [32], up-regulation of γ-aminobutyric acid (GABA) ergic neurons [33] and their cholinergic activity system including choline esterase inhibition [34]-[37].

These interactions considered the benefits for controlling the two trials that suffer from AD and investigated Melissa, which were observed due to reduced agitation and improving their cognitive (ADAS-cog) and behavioral function by following 16 weeks administration through alcoholic Melissa tincture mild group [38].

The alcoholic Melissa is initially studying for enhancing the responsibility through effects seen there. It is observed for clinical benefits to patients, which play an important role in a different response to terpene phytochemicals [39]. The unknown quantity is observed in subsequent plasma levels needed for bioactive to reach their CNS and compare the study-related materials through phytochemicals orally.

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E. Salvia Lavan Dulaefolia & Salvia Officinalis (Sage)

Sage is come from ancient Greeks where it is used it as a cognitive enhancer in their history and stretching back to prevent age-related decline in wisdom [40]. The bioactive monoterpenes are considered through two types of sage-like as 1,8 cineole & camphor, which are significantly used in monoterpenes through cholinesterase-inhibiting properties [40] with 1,8 cineole [41], [42]. In the healthy aged patient is produced secondary memory, accuracy & attention through CNS effects [43, 44] and obtained consumption capacity in terpene by S. Officinalis in the form of essential oil, which is found to tolerated their small group (n11) in AD patients (76-95 years old) [45]. The later study is beneficial for the reflected sample size through significant cognitive sites. About nineteen patient's individuals (65-80 years) with mild-moderate AD are considered for consumed an S.officinalis alcoholic tincture for 16 weeks and observed to control better result on ADAS-cog towards reduced agitation in the S. officinalis group [46].

F. Phenolic

More than 10,000 compounds have been described as polyphenols and they comprise a larger class in both flavonoid and non-flavonoid forms in AD. It is further classified sub-divided into isoflavones that occur in soya products, flavones found in sweet pepper, anthocyanins in berries, proanthocyanidins in fruits, flavonols in some fruits and vegetables like onions, flavanones in citrus fruits, flavanols into flavan-3-ols found in tea [47]. Their consumption occurs between polyphenol-rich diets and polyphenols, which decrease AD in human populations [48]. The total levels of flavonoids are consuming fruits and vegetables [49], which are associated against protection or slowed the progression of dementias AD [50].

G. Resveratrol

It is a derivative of non-flavonoid polyphenols, which may found in grapes and wine. Recently, there are many kinds of research, which responsible for benefits through many diseases including cancer [52], CVD [51] and their life extension range with models of animals [53]. They target the biological interaction between cyclooxygenase 1 and 2, the sirtuins, and the activity of kinases with DNA/RNA and lipoproteins respectively. The resveratrol is significantly able to exert their anti-inflammatory effects with directly interact in cell signaling and linked cardiovascular health respectively [54]. In animal models, resveratrol function may reduce through markers of pathology like amyloid-β-plaques [55] and their behavioral deficits, e.g., improving the response of learning and memory in resveratrol.

The investigation occurs in resveratrol by human volunteers with AD. Thus, the therapeutic measures are studied in amyloid-β-markers reduction by resveratrol significantly in the placebo group and loss of brain volume [56]. They are involved to tolerate the function of gastrointestinal problems with the loss of their weight by high dose after escalation as their side effects lower than 500 mg doses [57].

