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REVIEW ARTICLE

Comprehensive Review of Cannabis Including Cannabinoid Brain Function

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ABSTRACT

Cannabis sativa L. is cultivated for several thousand years. Cannabinoid research has been started from the 1940s and more than 100 species are structurally determined in recent years. The biosynthetic research of cannabinoids started using labelled compounds, followed by the isolation and cloning of their biosynthetic enzymes. Among them tetrahydrocannabinolic acid (THCA) synthase was found to be a flavoenzyme. This enzyme was overexpressed in a baculovirus system and crystallized. The exact structure was determined by X-ray crystallography resulting in determination of reaction mechanism. To efficiently promote THC metabolic studies anti-THCA monoclonal antibodies was prepared to isolate and structurally determine THC metabolites in vivo and define metabolic pathways. Two receptors CB1 and CB2 for cannabinoid were discovered and two endogenous ligands for them. Rapid progress is being made on the relationship between the endocannabinoid system and brain function. THC is currently marketed for nausea, vomiting, weight loss, and sleep apnea. CBD was approved for the treatment of intractable epilepsy. Therefore, dementia will be discussed in this review because dementia has recently become a major social issue worldwide. THC inhibits acetylcholinesterase and Aβ condensation in vitro. CBD showed antioxidant, anti-inflammatory and neuroprotective effects on mice treated with human Aβ protein. CBD and THC were used together, the therapeutic effect was much stronger than with CBD alone, and the effect showed an aspect of antagonistic response. Therefor, CBD is an excellent candidate for AD treatment as its mechanism of action and medicinal effects differ from those of other drugs, and it also acts as a prophylactic agent against AD without side effects such as dependence and/or hallucinogenic effects like THC. Clinical studies have been conducted with THC and/or CBD, or their products, and have shown anti-recognition effects, but of course side effects of THC have been observed and no conclusion has been reached as to whether THC or CBD is better for clinical use.

Keyword: *Cannabis sativa*, cannabinoid biosynthetic enzyme, metabolism, anti-THCA MAb, anti-dementia.

1. Introduction

Cannabis sativa L. belonging Cannabaceae, is a dioecious, annual grass that is cultivated for several thousand years worldwide and also grows wild (Fig.1).

Fig.1 Male (left) and female (right) flowering cannabis plants (collection of one of the author (Y.S.))

It is estimated that 3% of the world's population uses cannabis for mental relaxation, as can be easily guessed from the various names by which it is known in different parts of the world. Cannabis contains cannabidiol (CBD), tetrahydrocannabinol (THC), cannabinol (CBN), and cannabichromene (CBC) as a major cannabinoid (Fig. 2). The historical background of cannabinoids shows that Adams et al. structure-determined CBN[1], following Mechoulam and Shvo[2] and Gaoni and Mechoulam[3] determined the structures of THC and CBD, respectively, depending on their stereochemistry and doble bond position. Turner et al. [4] reported the number of 60 cannabinoids in 1980 resulting in 70 in 2005. Elsohly et al. report that the number has doubled to 120 species.[5] This is largely due to the rapid development of analytical methodology, in particular gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry resulted that 110 cannabinoids and 440 non-cannabinoid components such asterpenoids, flavonoids, and sterols were found[6].

Cannabis ingredients are known to be unstable against air oxidation, heating and light. For example, the authors have successfully synthesized cannabinolic acid (CBNA) and cannabicyclolic acid (CBLA) from tetrahydrocannabinolic acid (THCA) and cannabichromenic acid (CBCA), respectively, by photoreaction[7]. Contrary to this common knowledge, Pacifici et al. found that THCA and CBDA are usually easily decarboxylated by heat to give THC and CBD, respectively, however when stored as plants, THCA and CBDA can withstand storage for more than a year[8]. The authors believe that this finding is closely related to our findings[9]. The cannabinoids are protected by the essential oil components and are less sensitive to heat and other factors, and therefore can be preserved in their original form without decarboxylation, since THCA and CBDA are biosynthesized and accumulated in the glandular trichomes where the essential oil components are accumulated.[9]

The pharmacological activity of cannabinoids, particularly THC and CBD, has been widely studied[10] and their efficacy and safety have been noted[11]. The main cannabinoids are shown in Fig. 2. All of these except CBN (A) are original cannabinoids. As already mentioned, THC and CBD are the main medicinal components and are clinically applied for chemotherapy induced nausea and vomiting, decreased weight due to AIDS and drug resistant epilepsy.

The authors have conducted isolation of new cannabinoid[12], breeding studies of nontoxic Cannabis species[13], pharmacological studies of THC[14], biosynthesis[15] and metabolism[16] of cannabinoid. Recent cannabis research has developed around endocannabinoid and receptor research. However, since THC, CBD and synthetic-related cannabinoids are now medicines, the biosynthetic enzymes of cannabinoids which are found by authors are the main focusing of this article. The aim is to clarify how cannabinoid is biosynthesized in plants by purifying and isolating biosynthetic enzymes, clarifying their properties and providing an overall figure of cannabinoid production. On the other hand, it has become clear that cannabinoids are transported by fatty acid-binding proteins, stored in the ligand binding pocket and metabolized by CYP proteins. However, the actual metabolism of THC is unknown, and little is known about what metabolites of THC have strong affinity to the receptor. Therefore, all metabolites of THC isolated have been introduced for further research. Since THC and CBD have become intractable analgesics, appetite stimulants for AIDS patients and intractable epileptics, and since their potential as therapeutic cannabinoid agents for patients with Alzheimer's disease, which is now rapidly increasing worldwide, is being reported, the aim of this study was also to provide the latest clinical data and clear the mechanism of action resulting in basic data on the potential of THC, CBD or THC-CBD mixtures as new therapeutic agents for Alzheimer's disease.

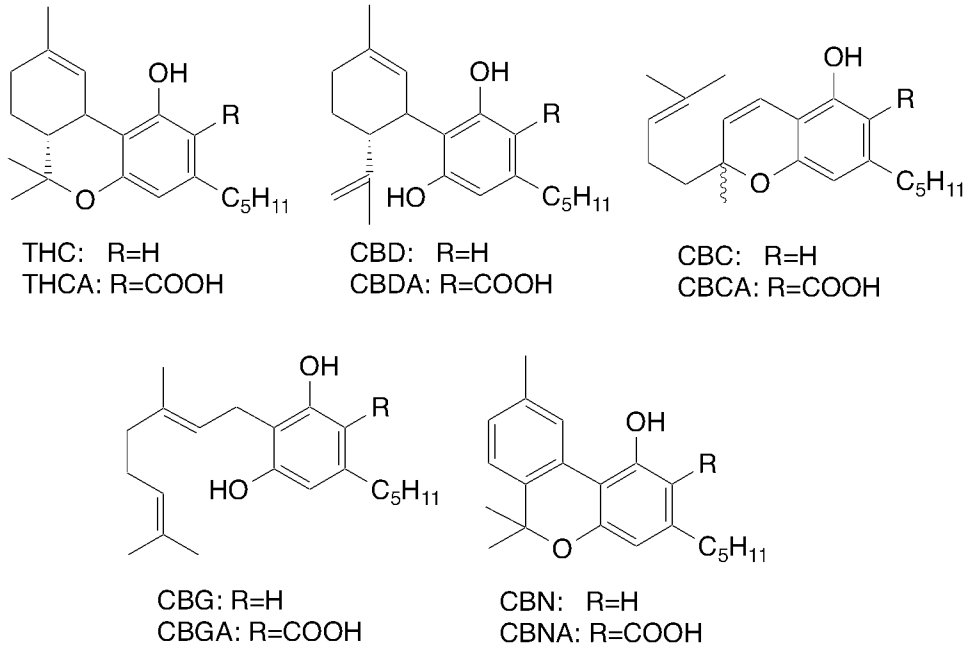

Fig. 2. Structures of major cannabinoids.

