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Evaluating the therapeutic potential of cannabis in Parkinson's Disease: An overview of the latest knowledge

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ABSTRACT

The progressive brain damage associated with Parkinson's disease (PD) develops over an extended duration. This disease is characterized by motor symptoms, particularly bradykinesia, stiffness, and dystonia. There are also non-motor manifestations such as pain, anxiety, and sleep disturbances. Levodopa and other common medications help relieve motor symptoms but are less effective at delaying the progression of the disease. This study reviews possible medical uses of cannabis for Parkinson's disease treatment. The key aspects to consider are its functionality and its advantages and drawbacks. Cannabidiol (CBD) and Δ^9 -tetrahydrocannabinol (THC), among other plant-based compounds of cannabis, modulate the endocannabinoid system. Evidence suggests that cannabinoids may reduce neuroinflammation and oxidative stress, two processes that lead to neuronal damage. In clinical studies, both motor and non-motor symptoms improve with cannabis. It turns out that this method of treatment is an effective solution among people suffering especially from rigidity, tremors, anxiety, and sleep disturbances. However, the use of cannabis can result in drawbacks, including psychiatric effects and addiction.

Keywords: Parkinson's disease, Marijuana, cannabinoids, addiction

1. INTRODUCTION

Parkinson's disease (PD) affects nearly one per thousand in the population. The probability of developing this disease grows as a person ages, with a 1% annual increase in risk for individuals over 60 years old (Reeve et al., 2014). Degeneration of dopaminergic neurons, which results in difficulty performing voluntary movements, is the main neuropathological alteration that causes

Parkinson's disease symptoms. Bradykinesia, tremor, and stiffness are among the motor symptoms of Parkinson's disease, resulting in the decline of dopaminergic neurons in the substantia nigra area of the brain. Another important pathogenic characteristic is the existence of Lewy bodies that contain alpha-synuclein.

As the disease progresses, Lewy body pathology can expand to other parts of the brain, resulting in non-motor symptoms such as loss of smell, sleep difficulties, and cognitive impairment. Genetic factors also play a role in PD, with 5-10% of cases linked to genetic mutations (Simon et al., 2020). There are wide variations in how Parkinson's disease (PD) develops; some patients develop symptoms gradually, while others experience a sudden decline in their condition. The main goal of treating Parkinson's disease is to treat symptoms with medications such as levodopa, which improves motor function and alleviates movement problems.

Research on the mechanism of disease development continues, and researchers are working to create more efficient methods of treating and preventing it. Marijuana has over 100 different phytocannabinoids. Whereas cannabidiol (CBD), a non-psychoactive molecule, is frequently mentioned for its potential benefits in treating neurological illnesses, Δ^9 -Tetrahydrocannabinol (Δ^9 -THC, THC) is the primary psychoactive substance in this plant (Babayeva et al., 2016). Despite strong evidence from recent studies supporting the therapeutic benefits of medical marijuana, increased availability of cannabis and cannabinoid products is associated with potential side effects, including addiction, impairments in working memory, anxiety, and depression (Lowe et al., 2019).

Cannabinoid receptors are found in nearly every body system, making them potentially useful in treating various medical conditions, including mood and movement disorders such as Parkinson's (Kluger et al., 2015). Most cannabinoids' actions are related to the type 1 receptor subtype (CB 1) and type 2 (CB 2), which are widely distributed in the striatum and other regions of the basal ganglia. These receptors are crucial for controlling dopamine activity and motor functions. Studies suggest that impairment of these receptors may be associated with dyskinesias (Romero et al., 2002). The goal of this article is to compare the advantages and disadvantages of treating Parkinson's disease with medical marijuana and to assess its therapeutic potential.

2. METHODOLOGY

A search was conducted using open-access medical databases, including PubMed, with keywords such as "Marijuana" and "Parkinson" to identify relevant studies published between 2002 and 2023. The articles used to write this review are selected based on their titles and abstracts. The review seeks to explore how marijuana may impact the treatment of Parkinson's disease, with a particular focus on its role in addressing motor symptoms, also showing potential benefits compared to existing treatment methods. The analysis of the existing literature allowed us to summarize in this article the potential benefits of using marijuana in PD, in particular, the safety and effectiveness of such therapy. The main areas we focused on were symptom reduction, treatment outcomes, and comparison to existing treatment options. The review aimed to contribute to a better understanding of whether marijuana could serve as a viable adjunct or alternative in Parkinson's disease management.

3. RESULTS AND DISCUSSION

Mechanism of action of marijuana

The identification of THC as the primary psychoactive component in cannabis prompted more studies on the particular molecules under the impact of cannabinoids. According to Pacher et al., (2006), its effects on the neurological system, including euphoria, relaxation, and changes in perception, inspired researchers to search for the receptors used by this molecule to affect the body. During the research, two primary cannabinoid receptors have been identified: CB1 and CB2. These receptors are part of the G-protein-coupled receptor family (GPCRs) and are essential for the functioning of the endocannabinoid system.

