IJPSR (2022), Volume 13, Issue 6 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 23 August 2021; received in revised form, 25 September 2021; accepted, 09 November 2021; published 01 June 2022

REVIEW ON ACTIVITY OF CANNABIS TREATMENT ON PARKINSON'S DISEASE

Douglas Zorinmawia Chhakchhuak, G. Swetha Saniya Tabassum and Anjali Raj *

Department of Pharmacology, Pharmacy # 6/9, 1st Cross, Begur Road, Hongasandra, Bengaluru - 560041, Karnataka, India.

Keywords:

Levodopa, Cannabidiol (CBD), Cannabinoid, Cannabis, Delta-9-tetrahydrocannabinol (THC), Parkinson's disease, Tremor

Correspondence to Author:
Dr. Anjali Raj

Assistant Professor,
Department of Pharmacology,
Pharmacy, # 6/9, 1st Cross, Begur Road, Hongasandra, Bengaluru - 560041, Karnataka, India.

E-mail: anjiii1911@gmail.com

ABSTRACT: As new treatments and medication are growing rapidly, neurologists are also toward expanding treating patients with idiopathic Parkinson's disease and facing questions regarding cannabis as a treatment elective, particularly for levodopa-safe Parkinson's symptoms. Cannabinoids compounds like delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) are the most abundant chemicals present. Whereas THC is psychotropic chemical that tends to cause individuals to feel "high," while CBD is no psychotropic chemical. Nonetheless, other than cannabis, plant cannabinoids are also produced by the mammalian body, called endocannabinoids. Endocannabinoids are neurotransmitters that bind to cannabinoid receptors and cannabinoid receptor proteins expressed throughout the central nervous system, including the brain and peripheral nervous system. So, these endocannabinoid receptors can be of two types cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R), which are G-protein coupled receptors. The first receptor, CB1R receptors are particularly abundant in the hippocampus, frontal cortex, basal ganglia, hypothalamus and cerebellum, spinal cord and peripheral nervous system. They can also be found in inhibitory GABA-ergic neurons and excitatory glutamatergic neurons. Whereas CB2R receptor is most abundantly found on cells of the immune system hematopoietic cells and glial cells. CB2R receptor is mainly found in the periphery under normal healthy conditions, but in the case due to disease or injury, this regulation occurs within the brain, and CB2R is therefore expressed in the brain in disease or injured person.

INTRODUCTION: The most common neuro-degenerative disorder can be said as Parkinson's disease (PD). PD is the gradual loss of dopaminergic neurons that destroy the basal ganglia, which is an important part of the brain for coordinated movement. Patients with PD experience motor symptoms, including bra-dykinesia (slowness and poverty of movement), resting tremor, muscular rigidity, and gait (impairment of postural balance).

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(6).2221-29

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(6).2221-29

Other than motor symptom, nonmotor symptoms can also appear which include excessive sweating, depression or, in late stages dementia. These changes are commonly cause by a loss of the pigmented dopaminergic neurons of the substantia nigra (SN) which innervate the striatum. In recent year, investigation have shown the considerable progress in understanding the pathophysiology of PD.

Several factors causing neuronal damage are probably involved [1], their common denominator seems to be an oxidative stress. So, this oxidative stress which causes imbalance between the formation of cellular oxidants and the antioxidative processes in SN neurons, which lead to excessive formation of hydrogen peroxide and oxygen-

derived free radicals that can seriously damage the neurons and which in turn lead to neuronal cell death [2]. Marijuana refers to the dried flowers, stems, seeds, and leaves derived from the cannabis *sativa* plant various Phytocannabinoids [3]. So, phytocannabinoids are used to differentiate the plant-derived cannabinoids from the synthetic cannabinoids and the structurally different endogenous cannabinoids (endocannabinoids). The Cannabis sativa plant, including Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), has various potency effects on diseases like cancer, glaucoma, and multiple sclerosis. There are several evidences demonstrate that dopamine depletion causes a dramatic rearrangement in the striatal endocannabinoid system, endocannabinoid (ECB) plays a vital role in neuronal regulation and immune function within the central nervous system (CNS) and is altered in several movement disorders; this occurrence can be seen in both rodent and primate models of PD, as well as in PD patients. In fact, close interactions exist between endocannabinoids and the dopaminergic system in the regulation of synaptic function and regulation of motor behaviour, through specific G protein-coupled cannabinoid receptors (CB1 and CB2) in the basal ganglia [4].