2. Biosynthesis and metabolism of cannabinoids

Cannabis plants are classified into two phenotypes such as THCA called as a medicinal type-marihuana and CBDA called as a fiver type-marihuana strains coexisting CBCA which is a major cannabinoid in younger stage and the major cannabinoid content such as THCA or CBDA is increasing comparing to that of CBCA as it matures[17]. With the aim of breeding for fibrous cannabis, a variety that contains an ignorable amount of THCA and in which CBDA is the main cannabinoid was successfully fixed after eight years of repeated selective breeding, named the CBDA variety[13]. Phenotypes for the alkyl group part of cannabinoids also exist. Isolation of propyl cannabinoids has been reported[18], and the authors have also isolated and determined the structures of genuine cannabinoids such as tetrahydrocannabivarinic acid (THCVA), cannabidivarinic acid (CBDVA), cannabichromevarinic acid (CBCVA) and cannabigerovarinic acid (CBGVA), which are carboxylic acid types, from Thai cannabis[12]. We continued to demonstrate the biosynthetic pathway of propyl cannabinoids using labelled compounds, and although the interrelationships between propyl cannabinoids were clear, we were unable to confirm the phenotype-related relationship between pentyl-type and propyl-type cannabinoids[19]. Recently Meijer et al. concluded that phenotypes also exist for propyl cannabinoids and are due to genetic factors[20].

Biosynthetic studies of cannabinoids started in the 1960s using isotope tracers resulted that cannabinoids are formed by the coalescence of both the acetate-malonic acid and mevalonic acid pathways[19]. On the other hand, it was suggested that hexanoyl-CoA formed by acyl-activating enzymes is a precursor for cannabinoids[21]. Fellermeier and Zenk confirmed that olivetolate and monoterpene were conjugated by a transferase to give CBGA[22] transforming to further CBDA, THCA and CBCA individually. The authors found that olivetol synthase, a polyketide synthase was an essential enzyme for the cannabinoid biosynthesis[23]. As mentioned above the biosynthetic pathway of cannabinoids was identified, the main cannabinoid biosynthetic enzymes, THCA synthase[24], CBDA synthase[25] and CBCA synthase[26] were successfully purified and isolated. Among them, the structural elucidation of THCA synthase, which is involved in THCA production and can also be applied to the breeding of fully THCA-negative CBDA strain, was initiated.

The cloning of THCA synthase, followed by the generation of a transgenic protein[27], revealed that this enzyme contains important insights. THCA synthase was found to be a flavoenzyme with high homology to berberine bridge enzyme, i.e. an enzyme that produces scoulerine by oxidative cyclisation of reticuline[28]. This finding was successfully demonstrated by mass expression of a recombinant enzyme using a baculovirus-insect cell system[23,27,29]. CBDA synthase was similarly cloned and found to be a flavoenzyme like THCA synthase by mass expression of the recombinant enzyme[30].

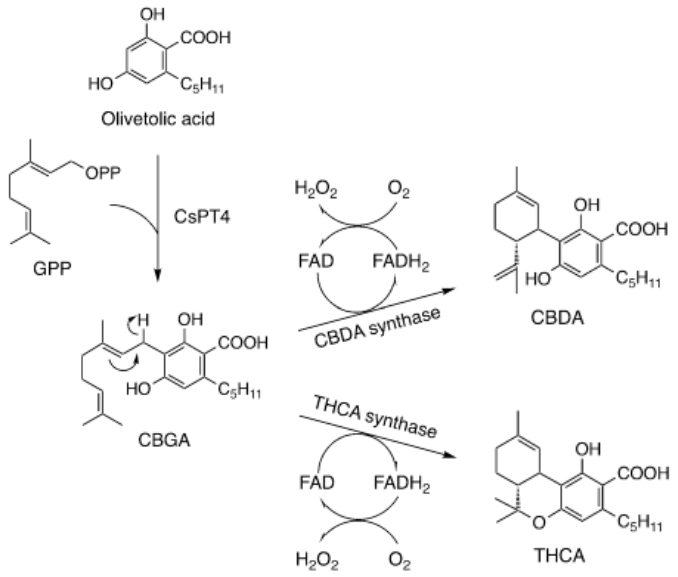

Fig.3. Biosynthetic pathway of CBDA and THCA

Another cannabinoid production-related enzyme, cannabinoid prenyltransferase 4 (CsPT4), has recently been discovered in C. *sativa*[31].

Based on the data obtained so far on THCA synthase, its crystallization was carried out to elucidate the crystal structure. This enzyme was overexpressed in a baculovirus system and crystallized[32]. The exact structure was determined by X-ray crystallography at 75 Å resolution (Fig.4-A)[33].

Fig.4 Structure of THCA synthaseA X-ray crystallographyBProposed structure of THCA synthase-CBGA complex
Green: CBGA, Blue: FAD, Black circle: hydrophobic region

As already mentioned, THCA synthase is bound to a flavin adenine dinucleotide (FAD), locating at histidine 114 which has succeeded in creating a mutant that has completely lost its activity by introducing a mutation in the molecule[27]. Moreover, having identified tyrosine 484 in the active pocket of THCA synthase as a dissociable amino acid residue, it was confirmed that conversion of tyrosine 484 to phenylalanine completely abolished its activity[27]. The proposed complex of THCA synthase and CBGA is indicated in Fig. 4-B. Further, Fig.5 shows the proposed catalytic mechanism of THCA synthase.

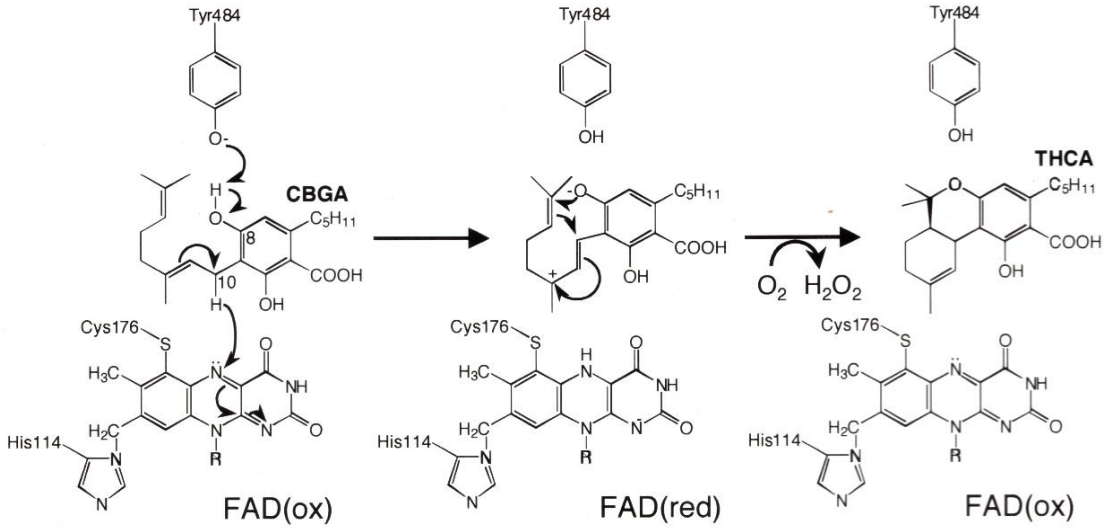

Fig.5. Proposed catalytic mechanism of THCA synthase

CBGA is found as a substrate, while THCA remains in the reaction pocket as a product; THCA synthase activity is clearly reduced in active site mutation experiments, but is not completely lost. This indicates that CBGA is bound to the active site resulting that a reaction mechanism was deduced, as shown in Fig. 5.