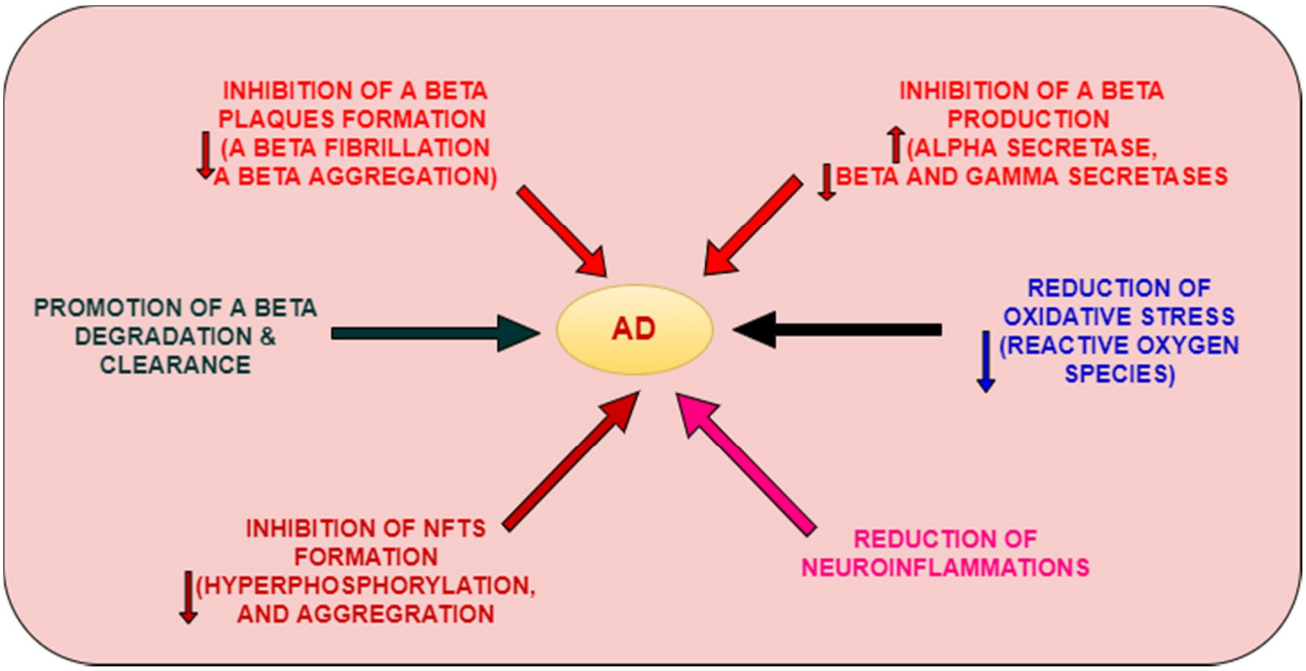

Figure 1- Schematic representation of different mechanisms associated with Alzheimer's disease.

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III. ROLE OF ASSOCIATED RECEPTORS IN ALZHEIMER'S DISEASE

Associated Receptors	Human Expression Area in CNS	Major Role in AD	References
Myeloid cells 2 (TREM-2) with triggered receptor expressed on Immunoglobulins superfamily	Located in Midbrain	Involved in inflammatory response, microglial survival, dendritic cell maturation, phagocytosis and others	[58]-[61]
GABAR (Gamma-Aminobutyric Acid receptor) and Ionotropic receptor	Present in Cerebral cortex	Regulates the function of learning, controls the glutamate, enhanced memory, cognitive function, release and reduces APP toxicity	[62]-[64]
G-protein-coupled receptor family and 5 HTR6 (5-hydroxytryptamine 6 receptor)	Located in Basal ganglia	Pyramidal neurons can migration at corticogenesis, which regulates the activity of GABA ergic, glutamatergic, and their cholinergic activity, TOR signaling activates and Involved in cognition, anxiety, memory, and mood.	[65[, [66]
Ionotropic receptor and NMDAR (N-methyl-D-aspartate receptors)	Position occur in Cerebral cortex and hypothalamus	Responsible in CNS development and improvement which is involved in synaptic plasticity, essential function for learning and memory	[67], [68]
G-protein-coupled receptor family and CNR (Cannabinoid receptor)	Located in Cerebral cortex	Disrupt the activity of AD and reduce the symptoms, function express in neurodegeneration, neuroinflammation, and improving the spatial memory	[69]-[72]
Toll-like receptor family and TLR4 (Toll-like receptor 4)	Present in Hippocampus	Induces CREB signaling activity pathways and may regulates their neuron survival, neuronal gene expression, and neurogenesis in their adult sub ventricular zone	[73]-[75]
G-protein-coupled receptor family and GPR40 (G-protein-coupled receptor 40)	Located in Spinal cord	Increase the activity of neurogenesis, which inhibits the neuronal apoptosis activity, and protecting the nerves and decreasing brain damage	[76], [77]
Chemokine receptor family and CCR2 (C-C chemokine receptor type 2)	Present in Pons and medulla	Promotes there monocyte activity through APP deposition sites at phagocyte APP proteins position.	[78]
Lipoprotein receptor family and LDLR (Low-density lipoprotein reeptor)	Present in Pons and medulla	Increasing the mediate activity in APOE expression induced due to APP protein	[79]
Nuclear receptor family and LXR (Liver X receptor β)	Located in Cerebral cortex	Regulates the level of inflammation and also regulate the level of cholesterol homeostasis ain CNS, which found their position in neurogenesis, APP processing, and microglial phagocytosis modulation.	[80]-[82]
Immunoglobulins superfamily and RAGE (Receptor for advanced glycation end products)	Present in Cerebellum	Involved in neuronal death and inflammation with their APP transport activity, cerebral blood flow process, and oxidative stress activity.	[83], [84]