Cannabinoid receptors and endogenous cannabinoids isolation in the nervous system is proposed by Raphael Mechoulam [5] and his colleague, and their discovery that the endocannabinoid system is capable of modulating numerous physiological processes, such as pain, eating behaviour, memory, and mood, have paved the way for systematic research into the effects of cannabis on a variety of chronic diseases [6]. Until that is March 10, 2017, cannabis flowers and their extracts can be prescribed on a narcotic drug prescription form without limitation to specific indications [7]. The discovery of high concentrations of cannabinoid receptors in the basal ganglia can trigger an increasing interest in the therapeutic potential of cannabinoids for the treatment of diseases like Parkinson's disease (PD) and other movement disorders. Hence, Public awareness of such a topic was raised by anecdotal reports of considerable improvement of PD symptoms after cannabis consumption that were shared *via* social networks and published in the general press.

1. Terminology of Cannabis: Marijuana, also known as cannabis *sativa* is an herbaceous plant that has versatile uses and effects. However, the leaves and resinous extracts of the plant can be consumed by eating, smoking, or even inhaling vapors. Moreover, cannabis hemp seeds can also be used for producing oil for cooking, lighting, and wood surface coatings. Until recently, the main interest in this plant is that it has a rich source of cannabinoids. These cannabinoids are chemical substances consumed largely for recreational and spiritual purposes and for their medicinal effects. The difference in the chemical structure of cannabinoids explains the difference in their psychoactive and therapeutic effects. The two cannabinoids of greatest interest today are cannabidiol (CBD) and (Delta)9-Tetrahydrocannabinol (Δ9- or D9-trahy--drocannabinol; THC). CBD is one of the major non-psychoactive Phyto-cannabinoids which is present in cannabis such that nearly 40% of cannabis extracts are comprised of CBD and CBD is also a substance in cannabis that is thought to have potential medicinal applications [8] lack psycho-activity and not interfere with psychomotor learning or neuropsychological functions. Whereas THC, the other main active component in cannabis, is also responsible for the mood-altering effects, and unlike CBD, THC has potent adverse psychoactive effects, inducing anxiety and paranoia [9], the interesting prospect is the possibility that CBD may be capable of counteracting adverse psychoactive effects of THC in humans [10].

2. Current Problem Face with PD Medical Treatment: Direct-acting dopamine receptor agonists have been a major focus of PD drug development over the past decades. In recent years, their potential to provide more continuous dopaminergic receptor stimulation than levodopa has been the subject of both preclinical and clinical research. Dopamine agonists were investigated for a better substitution of dopaminergic in PD than levodopa due to having a longer half-life and because some are amenable to continuous parenteral drug delivery through different routes. In fact, most dopamine agonists studied in clinical trials have shown consistent efficacy in reducing motor response [11]. Nonetheless, data from comparative studies between different agonists and

greater efficacy of agonists with longer half-lives, or continuous transdermal delivery on motor fluctuations, has not been established. Henceforth, studies in parkinsonian in primates have shown that treatment with short-acting dopamine agonists, but not with longer-acting ones, induces dyskinesias, supporting the hypothesis of pulsatile dopamine receptor stimulation as a critical factor for the development of dyskinesias [12]. At a clinical level, there is large evidence to support that continuous dopaminergic drug delivery can revert pre-existing levodopa-induced dyskinesias. This was observed with intraduodenal infusions of levodopa itself, which were found to smooth out motor oscillations and reduce dyskinesia severity despite more or less unchanged total daily dose [13]. In similar observations were made in studies of continuous s.c. Infusions of the dopamine agonists, lisuride or apomorphine, in which concomitant levodopa was usually reduced while the agonist was infused at rates to ensure maximal dystonic posturing reduction [14].