As already mentioned, THC and CBD are the main cannabinoids used for medical purposes, so the possibility of breeding, i.e. breeding varieties with high content of both cannabinoids including biosynthetic enzyme, is discussed. It is important to breed varieties that produce high yields of THC or CBD for medicinal uses, respectively. Mutations against THCA synthase inhibit THCA biosynthesis, while CBDA increases[27]. This methodology is considered to be the most powerful method for molecular breeding of *Cannabis* species, but unfortunately it has not led to the success of regeneration from transgenic *Cannabis* cells.

A sensitive analytical method using anti-THCA monoclonal antibody (MAb)[34,35] is useful in a wide range of fields such as metabolic pathway of THC[36,37] as discussed following and forensic area[38] and further a method of obtaining single chain fragment variable (scFv) antibody from hybridoma cell lines for the breeding of cannabinoid accumulation is important for production of THC and/or CBD as a medicine because the authors succeeded a unique breeding technology, "missile-type molecular breeding" method in which introduction of scFv genes into host plants increases antigen molecules by about 3-fold.[39-42]. Although this methodology has not been succeeded in Cannabis, THCA content increased almost three-fold compared to the original plant when the scFv gene from the anti-THCA MAb is introduced into cannabis plants of THCA strain. Since recently, Luo et al. have successfully used yeast to create CBGA, CBDA, THCA and cannabidivarinic acid (CBDVA) production matrics[31], the introduction of the scFv gene into this method may enable high-content breeding without going through cannabis plant cells.

We confirmed that THC is metabolized to the oxidative derivatives promptly resulted that their activities are changed one by one[36,37]. As mentioned previously it is easily suggested that anti-THCA MAb can recognize almost all oxidative THC products. Moreover, Eastern Blotting System[43] is a method that allows simultaneous detection of related compounds, so we plan to introduce it into THC metabolite studies. In vitro and in vivo investigations indicated that quick THC oxidation reactions occur at various sites on the THC molecule, and THC metabolites in which hydroxyl, epoxy, carbonyl and carboxylic acid groups are introduced by the oxidation process have been isolated and structurally elucidated and the metabolic pathway is confirmed as shown in Fig.6[37]. Metabolic studies of THC are also important in drug discovery, as its bioavailability differs depending on its structure, and its affinity to enzymes and/or receptors is also greatly affected. It was mentioned that MAb can discriminate between various THC metabolites with different oxidation processes, but it was found that it can also discriminate between stereoisomers as well. The β-isomer of 7-hydroxy-Δ8-THC and 8-hydroxy-Δ9-THC, respectively, was found to be slightly more reactive than the α-isomer. However, the double bond isomers could not be

distinguished between the two. It was mentioned that anti-THCA MAb has a broad cross-reactivity to THC metabolites, but this MAb does not react with endocannabinoids, cholesterol, testosterone, β-carotene etc, so it could be used for THC kinetic studies[36,37].

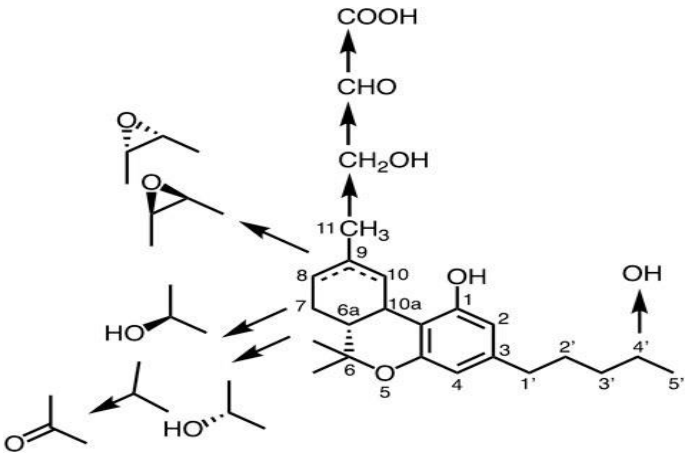

Fig.6. Metabolic pathway of THC

Recently, Elmes et al. reported that fat-soluble THC and CBD are transferred by fatty acid-binding proteins (FABP1)[44]. Subsequently, a pathway was identified in which THC is transferred and stored in the ligand binding pocket by FABP1 before being transferred to CYP450 enzymes for metabolism[45]. It is easily suggested that our anti-THCA MAb will be very useful in the above studies to track the movement of THC metabolites in vivo too.

3. Therapeutic cannabinoids

Research on endocannabinoids has made remarkable progress in recent years. CB1[46] and CB2[47], two types of THC receptors, were isolated in the brain and macrophage, respectively and cloned and sequenced. This led to research into receptor ligands resulting in discovers of arachidonoylethanolamide (anandamide) and 2-arachidonyl glyceride by Devane et al.[48] and Sugiura et al.[49], respectively. Developments in endocannabinoid research have indicated that pharmacological properties of a ligand, anandamide are similar to the central nervous system (CNS) and peripheral systems with THC, especially with regard to the inhibitory effects for memory and motor activity[50-52], ocular blood pressure and heart rate[53,54], regulation of hormones such as the hypothalamus pituitary-adrenal axis[55,56], neurotranusmission mediated by dopamine, acetylcholine, noradrenalin, endorphin and glutamate[57,58], and the immune response[59,60]. Hua et al. determined the crystal structure of human CB1 and revealed the basic properties of the receptor resulting in the antagonist binding site[61]. Moreover, the crystal structure of the human CB2 receptor has been determined by mutagenic and molecular docking methodologies, revealing its function and selectivity between CB2 and CB1. Further studies on antagonists and agonists for CB2 receptors have revealed the mechanism of CB2 receptor activation[62]. These functions are closely related to the CNS resulted that therapeutic cannabinoids have been discussed widely and can facilitate rational drug design.

