CNS & Neurological Disorders - Drug Targets, 2020, *19*, 334-343

SYSTEMATIC REVIEW ARTICLE

Impact of Cannabis-Based Medicine on Alzheimer's Disease by Focusing on the Amyloid β-Modifications: A Systematic Study

Tahereh Farkhondeh[1], Haroon Khan[2], Michael Aschner[3], Fariborz Samini[4], Ali M. Pourbagher-Shahri[5], Hamed Aramjoo[6], Babak Roshanravan[7], Christopher Hoyte[8], Omid Mehrpour[9,10] and Saeed Samarghandian[11,*]

[1]*Medical Toxicology and Drug Abuse Research Center (MTDRC), Birjand University of Medical Sciences (BUMS), Birjand, Iran;* [2]*Department of Pharmacy, Abdul Wali Khan University, Mardan 23200, Pakistan;* [3]*Department of Molecular Pharmacology, Albert Einstein College of Medicine, Forchheimer 2091300 Morris Park Avenue, Bronx, NY 10461, USA;* [4]*Department of Neurosurgery, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran;* [5]*Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran;* [6]*Student Research Committee, BSc Student in Lab Sciences Technology, Birjand University of Medical Sciences, Birjand, Iran;* [7]*Student Research Committee, Birjand University of Medical Sciences, Birjand, Iran;* [8]*School of Medicine, University of Colorado, Aurora, CO, USA;* [9]*Arizona Poison & Drug Information Center, the University of Arizona, College of Pharmacy, Tucson, Arizona, AZ, USA;* [10]*Medical Toxicology and Drug Abuse Research Center (MTDRC), Birjand University of Medical Sciences (BUMS), Birjand, Iran;* [11]*Noncommunicable Diseases Research Center, Neyshabur University of Medical Sciences, Neyshabur, Iran*

ARTICLE HISTORY

Received: April 29, 2020
Revised: May 22, 2020
Accepted: June 07, 2020

DOI:
10.2174/1871527319666200708130745

Abstract: Deposition of Amyloid-beta (Aβ) peptide in the brain is the leading source of the onset and progression of Alzheimer's Disease (AD). Recent studies have suggested that anti-amyloidogenic agents may be a suitable therapeutic strategy for AD. The current review was proposed to address the beneficial effects of cannabis-based drugs for the treatment of AD, focusing primarily on Aβ modifications. Keywords related to AD, Aβ, and cannabis-based on MeSH were identified and were searched in PubMed, Google Scholar, Scopus, Ovid-Medline, and Web of Science from inception until 15 March 2020. The full text of identified papers was obtained and assessed based on exclusion and inclusion criteria. The review is based on articles that have focused on AD and the amyloidogenic pathway. A total of 17 studies were identified based on the inclusion criteria; however, nine studies qualified for this systematic review. The maximum and minimum cannabis dosages, mostly CBD and THC in animal studies, were 0.75 and 50 mg/kg, respectively. Cannabis (CBD and THC) was injected for 10 to 21 days. The findings of the 9 articles indicated that cannabis-based drugs might modulate Aβ modifications in several AD models. Our findings establish that cannabis-based drugs inhibited the progression of AD by modulating Aβ modifications.

Keywords: Amyloid-beta, Alzheimer's disease, cannabis, cannabinoids, cannabidiol, molecular assays.

1. INTRODUCTION

Alzheimer's Disease (AD) is one of the critical age-related neurodegenerative diseases and the leading cause of cognitive dysfunction globally [1]. The incidence rate of AD is increasing [2].

The incidence of AD and other types of dementia is estimated to reach 82 million in 2030 and 152 million in 2050 [3, 4]. Much of this elevation is related to the people from low- and middle-income countries. Thus, numerous studies have been focused on identifying the etiology and treatments for AD. There are multiple factors involved in the progression and origin of AD that has yet to be fully understood [5].

One of these factors is the amyloid-beta (Aβ), which acts as a primary function in the progression and initiation of AD [6]. Aβ is generated *via* the proteolytic reaction of Amyloid Precursor Protein (APP), which processed by two enzymes secretases, including β and γ [7]. Aβ deposition in the brain is considered as an early toxic pathogenesis event of AD, in which over-production of Aβ or impairment in its removal is a critical factor in the progression and origin of AD [8]. However, several clinical investigations based on anti-amyloidogenic therapies have shown a mild benefit for these

*Address correspondence to this author at the Noncommunicable Diseases Research Center, Neyshabur University of Medical Sciences, Neyshabur, Iran; Tel: 09151200945; E-mail: samarghandians1@nums.ac.ir

1996-3181/20 $65.00+.00

therapies regarding cognitive impairment, even though some of them have shown a dramatic decrease in brain levels of Aβ [9, 10]. On the contrary, some of these therapeutics agents may accelerate AD progression [10, 11].

Despite controversial findings of the amyloidogenic-based therapies, accepting or rejecting this strategy for the treatment of AD is still debatable. Hence, many pre-clinical and clinical research has been designed to discover the impact of novel natural and chemical therapeutic agents against Aβ production and deposition [12-15].

Cannabis or marijuana is a psychoactive agent that is extracted from Cannabis plants' leaves and flowers. This plant belongs to the Cannabaceae family and includes four species: *Cannabis ruderalis, Cannabis afghanica, Cannabis indica,* and *Cannabis sativa* [16]. Crossbreeding occurs between these species; thus, all of them are included in Cannabis sativa as one classification [16]. Chemical compounds in cannabis are known as cannabinoids, and among them, Cannabidiol (CBD) is the main ingredient. Generally, cannabinoid-based plants are divided into five categories. Category I contains plants with high levels of Δ9-THC; category II are plants with an equal amount of psychoactive and non-psychoactive cannabinoids; categories of III and IV are comprised of high amounts of non-psychoactive cannabinoids and very low levels of psychoactive compounds; category V is not composed of cannabinoids [16]. Cannabis has two classes, including drug-type and the fiber-type for both medicinal and forensic applications. The drug-type of cannabis has a high amount of psychoactive Δ9-THC that is commonly used in medicine. Fiber-type cannabis consisted of Cannabidiol (CBD) and almost free of Δ9-THC, is used in food and textile [17]. Almost 113 types of cannabinoids have been found in cannabis [18]. Δ9-Tetrahydrocannabinolic acid (Δ9-THCA) and Δ9THC are found mostly in drug-type plants, and cannabinoic acids are abundant in fiber-type plants [17]. Very low levels of Cannabichromene (CBC), Cannabichromenic Acid (CBCA), Cannabinol (CBN), and Cannabinolic Acid (CBNA), and two oxidative degradation products of Δ9THCA and Δ9-THC are found in aged cannabis [19-23]. These compounds act as partial agonists/ antagonists at the cannabinoid receptors, including CB2 and CB1 [24]. The receptors of CB1are mostly concentrated on the brain and CNS, and CB2 receptors are located on the peripheral nervous system and the immune system [24].

Cannabis-based drugs exert neuroprotective, antioxidant, and anti-inflammatory effects. Use of Cannabis in folk medicine is effective against some disorders, including vomiting, nausea, and chronic pain related to chemotherapy, and spasticity due to chronic neurologic diseases [25-27]. Recent studies have indicated that Cannabis-based drugs can decrease Aβ synthesis, deposition, and aggregation [28-31]. Therefore, cannabis-related intervention strategies may be effective therapies in AD. The current study has been designed to systematically review the available experimental studies which discuss the impact of cannabis-based medicines in reducing the Aβ. Also, mechanisms related to the protective effects of cannabis against Aβ-induced Alzheimer's disease have been discussed.