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Nuclear receptor family and RXR (Retinoid X receptor)	Present in Cerebral cortex	Stimulates the activity of physiological mechanisms of APP elimination, decreasing the pathways activity in APP-induced deficits	[85]-[87]
Toll-like receptor family and TLR5 (Toll-like receptor 5)	Located in Thalamus	Involved in APP oligomers and fibrils process and occur in forming complexes that block APP toxicity activity.	[88]-[90]
Nuclear receptor family and ER (Estrogen receptors)	Located in Basal ganglia and hippocampus	Increases the activity of neural plasticity and neurogenesis, which shown effect in cognitive functions and their brain regenerative potential activity. Beneficial effects are performing to enhance the brain inflammatory pathways.	[91]-[93]
Nuclear receptor family and VDR (Vitamina D receptor)	Located in Cerebral cortex and hippocampus	Interacts occur to stimulate with SMAD3 and regulating the activity of APP transcription through TGFβ signaling. Suppress the APP gene promoter activity in AD.	[94]
Lipoprotein receptor family and OLR1 (Oxidized low-density lipoprotein receptor 1)	Present in Midbrain	involved to uptake and internalization their low density oxidized activity in lipoprotein (oxLDL), which involved in AD.	[95]
Nuclear receptor family and Peroxisome proliferatoractivated γ receptor (PPARγ)	Located in Amygdala	Involved in lipid metabolism pathways activity and responsible to immune response, which implicated in AD etiology. PPARγ acts like as transcriptional regulator activator activities of several genes, which may involve in AD pathogenesis	[96]-[98]
Chaperone protein and Sigma-1 receptor (σ1R)	Present in Cerebral cortex	Acetylcholinesterase, 5-lipoxygenase, and monoamine oxidase inhibiting the activity. Protects their neurons activity against oxidative stress and contributing to neuronal tissues repair.	[99]
G-protein-coupled receptor family and CaSR (Calcium sensing receptor)	Located in Cerebral cortex and hippocampus	Involved in hippocampal neurons degeneration system. APP enhanced the intracellular calcium during opening calcium-permeable cationic channels in hippocampal neurons	[100]
Nicotinic Receptors and AChR (Acetylcholine receptors)	Present in Cerebral cortex and cerebellum	Interacts involved in APP protein and exert positive effects on their memory and attention.	[101], [102]
Calcium channels and Ryanodine receptor 3 (RyR3)	Located in Basal ganglia	Synaptic transmission and synaptic plasticity play negative effect, which associated with their memory loss and age-related cognition decline.	[103]-[105]
Chemokine receptor family and Chemokine receptor CX3C 1 (CX3CR1)	Present in Midbrain, pons, and medulla	Maintains the support synaptic system with microglial and performs the activity of IL-1β dependent cognitive functions.	[106]
Glucocorticoid receptor family and Glucocorticoid receptor (GCRs)	Located in Cerebellum	Responsible to generate the activity of APP protein in their brain.	[107], [108]
NOD-like receptor family and NLRP3 (NOD-like receptor pyrin domain-containing-3)	Present in Pons and medulla	The NLRP3 is stimulating the activation of IL-18 production and also activate the IL-1β activity in their oxidative stress and inflammatory response in AD pathogenesis.	[109]-[112]

Table 2- Mechanism associated receptor of Alzheimer's disease in human.

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IV. ROLE OF SELECTED PROTEINS IN ALZHEIMER'S DISEASE

A. Apolipoprotein E

The human apoE protein has 299 types of amino acid glycoprotein with their variable posttranslational sialyation levels by threonine 194 residue with O-linked glycosylation [113]. They are expressed in several organs and liver, which occur in highest expression through by the brain, and also a major type of apoE neuronal cells express apoE in the brain [114], [115]. In the plasma membrane, the lipoprotein is present and associated with other apolipoproteins, whereas, brain apoE and 2 other apolipoprotein apo J and apo A-1 are present in high density-like lipoprotein particles [115], [116]. ApoE is containing lipoprotein particles, which released cholesterol from supporting synaptogenesis and improving synaptic connections *in vivo* [117]. Other apoE proteins found in the brain including apoA-I, apoA-II, apo-IV, apoD, apoE, apoH, and apoJ. While apoA-I and apoJ in Aβ fibrillogenesis were used for clearance investigation [118]. Both apoA-I and apoJ are found to binding the Aβ and are involved to prevent the activity of Aβ aggregation in vitro [119]-[121].