In addition, clinical studies have shown that dyskinetic responses to single-dose levodopa challenges were markedly reduced following several months of continuous s.c. apomorphine infusions [15].

So, due to these several problems with the long-term use of levodopa causing dyskinesia, replacement therapy is being investigated for better treatment of PD.

3. Cannabinoid Receptors Relations to CNS Dysfunction: ECB act as a retrograde messenger on presynaptic cannabinoid receptors, albeit additional molecular targets might be involved. Cannabinoid receptors can be divided into two major subtypes, which are CB1R and CB2R [16] **Fig. 1**. This CB2R is mostly found in the immune system, whereas CB1R is highly expressed and localized to several area regions of the brain, with a reported expression in neurons, astrocytes, oligodendrocytes, and neural stem cells [17].

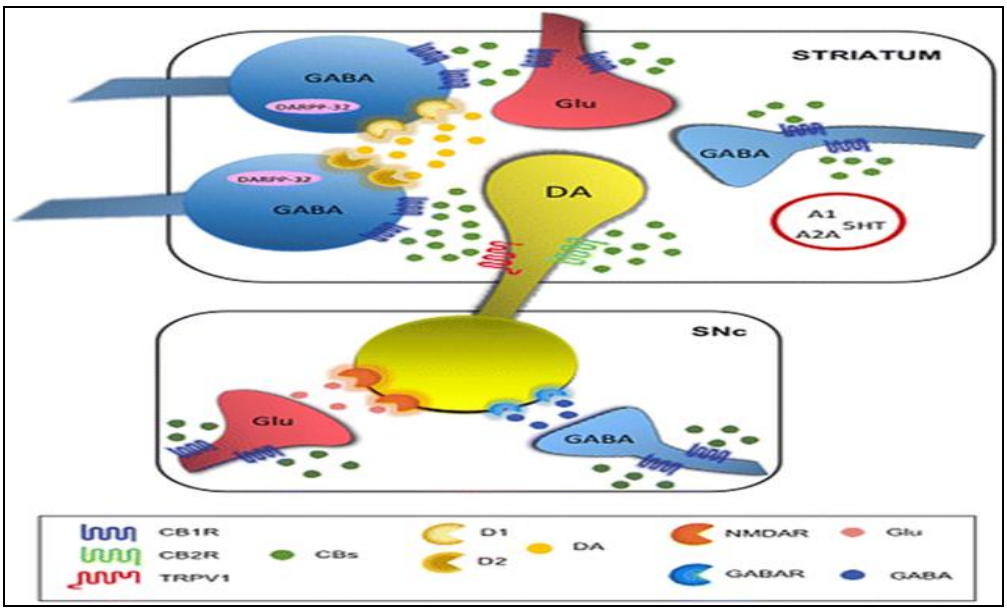

FIG. 1: SCHEMATIC REPRESENTATION EXPLAINING THE INTERACTIONS BETWEEN CANNABINOID SYSTEM AND DOPAMINERGIC TRANSMISSION AT BASAL GANGLIA LEVEL

There is noticeably high expression of CB1R in the cerebellum, particularly on its input into Purkinje cells from the inhibitory basket and stellate interneurons and excitatory climbing fibers, which arise from granule cells, thus indicating the crucial role of CB1R in cerebellar function. In addition, it also shows that CB1R knockout mice, as well as chronic marijuana users or animals administered CB1R agonists, have a clear impairment of eyeblink conditioning, an epitome of cerebellar cortex function [18]. 2-Arachidonoylglycerol (2-AG) and Arachidonoylethanolamide (AEA), two arachidonic acid derivatives, are the major component of endocannabinoids in the brain, cerebellum. At the same time, CB1R is predominantly activated by 2-AG. Increase in the concentration of postsynaptic Ca2+ either by entry through voltage-gated Ca2+ channels or by the

activation of type 1 metabotropic glutamate receptors which causes the release of 2-AG synthesized from diacylglycerol, which is nothing but the reaction catalyzed by diacylglycerol lipase-alpha in the Purkinje cells, with the overall effect of activation of presynaptic CB1R [19]. Moreover, some studies reported the high density of CB1Rs in the striatum and AEA presence throughout the basal ganglia, particularly in the globus pallidus and substantia nigra. Crosstalk between the dopaminergic transmission and ECB signaling in the striatum nigra can be considered great evidence that shows CB1R activation by ECB retrograde signaling and has a great potential to decrease glutamate release in dopaminergic D2 receptor-dependent manner [20].