2. METHOD

2.1. Search Strategy

In the systematic section, the methodology was established on the PRISMA. The following databases were searched from inception until 15 March 2020: PubMed, Google Scholar, Scopus, Ovid-Medline and Web of Science. The keywords related to Alzheimer's disease, amyloid beta and cannabis according to MeSH, consisted of the following: "Cannabis" OR " Cannabi" OR " Hemp Plant" OR " Hemp Plants" OR "Plants" OR "Hemp Marihuana" OR "Marijuana" OR "Cannabis indica" OR "Hemp" OR "Hemps" OR "Ganja" OR "Ganjas" OR "Hashishs" OR "Hashish" OR "Bhang" OR "Bhangs" OR "Cannabis sativa" OR "Cannabinoids" OR "Cannabidiol" OR "Cannabinol" OR "Dronabinol" AND "Amyloid beta Peptides" OR "beta-Peptides, Amyloid" OR "Alzheimer's ABP" OR "ABP, Alzheimer's" OR "Alzheimer ABP" OR "Alzheimer's ABP" OR "Alzheimer's Amyloid Fibril Protein" OR "Amyloid AD-AP" OR "AD-AP, Amyloid" OR "Amyloid AD AP" OR "beta-Amyloid Protein" OR "Protein, beta-Amyloid" OR "beta Amyloid Protein" OR "Amyloid beta-Protein" OR "Amyloid beta Protein" OR "beta-Protein, Amyloid" OR "Amyloid beta-Proteins" OR "Amyloid beta Proteins" OR "beta-Proteins, Amyloid" OR "Amyloid Fibril Protein, Alzheimer's" OR "Amyloid Protein A4" OR "Protein A4, Amyloid" OR "Alzheimer beta-Protein" OR "Alzheimer beta Protein" OR "beta-Protein, Alzheimer" OR "Amyloid beta-Peptide" OR "Amyloid beta Peptide" OR "beta-Peptide, Amyloid". During the search in the mentioned databases, no restriction was considered for article language. We also hand-searched the reference section of selected articles to find more related articles.

2.2. Inclusion Criteria

The founded studies were selected with the following criteria:

1) Experimental studies
2) Reported amyloid-beta modification during the study
3) Language is English.
4) Investigation of the effect of cannabis-based drugs on amyloid-beta protein levels, gene expression, synthesis, deposition, aggregation, and degradation.

2.3. Exclusion Criteria

1) Not identified results and methods
2) Duplicated studies

2.4. Data Extraction

Three authors (B.R, T.F, and A.M.P.S) extracted the data after a careful reading of the full text of the included studies as follow: first author, publication year, Alzheimer's disease model, age, pharmacological agents, dose, route and duration of administration, amyloid-beta detection method, findings of molecular assays. Any inconsistencies in the evaluation of articles were assessed by the fourth author.

3. RESULTS

3.1. Systematic Findings

3.1.1. Article Search Findings

A total of 153 articles were obtained from all searched databases. Ninety-five duplicate articles were excluded according to title evaluation. Next, abstracts of 58 articles were assessed according to the inclusion criteria, and 17 articles were selected for further evaluation. After careful assessment of the remaining papers, 9 articles were included in the systematic review. Fig. (**1**) shows the PRISMA Flowchart of the literature search and strategy for the selection of relevant documents. The most prevalent reasons for exclusion of articles were lack of information on the Aβ modifications in the methodology section, or some of them only focused on the behavioral tests in AD models without attention directed to the role of Aβ. Table **1** provides a summary of the selected studies.

3.1.2. AD Models

Mice were used in four articles: Chen *et al.* 2010; Aso *et al.* 2015; Aso *et al.* 2016; and Watt *et al.* 2020 [28-31] and cell lines were used in five: Cao *et al.* 2014; Janefjord *et al.* 2014; Scuderi *et al.* 2014; Libro *et al.* 2016; and Eggers *et al.* 2019 [32-36]. Animal studies that employed transgenic mice, including APP/PS1, APP23/PS45, APPswe/PS1E9, and CB2 HET mice as AD models were: Chen *et al.* 2010; Aso *et al.* 2015; Aso *et al.* 2016; Watt *et al.* 2020 [28-31].

Among them, one study used mice 1 to 2.5-month-old: Chen *et al.* 2010 [30], and 3 other studies investigated mice between 6 to 12-month-old. Scuderi *et al.* 2014, Aso *et al.* 2015, and Libro *et al.* 2016 used N2a/APPswe cells, SHSY5YAPP+ Cells, and mesenchymal stem cells, respectively [28, 33, 36]. Eggers *et al.* 2019 and Janefjord *et al.* 2014 investigated the effect of Aβ 1-42 on the PC12 and SH-SY5Y, respectively [32, 35].

3.1.3. Treatment Procedures

The cannabis-based drugs were used in the selected studies, including THC (four studies), CBD (five studies), mimulone, diplacone, and cannflavin A (one study), synthetic cannabis such as Abn-CBD (one study) and HU210 (one study).

In animal studies conducted by Aso *et al.* 2015 and Aso *et al.* 2016, THC, CBD, and THC plus CBD were used [28, 29]. One animal study investigated the impact of THC [31] and one other used HU210 [30]. *In vitro* study by Cao *et al.*

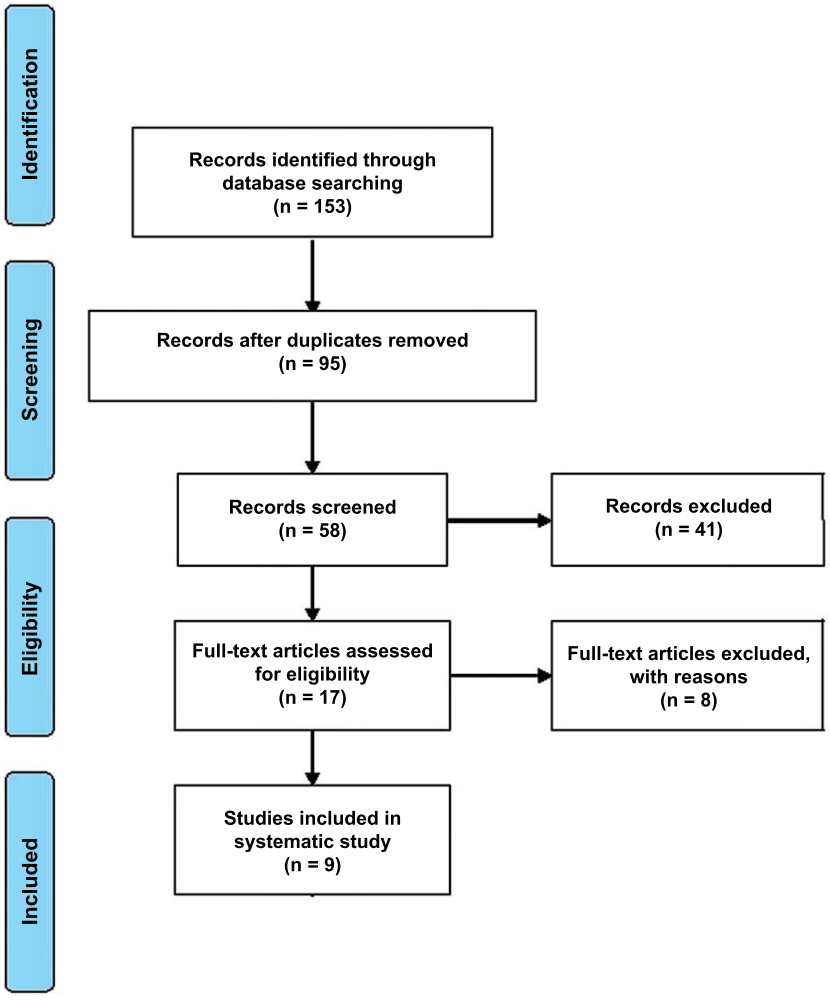

Fig. (1). PRISMA flowchart of the literature search and strategy for the selection of relevant documents. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Table 1. A summary of the selected studies.