It is well known that long-term cannabis use can lead to a condition known as marihuana psychosis, which causes mental disorders and mental instability. Furthermore, repeated use of cannabis by young people is said to reduce short-term potency, thereby causing anhedonia syndrome and making them lazy[63]. Recently, however, the idea of decriminalization of cannabis has spread around the world and the medical cannabis swell has grown rapidly[64]. Recently Jefsen et al. reported that the prospective population-based cohort study using the Danish National Register included all survivors aged 16 years and over showed that Cannabis use disorder has been found to be associated with an increasing risk of psychotic and non-psychotic bipolar disorder and unipolar depression[65]. These findings may inform policy on the legal status and management of cannabis use Moreover, in order to realize the concept of medical cannabis and provide a manual for doctors to prescribe cannabis, Brunetti et al. propose the establishment of precise methods for analyzing cannabinoids in various types of cannabis, the determination of the exact concentration of cannabinoids and the appropriate amount of cannabis to be used[66]. It is an undisputed fact that these discoveries have rapidly advanced the concept of medical cannabis, promoted the medical application of cannabinoids and drug development research involving cannabinoids, namely THC and CBD resulted that THC has been

approved by the Food and Drug Administration as a safe and appropriate treatment for vomiting and nausea that commonly occur with cancer drug therapy and for weight loss in HIV/AIDS. THC is currently marketed under the trade names Dronabinol, Adversa, Syndros, Marinol, and Reduvo for applications such as nausea, vomiting, weight loss, and sleep apnea. CBD, on the other hand, was approved for the treatment of intractable epilepsy in the USA in 2018 and in Europe in 2019, respectively.

With regard to illnesses dementia has recently become a major social issue worldwide. The type of dementia is clearly indicated in "The Diagnostic and Statistical Manual of Mental Disorders" specified dementia[67]. The rapid increase in the number of people with dementia in recent years has created a major crisis worldwide. To give an example of the estimates in Japan, the number of sensitized persons is expected to exceed 10 million in 2050, compared to 7.3 million in 2025[68]. This situation is seen all over the world[69]. The ratio of the number of people with dementia to the global population aged 60 and over is higher in Europe, the USA and Japan, at more than 6%, and lower in Asia and African countries, in the 3% range.[70] We consider it an important matter to investigate the factors behind this. In fact, epidemiological studies on lifestyle and eating habits have shown that wine[71] or fish[72] reduce AD in older people. For these reasons, there is a strong need for methods and natural products for the prevention of AD all over the world. AD is the most common form of dementia in older people, accounting for 30% of cases, and is estimated to affect 33 million people worldwide. It is generally accepted that AD is influenced by inflammation and oxidative stress in the brain, which leads to the accumulation of amyloid-β (Aβ) plaques and phosphorylation of tau protein in the brain, resulting in necrosis of cranial nerves and the development of dementia. AD generally increases with age, but as noted above, it is also clear that eating habits and lifestyle are associated with the dementia development. Research into natural products with anti-cognitive activity, particularly those with acetylcholinesterase inhibitory activity, has been widely developed and many active components have been identified[73,74]. Nevertheless, the only natural product with a medicinal use as an acetylcholinesterase inhibitor is galantamine containing in *Galanthus caucasicus* and *G. woronowii*. Alternatively, synthetic acetylcholinesterase inhibitors such as donepezil and rivastigmine, and N-methyl-D-aspartate receptor antagonist memantine, are available[75], but each causes nausea, diarrhea, weight loss[76] and hallucinations, fatigue and dizziness[77], respectively.

Marijuana is listed as a mafen in the 120 kinds of supernatural medicines (herbal medicines that, when used daily in moderate amounts, do no harm and contribute to improved health) in the Chinese book of Shen Nung Hon Ching, which states that "when taken in moderate doses for a long time, it will lead to the state of a god or hermit, to divine clarity and gradually lighten the body's movements" and is expected to activate the brain function. Investigations into the anti-cognitive activity of cannabinoids have shown that THC inhibits acetylcholinesterase and Aβ condensation in an in vitro evaluation system[78]. On the contrary, CBD has been shown to be a potent antioxidant, as is the dihydroxy form, although the mechanism and receptor issues are unresolved with regard to its anti-cognitive activity[79,80]. Neurotoxicity induced by Aβ infusion was protected by CBD in an in vitro system. In addition, CBD inhibits intracellular signaling pathways and suppresses tau protein phosphorylation[81] and NO production[82] in Aβ protein inducing investigations in vitro. Administration of CBD to mice injected with Aβ protein in the hippocampus suppressed interleukin-1β and NO expression in a dose-dependent manner[83]. These results indicate that CBD inhibits oxidative stress and tau phosphorylation in AD patients without hallucinations or other side effects such as those exhibited by THC. Georgia and Karl presented in vivo studies on the preventive and therapeutic effects of CBD on AD[84]. Watt and Karl also reviewed that CBD has possibility for AD therapy. CBD showed antioxidant, anti-inflammatory and neuroprotective effects on mice treated with human Aβ protein, but caused Aβ plaques in the hippocampus and cortex in APPxPS1 transgenic mice. CBD reduces Aβ plaques caused by reactive gliosis and simultaneously reduces iNOS and interleukin-1β protein levels. This phenomenon reduces inflammation and thus neurogenesis in brain tissue resulted that cognitive function is prevented in AD animal model[85]. When CBD and THC were used simultaneously, the therapeutic effect was much stronger than with CBD alone, and the effect showed an aspect of antagonistic response. From the results of the above studies, CBD is an excellent candidate for AD treatment as its mechanism of action and medicinal effects differ from those of many other drugs, and it also acts as a prophylactic agent against AD. More importantly, as mentioned above, CBD has no side effects such as dependence and/or hallucinogenic effects like THC. Recently, as research on CBD and THC has increased, various systematic reviews have been reported. Kim et al. review a number of studies on the use of cannabinoids for dementia and opine that CBD is effective not only in the treatment of AD but also in

prevention. Studies with PC-12 cells have shown that CBD protects against Aβ neulotoxicity and oxidative stress and inhibits acetylcholinesterase resulting in promotion of memory, and activates neurogenesis in the hippocampus and reduces ROS production and fatty acid peroxidation and so on. They stated clearly that mixed administration of CBD and THC was far more memory-enhancing than CBD or THC alone, although THC side effects did occur[86]. Twelve investigations covered inclusion criteria. Designs of study seemed to be dispersed such as randomized controlled trials (50%) and cannabinoids, dronabinol (33%), nabilone (25%) or THC (42%). It became evident that dronabinol and THC demonstrated significant enhancement against neuropsychiatric scores. Sedation has been observed as a side effect in many cases. There is no doubt that cannabinoids may be useful in refractory diseases being safe and mild although no systematic studies have been conducted to date yet. In summary, the author suggests that it is necessary to conduct experiments with higher doses of cannabinoids and to investigate according to formulations with suitable bioavailability to determine the appropriate use of cannabinoids[87]. The following high volume clinical trials are based on this suggestion. A high dose of 9.9 mg of THC and 18.0 mg of CBD for two months in female dementia patients with severe behavior problems improved rigidity, one of the behavior problems, and improved daily care in severe dementia patients[88]. Charernboon et al. reported that THC is effective against the cognitive symptoms of dementia in a systematic review of randomized controlled trials although evidence was not convincing[89]. The above-mentioned anti-perception activity of the natural drugs THC and CBD has been discussed, but there are some drawbacks as drugs. When the cannabis plant itself is used, it is necessary to determine the THC and CBD content for each lot. In addition, as the authors have succeeded in converting THCA to CBNA by photoreaction[7], THC is converted to CBN by the influence of light and air oxidation, so the potency needs to be checked frequently. Further when CBD is taken internally, there may be a possibility of cyclisation due to strong acidity in the stomach, which could lead to conversion to THC. Because of these problems, it will be necessary to continue to study various aspects of the use of THC and CBD as drugs.