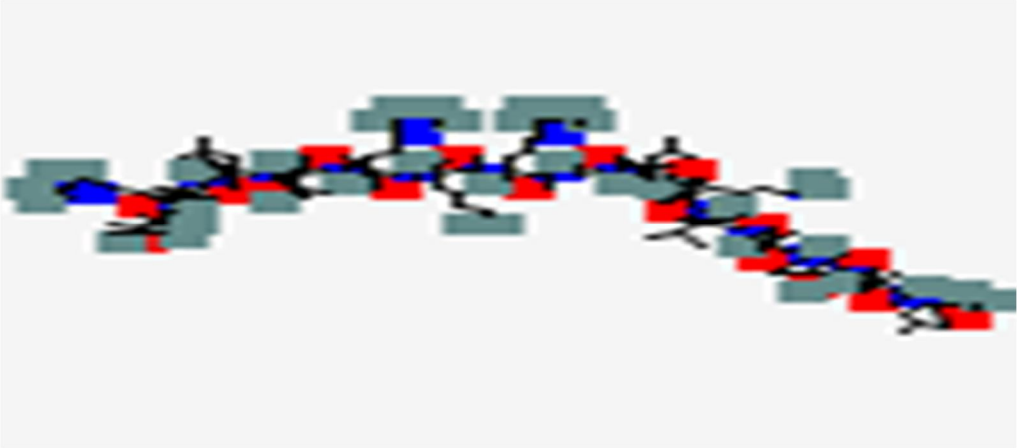

Figure 2- Chemical structure of Apolipoprotein in Alzheimer's disease.

B. Cathepsin D

Cathepsin D is s protein, which encoded due to the CTSD gene in humans [122]. It can compose of a protein dimer of disulfide linked light and heavy chains and also encoded the lysosomal aspartyl protease. Both of them are produced by a single protein precursor. It is ubiquitously involved to distribute in lysosomes and contains aspartic endo-protease [123], [124]. This can degrade proteins and active precursors for the synthesis of bioactive proteins during pre-lysosomal compartments [125]. This proteinase is involved in members of the peptidase A1 family, which is similar to narrower than pepsin A.

Cathepsin D may also break down the intracellular protein, which plays an important role in APP processing. They also activate the function of cleavage and activation due to ADAM30 through APP degradation. This is involved in Alzheimer's patients and also in breast cancer by pathogenesis activity.

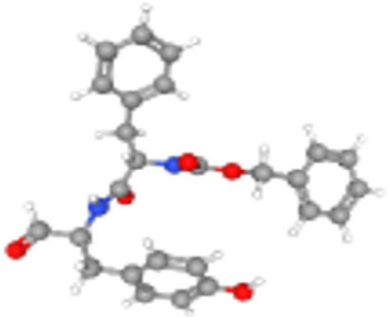

Figure 3- Chemical structure of Cathepsin D in Alzheimer's disease.

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C. Galypican-1

Glypican-1 is a protein, which encoded by the GPC1 gene in humans [126]. The glypican-1 has a cell surface of heparin sulfate proteoglycans in AD. It can compose during membrane-associated protein core, which is substituted by heparin sulfate chains. There glypican-1 related integral membrane proteoglycan family members (GRIPS), consist of a type of core protein, which anchored through glycosylphosphatidylinositol linkage (cytoplasmic membrane). They occur to control the function of cell growth regulation and cell division, which interacts with SLIT2 [127].