Author	Experimental AD Model	Type, Dosage, and Duration of Cannabis-Based Drug	Findings
Aso *et al.* 2015	AβPP/PS1 transgenic mice	THC, CBD, THC+CBD; 0.75 mg/kg each; Intraperitoneal injection; once a day for 5 weeks	Significant decrease in soluble Aβ42 peptide levels; change in plaques composition; reduced astrogliosis, microgliosis, and inflammatory-related molecules (more significant with THC +CBD compared to THC or CBD alone; THC + CBD produced redox protein thioredoxin 2 and the signaling protein Wnt16
Aso *et al.* 2016	CB2 HET mice	THC, CBD, THC+CBD; 0.75 mg/kg each; Intraperitoneal injection; once a day for 5 weeks	Lack of CB2 exacerbates cortical Aβ deposition and increases the levels of soluble Aβ40; CB2 receptor deficiency had no effect on viability, memory impairment, tau hyperphosphorylation in dystrophic neurites. Cannabis-based medicines had positive effects on cognitive function
Cao *et al.* 2014	N2a/AβPPswe cell line	THC solution; 0 nM, 0.25 nM, 2.5 nM, 25 nM, 250 nM, and 2500 nM; 6, 24, 48 h	Dose-dependent reduction in Aβ40 level after 6 h and 24 h; dose-dependent was conserved in Aβ40 level after 48 h; prevented Aβ aggregation; Reduced total GSK-3 levels; enhanced mitochondrial function; no additive effect in combining caffeine and THC; No toxicity was observed
Chen *et al.* 2010	APP23/PS45 mice	HU210; 0, 10, or 50 mg/kg twice daily; Intraperitoneal injection; 10-20 days	No improvement in spatial memory; no effect on A 40 or A 42 levels; no effect on APP processing and A generation or deposition; no change in the amount of APP C-terminal fragments
Eggers *et al.* 2019	PC12 cells exposed to AB1-42	mimulone (10 μM), diplacone (1 μM), cannflavin A (10 μM); 1-200 μM; 48h	Cannflavin A and diplacone had active anti-fibrillar effects against Aβ; cannflavin A (10μM) reduced membrane-bound Amylo-glo binding; cannflavin A and mimulone reduced the density of Aβ1–42 aggregates; Cannflavin A increased cell viability and inhibited Aβ1–42 neurotoxicity, reducing Aβ aggregate adherence to PC-12 cells; mimulone and more significantly diplacone showed concentration-dependent neurotoxicity
Libro *et al.* 2016	Mesenchymal Stem Cells	CBD; 5μM; 24h	Downregulated genes of tau phosphorylation and secretases involved in A generation; inhibited the expression of GSK3 by promoting PI3K/Akt signaling
Janefjord *et al.* 2014	SH-SY5Y cells exposed to AB1-42	CB ligands; 10 μM; 24h	Significant inhibition of ThT fluorescence over 14 h; no significant overall effect on ThT fluorescence, 2-AG altered Ab fibril morphology
Scuderi *et al.* 2014	SHSY5Y*APP*+ Cells	CBD; 10^{-9}-10^{-6}M; 24h	Increase the PPARγ expression, CBD-mediated decrease in both the C83 and C99 fragments; progressive reduction of Aβ peptide expression in cell lysates; decreased APP expression
Watt *et al.* 2020	APPswe/PS1E9 mice	CBD; 50 mg/kg, Once daily; Intraperitoneal injection; 3 weeks	Improved social recognition memory, spatial memory, reduce insoluble Aβ40 levels in the hippocampus; No effect on neuroinflammation, neurodegeneration, or PPARγ markers in the cortex

2014, THC was used, and in the research by Eggers *et al.* 2019, they showed the impact of mimulone, diplacone, and cannflavin A [34, 35]. Libro *et al.* 2016 and Scuderi *et al.* 2014 used CBD [33, 36]. Janefjord *et al.* 2014 used Abn-CBD, CBD, and THC [32]. The doses of CBD, THC, and HU210 in animal studies were 0.75 mg/kg once daily [28, 29], 50 mg/kg once daily [31], 10, or 50 mg/kg twice daily [30], respectively. The doses of CBD used by *in vitro* studies were 5μM or 10 μM or 10^{-9} to 10^{-6} M [33, 36]. The doses of THC used by an *in vitro* study was 0.25-2500 nM [34]. The doses of mimulone, diplacone, cannflavin A was between 1-200μM [35]. The dose of Abn-CBD was 10 ml [32]. Cannabis-based drugs were administrated intraperitoneally in all animal studies. Cannabis in animal studies was injected within 10 to 35 days. The cell cultures were incubated with cannabis between 6h to 48 h.

3.1.4. Laboratory Techniques for Assessing Aβ Modification

Several molecular assays were used to evaluate the impact of the cannabis-based drug on the Aβ modification including immunohistochemistry [28-30], ELISA [28-31], immunofluorescence [28, 29, 33], Quantitative PCR [28], real-time PCR [36], RNA microarray [28], western blotting [28, 30, 31, 34], Thioflavin T fluorescence [30, 32, 34, 35],

and Transmission electron microscopy [35]. These assays indicated the Aβ modification at the protein levels and gene expression and morphological changes.

3.1.5. Findings on the Impact of Cannabis on Aβ Modifications

3.1.5.1. Cannabis and Aβ Modifications at Protein Levels and Gene Expression

Chen B *et al.* 2010 reported that HU210 (10 or 50 μg/kg twice daily) did not affect the Aβ levels in the hippocampus of APP23/PS45 mice [30]. Watt *et al.* 2020 indicated that CBD (50 mg/kg, for 3 weeks) decreased insoluble Aβ40 levels in the hippocampus of APPswe/PS1E9 mice [31]. Aso *et al.* 2015 found that THC + CBD (0.75 mg/kg, once a day for 5 weeks) dramatically decreased soluble Aβ42 peptide levels in APP/PS1 mice [28].

3.1.5.2. Cannabis and Aβ Generation and Degradation

Chen B *et al.* 2010 reported that HU210 (10 or 50 μg/kg twice daily) did not affect the Aβ generation and Aβ Precursor Protein (APP) processing in the hippocampus of APP23/PS45 mice [30]. APP can cleave through activating of α-secretase within the Aβ domain for releasing preclude Aβ generation and soluble APPα. CBD at dose 5 μM for 24 h decreased Aβ generation a *via* downregulating the genes β-(BACE-1) and γ-secretases (APH1A, PSENEN, NCSTN, PSEN2, and PSEN1) that are involved in coding for the secretases in the generation of Aβ in CBD-GMSCs, and also genes upregulated coding for the involved enzyme in Aβ degradation (IDE, ECE1, and ACE1) [36]. Janefjord *et al.* 2014 indicated that THC, CBD, and Abn-CBD did not affect the Aβ fibril formation and morphology in SH-SY5Y exposed to Aβ 1-40 [32].

Scuderi *et al.* 2014 found that CBD (10-9 to 10-7 for 24 h) reduced the expression of APP and Aβ in SHSY5YAPP+ Cells [33].

3.1.5.3. Cannabis and Aβ Deposition and Aggregation

Cao *et al.* 2014 indicated that THC (2500, 250, 25, 2.5, and 0.25 nM) prevented Aβ aggregation dose-dependently by direct interaction with Aβ in N2a/APPswe cells [34]. Chen B *et al.* 2010 reported that HU210 [10 or 50 μg/kg twice daily) did not affect the Aβ deposition in the hippocampus of APP23/PS45 mice [30]. Eggers *et al.* 2019 studied the effects of mimulone, diplacone, cannflavin A, flavonoids of cannabis, at doses between 1-200 μM on the Aβ aggregation in PC12 exposed to AB1-42. Among them, cannflavin A (10μM) abrogated Aβ aggregation by decreasing membrane-bound Amylo-glo binding and also decreasing the density of Aβ1–42 aggregates [35].

Aso *et al.* 2015 reported that THC + CBD (0.75 mg/kg, once a day for 5 weeks) changed Aβ plaque composition [28]. They also found that THC + CBD (0.75 mg/kg, once a day for 5 weeks) could not change Aβ plaque composition and deposition in CB2 deficiency APP/PS1 mice [29]. It indicates the role of CB2 receptor in the protective impact of the combination of THC+CBD. However, no significant differences were seen in the tau phosphorylated levels at the Thr181 site in the vicinity of Aβ plaques in CB2 receptor deficiency and treatment groups and other APP/PS1 mice [29].

