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Cannabis & Alzheimer's: From adjunctive use in symptoms to neuromodulatory therapy

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ABSTRACT
This paper addresses the adjuvant use and neuromodulatory therapy of cannabis in Alzheimer's. It preliminarily considers the effects and risks of the medicinal use of cannabis, the anticonvulsant effect in epilepsy and the prospects for use in Alzheimer's. He argues for neuromodulatory use in Alzheimer's, in addition to the more restricted use to placate symptoms. And it concludes by pointing to the half-open perspectives and more recent investigations about the neuroprotective character of cannabis.

Keywords: Alzheimer's, Medical cannabis, Neuromodulation, Neuroprotection, VI Medical Cannabis Course of UNIFESP.

1 INTRODUCTION

The present text, Final Work of the VI Course on Medical Cannabis (August to December 2021), was elaborated based on class records and systematization of readings of bibliographic survey carried out by this author on the theme *Cannabis + Alzheimer's*. The present study was preceded by another (SILVA, 2021), entitled *Marijuana & Mental Health***:** *therapeutic effects and risks of medicinal and hedonistic uses* (Final Work of the V Course on Medical Cannabis). We seek to deepen the general knowledge so far developed of the use of cannabis in the field of mental health, we resume some premises and syntheses reached, and then dive into the challenge of understanding the paths already trodden and the still to tread of the medical use of cannabis in Alzheimer's.

1.1 ON THE EFFECTS AND RISKS OF THE MEDICINAL USE OF CANNABINOIDS FOR MENTAL HEALTH

Initially, we highlight two aspects related to the therapeutic effects and risks of the medicinal use of cannabinoids in mental health: the possibilities and precautions of use as anxiolytics; and the challenges and risks of use in depression (SILVA, 2021).

The use of medical cannabis in psychiatric pathologies is controversial. Caution in the use of cannabis is redoubled in importance in cases of psychosis, anxiety and depression. But to limit ourselves to the first two, we emphasize that the dosage is of paramount relevance. The anxiolytic

property (anxiety reducer) exists, as long as it is well managed and properly managed. Treatments should be zealous in terms of dosages and composition.

Crippa, Zuardi and Hallack (2010) address the therapeutic use of cannabinoids in psychiatry. If the anticonvulsant effect in epilepsy is well accepted and there is positive clinical responsiveness, in anxiety and depression some caveats are common. The dosage is a relevant factor for therapeutic or negative effect in these cases. The dosage is always something relevant, a fundamental element to be considered in the management of the prescription. We only highlight that it is highlighted when it comes to the use in anxiety and depressive disorders. And the dosage is always relative to a certain type of drug. It is necessary in each case to select the best drug indication, taking into account its composition and the clinical picture in question. As we pointed out in a previous study (SILVA, 2021), selection and parsimony are fundamental in the psychiatric clinic:

> If in anxiety one dosage can be beneficial and another can intensify it, in depression euphoria can also be induced in certain doses. For Crippa, Zuardi and Hallak (2010, p.62), the "paradoxical findings" of delta 9-THC "could be explained by the observation that its effects on anxiety and mood seem to be dose-dependent", with "low to moderate doses" demonstrating "anxiolytic and euphoric properties", and "higher doses" being "anxiogenic" (SILVA, 2021, p.).

Murillo-Rodriguez, Pandi-Perumal, and Monti (2021) contribute to a number of current discussions on psychiatric use in the dossier "Cannabinoids and neuro psychiatric disorders." In the present work we will refer to one of the articles, related to recent advances on the neuroprotective potential of cannabinoids in Alzheimer's (PÉREZ-OLIVES, RIVAS-SANTISTEBAN; LILLO; NAVARRO; FRANCO, 2021). The topic of cannabinoids in neuropsychiatry is also explored in James' (2021a) clinical guide.

1.2 DIVERSITY OF CANNABINOID PROPERTIES AND COMPLEXITY OF THERAPEUTICS

The various cannabinoid properties act on concrete beings, contexts, and it is recommended that the Therapeutic-medicinal use of cannabinoids in mental health is always selective and parsimonious. The complexity of the therapy demands it.

The medicinal properties vary according to plant, form of cultivation and extraction. Malcher-Lopes and Ribeiro (2007) detail the pharmacological properties of different cannabinoids. We consider here only the two most covered: THC and CBD. THC is Antipyretic, Antiviral, Appetite Stimulator, Hypotensive and Psicotropic. And both THC and CBD are: Painkiller; Anxiolytic; Anticonvulsant; Antiemetic, Anti-inflammatory, Antioxidant Antitumorigen, Immunodepressant, Neuroprotective and Sedative. And they are specifics of CBD: Antipsychotic; Antispasmodic.

In the case of Alzheimer's, as well as other pathologies, the entourage effect of the interaction of the two cannabinoids tends to be considered as having the best therapeutic effect. We will highlight

in this work the neuroprotective aspect and the cannabis potential to lead the mastery of the organism, particularly, the neuromodulation harmonized to neurogenesis and homeostasis.

1.3 FROM THE ANTICONVULSANT EFFECT IN EPILEPSY TO THE PROSPECTS OF USE IN ALZHEIMER'S

In our previous study we already pointed out the anticonvulsant effect as "better known and perhaps better proven in medicinal studies of cannabinoids" (SILVA, 2021, p.12). The action on seizures cannot be understood as merely on the symptom. When a seizure is resolved, or its high frequency, especially in cases refractory to conventional medications, not only one symptom is reached, but the progressive etiology of the disease itself, concomitantly. An effect that ignites great hope. A better future for various health problems. In which more comprehensive actions of cannabis, in addition to the more immediate, circumscribed and/or already verified therapeutic effects, can be unveiled.

The action of cannabis on Alzheimer's raises many expectations. In the reduction of discomforts and symptoms, promotion of well-being and quality of life, is one of them. But hypotheses are also launched about acting on memory, and therapeutic effects, let's say, more daring and comprehensive.