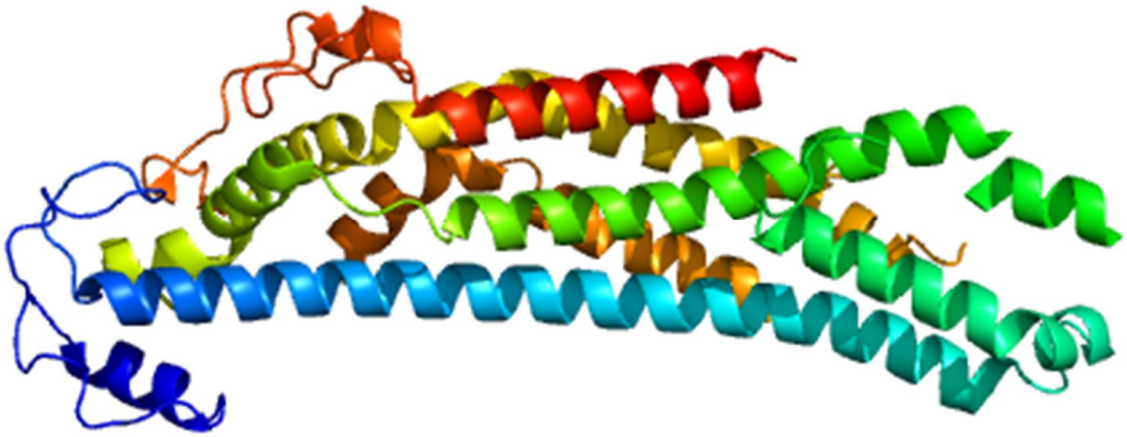

Figure 4- Chemical structure of Galypican-1 in Alzheimer's disease

D. Kallikrein-6

Kallikrein-6 is a type of protein, which encoded by the KLK6 gene in humans [127]-[129]. They have subgroups like serine proteases, which have diverse physiological functions with dual type-like and chymotrypsin-like substrate specificity. Their investigation suggests that kallikrein-6 has many implicated carcinogenesis, some novel cancer, and other biomarkers disease in AD [130]. In chromosome 19 cluster have fifteen located kallikrein-6 subfamily members. They regulate the activity of the enzyme by steroid hormones and are found to generate the amyloid genic fragments by the amyloid precursor protein in AD [131]. The different forms of isoform were identified by multiple alternatively spliced transcript genes and variants.

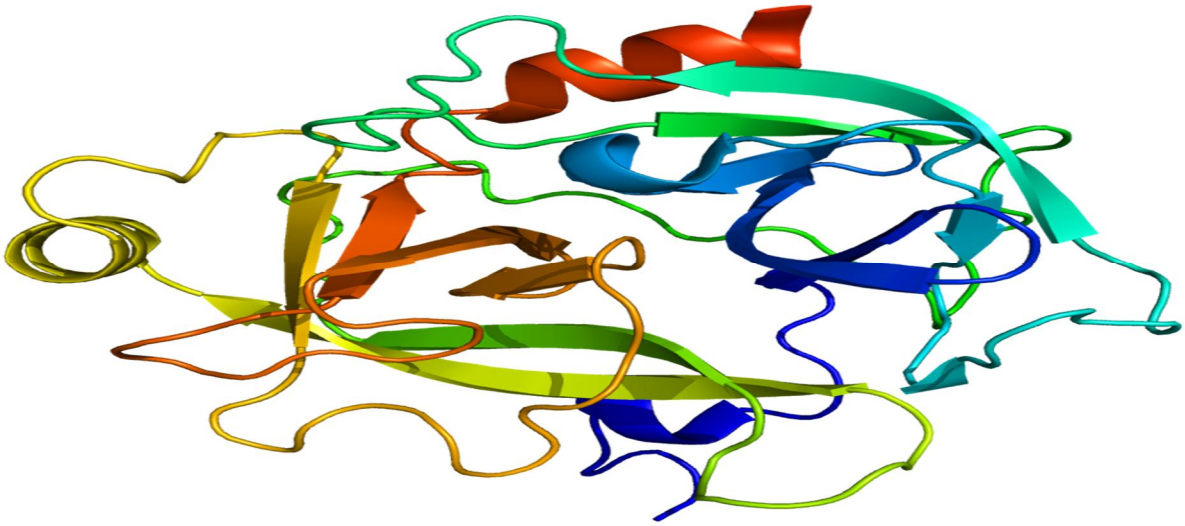

Figure 5- Chemical structure of Kallikrein-6 in Alzheimer's disease

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E. Drebrin Like Protein

It is like a protein, which plays an important role in actin cytoskeleton organizing protein and formation of cell projections. It may consider for actin the chemokine receptor CXCR4 to IS and actin polymerization at immunological synapses [IS]. It is involved in the localization of the dopamine receptor DRD1 to the dendritic spines and also in memory-related synaptic plasticity in the hippocampus. Drebrin expression may reduce in the hippocampus of AD patients [132], [133]. Thus, the reduction of drebrin has not restricted the activity of the hippocampus, which is obtained throughout the cerebral cortex [134]. The postsynaptic changes occur at the drebrin level then they distribute on synaptophysin a presynaptic protein in AD [135]. These changes showed their result in synaptic dysfunction and cognitive impairment in AD. It is also decreased the Down syndrome in the brain [135], which can be associated with cognitive defects [136], [137].