CB1 receptors are extensively spread throughout the central nervous system (CNS) and found in neurons, astrocytes, oligodendrocytes, and non-neuronal tissues such as the heart, lungs, and liver. CB1 is a key receptor for releasing neurotransmitters in the CNS, particularly in GABAergic neurons. By inhibiting the release of neurotransmitters such as GABA and glutamate, CB1 affects processes such as pain perception, mood, appetite, and memory (Fernández-Ruiz, 2009). Beyond the central nervous system, peripheral CB1 receptors significantly impact several physiological functions, such as muscle metabolism, fertility, and gastrointestinal motility (Schurman et al., 2020).

However, CB2 receptors are located mainly in immune cells and regulate inflammatory responses and immune functions. The discovery of selective receptor antagonists and the creation of mice that lack CB1 and CB2 receptors brought a breakthrough in research

on cannabinoid receptors (Pacher et al., 2006). These models have enabled more detailed studies of the effects of activating and blocking them in various tissues and during physiological processes. These studies have shown that the endocannabinoid system regulates CNS functions and inflammatory processes, the functioning of the circulatory system, and metabolic control. Understanding the roles of CB1 and CB2 and their endogenous ligands opens up potential pathways for developing new treatments for neurological, autoimmune, and metabolic disorders, including Parkinson’s disease.

Pros of marijuana use in PD

Using an animal model for Parkinson’s disease, the beneficial effects of CBD have been demonstrated, primarily through antioxidant processes that act independently of cannabinoid receptors. Although it does not cure tremors, it helps reduce the dystonia associated with Parkinson's disease. Among recreational cannabis users, researchers found positive associations between striatal and pallidal CBD concentrations (Maroon and Bost, 2018). Cannabis-based products are being studied for sleep issues in various disorders. Around 80% of patients with advanced-stage Parkinson’s disease experience sleep disturbances, for which effective treatment is challenging to find due to their complex, multifactorial nature and the lack of clearly defined causes (Zuzuárregui and During, 2020).

Some studies confirm the beneficial effect of marijuana on sleep disorders in PD patients, while others do not reach such conclusions, or the effect is only temporary (Figura et al., 2022). Compared to the mild effects observed in randomized, double-masked trials, patient perceptions of cannabis treatment are generally positive. Although the diversity of methods complicates comparisons, improvements in non-motor symptoms, primarily pain and anxiety, are often reported. Patients also noticed an improvement in Parkinson's disease motor symptoms, especially tremors and stiffness, which is consistent with the results of the unblinded studies. Interpretation is difficult because answers can vary between anonymous online surveys and responses collected by doctors (Figura et al., 2022).

Table 1 Summary of pros and cons of Marijuana use in PD

Aspect	Pros of Marijuana Use in PD	Cons of Marijuana Use in PD
Symptom management	CBD shows beneficial effects in reducing dystonia, though it does not cure tremors	Potential for addiction, respiratory problems, and cognitive decline
	Positive patient-reported improvements in motor symptoms (tremors, stiffness) and non-motor symptoms (pain, anxiety)	Δ9-THC associated with side effects such as anxiety, elevated heart rate (tachycardia), and cravings
Sleep disorders	Some studies report improvements in sleep disturbances for PD patients, though effects may be temporary	Results on sleep benefits are inconsistent, with some studies finding no significant improvements
Mental health	CBD may alleviate psychotic symptoms by enhancing endocannabinoid activity	Cannabis use is linked to anxiety, depression, psychosis, and mood disorders, especially in younger populations
Adolescent and young users	Limited benefits noted in this group	Adolescents are highly susceptible to long-term behavioral and neurological changes, including memory and concentration issues
General observation	Positive associations were noted between striatal and pallidal CBD concentrations among recreational cannabis users	Adverse effects on working memory, concentration, processing speed, and social behavior, with risk of anhedonia

Cons of marijuana use in PD

Despite their widespread availability for medical use, cannabis and cannabinoids carry many risks, including the potential for addiction, respiratory problems, and cognitive decline. Particularly in younger populations, their use is associated with inducing mental health issues such as anxiety, depression, and psychosis. Problems with working memory, decreased concentration and processing speed, anhedonia (reduced ability to feel pleasure), strange social behavior, and increased risk of anxiety and mood disorders are other negative consequences (MacCallum and Russo, 2018). Adolescents are particularly susceptible to long-lasting behavioral and neurological changes. While CBD may help alleviate psychotic symptoms by enhancing endocannabinoid activity, Δ^9 -THC has been found to result in side effects like anxiety, an elevated heart rate (tachycardia), and cravings (Babayeva et al., 2016).

