

A Review on Studies of Marijuana for Alzheimer's Disease – Focusing on CBD, THC

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Key Words

Marijuana, CBD(Cannabidiol), THC(Δ -tetrahydrocannabidiol), AD(Alzheimer's diseases)

Abstract

Objectives: This study was to discuss the research trend of dementia treatment using cannabis for the purpose of providing the basis of cannabis use for medical purposes in the future.

Methods: This study searched publications, which were registered to databases or published by Aug 22, 2019, and targeted the full-text or abstracts of these publications. We selected the final nine studies met all selection criteria.

Results: These results implied that the CBD components of cannabis might be useful to treat and prevent AD because CBD components could suppress the main causal factors of AD. Moreover, it was suggested that using CBD and THC together could be more useful than using CBD or THC alone.

Conclusion: We hope that there will be a solid foundation to use cannabis for medical use by continuously

evaluating the possibility of using cannabis for clinical purposes as a dementia treatment substance and cannabis can be used as a positive tool.

1. Introduction

The interest in senile disease is rising gradually because aging society has become a more common phenomenon. Types of dementia include AD, vascular dementia, paralytic dementia, Lewy body dementia, carbon monoxide induced dementia, and trauma dementia [1,2]. The onset of AD has continued to increase since 1995, while the prevalence of vascular dementia is gradually decreasing. Therefore, AD draws attention from researchers [3]. AD is a disease that is caused by the gradual degeneration and death of cerebral cortical cells. The main symptoms are memory loss, cognitive decline and behavioral disorders [4]. Histopathologically, overall encephalatrophy, senile plaques, and neurofibrinomatosis (NFT) are the common characteristics of AD [5]. Acquired cognitive deficits caused by AD have a significant impact on the social life and activity of the patients [6]. Moreover, active treatment of memory disorders greatly affects the prognosis of AD patients [3]. Consequently, many researchers acknowledge the need for a therapeutic drug to restore the memory and cognitive damages of AD patients, and various studies have been conducted.

There are three Cannabis species: *C. sativa*, *C. indica*,

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and *C. ruderalis* [7]. Cannabidiol (CBD), which is attracting attention as medical cannabis, belongs to cannabinoids [8]. Cacao, the main ingredients of chocolate, and the caryophyllene of black pepper also belong to cannabinoids [9].

Cannabis contains at least 113 kinds of cannabinoids. THC (Δ -tetrahydrocannabinol), CBD, CBG (Cannabigerol), and CBN (Cannabinol) are well-known cannabinoids and many studies have been conducted on them. [10] using rats have shown that THC killed cancer cells and reduced tumor size. It has been reported that CBG expands blood vessels and protects the nervous system [11]. Since CBN is effective for inflammation, pain control, and insomnia, patches containing CBN ingredients are commercially available for human use [12]. Despite these advantageous effects, its use is currently restricted in South Korea according to the Narcotics Control Act (Law No. 15939) in order to prevent health hazards due to drug abuse. However, cannabis is legally used for medical or recreational purposes in several states of the US [13]. Although the medical efficacy and effects of cannabis have been actively studied, cannabis research is quite lacking in South Korea. Therefore, the objective of this study was to discuss the research trend of dementia treatment using cannabis for the purpose of providing the basis of cannabis use for medical purposes in the future.

2. Materials and Methods

2.1. Search Method

This study searched publications, which were registered to databases or published by Aug 22, 2019, and targeted the full-text or abstracts of these publications. Three researchers independently searched electronic journals in EMBASE and Pubmed. Literature was searched using the keywords of "P(patient)&I(intervention)". The search terms P and I are presented in Table 1. After conducting a literature search, the lists of literature were merged into one document.

2.2. Selection criteria and outcome assessment

This study selected published studies using Cannabis sativa and its components for patients with dementia. The three researchers independently selected and excluded publications. When there was a discrepancy among them, all researchers discussed whether to include or exclude the publication. The extracted literature was analyzed first by in vivo and in vitro methods, and then by cannabis components used, and by subjects used to determine therapeutic effects.

3. Results

3.1. Description of the included studies

A total of 1,149 studies were searched through P & I cross-search, and 86 studies were identified after excluding duplicated studies. We first excluded studies that were not related with dementia or did not use Cannabis sativa and its components using the titles and abstracts of these publications and 21 were selected after the first screening. Afterward, we examined the contents of these 21 studies, five studies failed to obtain full text, five could not determine the efficacy of cannabis on dementia, and two were related to policy. Finally the final nine studies met all selection criteria [14-22] were selected (Fig. 1).