ECB signaling is bidirectionally linked to dopaminergic signaling within the basal ganglia. CB1, D2, and D1 dopamine receptors are localized in the striatum. In animal models, CB1 and D2 dopamine receptors have a common pool of G proteins, which link their signal transduction mechanisms [21]. In addition to this, D2 receptor stimulation resulted in the release of ECBs in the striatum. Although, stimulation of CB1 receptors completely inhibited the D1-dopamine receptor stimulating the activation of adenylyl cyclase and decreased GABA release from striatal afferents of dopaminergic neurons of the substantia nigra, which resulted in an increased firing of these cells [22]. Another receptor is involved in the control of movement; it is transient receptor potential vanilloid type 1 (TRPV1); these are expressed in sensory neurons and basal ganglia circuitry of dopaminergic neurons. TRPV1 receptors are molecular integrators of nociceptive stimuli activated by Endo vanilloids [23]. TRPV1 also interacts with ECB; particular anandamide is one of the major endogenous activators of TRPV1 [24]. Recent studies have shown that motor behaviour can be suppressed by activating vanilloid receptors 25, hinting that TRPV1 receptors can play a vital role in controlling motor function.

4. Therapeutic features of Cannabis: Cannabis and cannabinoid have an excellent therapeutic potential related to the effects of THC, CBD, and other cannabinoid compounds. Nonetheless, the high effect of THC in cannabis and cannabinoid may limit clinical use; due to this reason, the study on the therapeutic potential of THC alone is more limited. CNS effects of THC include disruption of psychomotor behavior, anti-nociceptive, stimulation of appetite, short-term memory impairment, and antiemetic effects [26]. Other known risk factors involved with long-term use of cannabis include diminished IQ and brain mass, lower cognitive function, low motivation, and poor judgment. It could hasten, worsen, unmask psychosis and chronic bronchitis [27]. Some evidence shows cardiovascular effects of THC shown in the chronic users of cannabis. Moreover, it was found to increase the risks of stroke and heart attack.

So, from this, we can indicate that THC extracted from the Phyto cannabinoids has shown to activate the platelets through CB1 and CB2 receptors, leading to increased GPllb-llla expression and activation of factor Vll, that have a potent thrombogenic protein resulting in stroke and heart attack [28]. Therefore, most research studies emphasize the therapeutic potentials of CBD due to the non-psychotropic chemical of CBD and the combination of THC with CBD. There are clinical research studies of CBD in a variety of neuropsychiatric disorders. Including Parkinson's disease, autistic spectrum disorder 29, anxiety disorder, schizophrenia, neuropathic pain, Huntington disease, Alzheimer's disease, hypoxic ischemic injury, and epilepsy [30].

5. Role of Endocannabinoid: The products extracted from the cannabis plant consist of a large number of Phytocannabinoids, a term used to differentiate cannabinoids derived from the plant, from those found in the body (*i.e.*, endocannabinoids) or those chemically synthesized (*i.e.,* endocannabinoids or exo-CBs), of about 100 phyto-CBs contained in the plant there are two significant ones, namely cannabidiol (CBD) and delta-9-Tetrahydrocannabinol (Δ9-THC). Cannabidiol (CBD) and Δ9-Tetrahydrocannabinol (Δ9-THC, THC) are the major constituents of marijuana [31] among the cannabinoids. Δ9-THC is a psychoactive agent with analgesic and muscle relaxant properties, whereas CBD is a non-psychoactive compound that is shown to have hypnotic, anxiolytic, antipsychotic, antioxidant, and neuroprotective effects [32], THC is a partial agonist at the cannabinoid receptor 1 (CB1) and receptor 2 (CB2). CBD, unlike those Δ9-THC has an

antagonistic or inverse agonistic property at the CB1 receptor; it also appears to regulate Δ9-THC-associated side effects like anxiety, tachycardia, and hunger. By inhibiting their inactivation, CBD also appears to have the same potentiation effect as endocannabinoids, hence alleviating psychotic symptoms [33]. Endocannabinoid (ECB) plays a vital role in neuronal regulation and immune function within the central nervous system (CNS) and is altered in several movement disorders. The cannabinoid receptors are expressed on multiple neuronal populated areas and microglial cells, hinting that activation of these different receptor populations can modulate basal ganglia function in one of various movements disorders [34].