3.2. Mechanisms Related to the Protective Effects of Cannabis Against Aβ-Induced Alzheimer Disease

Several studies showed an association between Aβ deposition, oxidative stress, apoptosis, and inflammation associated with AD [37-39]. Here, we discuss the beneficial impact of cannabis on the involved mechanisms of Aβ-induced AD. One of the primary critical pathologies of AD is microglial activation. Microglia, resident macrophages of the brain, has dual functions in the central nervous system. Under physiological conditions, microglia can protect the central nervous system against pathological events. In AD, overstimulation of microglia induces inflammatory cascades typically in patient's brains, leading to neurodegeneration [40-42]. The number of activated microglia is decreased following the Aβ removal [43]. Thus, pharmacological agents with inhibitory effects on microglial activity may be a suitable strategy for mitigating Aβ-induced neurotoxicity. In this context, several cannabinoids were effective against Aβ-induced activation of microglial, resulting in a reduction in the synthesis and release of NO [44] and TNF-α [45]. Cannabinoids (CBD, HU-210, WIN55, 212-2) inhibited Aβ-induced activation of microglia dependent on their CB2-selective agonist activities. This event is not related to its antioxidant activity [43]. Due to the leading role of cannabinoid receptors in the pathogenesis of AD, cannabinoids are active agents to prevent the AD process [32, 46]. Synthetic cannabinoids such as JWH-015 have been found to increase the phagocytosis of Aβ by mouse microglial cells [47] and promote the removal of Aβ from human tissue sections at low doses [48]. CBD was effective against Aβ induced oxidative stress and apoptosis in PC12 [49, 50]. CBD has anti-inflammatory activity in Aβ-treated neuronal cells. CBD blocked NO production (the stable metabolite of NO) in PC12 cells exposed to Aβ. The elevated NO content induced by Aβ generated by the inducible NOS isoform (iNOS) in PC12 was decreased by CBD treatment. Abnormal Aβ disposition in AD induces oxidative stress in AD [51], which is a key signal for an overstimulation of pro-inflammatory cytokines [52, 53]. Oxidative stress stimulates the "mitogen-activated protein kinases (MAPK) [54, 55]; among them, p38 MAPK plays a vital role in AD [56]. It was indicated that CBD decreased the phosphorylation of p38 MAPK that is involved in iNOS gene expression in rat glial [57]. CBD also blocked NF-kB activation induced by Aβ in PC12. CBD showed anti-apoptotic activity evidenced by a decrease in Bcl-2 overexpression in PC12 exposed to Aβ [49] through inhibition of p38 MAPK and NF-kB. CBD significantly decreased iNOS protein expression and NO levels through suppressing p38 MAPK activity in Aβ-induced PC12 cells. Oxidative stress may be the main pathway involved in the AD pathogenesis, which causes other cascade of AD events [58], thus antioxidants may be effective in AD. PC12 cells exposed to Aβ showed elevated ROS levels and lipid peroxidation [49, 59, 60]. CBD could decrease Aβ-induced ROS over-production and lipid peroxidation due to antioxidant effects [61]. It has been found that CBD reduced the oxidative stress induced by retinoid anhydroretinol in lymphoblastoid cells [62] and blocked hydrogen

peroxide-induced oxidative stress in neuronal cells [63]. CBD may potentiate the endocannabinoid action at CB1 receptors by inhibiting the uptake and the enzymatic degradation of the endocannabinoid anandamide [64]. Although, endogenous cannabinoids including noladin and anandamide were effective against Aβ-induced toxicity *via* activation of CB1 receptors in human teratocarcinoma cells but, the antioxidative effect of cannabidiol was a non-CB1 mediated protective effect of cannabinoids [65-67]. Aβ-induced neurotoxic effects in PC12 cells are related to an elevation in [Ca^{2+}] as a result of a free radical-mediated process and this effect may be blocked by antioxidants [68].

CBD decreased Aβ-induced elevation in [Ca2+]I, which confirmed its antioxidant activity [63]. Apoptosis is accompanied by the activation of the caspase [69]. CBD elevated pro-caspase 3 levels and reduced caspase 3 levels in PC12 cells exposed to Aβ, as evidenced by decreasing DNA fragmentation, showing that CBD has anti-apoptotic effects [70]. The impact of CBD on APP processing has been investigated by using transfected human neuroblastoma SHSY5YAPP+ cells [33]. CBD induced ubiquitination of APP and decreased Aβ peptide expression in cells, leading to lower apoptotic events [65]. The Peroxisome Proliferator-Activated Receptor-γ (PPARγ) antagonist inhibited these impacts of CBD, while α-, β- and γ-secretases involvement were ruled out. PPARs are ligand-activated transcription factors that consist of three isoforms (α, β/δ, and γ). Under physiological conditions, PPARγ receptors are expressed at low levels but an increase in pathological conditions such as AD [71]. It was found that activation of PPARγ resulted in APP expression [72] and increased the removal of Aβ [73]. CBD may exert a beneficial effect on the amyloidogenic pathway through a mechanism involving PPARγ [63].

Activation of PPARγ suppressed the gene expression of inflammatory cytokines *via* the inhibition of NFkB [74]. CBD binds to PPARγ, leading to the induction of PPARγ-related transcriptional activity [75]. CBD also blocks the Aβ-mediated expression of the NFkB p50/p65 complex, suppressing the NFkB pathway related to PPARγ [76]. The inhibition impact of CBD on NFkB causes a decrease in the levels of iNOS, GFAP, IL1β, TNFα, and S100B in Aβ-exposed rats [76]. PPARγ agonists have also been shown to reverse Aβ-mediated depression of LTP and cognitive processes in rat hippocampal slices [77]. Acute application of Aβ inhibited Long-Term Potentiation (LTP) and cognitive processes in the hippocampus of rats due to caspase-3 activation, Akt cleavage and increased activation of Glycogen Synthase Kinase 3β (GSK3β) [78]. Inhibition of early LTP induced by Aβ-mediated activation of GSK3β can be reversed by CBD [78]. CBD also attenuated Aβ-induced an elevation in the caspase-3 activity [50, 79], through improving mitochondrial function. β-catenin is triggered by PPARγ to modulate anti-inflammatory gene expression. The stimulatory effect of CBD on inhibited β-catenin by Aβ suggests a regulatory role of CBD in the Wnt signaling pathway [80]. PPARγ stimulation reduced the activity of GSK3β [81], leading to improved LTP. An interaction between CBD, PPARγ, and the Wnt/β-catenin pathway showed a significant role in the protective impact of CBD in AD [82]. CBD raised Wnt/β-catenin by induction of PPARγ and inhibition of Aβ production. CBD also decreased mitochondrial dysfunction and ROS production associated with amyloid aggregation [82].