The Disease of Alzheimer's (AD) is the most common neurodegenerative disease of dementias related to senility (MANZARO, 2017). In this work we consider that cannabis medicine can improve quality of life. Promote restorative sleep. Improvement of appetite and pain. But our fundamental question is: how would its modulating action of the organism and its effects on metabolism take place? Can neuroprotective effects slow down mnemic or memory losses? These are questions necessary for the deepening of investigations that bring relatively promising hypotheses for the prevention and treatment of the disease and that do not limit the use of cannabis to the placation of symptoms.

In class 12 of the VI Course of 10/26/2021, Professor Sidarta Ribeiro made mention of the "cannabinoid revolution". It addressed the neurobiological mechanisms of THC, tuned to the CB1 receptor, and CBN, an oxidized, non-enzyme-based product of THC, tuned to the CB2 receptor. He pointed out the use of the cannabinoid in diseases related to excess neural synchronization, such as epilepsy. Such an excess generates the seizure. In this disease the cannabinoid can desynchronize without impairing neuronal activity, unlike conventional medicine, which lowers activity but generates drowsiness. It considered several positive aspects of the use of cannabinoids, in the immune response, appetite, sleep, anxiety, emotion, pain, locomotion, cardiovascular and respiratory functions, intraocular pressure, inflammation, reproduction, sex, as well as pointed to *remodeling of neural circuits*, formation of new memories, extinction of traumatic memories, *neuroprotection, neurogenesis,* perception, motor coordination, flow of thoughts, creativity, emotion, etc. (emphasis added). It considered diseases with decreased neurogenesis (such as depression and Alzheimer's) and the

mitigating effects with the use of medical cannabis. In addition, decreased oxidative stress, neuroinflammation and the formation of amyloid plaques and neurofibrillary tangles typical of Alzheimer's disease (AD). Already *in live* "The use of medical cannabis in dementia processes" (11/11/2021), Professor Sidarta reiterated the potential for cannabis cell regeneration and new synapses in the face of decreased connectivity. He clarified the accumulation of malformed proteins and neural circuits in AD. He referred to the genesis of connections, that is, he argued that phytocababinoids promote neurogenesis and plasticity. In relation to the problems of cognition, there is the triad: delay; mitigate; rescue. He mentioned that there is a mismatch between the clinic (use for years in Canada, for example), and the scientific evidence. Mismatch between the clinician and the published. And under the metaphor *of Ippon* (a term that means in martial arts the last or perfect blow), he admitted that with regard to AD - unlike what happened with epilepsy, based on the findings of the Israeli PhD Raphael Mechoulan - a "Ippon article" has not yet been published, which could be considered a full proof of therapeutic efficacy.

Nevertheless, more recent studies by the renowned Mechoulan on cannabinoids in health and disease (KOGAN; MECHOULAN, 2007), as well as others, indicated by Professor Siddhartha in that class, are encouraging. We are referring to the contributions of *in vivo evidence* study for therapeutic properties of cannabidiol (CBD) for Alzheimer's disease (WATT; KARL, 2017). And two others about the decrease in neurogenesis. One of them addresses the CB1 receptor of cannabinoids in rats (JIN; XIE; KIM; PARMENTIER-BATTEUR; SUN; MAO; CHILDS; GREENBERG, 2004). Jim et.al (2004) indicate that pharmacological studies suggest the role of the cannabinoid receptor, CB1, in the regulation of adult brain neurogenesis. And another, also experimental with rats, which indicates promotion of neurogenesis of the embryonic and adult hippocampus, in order to produce anxiolytic and antidepressant effects (JIANG; ZHANG; XIAO; CLEEMPUT; JI; BAI; ZHANG, 2005). Jiang et. al. (2005) investigated the synthetic cannabinoid HU210.

In the study by Watt and Karl (2017), like several others, the accumulation of beta-amyloid protein plaques and hyperphosphorylation of the tau protein in AD is indicated. Beta-amyloid comes from a larger protein present in the fatty membrane of nerve cells. The plaques block signaling between cells at synapses or even activate immune cells that cause inflammation. And the hyperphosphorylation of the tau protein blocks the intracellular traffic of proteins (neurotrophic; functional) so as to generate loss or decrease in axonal or dendritic transport in neurons. That is, there is neuroinflammation and oxidative stress. The authors point out that conventional remedies do not stop or reverse the disease. And that cannabidiol (CBD) is proven (*in vitro*) to be a phytocannabinoid with neuroprotective, anti-inflammatory, and antioxidant properties. A potential multifunctional treatment option for Alzheimer's is thus being investigated. In this case, the study investigated the *in vivo* effects of CBD on animals. It points to CBD's ability to reduce reactive gliosis and neuroinflammatory response. And not only. It

can also produce neurogenesis. Also, reversal and prevention of the development of cognitive deficits in rats with AD. They point out that such potentialities are more promising when the CBD-THC combination. But they do indicate that research is needed to assess the long-term potential of what they describe about CBD.

2 CANNABIS IN ALZHEIMER'S DISEASE (AD): IN ADDITION TO ADJUNCTIVE USE, NEUROMODULATORY PROTAGONISM

Alzheimer's is progressive and insidious. It involves progressive synaptic and neuronal loss. The beneficial effects of the use of cannabinoid medication, in addition to well-being in aspects such as food, sleep, pain, interaction and behavior, may occur due to its action on the deficiency of the endocannabinoid system, which influences metabolism, homeostasis and the nervous and immune systems.

2.1 USE TO PLACATE SYMPTOMS

We can consider a type of use more aimed at placating symptoms. Liu, Chau, Ruthirakuhan, Lanctôt & Herrrmann (2015) point to case studies in which THC reduces symptoms of agitation and aggressiveness characteristic of AD. Ruthirakuhan, Lanctôt, Vieira & Herrrmann (2019) in a meta-analysis evaluated effects of natural and synthetic cannabinoids. They point to the reduction of the symptom of agitation with the use of synthetic THC, but with an adverse effect of sedation.