4. Conclusion

Compared to the cannabinoid field, the development of the endocannabinoid field in recent years has been spectacular. Therefore, in this review, the authors have isolated and cloned enzymes in the biosynthetic pathway of cannabinoids, and clarified the overall structure of THCA synthase by x-ray analysis. A new breeding technology for cannabinoid is proposed, which will greatly contribute to the production of cannabinoid, especially THC and CBD. The way in which cannabinoids are made has been clarified, and now the metabolism is touched upon. The use of anti-THCA MAb, which has a broad affinity for cannabinoids, as a new method for metabolic studies shows that it is possible to systematically and efficiently elucidate the metabolic pathways of THC. We hope that this will be a pioneer in THC kinetics and kinetic studies in the body and brain in the future.

Recent neuronal research[84] have shown that THC and/or CBD blocks Aβ-induced neurotoxicity, hyperphosphorylation of tau protein, iNOS and interleukin-1β, and has unique activity compared to existing anti-dementia drugs. The anti-recognition activity of THC and CBD in in vitro, in vivo and clinical trials is shown in Fig. 7. CBD is gaining attention due to its anti-dementia activity as well as its effectiveness in treating intractable seizures, especially intractable pilepsy without the risk of the psychological side effect like THC. Clinical studies have been conducted with THC and CBD, or their combination, and have shown anti-recognition effects, but of course side effects of THC have been observed and no conclusion has been reached as to whether THC or CBD is better for clinical use.

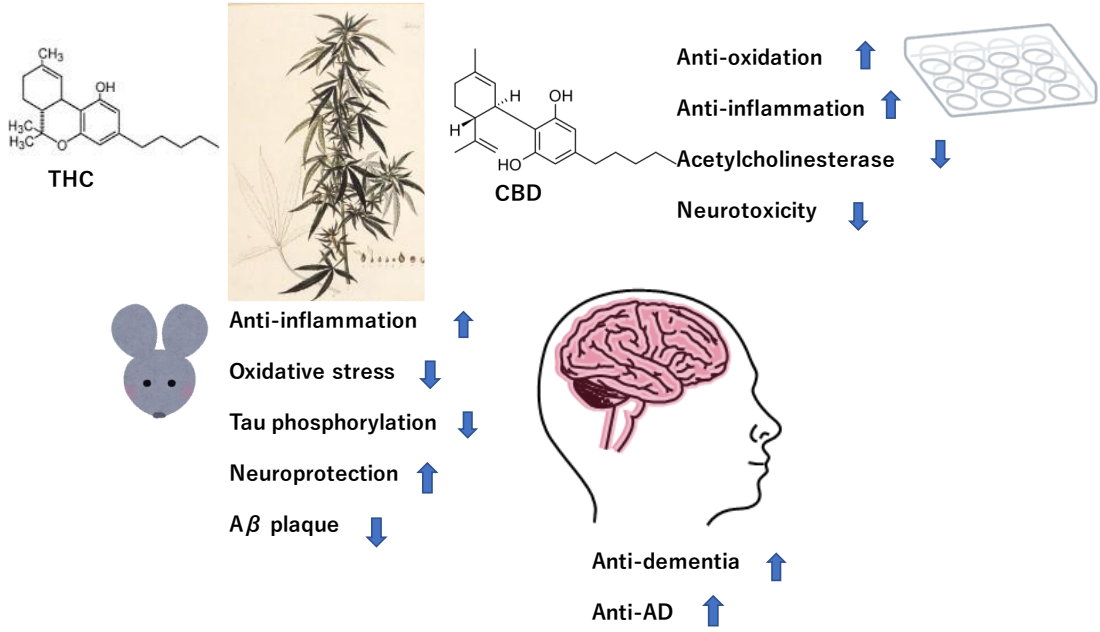

Fig.7. Anti-dementia activities of THC and CBD

The prospective population-based cohort study showed that cannabis use disorder has been found to be associated with an increasing risk of psychotic and non-psychotic bipolar disorder and unipolar depression in future[65]. This is an area that needs further discussion, as it is taken as an indication that cannabinoid, and especially THC, use as well as cannabis users may cause depressions in later years.

Conflicts of Interest: All authors have completed the ICMUE uniform disclosure form.

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References

1. Adams R, Baker BR, Wearn RB. Structure of Cannabinol. III. Synthesis of Cannabinol, 1-Hydroxy-3-N-Amyl-6,6,9-Trimethyl-6-Dibenzopyran1. *J Am Chem Soc.* 1940;62:2204–2207. doi:10.1021/ja01865a083.
2. Mechoulam R, Shvo Y. Hashish I. The Structure of Cannabidiol. Tetrahedron. 1963;19:2073–2078. doi:10.1016/0040-4020(63)85022-x.
3. Gaoni Y, Mechoulam R. Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish. J Am Chem Soc. 1964;86:1646–1647. doi:10.1021/ja01062a046.
4. Turner CE, Elsohly MA, Boeren EG. Constituents of Cannabis Sativa L. XVII. A Review of the Natural Constituents. J Nat Prod. 1980;43:169–234. doi:10.1021/np50008a001.
5. ElSohly MA, Radwan MM, Gul W. Chandra S. Galal A. Phytochemistry of Cannabis Sativa L in Phytocannabinoids, Progress in the Chemistry of Organic Natural Products. Editors Kinghorn ADH. Gibbons FS. Kobayashi J. 2017;103:1–36.doi:10.1007/978-3-319-45541-9_1.
6. Solymosi K, Köfalvi A. Cannabis: A Treasure Trove or Pandora's Box? Mini Rev. Med Chem. 2017;17:1223–1291. doi:10.2174/1389557516666161004162133.
7. Shoyama Y, Oku R, Yamauchi T, Nishioka I. Cannabis. VI. Cannabicyclolic Acid. Chem Pharm Bull. 1972;20:1927–1930. doi:10.1248/cpb. 20.1927.
8. Pacifici R, Marchei E, Salvatore F, Guandalini L, Busardò FP, Pichini S. Evaluation of Long-Term Stability of Cannabinoids in Standardized Preparations of Cannabis Flowering Tops and Cannabis Oil by Ultra-high performance Liquid Chromatography Tandem Mass Spectrometry. Clin Chem Lab Med. 2017;56:94–96. doi:10.1515/cclm-2017-0758.
9. Morimoto S, Tanaka Y, Sasaki K, Tanaka H, Fukamizu T, Shoyama Y. et al. Identification and Characterization of Cannabinoids that Induce Cell Death through Mitochondrial Permeability Transition in Cannabis Leaf Cells. J Biol Chem. 2007;282:20739–20751. doi:10.1074/jbc.M700133200.
10. Friedman D, French JA, Maccarrone M. Safety, Efficacy, and Mechanisms of Action of Cannabinoids in Neurological Disorders. Lancet Neurology. Lancet Neur. 2019;18:504–512. doi:10.1016/S1474-4422(19)30032-8.
11. Cohen K, Weizman A, Weinstein A. Positive and Negative Effects of Cannabis and Cannabinoids on Health. Clin Pharmacol Ther. 2019;105:1139–1147.doi:10.1002/cpt.1381.
12. Shoyama Y, Hirano H, Makino H, Umekita N, Nishioka I. Cannabis X The isolation and structures of four new propyl cannabinoid acids, tetrahydrocannabivarinic acid, cannabidivarinic acid, cannabichromenic acid and cannabigerovarinic acid from Thai Cannabis, 'Meao variant', Chem Pharm Bull. 1977;25:2306-2311.
13. Shoyama Y. Biological aspects on marihuana, Cannabis sativa L, and biotechnological investigation on medicinal plants, Winged been, some other vegetables and medicinal plants in the tropics and subtropics. Editors Herath W, Uemoto S.1993;141-200. Tokushu Nousanbutsu Kyokai, Tokyo.
14. Nagai N, Egashira N, Sano K,, Ogata A, Mizuki A, Mishima K, Iwasaki K, Shoyama Y, Nishimura R,Fujiwara M. Antipsychotics improve Δ9-tetrahydrocannabinol-induced impairment of the prepulse inhibition of the startle reflex in mice, Pharmacol Biochem Behav. 2006;84:330-336.
15. Taura F, Sirikantaramas S, Shoyama Y, Shoyama Y, Morimoto S. Phytocannabinoids in Cannabis sativa: Recent studies on biosynthetic enzyemes. Chem. Biodiversity, 2007;4:1649-1663.
16. Watanabe K, Matsunaga T, Kimura T, Funahashi T, Yamaori S, Shoyama Y, Yamamoto I. Stereospecific and regioselective hydrolysis of cannabinoid esters by ES46.5K, an esterase from mouse hepatic microsomes, and its differences from carboxylesterases of rabbit and porcine liver, Biol Pharm Bull. 2005;28:1743-1747.
17. Kushima H, Shoyama Y, Nishioka I. Cannabis XII. Variations of cannabinoid contents in several strains of Cannabis sativa L. with leaf-age, season and sex. Chem Pharm Bull. I980;28:594-598.
18. de Zeeuw RA, Wijsbeek J, Breimer DD, Vree TB, van Ginneken CAM, van Rossum JM. Cannabinoids with a Propyl Side Chain in Cannabis: Occurrence and Chromatographic Behavior Sci. 1972;175:778-779. doi: 10.1126/science.175.4023.778.
19. Shoyama Y, Hirano H, Nishioka I. Biosynthesis of propyl cannabinoid acid and its biosynthetic relationship with pentyl and methyl cannabinoid acid. Phytochemistry. 1984;23:I909-1912.
20. de Meijer EPM, Hammond KM. The inheritance of chemical phenotype in *Cannabis sativa* L. (V): regulation of the propyl-/pentyl cannabinoid ratio, completion of a genetic model. Euphytica. 2016;210:291-307. doi.org/10.1007/s10681-016-1721-3.