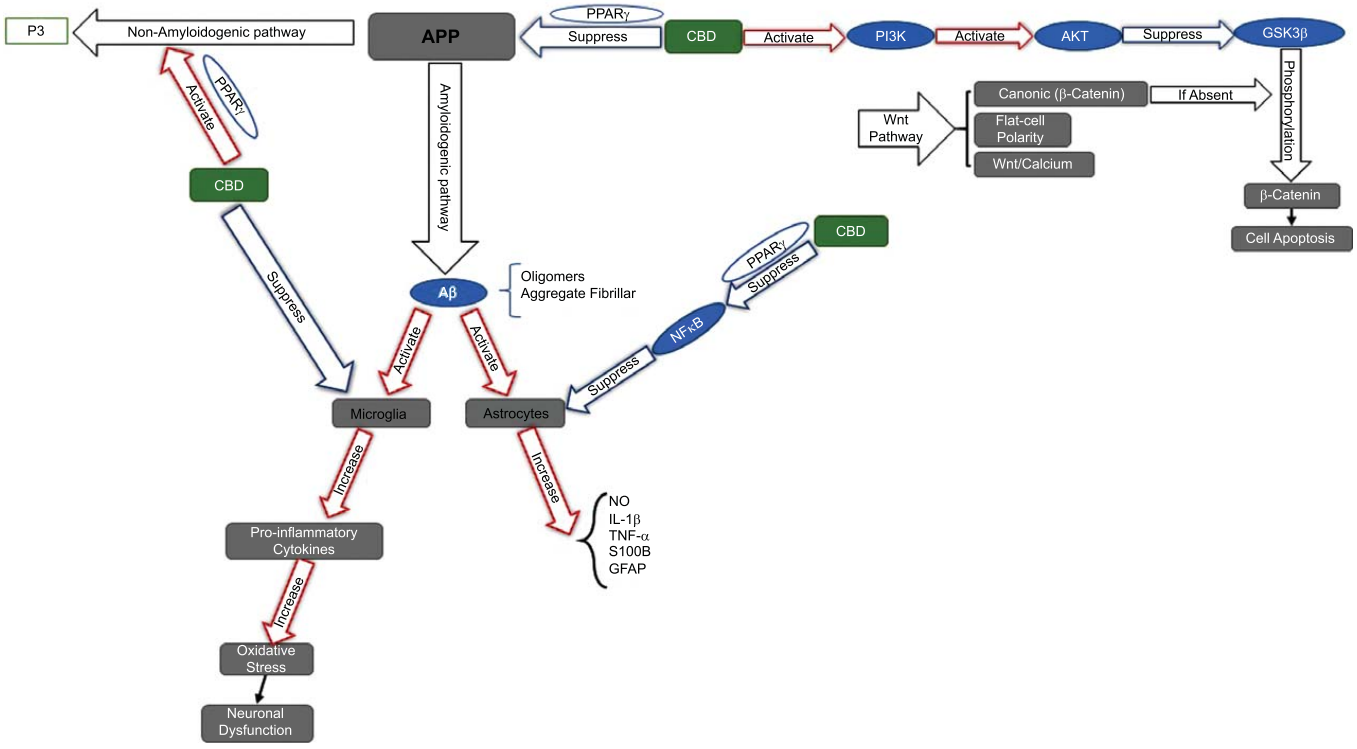

Fig. (2). Schema of interaction between Cannabis-Based Drugs (CBDs) and Aβ pathway-induced Alzheimer's disease. (*A higher resolution/ colour version of this figure is available in the electronic copy of the article*).

The Wnt pathway consists of the Wnt/β-catenin or canonic pathway, Wnt/Jun N-terminal Kinases (JNK), and the Wnt/calcium pathway. Aβ can affect the Wnt pathway both indirectly or directly through binding to the extracellular domains of the frizzed receptor protein blocking the Wnt/β-catenin pathway [83]. CBD decreased tau protein hyperphosphorylation in AD *via* Wnt/þ-catenins pathway rescue in PC12 cells exposed to Aβ-treated [80]. PI3K/Akt signaling also played a crucial role in AD pathogenesis by phosphorylating tau and inducing Aβ generation [84]. It has been indicated that cannabinoids can regulate the PI3K/Akt/GSK3β pathway [85, 86]. CBD prevented Aβ deposition *via* the activation of the TRPV1 channel, a calcium-permeable channel, and interact with PI3K [87]. TRPV1 activation by CBD can effect the PI3K/Akt signaling, leading to the inactivation of GSK3β *via* the phosphorylation at serine-9, resulting in decreased tau phosphorylation and Aβ generation [36]. Cannabidiol blocked Aβ-induced tau protein hyperphosphorylation in PC12 cells, leading to a decrease in the Neurofibrillary Tangles (NFTs) production, an important hallmark of AD [80]. This impact was related to a decrease in p-GSK3β [80].

CBD can also increase brain-derived neurotrophic factor (BDNF), resulting in combat against excitotoxicity and neuronal plasticity; all of these processes have a main role in AD [88-90]. However, there is yet no study about the effect of CBD-induced BDNF on the pathological processes of AD. In addition, there is not enough evidence about the impact of CBD on autophagy signaling, which has a role in AD pathogenesis [91]. The disruption of these processes leads to the deposition of aggregated proteins, changed the mitochondrial function that might exacerbate the AD process [91]. Until now, one study has indicated the stimulatory effects of CBD on autophagy in a tauopathy model [92]. CBD can also regulate cerebral blood, including vasodilatation of brain blood vessels flow and elevation of cerebral blood flow that contribute to its protective effect against AD [93-95].

Fig. (**2**) indicates mechanisms related to the protective effects of cannabis against Aβ-induced AD. CBDs activate PI3K/Akt, resulting in the suppression of GSK-3β activity, which leads to the decrease of apoptosis in AD. CBDs act *via* PPAR gamma activation and stimulate the ubiquitination of APP, leading to inhibition of Aβ formation. Inhibition of Aβ decreases the activation of microglia and astrocyte, which leads to the diminishing of inflammation and oxidative stress in AD. AD, Alzheimer's disease; APP, amyloid precursor protein; CBDs, cannabis-based drugs; GSK-3β, glycogen synthase kinase3beta; PPARγ, peroxisome proliferator-activated receptor-gamma; PI3K-Akt, phosphatidylinositol 3-kinase-protein kinase B

CONCLUSION

AD is the most common cause of memory impairment, and it is estimated that the morbidity rate of AD will reach 1 in every 85 people worldwide in 2020. According to the high burden of AD, suitable treatments should be found to delay the onset of AD and prevent its progression. Today, several experimental studies have been focused on the therapeutics agents inhibiting the toxic impact of A*β* in the AD pathophysiology. Several studies also indicated the protective effects of natural agents against the A*β*'s influence in the AD. Unluckily, present therapeutic agents can decrease AD symptoms, without inhibiting its progression. The findings in the current systematic investigation propose that cannabis-based medicine could be able to reduce AD symptoms and prevented the progression of AD by modulating an amyloidogenic pathway. We found that cannabis agents, particularly CBD and THC with different doses of 0.75 mg/kg to 50 mg/kg for 10 to 21 days, decreased Aβ at the protein levels and gene expression, deposition, and aggregation.

However, there is concern about the prescribing of cannabis derivatives in medicine due to psychoactivity of some of them, particularly Δ9-THC, that may impair memory mainly through CB1 receptors after long-term use [96]. However, the therapeutic effects of cannabis derivatives should be separated from the negative effects of Δ9-THC on cognitive function associated with recreational use [97].

Although MTT assays confirmed the safety of cannabis drugs, more in-depth animal studies are needed to find the outcome of long-term cannabis therapy and to understand the adverse effects of cannabis. When these data are provided, the pre-clinical findings could be realized as cannabis is safe for human use. Finding the pharmacology of cannabis-based drugs in more detail will be useful for confirmation or rejection of these agents for AD therapy. Finally, more animal studies should be designed to determine useful doses and duration of treatment with cannabis-based drugs on the modulation of Aβ without toxic effects.

AUTHORS CONTRIBUTIONS

Tahereh Farkhondeh, Fariborz Samini and Saeed Samarghandian designed the study. All authors wrote the manuscript and designed tables and figures. Saeed Samarghandian, Omid Mehrpour, Michael Aschner, and Haroon Khan revised the manuscript. Ali Mohammad Pourbagher-Shahri, Babak Roshanravan, and Hamed Aramjoo obtained data.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Gómez-Gómez ME, Zapico SC. Frailty, cognitive decline, neurodegenerative diseases and nutrition interventions. Int J Mol Sci 2019; 20(11): 2842. http://dx.doi.org/10.3390/ijms20112842 PMID: 31212645

[2] Mayeux R, Stern Y. Epidemiology of Alzheimer disease. Cold Spring Harb Perspect Med 2012; 2(8): a006239. http://dx.doi.org/10.1101/cshperspect.a006239 PMID: 22908189

[3] Organization WH. The epidemiology and impact of dementia current state and future trends. Available from: https://www.who.int/mental_health/neurology/dementia/dementia_thematicbrief_epidemiology.pdf

[4] Prince M, Guerchet M, Prina M. The global impact of dementia 2013-2050: Alzheimer's Disease International 2013. Available form: https://www.researchgate.net/publication/259193075_The_Global_Impact_of_Dementia_2013-2050

[5] Farlow MR. Etiology and pathogenesis of Alzheimer's disease; AJHP 1998; 55(Suppl 2): S5-S10. http://dx.doi.org/10.1093/ajhp/55.suppl_2.S5