The advantage of marijuana over other medications used in PD

The advantage of marijuana over other medications for Parkinson's disease (PD) lies primarily in its ability to alleviate both motor and non-motor symptoms, especially in patients who do not respond well to conventional treatments (Kluger et al., 2015).

Symptomatic Relief

One of the key benefits of cannabis-based therapies, especially cannabidiol (CBD) and tetrahydrocannabinol (THC), is their ability to alleviate symptoms such as dyskinesia, pain, anxiety, and sleep disorders. Numerous studies have demonstrated that cannabis has the potential to reduce motor fluctuations and improve overall mobility in patients who experience levodopa-induced dyskinesia, a common complication of standard treatment for Parkinson's disease (Kogan and Mechoulam, 2007). Additionally, cannabinoids have shown significant potential in the treatment of chronic pain, which is common in Parkinson's disease patients and is often not adequately treated with traditional medications (Figura et al., 2022).

Neuroprotective and Disease-Modifying Effects

Researchers believe that cannabis has neuroprotective qualities, which are not typically associated with many standard Parkinson's disease medications. According to preliminary research, cannabis may help reduce oxidative stress and neuroinflammation, two factors that accelerate the onset of neurodegenerative conditions like Parkinson's disease. According to some studies, cannabinoids can regress the course of the disease by modifying these processes. For this reason, cannabis may be a helpful adjunct therapy for both disease-modifying treatment and symptom management, something that existing medications cannot provide (Goldberg et al., 2023).

Better Tolerability

Commonly used medications for Parkinson's disease, including treatments like levodopa and dopamine agonists, can cause numerous side effects over time, including nausea, dyskinesia, and mental deterioration. In contrast, cannabis-based therapies are often better tolerated and result in fewer and milder side effects. For patients who are unable to cope with the adverse effects of conventional Parkinson's disease medications, cannabis becomes a tempting substitute (Patel et al., 2019). Despite the encouraging results, scientists should do more clinical trials to fully determine the best doses, administration techniques, and long-term consequences of cannabis use for Parkinson's disease. Although marijuana appears to be potentially beneficial in the treatment of Parkinson's disease, its placement in therapy remains a problem due to the lack of large-scale research on its effects.

Ethical Considerations in the Use of Medical Cannabis for Parkinson's Disease Patients

The application of medical cannabis for managing Parkinson's disease (PD) symptoms raises several significant ethical concerns, particularly when balancing the potential benefits with possible risks. Although cannabis and cannabinoids have shown promise in easing specific symptoms linked to Parkinson's disease, there remains much uncertainty regarding the long-term use and effectiveness of such treatment. Due to this fact, such therapy's introduction may be questionable regarding safety and equal access to treatment among patients from different social groups. One of the critical ethical issues regarding the use of medical cannabis for Parkinson's disease is ensuring that patients receive safe treatment that is supported by solid evidence.

While some studies suggest that cannabinoids may help lessen motor symptoms like tremors and stiffness, along with nonmotor symptoms such as pain, sleep problems, and anxiety, these results are still in the early stages and require more in-depth research (Kluger et al., 2015). Marijuana and cannabinoids may act by modulating the functioning of the central nervous system and changing

the production of neurotransmitters. Still, the mechanisms of their action are not fully understood, which raises doubts about conducting such therapy (Balash et al., 2017). However, since patients with Parkinson's disease already experience cognitive decline and motor dysfunction, this therapy could potentially be used. Before inducing such therapy, physicians should comprehensively inform every patient about treatment and its potential benefits and risks.

About medical cannabis, patients should understand that although some studies suggest it might have benefits, there remains a substantial lack of large-scale, high-quality clinical trials to conclusively establish its effectiveness in treating Parkinson's disease (Carroll et al., 2004). Given this uncertainty, healthcare providers have a moral responsibility to ensure patients are informed about the potential therapeutic effects and the possible side effects, including dizziness, dry mouth, cognitive disturbances, and even the risk of dependency (Borgelt et al., 2013). Providing the patient with information about possible complications of therapy allows him to make a reliable analysis and decide whether to undertake it.

The availability of medical marijuana is another issue that the medical community must overcome to ensure optimal levels of treatment for patients. However, in many regions of the world, it is costly, and insurance rarely covers the costs of such therapy, and patients cannot afford to pay for the treatment themselves. Moreover, it remains illegal in many countries, but its use for medical purposes is becoming increasingly common (Shover and Humphreys, 2019).

Future Directions and Innovative Approaches in Cannabinoid-Based Therapies for Parkinson's Disease

Research on the use of medical marijuana and cannabinoids in Parkinson's disease (PD) has gained notoriety in recent years, which has led to studies on their effectiveness in the treatment of various diseases. Currently, research is focused on new delivery methods, combining marijuana with other drugs and discovering new molecular targets that cannabinoids act on.