21. Stout JM, Boubakir Z, Ambrose SJ, Purves RW, Page JE. The Hexanoyl-CoA Precursor for Cannabinoid Biosynthesis Is Formed by an Acyl-Activating Enzyme in Cannabis Sativa Trichomes. Plant J. 2012;71:353–365. doi:10.1111/j.1365-313X.2012.04949.x.
22. Fellermeier M, Zenk MH. Prenylation of Olivetolate by a Hemp Transferase Yields Cannabigerolic Acid, the Precursor of Tetrahydrocannabinol. FEBS Lett. 1988;427: 283–285. doi:10.1016/s0014-5793(98)00450-5.
23. Taura F, Tanaka S, Taguchi C, Fukamizu T, Tanaka H, Shoyama Y. et al. Characterization of Olivetol Synthase, a Polyketide Synthase Putatively Involved in Cannabinoid Biosynthetic Pathway. FEBS Lett. 2009;583:2061–2066. doi:10.1016/j.febslet.2009.05.024.
24. Taura F, Morimoto S, Shoyama Y, Mechoulam R. First Direct Evidence for the Mechanism of DELTA1-tetrahydrocannabinolic Acid Biosynthesis. J Am Chem Soc. 1995;117:9766–9767. doi:10.1021/ja00143a024.
25. Taura F, Morimoto S, Shoyama Y. Purification and Characterization of Cannabidiolic-Acid Synthase from Cannabis Sativa L. J Biol Chem. 1996;271: 17411–17416. doi:10.1074/jbc.271.29.17411.
26. 26.Morimoto S, Komatsu K, Taura F, Shoyama Y. Purification and Characterization of Cannabichromenic Acid Synthase from Cannabis sativa. Phytochemistry. 1998; 49:1525–1529. doi:10.1016/s0031-9422(98)00278-7.
27. Sirikantaramas S, Morimoto S, Shoyama Y, Ishikawa Y, Wada Y, Shoyama Y. et al. The Gene Controlling Marijuana Psychoactivity: Molecular Cloning and Heterologous Expression of Delta1-tetrahydrocannabinolic Acid Synthase from Cannabis sativa L. J Biol Chem. 2004;279:39767–39774. doi:10.1074/jbc.M403693200.
28. Dittrich H, Kutchan TM. Molecular Cloning, Expression, and Induction of Berberine Bridge Enzyme, an Enzyme Essential to the Formation of Benzophenanthridine Alkaloids in the Response of Plants to Pathogenic Attack. Proc Natl Acad Sci U S A. 1991;88:9969–9973. doi:10.1073/pnas.88.22.9969.
29. Sirikantaramas S, Taura F, Tanaka Y, Ishikawa Y, Morimoto S, Shoyama Y. et al. Tetrahydrocannabinolic Acid Synthase, the Enzyme Controlling Marijuana Psychoactivity, Is Secreted into the Storage Cavity of the Glandular Trichomes. Plant Cell Physiol. 2005;46:1578–1582. doi:10.1093/pcp/pci166.
30. Taura F, Sirikantaramas S, Shoyama Y, Yoshikai K, Shoyama Y, Morimoto S. Cannabidiolic-acid Synthase, the Chemotype-Determining Enzyme in the Fiber-type Cannabis sativa. FEBS Lett. 2007;581:2929–2934. doi:10.1016/j.febslet.2007.05.043.
31. Luo X, Reiter MA, d'Espaux L, Wong J, Denby CM, Lechner A et al. Complete Biosynthesis of Cannabinoids and Their Unnatural Analogues in Yeast. Nature. 2019;567:123–126. doi:10.1038/s41586-019-0978-9
32. Shoyama Y, Takeuchi A, Taura F, Tamada T, Adachi M, Kuroki R et al. Crystallization of Delta1-tetrahydrocannabinolic Acid (THCA) Synthase from Cannabis Sativa. Acta Crystallogr Sect F Struct Biol Cryst Commun. 2005;61:799–801. doi:10.1107/S1744309105023365.
33. Shoyama Y, Tamada T, Kurihara K, Takeuchi A. Taura F, Arai S et al. Structure and Function of Δ1-tetrahydrocannabinolic Acid (THCA) Synthase, the Enzyme Controlling the Psychoactivity of Cannabis Sativa. J Mol Biol. 2012;423:96–105. doi:10.1016/j.jmb.2012.06.030.
34. Goto Y, Shima Y, Morimoto S, Shoyama Y, Murakami H, Kusai A, Nojima K. Determination of tetrahydrocannabinolic acid-carrier protein conjugate by matrix-assisted laster desorption/Ionization mass spectrometry and antibody formation, Org Mass Spectr. 1994;29:668-671.
35. Tanaka H, Goto Y, Shoyama Y. Monoclonal antibody based enzyme immunoassay for marihuana (cannabinoid)compounds. Immunoassay. 1996;17:321-342.
36. Watanabe K, Matuda M, Tateoka Y, Kimura T, Matsunaga T, Tanaka H, Shoyama Y, Yamamoto I. Cross-reactivity of varrious tetrahydrocannabinol metabolites with a monoclonal antibody against tetrahydrocannabinolic acid, J Health Sci. 2000;46:310-313.
37. Watanabe K, Matsunaga T, Kimura T, Funahashi T, Yamaori S, Shoyama Y, Yamamoto I. Stereospecific and regioselective hydrolysis of cannabinoid esters by ES46.5K, an esterase from mouse hepatic microsomes, and its differences from carboxylesterases of rabbit and porcine liver, Biol Pharm Bull. 2005+28:1743-1747,
38. Tanaka H, Shoyama Y. Monoclonal antibody against tetrahydrocannabinolic acid distinguishes Cannabis sativa samples from different plant species. Foren Sci Int. 1999;106:135-146.
39. Putalun W, Taura H, Qing W, Matsushita H, Tanaka, H, Shoyama Y. Anti-solasodine glycoside single-chain Fv antibody stimulates biosynthesis of solasodine glycoside in plants. Plant Cell Rep. 2003;22:344-349.
40. Putalun W, Tanaka H, Sakamoto S, Shoyama Y. Molecular breeding of solasodien glycoside for *Solanum khasianum* using anti-solamargine sin-