[6] Murphy MP, LeVine H III. Alzheimer's disease and the amyloid-beta peptide. J Alzheimers Dis 2010; 19(1): 311-23. http://dx.doi.org/10.3233/JAD-2010-1221 PMID: 20061647

[7] Chow VW, Mattson MP, Wong PC, Gleichmann M. An overview of APP processing enzymes and products. Neuromolecular Med 2010; 12(1): 1-12. http://dx.doi.org/10.1007/s12017-009-8104-z PMID: 20232515

[8] Zhang X, Fu Z, Meng L, He M, Zhang Z. The early events that initiate β-amyloid aggregation in Alzheimer's disease. Front Aging Neurosci 2018; 10: 359. http://dx.doi.org/10.3389/fnagi.2018.00359 PMID: 30542277

[9] Klein G, Delmar P, Voyle N, *et al.* Gantenerumab reduces amyloid-β plaques in patients with prodromal to moderate Alzheimer's disease: a PET substudy interim analysis. Alzheimers Res Ther 2019; 11(1): 101. http://dx.doi.org/10.1186/s13195-019-0559-z PMID: 31831056

[10] Huang L-K, Chao S-P, Hu C-J. Clinical trials of new drugs for Alzheimer disease. J Biomed Sci 2020; 27(1): 18. http://dx.doi.org/10.1186/s12929-019-0609-7 PMID: 31906949

[11] Neugroschl J, Sano M. Current treatment and recent clinical research in Alzheimer's disease. Mt Sinai J Med 2010; 77(1): 3-16. http://dx.doi.org/10.1002/msj.20165 PMID: 20101716

[12] Yager D, Watson M, Healy B, Eckman EA, Eckman CB. Natural product extracts that reduce accumulation of the Alzheimer's amyloid beta peptide: selective reduction in A beta42. J Molecul Neurosci 2002; 19(1-2): 129-133.

[13] Kuruuzum-Uz A, Suleyman H, Cadirci E, Guvenalp Z. Demirezer LOJZfNC. Investigation on anti-inflammatory and antiulcer activities of Anchusa azurea extracts and their major constituent rosmarinic acid. Zeitschrift für Naturforschung C 2012; 67(7-8): 360-366.

[14] Asadi S, Ahmadiani A, Esmaeili MA, *et al. In vitro* antioxidant activities and an investigation of neuroprotection by six Salvia species from Iran: a comparative study. Food Chem Toxicol 2010; 48(5): 1341-9. http://dx.doi.org/10.1016/j.fct.2010.02.035

[15] Li N, Wang J, Ma J, Gu Z, Jiang C, Yu L, *et al.* Neuroprotective effects of cistanches herba therapy on patients with moderate Alzheimer's disease. evidence-based complementary and alternative medicine. eCAM 2015; 2015: 103985. http://dx.doi.org/10.1155/2015/103985

[16] McPartland JM. Cannabis systematics at the levels of family, genus, and species. Cannabis Cannabinoid Res 2018; 3(1): 203-12. http://dx.doi.org/10.1089/can.2018.0039 PMID: 30426073

[17] Piluzza G, Delogu G, Cabras A, Marceddu S, Bullitta S. Differentiation between fiber and drug types of hemp (*Cannabis sativa* L.) from a collection of wild and domesticated accessions. Genet Resour Crop Evol 2013; 60: 2331-42. http://dx.doi.org/10.1007/s10722-013-0001-5

[18] Atakan Z. Cannabis, a complex plant: different compounds and different effects on individuals. Ther Adv Psychopharmacol 2012; 2(6): 241-54. http://dx.doi.org/10.1177/2045125312457586 PMID: 23983983

[19] DeLong GT, Wolf CE, Poklis A, Lichtman AH. Pharmacological evaluation of the natural constituent of *Cannabis sativa*, cannabichromene and its modulation by Δ(9)-tetrahydrocannabinol. Drug Alcohol Depend 2010; 112(1-2): 126-33. http://dx.doi.org/10.1016/j.drugalcdep.2010.05.019 PMID: 20619971

[20] Niesink RJ, Rigter S, Koeter MW, Brunt TMJA. Potency trends of Δ9-tetrahydrocannabinol, cannabidiol and cannabinol in cannabis in the Netherlands: 2005-15. Addiction 2015; 110(12): 1941-50.

[21] Harvey DJ. Cyclic alkylboronates as derivatives for the characterization of cannabinolic acids by combined gas chromatography and mass spectrometry. Biomed Mass Spectromet1977; 4(2): 88-93.

[22] Dussy FE, Hamberg C, Luginbühl M, *et al.* Isolation of Δ9-THCA-A from hemp and analytical aspects concerning the determination of Δ9-THC in cannabis products. Forensic Sci Int 2005; 149(1): 3-10.

[23] Morimoto S, Komatsu K, Taura F, Shoyama Y. Purification and characterization of cannabichromenic acid synthase from *Cannabis sativa*. Phytochemistry 1998; 49(6): 1525-9. http://dx.doi.org/10.1016/S0031-9422(98)00278-7 PMID: 9862135

[24] Amouzeshi A, Pourbagher-Shahri AM. Effects of endocannabinoid system, synthetic and nonsynthetic cannabinoid drugs on traumatic brain injury outcome: a narrative review. J Surgery Trauma 2019; 7(1): 3-14.

[25] Martín-Sánchez E, Furukawa TA, *et al.* Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med 2009; 10(8): 1353-68.

[26] Machado Rocha FC, Stefano S, De Cassia Haiek R, *et al.* Therapeutic use of *Cannabis sativa* on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. Eur J Cancer care 2008; 17(5): 431-43.

[27] Collin C, Davies P, Mutiboko I, Ratcliffe S. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur J Neurol 2007; 14(3): 290-96.

[28] Aso E, Sánchez-Pla A, Vegas-Lozano E, Maldonado R. Cannabis-based medicine reduces multiple pathological processes in AβPP/PS1 mice. J Alzheimer Dis 2015; 43(3): 977-91.

[29] Aso E, Andres-Benito P, Carmona M, *et al.* Cannabinoid receptor 2 participates in amyloid-β processing in a mouse model of Alzheimer's disease but plays a minor role in the therapeutic properties of a cannabis-based medicine. J Alzheimer Dis 2016; 51(2): 489-500.

[30] Chen B, Bromley-Brits K, He G, Cai F, Zhang X, Song WJCAR. Effect of synthetic cannabinoid HU210 on memory deficits and neuropathology in Alzheimer's disease mouse model. Curr Alzheimer Res 2010; 7(3): 255-61.

[31] Watt G, Shang K, Zieba J, *et al.* Chronic treatment with 50 mg/kg cannabidiol improves cognition and moderately reduces Aβ 42 levels in 12-month-old male AβPP swe/PS1ΔE9 transgenic mice. J Alzheimer Dis 2020; 74(3): 937-50.

[32] Janefjord E, Mååg JL, Harvey BS, Smid SDJC. Cannabinoid effects on β amyloid fibril and aggregate formation, neuronal and microglial-activated neurotoxicity *in vitro.* Cell Mol Neurobiol 2014; 34(1): 31-42.

[33] Scuderi C, Steardo L, Esposito GJPr. Cannabidiol promotes amyloid precursor protein ubiquitination and reduction of beta amyloid expression in SHSY5YAPP+ cells through PPARγ involvement. Phytother Res 2014; 28(7): 1007-13.

[34] Cao C, Li Y, Liu H, Bai G, Mayl J, Lin X, *et al.* The potential therapeutic effects of THC on Alzheimer's disease. J Alzheimer Dis 2014; 42(3): 973-84. http://dx.doi.org/10.3233/JAD-140093

[35] Eggers C, Fujitani M, Kato R, *et al.* Novel cannabis flavonoid, cannflavin A displays both a hormetic and neuroprotective profile against amyloid β-mediated neurotoxicity in PC12 cells: comparison with geranylated flavonoids, mimulone and diplacone. Biochem Pharmacol 2019; 169: 113609.