Nocetti and Ribeiro (2020), in a broader perspective, also address the use of cannabis in AD. They consider it as an "adjuvant" drug (in the title of the article) and an "adjuvant" medication (in the body of the text) in the treatment of AD. We will return to this point, for a reflection on this subtle difference between these adjectives in the title and body of the text, and the possible reason for their use, since neuromodulation is considered, competently and explicitly, by the authors.

In general, the multiple references to disease harm reduction and symptom mitigation can perhaps be explained by the fact that many articles are reviewed, there are insufficient human studies, and there is no complete proof of the comprehensive therapeutic potential of cannabis in Alzheimer's. There is still a complexity of genetic variables, individual / singular, and many processes still under investigation regarding the endocannabinoid system (MOREIRA, 2008). We shall also return to these hypotheses.

But is the use of cannabinoids limited to placating major or secondary symptoms of the disease, to being an adjunct to other treatments, or merely a specific form of palliative care? Or yet, to limit oneself to providing some situations of well-being? Let's see what some studies tell us.

Carvalho and Mello (2020) point out that the limited efficacy of drugs used in AD in combating the degeneration of neurons, senile plaques and neurofibrillary tangles motivate research on the

identification of the therapeutic potential of cannabidiol. They seek to demonstrate cannabidiol as a therapeutic "alternative" (CARAVALHO; MELLO, 2021, p.1). The term "alternative" also appears in the title of the article by Lemos, Barcelar and Fialho (2017), who criticize the adverse effects of conventional drugs. If they indicate that it is an "alternative", apparently without positioning themselves in favor of cannabis being a protagonist of the therapy, they indicate not only the action of delaying the progressive effects of Alzheimer's, or of applicability on "neuropathic pain", "nausea and vomiting" (in these cases in patients using chemotherapy), but also more substantive reductions than the mere attenuation of symptoms, such as that of excitotoxicity" (cause of Alzheimer's neural injury), decreased neural damage, protection of cells from nitrosative stress, and even CBD's ability to "create new neurons," "retrieval of memories," "improve cognition," protect the nervous system, and "antioxidant" action (LEMOS; BARCELAR; FIALHO, 2017, p.3).

Oliveira, Moraes and Fattori (2021, p.1-2) refer to the articles by Nocetti and Ribeiro (2020) and Lemos, Barcelar and Fialho (2017), and follow them in a similar line: they refer to the "reduction of the adverse effects of conventional drugs"; also in relation to the use of medicines and products, they consider it "alternative or complementary", and also mention "delay" of the "progressive effects of AD" and "neurodegeneration", and also, "creation of new neurons." They refer to the amyloid hypothesis of the "complex pathological cascade" that "culminates in disseminated synaptic and neural dysfunction"; hypothesis that has as "key process an imbalance between the production and clearance of peptide A-Beta", "dysregulation in synaptic structure and function", "oxidative stress" and "alteration of homeostasis" (OLIVEIRA, MORAES, FATTORI, 2021, p.4). And they affirm: "it becomes necessary to search for *supporting resources*" (OLIVEIRA, MORAES, FATTORI, 2021, p.6, our emphasis). The final highlight of the article is also highlighted, in which they refer to "endocannabinoid signaling" and the *"modulation* of various brain functions", as well as the "neuroprotective effects of cannabinoids" (OLIVEIRA, MORAES, FATTORI, 2021, p.6-7, our emphasis).

Some terms of specialized titles in the discussion of the topic *Cannabis & Alzheimer's* of relevance can be briefly highlighted: Cao et. al. (2014) refer to the "potential" of the therapeutic effects of THC in AD. Esposito et. al. (2006a) refer to the inhibition factor of cannabidiol in Beta-Amyloid and Tau Protein. In another article, Esposito et. al. (2006b) indicate again the same factor of inhibition of Beta-Amyloid, this time analyzing physiological and biochemical mechanisms involving the CB1 receptor. And detailed discussions about cannabinoids and reduction of structural and not merely symptomatic pathological aspects of AD, which require deepening that is beyond the scope of this work, are presented by Aso et. al. (2003; 2012; 2015) and Tolón et. (2009).

Camargo Son et. al. (2019) address the use of cannabidiol and delta 9-TH in Alzheimer's and Parkinson's. Indicate reduction of motor and cognitive symptoms. But in addition, also the

neuroprotective action. The results are explained by the antioxidant effects, CB1 receptor antagonists and PPAR-gamma receptor activation. They consider adverse effects such as drowsiness and dry mouth. Further research on adverse therapeutic effects is recommended, with higher doses and periods of exposure, so that the substances can be considered more effective and safe therapeutic options.

Marsicano et.al (2002) focus on the endogenous cannabinoid system in the extinction of aversive memory. It is known that AD patients have significant recent memory impairments, not reversible and only potentially attenuated in their progressive rate of degradation (by conventional and cannabis drugs, which in this aspect act in a non-antagonistic way). And that interestingly some memories and negative emotional conditioning tend to persist. It is about such memories and conditionings that Marsicano et. al. refer to. The same is pointed out by Malcher-Lopes and Ribeiro (2007), whose quote below refers us again to the important memory of management, dosage, under the principles of selectivity and parsimony:

> The amygdala acts on the emotional response, the formation of aversive (negative) memories, and the perception of fear and stress. The presence of CB1 in the amygdala is responsible for the erasure of traumatic memories and this helps to explore the relaxing effects and decreased anxiety caused by marijuana. In some people, depending on the dose and emotional state, the action of marijuana on the amygdala can generate opposite effects, with the transient emergence of paranoid thoughts (MALCHER-LOPES; RIBEIRO, 2007, p.55).

So, still that there are many allusions to effects of placating symptoms, in some cases are reductions of symptoms related to something much more comprehensive and that, in this sense, suggest a therapeutic cannabis action also much more comprehensive.