Cannabinoid 1 (CB1) receptor is the most common cannabinoid receptor that is found throughout the CNS, with high levels of expression in the basal ganglia [35]. This CB1 receptor is found on the presynaptic cortical-striatal glutamatergic nerve terminals and decreases the influx of calcium, thereby decreasing glutamate release from the nerve terminal [36]. Medium spiny GABAergic neurons within the striatum express CB1 receptors on dendrites and on their presynaptic terminals, which project to the internal and external segments of the globus pallidus and substantia nigra pars reticulata, and are involved in inhibition of GABA release from presynaptic terminals [37] CB1 receptors are also found on striatal interneurons and on the glutamatergic neurons projecting from the subthalamic nucleus to the internal segment of the globus pallidus [38]. The cannabinoid 2 (CB2) receptors are primarily found on the CNS of glial cells and a subset of a neuronal populated area in the cerebellum and brainstem [39].

Moreover, CB2 receptors are widely expressed outside the CNS, especially on immune cells. The expression of the CB2 receptor has increased on activation of microglial cells. Through the binding of these receptors, the endocannabinoids also decrease in activation of proinflammatory pathways and cytokine production. These CB1 and CB2 receptors are G protein-linked receptors coupled to intracellular signaling pathways, which can modulate several downstream signaling cascades that alter protein function, gene expression and proinflammatory mediators and release of neurotransmitter [40].

6. Cannabis as Neuroprotection in PD: In early years, in animals' studies demonstrated an effect of cannabinoids on the catecholaminergic and dopaminergic systems [41]. So, a compound like Cannabinoid receptor 1 (CB-1R) and the endocannabinoid ligands anandamide and 2-arachidonylglycerol (2-AG) occur in high concentrations in the dopaminergic system, including the striatum, where they modulate dopaminergic transmission as a retrograde feedback system on presynaptic glutamatergic and GABAergic nerve endings.

In the late 1970s, an *in-vitro* study shows conflicting evidence, demonstrating an increase 42 and a dose-dependent decrease in dopamine synthesis and release. In contrast, *in-vivo* studies demonstrate an increase in dopamine release in the prefrontal cortex, striatum, and nucleus acumens. Hence, an increased firing rate of dopaminergic neurons after acute THC exposure can be assumed, resulting in augmented dopamine synthesis and release. Surprisingly, both acute and chronic THC exposure indicates a result in different effects on neuronal firing rate, transmitter synthesis, transmitter release, and reuptake within the dopaminergic system [43]. Endocannabinoid system (ECS) activity increase has been detected in a PD animal model and human tissue analyses from PD patients; this also includes upregulation of cannabinoid receptors [44], an accumulation of cannabinoid receptor agonists, and even reduction in their degradation[45]. This ECS adaptation can be reversed by chronic levodopa substitution in an animal model [46].

Regarding the effect of CB-1R on motor function, experimental studies have shown heterogeneous and partially conflicting results. CB-1R direct activation can reduce dopamine release and show an increase in bradykinesia in MPTP (1-methyl – 4 – phenyl - 1, 2, 3, 6 -tetrahydropyridine) induced PD in animals model [47]. Improvement of motor impairment with cannabinoid receptor agonists can be seen in another report, possibly due to receptor-independent mechanism of action [48]. Moreover, alleviation of levodopa-induced dyskinesia has been reported for cannabinoid receptor agonists and antagonists [49]. Furthermore, ECS activation may confer neuroprotective such as direct receptor-independent mechanisms or activation of anti-

inflammatory cascades in glial cells via cannabinoid receptor 2 (CB-2R) [50] and anti-glutamatergic.