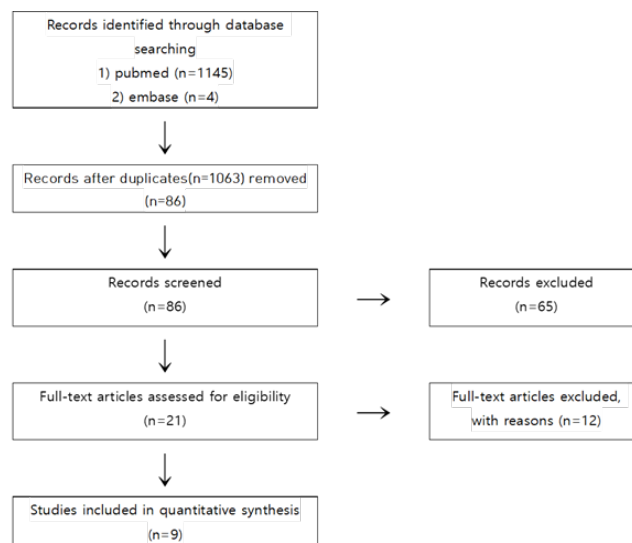


Figure 1 Flowchart of trial selection process

3.2. In vitro studies using CBD for AD

Four out of five in vitro studies using CBD were performed on PC12 neuronal cells. The results showed that CBD activated the Peroxisome Proliferator-Activated Receptor- γ (PPAR γ) through the Wnt/ β -catenin pathway. As a result, it protected PC12 cells from A β neurotoxicity and oxidation stress, increased cell survival, reduced ROS production, reduced lipid peroxidation, inhibited the hyperphosphorylation of tau protein, and inhibited AChE [14-17]. A study conducted on SH-SY5YAPP⁺ cells showed that it reduced A β production and actually decreased the APP full length protein levels. Additionally, CBD affected the selective activation of PPAR γ [18].

3.3. In vivo studies using CBD for AD

Two in-vitro studies using CBD treated the right dorsal hippocampus of mice with human A β (1-42) peptide and applied CBD to evaluate the effects of CBD on neurotoxicity and inflammation. The results showed that CBD significantly inhibited the expression of GFAP, mRNA, and protein and reduced the expression of iNOS and IL-1 β protein. 19) Moreover, the effects of CBD were confirmed

Table 1 Molecular Targets in Rheumatoid Arthritis

	List
P	'Alzheimer's Disease', 'Dementia, Senile', 'Senile Dementia', 'Dementia, Alzheimer Type', 'Alzheimer Type Dementia', 'Alzheimer-Type Dementia (ATD)', 'Alzheimer Type Dementia (ATD)', 'Dementia, Alzheimer-Type (ATD)', 'Alzheimer Type Senile Dementia', 'Primary Senile Degenerative Dementia', 'Dementia, Primary Senile Degenerative', 'Alzheimer Sclerosis', 'Sclerosis, Alzheimer', 'Alzheimer Syndrome', 'Alzheimer Dementia', 'Alzheimer Dementias', 'Dementia, Alzheimer', 'Dementias, Alzheimer', 'Senile Dementia, Alzheimer Type', 'Acute Confusional Senile Dementia', 'Senile Dementia, Acute Confusional', 'Dementia, Presenile', 'Presenile Dementia', 'Alzheimer Disease, Late Onset', 'Late Onset Alzheimer Disease', 'Alzheimer's Disease, Focal Onset', 'Focal Onset Alzheimer's Disease', 'Familial Alzheimer Disease (FAD)', 'Alzheimer Disease, Familial (FAD)', 'Alzheimer Diseases, Familial (FAD)', 'Familial Alzheimer Diseases (FAD)', 'Alzheimer Disease, Early Onset', 'Early Onset Alzheimer Disease', 'Presenile Alzheimer Dementia'
I	'Cannabi', 'Hemp Plant', 'Hemp Plants', 'Plant, Hemp', 'Plants, Hemp', 'Cannabis indica', 'Cannabis indicas', 'indicas, Cannabis', 'Marihuana', 'Marihuanas', 'Marijuana', 'Marijuanas', 'Ganja', 'Ganjas', 'Hashish', 'Hashishs', 'Hemp', 'Hemps', 'Bhang', 'Bhangs', 'Cannabis sativa', 'Cannabis sativas', 'sativas, Cannabis'

with and without the antagonist of PPAR γ [20]. It was found that the blocking of PPAR γ mitigated the effects of CBD on neural damage and CBD stimulated the neurogenesis of the hippocampus through interactions [20].