It is worth considering one more example: the use for sleep induction (symptom of insomnia, also related to anxiety) or combating irregular or turbulent sleep. James (2021b) addresses the use of cannabis in sleep. What is clear, is that this use is much broader than the more immediate, to placate symptoms. It is not only achieved insomnia or sleep turbulent. The action takes place on the circadian cycle. That is, it acts positively in the orientation of the organism between day and night, in the hormonal production in wakefulness and sleep. As seen in the Class of the day 27/11 with professors Nivaldo Vanni and Guilherme Martins, cannabis can act in order to compensate for the deficiency of the hormone melatonin, which regulates the cycle. Cannabis extract nabiximols is pointed out by James (2021b) as having a beneficial effect in coping with sleep disorders. It is also pointed out that endocannabinoids 2-AG and anandamide (AEA) modulate the activity of sleep-associated neurotransmitters, including GABA and glutamate. Still, the CB1 receptor develops its activity during REM sleep.

Before we synthesize aspects of neuromodulatory use in the following item, it is worth making some comments and systematizations about the important article, already briefly alluded to, by Nocetti

and Ribeiro (2020), entitled "Use of cannabinoids as an adjuvant in the treatment of Alzheimer's Disease".

Nocetti and Ribeiro (2020, p.1) characterize the symptoms in Alzheimer's in the Abstract of the article: "neuroanatomical and biochemical changes in the cerebral cortex". And when they comment that "drug treatment" (conventional) "has little efficacy in more advanced stages of the disease", they refer to the search for "adjuvant resources" (medication canabbica) (NOCETTI; RIBEIRO, 2021, p.104). It is curious the use of the term "adjuvant" in the title and the "coadjuvant" in the Abstract, and this is repeated on page 2 in the following statement: "It is evident the need for resources *Supporting* capable of reducing the adverse effects of conventional pharmacological therapies, thus benefiting AD carriers" (NOCETTI; RIBEIRO, 2021, p.105, emphasis added).

If we turn to the dictionary, we find a distinction between "adjuvant" and "adjunct". Adjuvant is what provides help, help. Being that, in pharmacology, it is said of the drug that, administered with some other, or added to the formula of this, reinforces its action. Well. Already supporting is said to what helps, assists or contributes to a common goal. But it also has a second meaning, not of the pharmacological area, but of cinema and radio: it is said of actor or actress who plays a secondary role.

When we take the article as a whole, or even confining ourselves to the Abstract, when referring to the endocannabinoid system, there is something that is relatively out of touch, whether we stick with the term adjuvant or stay with the adjuvant, namely: "The endocannabinoid system has gained scientific *prominence* as a *therapeutic target* in the treatment of Alzheimer's disease" (NOCETTI; RIBEIRO, 2021, p.104, emphasis added). We assert that such prominence is given by cannabis medicine, since only cannabis acts directly on this "target". And if that's the "target," cannabis would be, let's say, under metaphor, the lead actor, not the supporting actor. This does not invalidate the proposition of conciliatory possibilities with conventional treatment; and we can understand the most common meanings and synonyms of the terms adjuvant or coadjuvante (help; help). We also know, as in the case of inflammation-pain, that we can combine corticosteroids and cannabis, reducing side effects of the former by lowering its dose and including cannabis, aiding the anti-inflammatory-analgesic action, and also adding the beneficial effects of cannabinoids (sleep; food; anxiety). In this case, cannabis "helps" the corticosteroid. Using a metaphor again, we can consider that the husband who says he "helps" to wash dishes, certainly has not overcome the macho attitude. And so we ask: how long would we be limited to the auxiliary use of the cannabinoid? We don't want to forge an all-or-nothing stance; And we also know that there are cases where the corticosteroid is definitely replaced by cannabis, and others where the two are reconciled. How will the use of cannabinoids evolve in the case of AD? Will it ever be possible, with the development of research and evidence that is more rigorous and consistent and more consistent, to have cannabis medicine as its protagonist therapeutic

agent? This is what we want to problematize, without at any time failing to recognize the relevance and richness of the contents worked on in the article.

Therefore, we consider that the term "adjuvant" may bring some misunderstanding, and that the "adjuvant" is the most appropriate. It should also be in the body of the text and not just in the title. For it would be more consistent with the path that unfolds with the "cannabis revolution", to use the term used by Professor Siddhartha. Path that we identify in the following passage from Nocetti and Ribeiro (2021, p.104): "The modulation of the endocannabinoid system presented high therapeutic potential", "because it was able *to slow* the progression of Alzheimer's disease, *reducing* neuroinflammation, the accumulation of beta-amyloid protein and the hyperphosphorylation of tau protein". To which they add: "The *neuroprotective* effects of cannabinoids favor *neurogenesis,* attenuate neuropsychiatric symptoms and improve memory, behavior and learning" (NOCETTI; RIBEIRO, 2021, p.104, emphasis added). On the one hand, reduction, decrease, attenuating aspects of suffering and pathology, and on the other, modulation, neurogenesis, and even as we have seen, mentioned by other authors, "creation of synapses", that is, factors that go beyond the palliative aspects, and that clearly indicate a health-promoting action - which, in the face of a degenerative pathology, will always have a mitigating effect - there would not be, in this distinction, a negation of this aspect.

We consider that the non-existence of the scientific article "Ippon", in the humorous Professor Sidarta's expression - undoubtedly the result of prohibitions and prejudices that hinder the parsimonious and selective use of cannabis in health, and particularly in mental health (SILVA, 2021) - has weight in a certain oscillation between the emphasis of cannabis as a merely additional element to conventional treatment, collaborative with conventional medicines and / or symptom placation (both of the symptoms of the disease and of the side effects of conventional medicines themselves), and the emphasis on its asset *potential* comprehensive therapeutics. Yes, the *potential*, there is still a need to point out with some caution what is glimpsed with cannabis in AD (and that as we have pointed out, differs from the *"status"* achieved by its use in epilepsy). The still circumscribed scope of clinical scope and its mismatch in comparison with objective scientific scopes, in randomized double-blind studies, the need for dialogue with skeptical views with cannabis medicine, may indeed require a prudent stance.