7. Cannabinoid System Activity Changes in PD: Recently, several studies show an important role of the endocannabinoid system in PD. Endocannabinoid system compounds are highly expressed in the neural circuit of basal ganglia, which is part of a complex neuronal system. So, this neuronal system coordinates activities from different cortical regions that directly or indirectly participate in controlling movement. The ECB's system in the basal ganglia bidirectionally interacts with dopaminergic, GABAergic, and glutamatergic signaling systems [51]. These endocannabinoids play an important role in controlling transmission at synapses between cortical and striatal neurons, inducing a particular form of synaptic plasticity and modulating basal ganglia activity and motor functions [52].

PD associated progressive loss of dopaminergic neurons leads to lowering the striatal levels of dopamine. So, these low levels of dopamine result in the alteration of the equilibrium between the direct and the indirect basal ganglia pathways and ECB signaling [53]. The cannabinoid signaling system mentioned above shows a biphasic pattern of changes during the progression of PD [54]. In early and presymptomatic PD stages, characterized by a neuronal malfunction with little evidence of neuronal death, are associated with desensitization or downregulation of CB1R and aggravation of various cytotoxic effects such as oxidative stress excitotoxicity and glial activation [55].

Nonetheless, the intermediate and advanced stages of PD are characterized by a deep nigral degeneration and the manifestation of major Parkinsonian symptoms associated with up regulatory responses of CB1R and the endocannabinoid ligands. Hence, this could help explain the potential of CB1Rligands in alleviating common symptoms of PD. In the brain area, CB1R is expressed by GABAergic neurons that stimulate globus pallidus and substantia nigra's external and internal segments. CB1R is also present in the various region like the corticostriatal glutamatergic terminals, in the excitatory projections from the subthalamic nucleus to the internal segment of the globus pallidus and the substantia nigra [56]. In the striatum, CB1R has expressed in parvalbumin immune-reactive interneurons, nitric oxide synthase-positive neurons and cholinergic interneurons [57]. Animal models of PD depicted an increase in the density of CB1R, levels of endogenous ligands, and even the CB1R, which binds to the basal ganglia [58]. Endogenous cannabinoids activate CB1R on presynaptic axons, which lead to reduced neurotransmitter and glutamate release, working as retrograde synaptic messengers released from postsynaptic neurons. Likewise, activation of CB1R inhibits both glutamate release from substantia nigra afferents and GABA release from striatal afferents. Simultaneously, presynaptic activation of CB1R in the external segments of the globus pallidus can lead to an increase in GABA levels by decreasing GABA reuptake from striatal carrying toward to the nucleus and reducing the GABA release from striatal toward the substantia nigra. In regards to this evidence, it is thought that ECB controls the function of the basal ganglia neuronal system. The presence of ECB systems in different neural structures and their interaction with dopaminergic, glutamatergic and GAB aergic neurotransmitter signaling systems make the components of ECB system an ideal target for a novel non-dopaminergic treatment of PD.

CONCLUSION: Recent studies show that cannabis and its compounds could serve a spromising therapeutic agent in the treatment of neurodegenerative and movement disorders, including Parkinson’s disease. So, we have searched for any scientific evidence that indicates the potential use of cannabis and its related compounds for PD treatment. The current treatment of PD only provide relief of motor symptoms and are associated with adverse effects such as dyskinesia. Moreover, they do not slow the progression of the disease. Therefore, there is an urgent need for a safer drug that can treat both motor and nonmotor symptoms of PD and drugs that slow the progression of the disease. These actions of cannabinoids are mostly through G protein-coupled cannabinoid CB1 (CB1R) and G protein-coupled cannabinoid CB2 (CB2R) activation. So, we can see that cannabinoid receptors and endocannabinoids are most abundant

in the brain areas involved in the management of motor function and have a significant role in modulating many motor functions. Nonetheless, the exact molecular mechanisms of cannabinoid signaling in the pathogenesis of motor-related diseases have not been fully understood, and there are still various significant gaps in our understandings of their influence on motor pathways. Still, medical cannabis appears to have a huge benefit among some of the patients enduring tremor-associated diseases. Therefore, there is a need to improve and develop novel therapeutic strategies using cannabinoid-based medicines with fewer side effects. SO, in this review, we can reasonably conclude that cannabinoids have a potential effect for the management of Parkinson's symptoms and other neuro diseases and some patients with motor-related diseases.