[36] Libro R, Diomede F, Scionti D, *et al.* Cannabidiol modulates the expression of Alzheimer's disease-related genes in mesenchymal stem cells. Int J Mol Sci 2016; 18(1): 26. http://dx.doi.org/10.3390/ijms18010026 PMID: 28025562

[37] Cai Z, Zhao B. Ratka AJNm. Oxidative stress and β-amyloid protein in Alzheimer's disease. Redox Biol 2018; 14: 450-64.

[38] Farajdokht F, Amani M, Bavil FM, *et al.* Troxerutin protects hippocampal neurons against amyloid beta-induced oxidative stress and apoptosis. EXCLI J 2017; 16: 1081-89.

[39] Pugazhenthi S, Wang M, Pham S, Sze C-I. Eckman CB. Downregulation of CREB expression in Alzheimer's brain and in Aβ-treated rat hippocampal neurons. Mol Neurodegener 2011; 6(1): 60.

[40] Varnum MM, Ikezu TJAiete. The classification of microglial activation phenotypes on neurodegeneration and regeneration in Alz-

heimer's disease brain. Arch Immunol Ther Exp 2012; 60(4): 251-66.

[41] Streit WJ, Braak H, Xue Q-S, *et al.* Dystrophic (senescent) rather than activated microglial cells are associated with tau pathology and likely precede neurodegeneration in Alzheimer's disease. Acta Neuropathol 2009; 118(4): 475-85.

[42] Perry VH, Cunningham C, Holmes CJNRI. Systemic infections and inflammation affect chronic neurodegeneration. Nat Rev Immunol 2007; 7(2): 161-7. http://dx.doi.org/10.1038/nri2015

[43] Ramírez BG, Blázquez C, del Pulgar TG, Guzmán M. Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation. J Neurosci 2005; 25(8): 1904-13.

[44] Waksman Y, Olson JM, Carlisle SJ. Therapeutics E The central cannabinoid receptor (CB1) mediates inhibition of nitric oxide production by rat microglial cells.J Pharmacol Exp Ther 1999; 288(3): 1357-66.

[45] Facchinetti F, Del Giudice E, Furegato S, Passarotto M, Leon AJG. Cannabinoids ablate release of TNFα in rat microglial cells stimulated with lipopolysaccharide. GLIA 2003; 41(2): 161-8.

[46] Martín-Moreno AM, Reigada D, Ramírez BG, *et al.* Cannabidiol and other cannabinoids reduce microglial activation *in vitro* and *in vivo*: relevance to Alzheimer's disease. Mol Pharmacol 2011; 79(6): 964-73. http://dx.doi.org/10.1124/mol.111.071290

[47] Ehrhart J, Obregon D, Mori T, *et al.* Stimulation of cannabinoid receptor 2 (CB2) suppresses microglial activation. J Neuroinflammation 2005; 2: 29. http://dx.doi.org/10.1186/1742-2094-2-29 PMID: 16343349

[48] Tolón RM, Núñez E, Pazos MR, *et al.* The activation of cannabinoid CB2 receptors stimulates in situ and *in vitro* beta-amyloid removal by human macrophages. Brain Res 2009; 1283: 148-54. http://dx.doi.org/10.1016/j.brainres.2009.05.098 PMID: 19505450

[49] Esposito G, De Filippis D, Maiuri MC, De Stefano D, Carnuccio R. Iuvone TJNl. Cannabidiol inhibits inducible nitric oxide synthase protein expression and nitric oxide production in β-amyloid stimulated PC12 neurons through p38 MAP kinase and NF-κB involvement. Neurosci Lett 2006; 399(1-2): 91-5.

[50] Iuvone T, Esposito G, Esposito R, Santamaria Rita, Rosa MD, Izzo AA. Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on β-amyloid-induced toxicity in PC12 cells. J Neurochem 2004; 89(1): 134-41.

[51] Chauhan V, Chauhan AJP. Oxidative stress in Alzheimer's disease. Pathophysiology 2006; 13(3): 195-208. http://dx.doi.org/10.1016/j.pathophys.2006.05.004

[52] Pavlides S, Tsirigos A, Vera I, *et al.* Transcriptional evidence for the "Reverse Warburg Effect" in human breast cancer tumor stroma and metastasis: similarities with oxidative stress, inflammation, Alzheimer's disease, and "Neuron-Glia Metabolic Coupling". Aging (Albany NY) 2010; 2(4): 185-99. http://dx.doi.org/10.18632/aging.100134 PMID: 20442453

[53] Agostinho P, Cunha RA, Oliveira C. Neuroinflammation, oxidative stress and the pathogenesis of Alzheimer's disease. Curr Pharm Des 2010; 16(25): 2766-78.

[54] Kurata S. Selective activation of p38 MAPK cascade and mitotic arrest caused by low level oxidative stress. J Biol Chem 2000; 275(31): 23413-6.

[55] Kefaloyianni E, Gaitanaki C, Isidoros B. ERK1/2 and p38-MAPK signalling pathways, through MSK1, are involved in NF-κB transactivation during oxidative stress in skeletal myoblasts. Cell Signal 2006; 18(12): 2238-51.

[56] Munoz L, Ammit AJJN. Targeting p38 MAPK pathway for the treatment of Alzheimer's disease. Neuropharmacology 2010; 58(3): 561-568. http://dx.doi.org/10.1016/j.neuropharm.2009.11.010

[57] De Stefano D, Maiuri MC, Iovine B, *et al.* The role of NF-κB, IRF-1, and STAT-1α transcription factors in the iNOS gene induction by gliadin and IFN-γ in RAW 2647 macrophages. J Molecul Med 2006; 84(1): 65-74.

[58] Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease. Free Radic Biol Med 1997; 23(1): 134-47. http://dx.doi.org/10.1016/S0891-5849(96)00629-6 PMID: 9165306

[59] Onoue S, Endo K, Ohshima K, Yajima T, Kashimoto KJP. The neuropeptide PACAP attenuates β-amyloid (1–42)-induced toxicity in PC12 cells. Peptides 2002; 23(8): 1471-8.

[60] Guan Z-Z, Yu W-F. Nordberg AJNi. Dual effects of nicotine on oxidative stress and neuroprotection in PC12 cells. Neurochem Int 2003; 43(3): 243-9.

[61] Cash AD, Perry G. Smith MA. Therapeutic potential in Alzheimer disease. Curr Med Chem 2002; 9(17): 1605-10.

[62] Chen Y, Buck J. Therapeutics E Cannabinoids protect cells from oxidative cell death: a receptor-independent mechanism. J Pharmacol Exp Ther 2000; 293(3): 807-12.

[63] Hampson A, Grimaldi M, Axelrod J. Wink DJPotNAoS. Cannabidiol and (−) Δ9-tetrahydrocannabinol are neuroprotective antioxidants. Proc Natl Acad Sci USA 1998; 95(14): 8268-73.

[64] Bisogno T, Hanus L, De Petrocellis L, *et al.* Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol 2001; 134(4): 845-52. http://dx.doi.org/10.1038/sj.bjp.0704327 PMID: 11606325

[65] Esposito G, Izzo AA, Di Rosa M. Iuvone T. Selective cannabinoid CB1 receptor-mediated inhibition of inducible nitric oxide synthase protein expression in C6 rat glioma cells. J Neurochem 2001; 78(4): 835-41.

[66] Esposito G, Ligresti A, Izzo AA, *et al.* The endocannabinoid system protects rat glioma cells against HIV-1 tat protein-induced cytotoxicity. Mechanism and regulation. J Biol Chem 2002; 277(52): 50348-54.

[67] Milton NGN. Anandamide and noladin ether prevent neurotoxicity of the human amyloid-β peptide. Neurosci Lett 2002; 332(2): 127-30. http://dx.doi.org/10.1016/S0304-3940(02)00936-9

[68] Zhou Y, Gopalakrishnan V, Richardson JS. Actions of neurotoxic β-amyloid on calcium homeostasis and viability of PC12 cells are blocked by antioxidants but not by calcium channel antagonists. J Neurochem 1996; 67(4): 1419-25.

[69] Nicholson DW. Thornberry NA. Caspases: killer proteases. Trends Biochem Sci 1997; 22(8): 299-306.

[70] Gschwind M. Huber G. Apoptotic cell death induced by β-Amyloid1-42 peptide is cell type dependent. J Neurochem1995; 65(1): 292-300.