For our part, it is only necessary to explain that we use the term supporting in this work with a connotation different from that of Nocetti and Ribeiro (2021), and that, although we problematize it, we consider it understandable, if not necessary. Here we use the connotation closest to secondary, to the sense of the artistic area. For it is our intention to try to indicate what is unfolding, even if at the risk of projecting something that takes a long time, or that does not even occur in the way we can conjecture today. Nevertheless, whatever the result that there may be of cannabis and the endonacabinoid system as its therapeutic target par excellence, which only the future will tell us, we

consider it necessary to assert the statement that one can no longer go back on the hypotheses and discussions about neuroprotective, neurogenic and neuromodulatory actions. And if a certain caution is needed, and a step or two steps back, boldness is also necessary, for this is the "cat's leap" of many of the social transformations.

2.2 NEUROMODULATORY USE

The use of cannabis as a neuromodulator in AD is distinguished from the use of symptom easing or adjuvant use by its greater scope in terms of the organism, related pathologies and etiological complexity.

Malcher-Lopes and Ribeiro (2007) present considerations about the endocannabinoid system and marijuana. The mental and neurobiological effects, the "cascades of biochemical reactions" (p.44), the effects on sleep and dream, "sexual appetite" (p.72), as well as the "immune effects" (p.74), "anticonvulsants" (p.82) and neuroprotective (p.83) are explained. Regarding the administration of THC in animal models of Alzheimer's, they indicate that there is inhibition of neurodegenerative and its symptoms, in addition to having beneficial effects on the behavioral disorders and lack of appetite present in this disease (p.84).

Malcher-Lopes and Ribeiro (2007, p.135), who refer to the neuroprotective aspects and anti-inflammatory effects, among others, understood as constitutive of numerous possibilities and therapeutic potentialities and well-being of the use of cannabinoids, mention that there is a "flexibilization" of "neuronal groups", in a passage in which they indicate "typical mental effects" of marijuana:

> The antiepileptic action, the short-term memory deficits, the perceptual alteration that converts even the most common stimuli into novelty, the loss of attention, the altered sensation of the passage of time, laziness, the increase in creativity and contemplative attitude, all these mental effects typically caused by marijuana may derive directly from the flexibilization of coordination between neuronal groups (MALCHER-LOPES; RIBEIRO, 2007, p.135).

Thus, we align ourselves with Malcher-Lopes and Ribeiro (2007, p.63) who, when they argue that the "endocannabinoid system" is one of the "main conductors in the orchestration of vital functions", or even when they consider that marijuana produces "complex" effects and indicative of the "fantastic potential of the endocannabinoid system as a target for new remedies"; being challenging the task of directing its effects and using them selectively (MALCHER-LOPES; RIBEIRO, 2007, p.64).

CBD reduces the formation of beta-amyloid protein and blocks the pathway that drives the accumulation of the TAU protein. And THC reduces amyloid beta protein. Synthetic cannabinoids also act positively, through activation of CB2 receptors that help remove beta-amyloid protein from human brain cells; and through CB1 receptors, which block the formation of neurofibrillary TAU protein

tangles. In rats, synthetic cannabinoids blocked the release of pro-inflammatory substances and TAU protein targeting CB2 receptors. In mice with AD (Alzheimer's disease), the combination of CBD and THC results in memory preservation and improved learning capacity. The therapeutic effects of THC and CBD may be indicated, even with studies still advancing. THC reduces agitation and aggressiveness, competitively inhibits acetylcholinesterase (such as conventional drugs used in the early/mildly moderate phases), decreases glutamate release with decreased neurotoxicity in the neurodegenerative cascade (also conventional drugs used in the moderate/severe phases), improves depression and fatigue, increases hunger and improves taste, decreases pain and disconnects pain and suffering. And CBD: improves memory, anxiety and sleep, decreases neuroinflammation (has antioxidant and neuroprotective effect) and has antipsychotic (reduces agitation) and anticonvulsant effects. In summary, all the benefits in terms not only of symptom allaying, but also of action on the health of the organism can be related to the modulation of the activities of neurotransmitters (Lecture 15 - Course VI - 11/23/2021 - Prof. Denise Lufti Pedra).

And Nocetti and Ribeiro (2021, p.105) also emphasize such a neuromodulatory role. When considering the pathophysiology of AD, we highlight, among other aspects, the "neuroanatomical alterations of the cortex", the "oxidative stress", the "neuroinflammation", the "calcium dysregulation", the "mitochondrial dysfunction", the "alterations of cholinergic transmission in the hippocampus" and "alterations of the homeostasis of the cytosolic calcium and the Wnt pathway". And they emphasize the neuromodulatory action of this neurotoxicity. When considering the endocannabinoid system (ECS) indicate that "ECS activation leads to neuroprotection", "reducing neural damage, inflammation and oxidative stress" (NOCETTI; RIBEIRO, 2021, p.105).

> In general, activation of cannabinoid receptors protects the hippocampus and granular neurons against excitotoxicity and glucose deprivation. The beneficial effects of cannabinoid receptor activation can be used effectively in the treatment of AD. Based on this information, the objective of this study is to evidence, from the review of preclinical (in *vivo and in* vitro) and clinical studies, the therapeutic potential of SEC in the treatment of AD (NOCETTI; RIBEIRO, 2021, p.105).

In the development and discussion of the article deepen the explanations about the modulation of the SEC. They address the regulation of synaptic transmission. CB1 receptors (located at neuronal endings) act as "modulators of excitatory or inhibitory neurotransmission", whereas CB2 receptors (located in immune system cells) "modulate cell migration and cytokine release" (NOCETTI; RIBEIRO, 2021, p.106). They also clarify that "endocannabinoids" are "lipid compounds" derived from the "degradation of the phospholipid membrane", and that they "act as neurotransmitters" (NOCETTI; RIBEIRO, 2021, p.106). And they add: "The increase in tonic of SEC" plays a "neuroprotective role" in "neurodegenerative processes," so that "cannabinoid activation" promotes "brain homeostasis and neuronal survival" (NOCETTI; RIBEIRO, 2021, p.106). Therefore, the

argument of an action far beyond the supporting one is evident, especially if we consider the critical connotation that we proposed to the use of this adjective. This is consolidated in the conclusion, in which they assert that the "modulation of the SEC, through the daily use of small doses of cannabinoids" implies an increase in the "neurogenic potential", in addition to "improvement of memory and behavior" (NOCETTI; RIBEIRO, 2021, p.108).