gle-chain Fv gene. Med Arom Plants. 2013;2: 3.doi: 10.4172/2167-0412.1000124.,
41. Sakamoto S, Taura F, Putalun W, Pongkitwitoon B, Tsuchihashi R, Morimoto S et al. Construction and Expression of Specificity-Improved Single-Chain Variable Fragments against the Bioactive Naphthoquinone, Plumbagin. Biol Pharm Bull. 2009;32:434-439.
42. Sakamoto S, Putalun W, Pongkitwitoon B, Juengwatanatrakul T, Shoyama Y,Tanaka H et al. Modulation of plumbagin production in Plumbago zeylanica using a single-chain variable fragment antibody against plumbagin. Plant Cell Rep. 2012; 31:103-110.
43. Shan S, Tanaka H, Shoyama Y. Enzyme-linked Immunosorbent Assay for Glycy.rrhizin Using Anti-glycyrrhizin Monoclonal Antibody and an Eastern Blotting Technique for Glucuronides of Glycyrrhetic Acid. Anal. Chem. 2001;73:5784–5790. doi:10.1021/ac0106997.
44. Elmes MW, Kaczocha M, Berger WT, Leung K, Ralph BP, Wang L et al. Fatty Acid-Binding Proteins (FABPs) Are Intracellular Carriers for Δ9-tetrahydrocannabinol (THC) and Cannabidiol (CBD). J Biol Chem. 2015;290:8711–8721.doi:10.1074/jbc.M114.618447.
45. Elmes MW, Prentis LE, McGoldrick LL, Giuliano CJ, Sweeney JM, Joseph OM et al. FABP1 Controls Hepatic Transport and Biotransformation of Δ9-THC. Sci Rep 2019;9:7588. doi:10.1038/s41598-019-44108-3.
46. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a Cannabinoid Receptor and Functional Expression of the Cloned cDNA. Nature. 1990;346:561–564. doi:10.1038/346561a0.
47. Munro S, Thomas KL, Abu-Shaar M. Molecular Characterization of a Peripheral Receptor for Cannabinoids. Nature. 1993;365:61–65. doi:10.1038/365061a0.
48. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G et al. Isolation and Structure of a Brain Constituent that Binds to the Cannabinoid Receptor. Science. 1992;258:1946–1949. doi:10.1126/science.1470919.
49. Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K et al. 2-Arachidonoylglycerol: a Possible Endogenous Cannabinoid Receptor Ligand in Brain. Biochem Biophys Res Commun. 1995;215:89–97. doi:10.1006/bbrc.1995.2437.
50. Lichtman AH, Dimen KR, Martin BR. Systemic or Intrahippocampal Cannabinoid Administration Impairs Spatial Memory in Rats. Psychopharmacol (Berl). 1995;119:282–290. doi:10.1007/BF02246292.
51. Romero J, García L, Cebeira M, Zadrozny D, Fernández-Ruiz JJ, Ramos JA. The Endogenous Cannabinoid Receptor Ligand, Anandamide, Inhibits the Motor Behavior: Role of Nigrostriatal Dopaminergic Neurons. Life Sci. 1995;56:2033–2040. doi:10.1016/0024-3205(95)00186-a.
52. Terranova JP, Michaud JC, Le Fur G, Soubrié P. Inhibition of Long-Term Potentiation in Rat Hippocampal Slices by Anandamide and WIN55212-2: Reversal by SR141716 A, a Selective Antagonist of CB1 Cannabinoid Receptors. Naunyn Schmiedebergs Arch Pharmacol. 1995;352:576–579. doi:10.1007/BF00169393.
53. Varga K, Lake K, Martin BR, Kunos G. Novel Antagonist Implicates the CB1 Cannabinoid Receptor in the Hypotensive Action of Anandamide. Eur J Pharmacol. 1995; 278:279–283. doi:10.1016/0014-2999(95) 00181-j
54. Weidenfeld J, Feldman S, Mechoulam R. Effect of the Brain Constituent Anandamide, a Cannabinoid Receptor Agonist, on the Hypothalamo-Pituitary-Adrenal axis in the Rat. Neuroendocrinol. 1994;59:110–112. doi:10.1159/000126646.
55. Wenger T, Tóth BE, Martin BR. Effects of Anandamide (Endogen Cannabinoid) on Anterior Pituitary Hormone Secretion in Adult Ovariectomized Rats. Life Sci. 1995; 56:2057–2063. doi:10.1016/0024-3205(95)00189-d.
56. Giannikou P, Yiannakakis N, Frangkakis G, Probonas K, Wenger T. Anandamide (Endogen Cannabinoid) Decreases Serum Prolactin in Pregnant Rat. Neuro Endocrinol Lett. 1995;17:281–287.
57. Ishac EJ, Jiang L, Lake KD, Varga K, Abood ME, Kunos G. Inhibition of Exocytotic Noradrenaline Release by Presynaptic Cannabinoid CB1 Receptors on Peripheral Sympathetic Nerves. Br J Pharmacol. 1996;118:2023–2028. doi:10.1111/j.1476-5381.1996.tb15639.x.
58. Wickens AP, Pertwee RG. Delta 9-Tetrahydrocannabinol and Anandamide Enhance the Ability of Muscimol to Induce Catalepsy in the Globus Pallidus of Rats. Eur J Pharmacol. 1993;250:205–208. doi:10.1016/0014-2999(93)90646-y.
59. Schwarz H, Blanco FJ, Lotz M. Anadamide, an Endogenous Cannabinoid Receptor Agonist Inhibits Lymphocyte Proliferation and Induces Apoptosis. J Neuroimmunol. 1994;55:107–115. doi:10.1016/0165-5728(94)90152-x
60. Schuel H, Goldstein E, Mechoulam R, Zimmerman AM, Zimmerman S. Anandamide (Arachidonylethanolamide), a Brain Cannabinoid Receptor Agonist, Reduces Sperm Fertilizing Capacity in Sea Urchins by Inhibiting the Acrosome