V. CONCLUSION

We know that there is a continuous fight against treatment of AD. It is suggested that the pathogenic mechanism will be considered for a better treatment strategy in clinical therapeutic research with minor or few side effects. Through this suggestion, nuclear receptors family with G-protein-couple receptors are involved in AD by expressing themselves and improving the function of the cerebral cortex's area and small size of the hippocampus, which involved taking a decision making, subjective thinking, perception, and attention-related memory. These existing molecules have the aim to control the symptoms and prevent AD. Different types of natural products, molecules, and proteins are used to prevent and treat AD in prospect.

A. Conflict Of Interest Statement

The authors declare that there is no conflict of interest.

VI. ACKNOWLEDGMENTS

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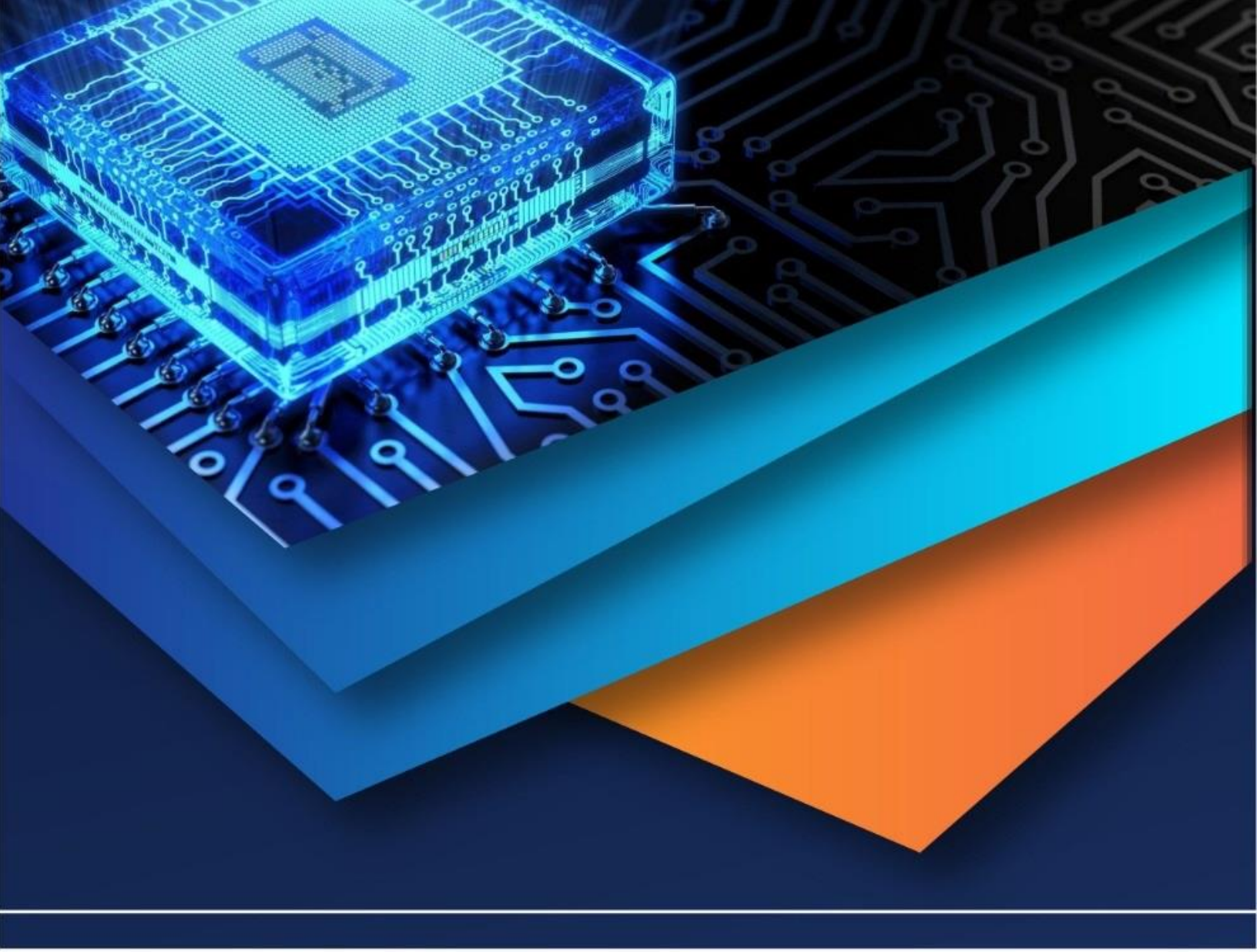

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