3 NEW PATHS TO ALZHEIMER'S: IS NEUROPROTECTIVE CANNABIS HERE TO STAY?

If assertiveness about the comprehensive therapeutic potential of cannabis in AD and health still has limitations, we can look at the question in another way, and instead of simply questioning it, ask: is it possible to go back to what has already been raised of hypotheses, debatES and clinical experiences that refer to neuroprotective action? Our answer to the question is no.

James (2021a) in his chapter on cannabinoids and neuropsychiatry describes the functioning of the endocannabinoid system and mentions: neuroprotection, and its action on oxidative stress, inflammation and mitochondrial dysfunction, among other aspects; neurogenesis, the formation of new neurons, with benefits to brain plasticity and limbic system functions (emotions; memory; behavior); and anxiolytic action.

Pérez-Olives et. al. (2021) address advances in the neuroprotection potential of cannabinoids in Alzheimer's (and also in Parkinson's and Huntington's disease). They indicate the delay of neuronal death and the existence of microglia activation as a protective phenotype. The cannabis extract SativexTM is referred to as approved for human therapy, and that such condition has favored studies on natural and synthetic cannabinoids. And, consequently, the expansion to cope with neurodegeneration and removal of intraneural amyloid in the case of AD.

The neuromodulatory action is related to the neuroprotective and vice versa, and both to the anti-neurodegenerative potential. The SEC study is here to stay. You can't turn your back on him. Although there are still many investigations to better understand the SEC and its relations with the nervous system, immune, metabolism and homeostasis. As already pointed out, lipid and mitochondrial dysregulation deserve special attention in the case of AD and its neurodegenerative processes.

For Moreira (2008, p.47), the "endogenous cannabinoid system" is one "of the most recent neurotransmitter systems studied, with many aspects to be elucidated". Among them the "enzymatic processes" of "synthesis and inactivation" of "cannabinoids" (MOREIRA, 2008, p.47). With this, it will be possible to develop compounds that act in these stages. The question of the role of CB1 and CB2 is also mentioned, as well as findings that unfold in relation to CB3. The "endocannabinoids" interact with "other systems", "such as opioids, dopamine, gamma-aminobutyric acid and glutamate" (MOREIRA, 2008, p.47). They are "modulators of these neurotransmitters", and some functional

aspects are still obscure (MOREIRA, 2008, p.47). Understanding the mechanisms of action of cannabinoids and especially the physiology of the cannabinoid system can shed light on pathological conditions in which this system is unbalanced, such as Alzheimer's. And, consequently, expand "new pharmacological approaches" that can be "transformed into therapeutic benefits" (MOREIRA, 2008, p.48).

Nocetti and Ribeiro (2021), as previously mentioned, indicate the SEC as a therapeutic target for Alzheimer's. They indicate that the "lipodromic analysis" points to low levels of anandamide (AEA). This reduction is inversely proportional to beta-amyloid protein levels.

> This relationship suggests that cognitive function is affected by AEA deficiency, which is regulated by peptide levels of beta-amyloid. In addition, changes in enzyme activity related to the synthesis/degradation of endocannabinoids have also been observed in the brains of AD patients. Previously, an increase in FAAH enzyme activity was observed in glial cells associated with neuritic plaque, as well as in peripheral blood mononucleated cells. This event may contribute to the degradation of AEA in senile plaques (NOCETTI; RIBEIRO, p.7).

Studies indicate the "neuroprotective, antioxidant, and antiapoptotic effect of CBD" in "cell culture" exposed to "beta-amyloid neurotoxicity" (NOCETTI; RIBEIRO, p.7). There is "reduced production of ROS" and "lipid peroxidation" (NOCETTI; RIBEIRO, p.7).

> Much of CBD's effects involve intracellular mechanisms closely linked to neuronal physiology. In hippocampal neurons, for example, CBD stimulates increased intracellular calcium concentration via mitochondrial uptake/release and activation of L-type (voltage-dependent) calcium channels. CBD is able to significantly reduce oxidative and nitrosative stress and neuronal damage promoted by the deposit of beta-amyloid protein, attenuating tyrosine hydroxylase depletion, dopamine levels, GABA and the *modulation* of induced nitric oxide synthase (iNOS) expression, decreasing the production of NADPH oxidase from ROS. Rajesh et. al. (2007) observed that pretreatment with CBD attenuated mitochondrial superoxide generation induced by lack of glucose concentration and NF-kB activation, along with expression of ICAM-I and VCAM-1 adhesion molecules in human coronary artery endothelial cells. These results suggest that CBD may exert a *desirable neuroprotective*, antioxidant, and anti-inflammatory role for the treatment of AD (NOCETTI; RIBEIRO, p.7-8, emphasis added).

In this way, one can see the level of detail that research has already achieved, and how the conjecture of a future treatment of AD under the reins of cannabis medicine makes sense, provided thatMany obscure or insufficiently understood aspects can be elucidated.

3.1 HALF-OPEN PERSPECTIVES, HYPOTHESES AND INVESTIGATIONS

As we have tried to demonstrate, the neuroprotective potential of cannabis in AD leads us to neurogenesis, or even to a complex metabolic action of neuromodulation. Regarding this broader possibility of the action of cannabis medicine in Alzheimer's, some studies point out important aspects, hypotheses that incite new debates, so that we seek here to indicate some paths that can provide new paths to Alzheimer's.

We have selected, for the discussion of this item, four articles whose points raised seem important to us for the fabric of new research and deepening. Points that can be connected and aligned by a wire that allows better grounding the neuroprotective and neurogenic potential, or, synthetically, neuromodulation and homeostasis.