Development of Novel Formulations

The development of new technologies in pharmacology has enabled the creation of breakthrough cannabinoid formulations, thanks to which their bioavailability has significantly increased, improving the quality of therapy. One of them are liposomal carriers and nanoemulsions. Thanks to their structure, they potentially could enhance the solubility and stability of cannabinoids and transport molecules more efficiently to the target tissues (Stella et al., 2021). Apart from that, transdermal patches are a part of controlled-release administration routes. This delivery form may reduce systemic side effects and provide sustained therapeutic levels of cannabinoids in the bloodstream, which is very important and beneficial in treatment (Alkilani et al., 2015).

Combination Therapies

One of the most optimistic potential uses of cannabinoids in PD lies in their synergistic potential when combined with existing medications. Traditional PD therapy, utilizing levodopa, could use a lower dosage and cause less bothersome side effects (Carroll et al., 2004). Researchers proposed co-administration of cannabidiol (CBD) with levodopa to mitigate levodopa-induced dyskinesias, which is a common complication in PD therapy (Dos-Santos-Pereira et al., 2016). Exploring other combinations could result in lower doses of traditional medications and fewer side effects of PD treatment, which cause better tolerance of therapy by patients.

Personalized Medicine

The different response of patients to marijuana therapy proves the need for an individual approach for each patient seeking treatment. One of the reasons for this phenomenon is genetic variability between patients; therefore, research suggests that doctors should adjust therapy based on the patient's genetic profile (Hryhorowicz et al., 2018). The correlation of the levels of various biomarkers in the blood with the response to treatment is also examined (Pisanu et al., 2022). Personalized medicine approaches could optimize cannabinoid therapy efficacy and safety in PD management.

Identification of New Molecular Targets

Cannabinoid receptors CB1 and CB2 have been discussing endocannabinoid systems for a while now. However, scientists found new receptors, such as GPR55 and TRPC, and discovered their role in modulating neuroinflammation and neuroprotection (Goldberg et al., 2023). Using these receptors as a grip point for synthetic THC analogs could open new options for PD treatment. Discovery and

understanding of the interaction between cannabinoids and these receptors could benefit the development of more effective PD therapeutic options.

Preclinical Models and Artificial Intelligence

The development of new technologies gives excellent hope for understanding and learning the mechanisms responsible for improving the functioning of patients with Parkinson's disease. One of the methods used for this is preclinical models, including pluripotent stem cell-derived neurons and organoids (Vandana et al., 2023). Thanks to these models, the mechanisms leading to beneficial effects in cannabis therapy are being identified. In addition, the increasingly rapid development of artificial intelligence and machine learning allows faster and more accurate analysis of increasingly large databases related to cannabis use in Parkinson's disease (Singh et al., 2023).

These activities may reveal specific patterns in the body's response to treatment with THC and thus better predict the response to such therapy in different patients with different dominant symptoms, which will allow for more precise and effective use of marijuana in treatment. These new technologies may accelerate the development and increase the effectiveness of treating Parkinson's disease. In summary, the future of cannabinoid-based therapies for PD lies in integrating innovative formulations, joint strategies, personalized medicine, new molecular targets, and advanced research methodologies (Table 1). Combining the above approach with already available knowledge may improve the treatment quality in patients with PD and certainly increase their quality of life.

4. CONCLUSIONS

This research shows that medical cannabis has much promise as an extra tool for treating Parkinson's disease (PD). Researchers have found that cannabinoids, especially cannabidiol (CBD), may help with both motor symptoms, such as tremors and stiffness, while also easing non-motor symptoms, including pain, nervousness, and sleep disorders. Research also suggests that marijuana may have a beneficial effect on brain and neuronal function by reducing neuroinflammation and oxidative stress. Despite its beneficial effects on PD patients, marijuana is not without its drawbacks. One of them is that different patients respond differently to treatment. In addition, other side effects may occur during therapy, such as memory loss, and the lack of a unified dosage system makes treatment control much more difficult.

During cannabis therapy, in patients who are particularly vulnerable to side effects, treatment should be carried out with greater caution, paying special attention to the dosage and the occurrence of severe symptoms. As for today, medical society needs to carry out more randomized controlled studies to find out how well cannabis works, what the best amount is, and if it is long-term safe for people with Parkinson's disease. Using pharmacogenomic and biomarker-driven methods together may also help tailor cannabinoid therapies to each patient, making them more effective and easier to handle. Medical cannabis is not a replacement for traditional Parkinson's disease treatments. Still, it is worth considering it in PD treatment because it could help these patients better control their symptoms and live a better overall life.

Author's Contributions

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All authors have read and agreed with the final, published version of the manuscript.

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The authors declare that there is no conflict of interests.

Data and materials availability

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