[71] Kitamura Y, Shimohama S, Koike H, *et al.* Increased expression of cyclooxygenases and peroxisome proliferator-activated receptor-gamma in Alzheimer's disease brains. Biochem Biophys Res Commun 1999; 254(3): 582-6. http://dx.doi.org/10.1006/bbrc.1998.9981 PMID: 9920782

[72] d'Abramo C, Massone S, Zingg JM, *et al.* Role of peroxisome proliferator-activated receptor gamma in amyloid precursor protein processing and amyloid beta-mediated cell death. Biochem J 2005; 391(Pt 3): 693-8. http://dx.doi.org/10.1042/BJ20050560 PMID: 15946122

[73] Camacho IE, Serneels L, Spittaels K, Merchiers P, Dominguez D. De Strooper B. Peroxisome proliferator-activated receptor γ induces a clearance mechanism for the amyloid-β peptide. J Neurosci 2004; 24(48): 10908-17.

[74] Heneka MT. Landreth GE. PPARs in the brain. Biochim Biophys Acta 2007; 1771(8): 1031-45.

[75] O'Sullivan SE, Sun Y, Bennett AJ, Randall MD. Kendall DA. Time-dependent vascular actions of cannabidiol in the rat aorta. Eur J Pharmacol 2009; 612(1-3): 61-68.

[76] Esposito G, Scuderi C, Valenza M, *et al.* Cannabidiol reduces Aβ-induced neuroinflammation and promotes hippocampal neurogenesis through PPARγ involvement. PLoS One 2011; 6(12): e28668. http://dx.doi.org/10.1371/journal.pone.0028668

[77] Costello DA, O'Leary DM, Herron CEJN. Agonists of peroxisome proliferator-activated receptor-γ attenuate the Aβ-mediated impairment of LTP in the hippocampus *in vitro*. Neuropharmacology 2005; 49(3): 359-66. http://dx.doi.org/10.1016/j.neuropharm.2005.03.009

[78] Jo J, Whitcomb DJ, Olsen KM, *et al.* Aβ 1–42 inhibition of LTP is mediated by a signaling pathway involving caspase-3, Akt1 and GSK-3β. Nat Neurosci 2011; 14(5): 545-7.

[79] Da Silva VK, de Freitas BS, da Silva Dornelles A, *et al.* Cannabidiol normalizes caspase 3, synaptophysin, and mitochondrial fission protein DNM1L expression levels in rats with brain iron over-

load: implications for neuroprotection. Mol Neurobiol 2014; 49(1): 222-33.

[80] Esposito G, De Filippis D, Carnuccio R, Izzo AA, Iuvone T. The marijuana component cannabidiol inhibits β-amyloid-induced tau protein hyperphosphorylation through Wnt/β-catenin pathway rescue in PC12 cells. J Mol Med 2006; 84(3): 253-8.

[81] Inestrosa NC, Godoy JA, Quintanilla RA, Koenig CS, Bronfman M. Peroxisome proliferator-activated receptor γ is expressed in hippocampal neurons and its activation prevents β-amyloid neurodegeneration: role of Wnt signaling. Exp Cell Res 2005; 304(1): 91-104.

[82] Vallée A, Lecarpentier Y, Guillevin R. Vallée JN. Effects of cannabidiol interactions with Wnt/β-catenin pathway and PPARγ on oxidative stress and neuroinflammation in Alzheimer's disease. Acta Biochim Biophys Sinica 2017; 49(10): 853-66.

[83] Boonen RA, van Tijn P, Zivkovic D. Wnt signaling in Alzheimer's disease: up or down, that is the question. Ageing Res Rev 2009; 8(2): 71-82.
http://dx.doi.org/10.1016/j.arr.2008.11.003 PMID: 19101658

[84] Hernández F, de Barreda EG, Fuster-Matanzo A, Lucas J. GSK3: a possible link between beta amyloid peptide and tau protein. Exp Neurol 2010; 223(2): 322-25.

[85] Trazzi S, Steger M, Mitrugno VM, Bartesaghi R, Ciani E. CB1 cannabinoid receptors increase neuronal precursor proliferation through AKT/glycogen synthase kinase-3beta/beta-catenin signaling. J Biol Chem 2010; 285(13): 10098-109.
http://dx.doi.org/10.1074/jbc.M109.043711 PMID: 20083607

[86] Ozaita A, Puighermanal E, Maldonado R. Regulation of PI3K/Akt/GSK-3 pathway by cannabinoids in the brain. J Neurochem 2007; 102(4): 1105-14.
http://dx.doi.org/10.1111/j.1471-4159.2007.04642.x
PMID: 17484726

[87] Hassan S, Eldeeb K, Millns PJ, Bennett AJ, Alexander SP, Kendall DA. Cannabidiol enhances microglial phagocytosis *via* Transient Receptor Potential (TRP) channel activation. Br J Pharmacol 2014; 171(9): 2426-39.
http://dx.doi.org/10.1111/bph.12615 PMID: 24641282

[88] Khaspekov LG, Brenz Verca MS, Frumkina LE, Hermann H, Marsicano G, Lutz B. Involvement of brain-derived neurotrophic factor in cannabinoid receptor-dependent protection against excitotoxicity. Eur J Neurosci 2004; 19(7): 1691-8.
http://dx.doi.org/10.1111/j.1460-9568.2004.03285.x
PMID: 15078543

[89] Lee J, Fukumoto H, Orne J, *et al.* Decreased levels of BDNF protein in Alzheimer temporal cortex are independent of BDNF polymorphisms. Exp Neurol 2005; 194(1): 91-6.
http://dx.doi.org/10.1016/j.expneurol.2005.01.026
PMID: 15899246

[90] Peng S, Garzon DJ, Marchese M, *et al.* Decreased brain-derived neurotrophic factor depends on amyloid aggregation state in transgenic mouse models of Alzheimer's disease. J Neurosci 2009; 29(29): 9321-9.
http://dx.doi.org/10.1523/JNEUROSCI.4736-08.2009
PMID: 19625522

[91] Scharfman H, Goodman J, Macleod A, Phani S, Antonelli C, Croll S. Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. Exp Neurol 2005; 192(2): 348-56.
http://dx.doi.org/10.1016/j.expneurol.2004.11.016
PMID: 15755552

[92] Casarejos MJ, Perucho J, Gomez A, *et al.* Natural cannabinoids improve dopamine neurotransmission and tau and amyloid pathology in a mouse model of tauopathy. J Alzheimers Dis 2013; 35(3): 525-39.
http://dx.doi.org/10.3233/JAD-130050 PMID: 23478312

[93] Wagner JA, Járai Z, Bátkai S, Kunos G. Hemodynamic effects of cannabinoids: coronary and cerebral vasodilation mediated by cannabinoid CB(1) receptors. Eur J Pharmacol 2001; 423(2-3): 203-10.
http://dx.doi.org/10.1016/S0014-2999(01)01112-8
PMID: 11448486

[94] Pacher P, Bátkai S, Kunos G. Cardiovascular pharmacology of cannabinoids. Handb Exp Pharmacol 2005; (168): 599-625.
http://dx.doi.org/10.1007/3-540-26573-2_20 PMID: 16596789

[95] Iring A, Ruisanchez É, Leszl-Ishiguro M, *et al.* Role of endocannabinoids and cannabinoid-1 receptors in cerebrocortical blood flow regulation. PLoS One 2013; 8(1): e53390.
http://dx.doi.org/10.1371/journal.pone.0053390 PMID: 23308211

[96] Maldonado R, Berrendero F, Ozaita A, Robledo P. Neurochemical basis of cannabis addiction. Neuroscience 2011; 5181: 1-17.
http://dx.doi.org/10.1016/j.neuroscience.2011.02.035

[97] Fadda P, Robinson L, Fratta W, Pertwee RG, Riedel G. Differential effects of THC- or CBD-rich cannabis extracts on working memory in rats. Neuropharmacology 2004; 47(8): 1170-9.
http://dx.doi.org/10.1016/j.neuropharm.2004.08.009
PMID: 15567426