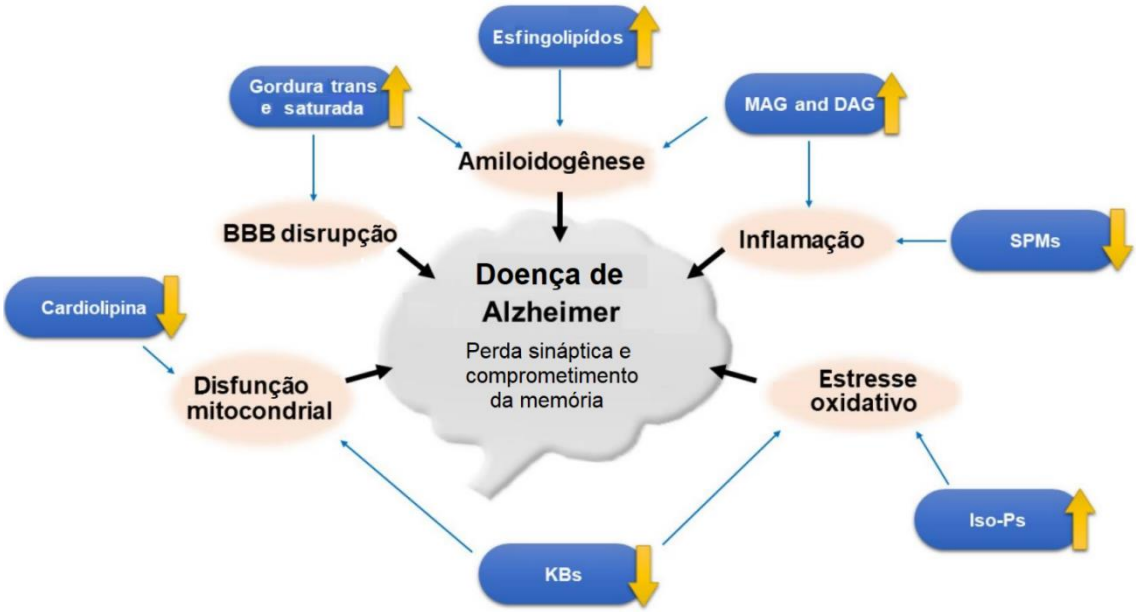
Kao, Ho, Tu, Jou & Tsai (2020, p.1) point to an analysis of lipid peroxidation so as to shed light on exaggerated inflammation and "aberrant lipid metabolism". Cadas, Gaillet, Beltramo, Venance & Piomelli (1996), in turn, deal with the biogenesis of anandamide. The release of this bioactive lipid is considered from an analysis of the mechanisms of its biogenesis. The understanding of lipid metabolism does not dispense with the discussion of elements related to brain energy. Castro, Martins and Tufi (2010) address the crucial role of mitochondria in providing energy to the brain. They indicate the relevance of mitochondrial stress in neurodegeneration. In a complementary way, Rao, Carlson and Yan (2013) specifically address the mitochondrial permeability transition pore as a potential drug target for neurodegeneration.

KAO, HO, TU, JOU & TSAI (2020) point out that knowledge of the connection between lipids and AD is crucial to unravel its metabolic aspects. AD is referred to as an "intriguing disease" in which there is "disruption of lipid homeostasis" (KAO; HO; YOU; JOU; & TSAI, 2020, p.1). They point out that lipids are basic components of cell membranes. They play a role in brain health and function. The interruption of lipid homeostasis generates neurological disorders, in the case of AD, neurodegeneration. The authors consider recent advances in lipid analytical methodology to be necessary and promising. His considerations are based on the observation of "fatty acid changes at the level of lipid rafts" and "lipid peroxidation in the initial stage of AD" (KAO; HO; YOU; JOU; & TSAI, 2020, p.1). Lipid peroxidation is pointed out as the main manifestation of oxidative stress in the CNS.

As we pointed out, in Alzheimer's there is "accumulation of amyloid protein in plaques due to overproduction or impaired elimination of β-amyloid peptides (Aβ)" and "deposition of neurofibrillary tangles (NFTs)" (KAO; HO; YOU; JOU; & TSAI, 2020, p.1). This results in synaptic loss and neurodegeneration. The authors indicate lipids as responsible for "50% of dry brain weight" and "basic structural component of neuronal cell membranes" (KAO; HO; YOU; JOU; & TSAI, 2020, p.1). As an early AD event, they identify "cerebral lipid peroxidation", which characterizes an "aberrant lipid metabolism" (KAO; HO; YOU; JOU; & TSAI, 2020, p.1). Patients with AD have increased "lipoid granules (adipose inclusions)" in "cells of the central nervous system (glia)." Lipids are mediators of immune responses, and the "permeability of the blood-brain barrier (BBB)" is higher in the elderly: "Cerebral hypoperfusion" and "loss of BBB integrity" result in "reduced energy availability and disrupted synapses, leading to impairments in memory and learning" (KAO; HO; YOU; JOU; & TSAI, 2020, p.3).

AD is a disease with "exaggerated inflammation" and "impaired inflammatory resolution"; resolution is regulated by "lipid mediators" (specialized pro-resolution mediators - SPMs) whose anti-inflammatory properties restore "inflammatory resolution and homeostasis" (KAO; HO; YOU; JOU; & TSAI, 2020, p.7).

"Dysregulated lipid homeostasis" is associated with aging and contributes to the "pathogenesis of AD" (KAO; HO; YOU; JOU; & TSAI, 2020, p.18). We present the figure elaborated by the authors on the roles of lipids in the pathogenesis of AD. As they state, "the mechanisms linking lipid dysregulation" and Alzheimer's "consist of changes in the gut microbiota and gut-brain axis, neuronal signaling pathway, BBB disruption, mitochondrial dysfunction, oxidative stress, and inflammation"; Such aspects lead to "synaptic loss" and "memory impairment." Lipids, illustrated below, play "essential roles in pathogenesis," and are proposed as "biomarkers" (KAO; HO; YOU; JOU; & TSAI, 2020, p.18).