3.4. In vivo studies using CBD-THC for AD

Two in-vivo studies using CBD and THC at the same time showed that the CBD+THC treatment was effective on the memory of A β PP/PS1 transgenic mice and the CBD+THC was more effective than CBD alone or THC alone treatments [21]. Moreover, the CBD+THC treatment reduced the GluR2/3 of aged A β PP/PS1 mice and increased the level of GABA-A R α 1 [22].

4. Discussion

The number of patients with dementia has been increasing gradually and it is predicted that it will reach 81.1 million in 2040 [23]. It is also forecasted that the number of patients with dementia will be 800,000 in South Korea in 2020 [24]. Additionally, the Ministry of Health and Welfare estimates that about 10% of the population aged 65 or older will suffer from dementia in 2025 and it will cost 30 tril-

lion KRW to treat them [25]. However, we yet do not have a solid treatment to cure dementia and the current standard medications mainly focus only on delaying dementia and recovering symptoms [26].

Therefore, we conducted this study to provide a basis for the treatment of dementia using cannabis, which is currently illegal in South Korea but known to be effective against neuroinflammation, while an effective method is needed for treating dementia, which is gradually becoming a social problem.

This study conducted P&I cross-search targeting publications published or registered to databases by Aug 22, 2019, using the full-text and abstracts of publications. Finally, nine studies [14-22] were selected and analyzed.

The results of these studies confirmed that CBD activated the peroxisome proliferator-activated receptor- γ (PPAR γ) through the Wnt/ β -catenin pathway to protect PC12 cells from A β neurotoxicity and oxidation stress, increase cell survival, reduce ROS production, reduce lipid peroxidation, inhibit the hyperphosphorylation of tau protein, inhibit AChE, and stimulate the neurogenesis of the hippocampus.

Additionally, CBD+THC treatment to A β PP/PS1 transgenic mice revealed that CBD+THC treatment was effective in memory and CBD+THC treatment was more effective than CBD alone or THC alone treatment. These results implied that the CBD components of cannabis might be

Table 2 Summary of the effects of CBD and CBD-THC combinations on AD

No.	Study ID	Model	Effect
IN VITRO STUDIES USING CBD			
1	Iuvone 2004	PC12 Neuronal Cells	Protected against A β neurotoxicity and oxidative stress, increased cell survival and decreased ROS production and lipid peroxidation
2	Esposito 2006	PC12 Neuronal Cells	Inhibited tau hyperphosphorylation
3	Eubanks 2006	PC12 Neuronal Cells	Prevented transcription of pro-inflammatory genes
4	Alexandre 2017	PC12 Neuronal Cells	A β -induced tau protein hyperphosphorylation is inhibited
5	Scuderi 2014	SH-SY5YAPP+ Cells	Induced APP ubiquitination and subsequently A β production and increased cell survival by reducing apoptotic rate
IN VIVO STUDIES USING CBD			
6	Esposito 2007	Mice inoculated with human A β 42 peptide	Attenuated A β induced neuroinflammatory responses by decreasing expression of pro-inflammatory gene and mediators
7	Giuseppe 2011	Mice inoculated with human A β 42 peptide	Reduced reactive gliosis
IN VIVO STUDIES USING CBD-THC			
8	Ester 2015	Young transgenic APPxPS1 mice (mixed background)	Improved memory deficits in the two-object recognition task and the active avoidance task. Decreased soluble A β 42 levels and changed plaque composition and reduced astroglia, microglia and inflammatory related molecules
9	Ester 2016	Aged transgenic APPxPS1 mice (mixed background)	APP/PS1 mice are associated with reduced GluR2/3 and increased levels of GABA-A α 1 in cannabinoid-treated animals

useful to treat and prevent AD because CBD components could suppress the main causal factors of AD. Moreover, it was suggested that using CBD and THC together could be more useful than using CBD or THC alone.

We hope that there will be a solid foundation to use cannabis for medical use by continuously evaluating the possibility of using cannabis for clinical purposes as a dementia treatment substance and cannabis can be used as a positive tool.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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