Reaction. Proc Natl Acad Sci U S A. 1994;91:7678–7682. doi:10.1073/pnas.91.16.7678.
61. Hua T, Vemuri K, Pu M, Qu L, Han GW, Wu Y et al. Crystal Structure of the Human Cannabinoid Receptor CB1. Cell. 2016;167:750–762. doi: 10.1016/j.cell.2016.10.004.
62. Li X, Hua T, Vemuri K, Ho JH, Wu Y, Wu L et al. Crystal Structure of the Human Cannabinoid Receptor CB2. Cell 2018;176:459–467 2019https://doi.org/10.1016/j.cell.2018.12.011.
63. Wang GS. Pediatric concerns due to expanded cannabis use: unintended consequences of legalization. J Med Toxicol. 2017;13:99-105. doi: 10.1007/s13181-016-0552-x
64. World drug report, 2021.
65. Jefsen OH, Erlangsen A, Nordentoft M, Hjorthoj C. Cannabis Use Disorder and Subsequent Risk of Psychotic and Nonpsychotic Unipolar Depression and Bipolar Disorder. JAMA Psychiatry. 2023;80:803-810. doi:10.1001/jamapsychiatry.2023.1256.Published online May 24, 2023.
66. Brunetti, P, Pichini S, Pacifici R, Busardò FP, Del RA. Herbal Preparations of Medical Cannabis: A Vademecum for Prescribing Doctors. Medicina (Kaunas). 2020;56:237. doi:10.3390/medicina56050237.
67. Anonymous. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) update. 2013.
68. National Institute of Public Health. 2015, MHLW Grants System [in Japanese]. NIDD00.do?resrchNum=201405037A. Available online: https://mhlw-grants.niph.go.jp/niph/searc.
69. Ferri CP, Prince M, Brayne C. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005;366:2112-2117.
70. Wimo A, Winblad B, Jönsson L. The worldwide societ costs of dementia: Estimates for 2009. Alzheimers Dement. 2010;6:98-103.
71. Orgogozo JM, Dartigues JF, Lafont S. Wine consumption and dementia in the elderly: a prospective community study in the Bordeaux area. Rev Neurol (Paris). 1997;153: 185-192.
72. Kalmijn S, Launer LJ, Ott A. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol. 1997;42:776-782.
73. Natarajan S, Shunmugiah KP, Kasi PD. Plants traditionally used in age-related brain disorders (dementia): an ethanopharmacological survey. Pharm Biol. 2013;51:492-523.
74. Ho YS, So KF, Chang RC. Drug discovery from Chinese medicine against neurodegeneration in Alzheimer's and vascular dementia. Chin Med. 2011;6:15. doi: 10.1186/1749-8546-6-15.
75. Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's Disease: Clinical Trials and Drug Development. Lancet Neurol. 2010;9:702–716. doi:10.1016/S1474-4422(10)70119-
76. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H. Cholinesterase Inhibitors for Patients with Alzheimer's Disease: Systematic Review of Randomised Clinical Trials. BMJ. 2005;331:321–327. doi:10.1136/bmj.331.7512.321.
77. Parsons CG, Danysz W, Quack G. Memantine Is a Clinically Well Tolerated N-Methyl-D-Aspartate (NMDA) Receptor Antagonist-Aa Review of Preclinical Data. Neuropharmacology. 1999;38:735–767. doi:10.1016/s0028-3908(99)00019-2.
78. Eubanks LM, Rogers CJ, Beuscher AE, Koob GF, Olson AJ, Dickerson TJ et al. A Molecular Link Between the Active Component of Marijuana and Alzheimer's Disease Pathology. Mol Pharm. 2006;3:773–777. doi:10.1021/mp060066m
79. Campillo NE, Páez JA. Cannabinoid System in Neurodegeneration: New Perspectives in Alzheimer's Disease. Mini Rev Med. Chem. 2009;9:539–559. doi:10.2174/138955709788167628
80. Iuvone T, Esposito G, De Filippis D, Scuderi C, Steardo L. Cannabidiol: a Promising Drug for Neurodegenerative Disorders? CNS Neurosci Ther. 2009;15:65–75. doi:10.1111/j.1755-5949.2008.00065.x.
81. Esposito G, De Filippis D, Carnuccio R, Izzo AA, Iuvone T. The Marijuana Component Cannabidiol Inhibits Beta-Amyloid-Induced Tau Protein Hyperphosphorylation through Wnt/beta-Catenin Pathway Rescue in PC12 Cells. J Mol Med (Berl). 2006;84:253–258. doi:10.1007/s00109-005-0025-1.
82. Esposito G, De Filippis D, Maiuri MC, De Stefano D, Carnuccio R, Iuvone T. Cannabidiol Inhibits Inducible Nitric Oxide Synthase Protein Expression and Nitric Oxide Production in Beta-Amyloid Stimulated PC12 Neurons through P38 MAP Kinase and NF-kappaB Involvement. Neurosci Lett. 2006;399:91–95. doi:10.1016/j.neulet.2006.01.047.
83. Esposito G, Scuderi C; Savani C, Steardo L, De Filippis D, Cottone P et al. Cannabidiol In Vivo Blunts Beta-Amyloid Induced Neuroinflammationby Suppressing IL-1beta and iNOS Expression. Br J Pharmacol. 2007;151:1272–1279. doi:10.1038/sj.bjp.0707337.
84. Georgia W, Karl T. In vivo Evidence for Therapeutic Properties of Cannabidiol (CBD) for Alzheimer's Disease. Front Pharmacol. 2017;8:20. doi:10.3389/fphar.2017.00020.

85. Watt G, Karl T. In Vivo Evidence for Therapeutic Properties of Cannabidiol (CBD) for Alzheimer's Disease. Front Pharmacol. 2017;8:20.doi:10. 3389/fphar.2017.00020
86. Kim SH, Yang JW, Kim KH, Kim JU, Yook TH. A Review on Studies of Marijuana for Alzheimer's Disease Focusing on CBD, THC. J Pharmacopuncture. 2019;22: 225–230. doi:10.3831/KPI.2019.22.030.
87. Hillen JB, Soulsby N, Alderman C, Caughey GE. Safety and Effectiveness of Cannabinoids for the Treatment of Neuropsychiatric Symptoms in Dementia: a Systematic Review. Ther Adv Drug Saf. 2019;15:10, 2042098619846993. doi:10.1177/2042098619846993.
88. Broers B, Patà Z; Mina A; Wampfler J, de Saussure C, Pautex S. Prescription of a THC/CBD-Based Medication to Patients with Dementia: A Pilot Study in Geneva. Med Cannabis Cannabinoids. 2019;2:56–59. doi:10.1159/000498924.
89. Charernboon T, Lerthattasilp T, Supasitthumrong T. Effectiveness of Cannabinoids for Treatment of Dementia: A Systematic Review of Randomized Controlled Trials. Clin Gerontol. 2021;44:16–24. doi:10.1080/07317115.2020.1742832