Roles of lipids in the pathogenesis of AD (In: KAO; HO; YOU; JOU; & TSAI, 2020, p.18).

As it turns out, the discussions of Kao et. al. (2020) on the roles of lipids in pathogenesis can be related and compared to those of the other authors of the three articles referred to in this item.

Cadas, Gaillet, Beltramo, Venance & Piomelli (1996, p.3934), in their approach to the biogenesis of anandamide, precisely indicate the role of this lipid as cannabinoid substances. Anandamine, according to the authors, may derive from the "cleavage of the precursor phospholipid NAPE" (CADAS et. al., p.3934). NAPE levels in neurons are regulated by ions. Such "regulation" can maintain the supply of "carabimimetic N-acylethanolamines" during the "synaptic activity and primary target neurons of the release of these bioactive lipids" (CADAS et. al., p.3934).

Castro, Martins and Tufi (2010, p.1), who emphasize the crucial role of mitochondria in providing energy to the brain, consider that their "deterioration" can have "harmful consequences" on the "function and plasticity of neurons", and consequently, on the "pathogenesis of neurological disorders" (CASTRO, MARTINS; TUFI, 2010, p.1). Mitochondria are subjected to high stress. Thus, the authors seek to understand the "mitochondrial stress control pathways", and thus better understand neurodegenerative processes (CASTRO, MARTINS; TUFI, 2010, p.1).

Rao, Carlson and Yan (2013, p.1267) indicate that the "mitochondrial permeability transition pore (mPTP)" plays a "central role" in "changes in mitochondrial structure and function". This leads to the neuronal lesion typical of AD. "The interaction of amyloid beta peptide with CypD potentiates mitochondrial and neuronal disturbance," Rao et states. al. (2013, p.1267), in order to bring interesting complements to the analysis of Castro, Martins and Tufi (2010)

Thus, we leave open to the experts some paths that can be aligned between these points of these four important articles briefly considered here.

3.2 CONNECTIONS AND PLASTICITIES

Malcher-Lopes and Ribeiro (2007, p.53) address the action of THC on "brain circuits" called "base nuclei" and the presence of CB1 in the cerebellum. They explain that in the "core *Accumbens*" the CB1 receptor is abundant; It is the region of the brain that participates in the "anticipation and processing of the sensations of pleasure and reward." (MALCHER-LOPES; RIBEIRO, 2007, p.54). They also present a detailed characterization of marijuana as a "tonic": cannabinoids promote a "disorganization of neuronal processing" that has as a consequence a "facilitation of the restructuring of memory traits", thus making it easy to understand that their use "facilitates the creative process and the generation of *Insights*" (MALCHER-LOPES; RIBEIRO, 2007, p.141-142). The tonic, they continue, acts as an "appetite stimulator" and "favors states of low anxiety", reducing "social tensions" in different contexts through its "anti-stressful action" (MALCHER-LOPES; RIBEIRO, 2007, p.142). Thus, such aspects can also be considered as potentially beneficial to Alzheimer's patients. When considering the "neurobiological effects of marijuana," they consider that CB1 activation promotes "reduced activity of inhibitory neurons," which enables "more active circuits." (MALCHER-LOPES; RIBEIRO, 2007, p.124). Finally, but not last, they consider that the joint results of studies from the last three decades suggest that "endocannabinoids" regulate "hippocampal modifications" by "*Modulation* of the activity of inhibitory neural networks that control the greater or lesser organization of memory processing" (MALCHER-LOPES; RIBEIRO, 2007, p.126).

And if the studies, with all the gaps and challenges still to be overcome, already indicate such elements, what will be said of the results that will come in the next three decades? Therefore, the paths are open to, perhaps, erect the protagonism of the neuromodulatory role of cannabis in Alzheimer's.

Connections and plasticities are key words that emerge from the conjectures that, for now, we can glimpse for coping with such a complex and intriguing disease.

4 FINAL CONSIDERATIONS

The future belongs to God, say the religious. While others say that history is made by men and that the social practices they lead produce transformations and advances, in historical cycles of alienation and estrangement guided by properties intrinsic to the development and ontology of the social being (LUKÁCS, 2010). We adopt this second perspective. And we ponder that nothing advances or transforms without difficulties. This is how they should or can occur. Counterpoints and dialogues are necessary for there to be solid foundations of our social constructions. And these never become eternal. In the scientific and health field, we can easily identify the contradictions, advances and setbacks of the processes of discussion, legitimation and consolidation of different perspectives of promotion, prevention and care. In the present work we seek to indicate supporting and protagonist aspects of cannabis in the treatment of Alzheimer's. And we emphasize the importance of making the neuromodulatory role predominant (neurogenic; neuroprotective; neurostabilizing). Parsimony and boldness. Dialogue and affirmation. Thoughtfulness and enthusiasm. These are necessary and intrinsic psychosocial components to the irreversible advancement of cannabis medicine, and by extension, cannabis medicine in the treatment of Alzheimer's. Psychoanalysis revolutionized the understanding of the therapeutics of neuroses, and later of psychoses, and even today there are those who question its scientificity. The Freirean perspective revolutionized the understanding of educational processes, and even today there are those who despise it or even label it as left-wing or other bizarre and unreasonable adjectives. These were contributions that took very important steps. And even if they still provoke resistance, they are irreversible, whether you believe them or not. Both Sigmund Freud and Paulo Freire were tireless in their trajectories, in the sense of assuming dialogical postures with what was faced (or even denied), without ever giving up their ethical convictions, and the practices and objectives they achieved. His achievements marked epochs and generations, but they never occurred in an ideal way and not even without mishaps, as indicated in his works "Terminable and endless analysis" (FREUD, 1985) and "Pedagogy of hope" (FREIRE, 2018). Similarly, this is the case with the achievements of the medicinal use of cannabis. With the contents and reflections systematized in this work, we hope to make our modest contribution to a more promising future for the life and health of Alzheimer's patients, with the hope that this can happen with the strengthening of cannabis medicine, since we risk saying that this is essential to the former.

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