ACKNOWLEDGEMENT: The authors would like to thank The Oxford College of Pharmacy, Bangalore, for the support and help provided in the completion of the

CONFLICTS OF INTEREST: Nil

REFERENCE:

1. Standaert D: Treatment of central nervous system degenerative disorders. Goodman & Gilman's the Pharmacological Basis of herapeutics 2006; 527-45.
2. Siracusa R, Scuto M, Fusco R, Trovato A, Ontario ML, Crea R, Di Paola R, Cuzzocrea S and Calabrese V: Anti-inflammatory and antioxidant activity of Hidrox® in rotenone-induced Parkinson's disease in mice. Antioxidants 2020; 9(9): 824.
3. Patil AS, Mahajan UB, Agrawal YO, Patil KR, Patil CR, Ojha S, Sharma C and Goyal SN: Plant-derived natural therapeutics targeting cannabinoid receptors in metabolic syndrome and its complications: A review. Biomedicine & Pharmacotherapy 2020; 132: 110889.
4. Radwan MM, Chandra S, Gul S and ElSohly MA: Cannabinoids, Phenolics, Terpenes and Alkaloids of Cannabis. Molecules 2021; 26(9): 2774.
5. García C, Palomo-Garo C, Gómez-Gálvez Y and Fernández-Ruiz J: Cannabinoid–dopamine interactions in the physiology and physiopathology of the basal ganglia. British journal of pharmacology 2016; 173(13): 2069-79.
6. Amato G, Khan NS, Maitra R. A patent update on cannabinoid receptor 1 antagonists (2015-2018). Expert opinion on therapeutic patents. 2019 Apr 3;29(4):261-9.
7. Gandor F and Ebersbach G: Cannabinoids in the Treatment of Parkinson's Disease. Neurology International Open 2017; 1(04): 307-11.
8. Fusar-Poli P, Allen P, Bhattacharyya S, Crippa JA, Mechelli A, Borgwardt S, Martin-Santos R, Seal ML, O'Carrol C, Atakan Z and Zuardi AW: Modulation of effective connectivity during emotional processing by Δ9-tetrahydrocannabinol and cannabidiol. International journal of neuropsychopharmacology 2010; 13(4): 421-32.
9. Colizzi M, McGuire P, Giampietro V, Williams S, Brammer M and Bhattacharyya S: Previous cannabis exposure modulates the acute effects of delta-9-tetrahydrocannabinol on attentional salience and fear processing. Experimental and Clinical Psycho-pharmacology 2018; 26(6): 582.
10. Hindocha C, Freeman TP, Schafer G, Gardener C, Das RK, Morgan CJ and Curran HV: Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: a randomised, double-blind, placebo-controlled study in cannabis users. European Neuropsychopharmacology 2015; 25(3): 325-34.
11. Nemade D and Thyagarajan Subramanian VS: An update on medical and surgical treatments of Parkinson's disease. Aging and Disease 2021; 0.
12. Girasole AE: The cellular and circuit mechanisms of hyperkinetic movement disorders (Doctoral dissertation, UCSF); 2019.
13. Syed N, Murphy J, Zimmerman JRT, Mark MH and Sage JI: Ten years' experience with enteral levodopa infusions for motor fluctuations in Parkinson's disease. Movement disorders: Official Journal of the Movement Disorder Society 1998; 13(2): 336-8.
14. Carbone F, Djamshidian A, Seppi K and Poewe W: Apomorphine for Parkinson's disease: Efficacy and safety of current and new formulations. CNS Drugs 2019; 33(9): 905-18.
15. Katzenschlager R, Poewe W, Rascol O, Trenkwalder C, Deuschl G, Chaudhuri KR, Henriksen T, Van Laar T, Spivey K, Vel S and Staines H: Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial. The Lancet Neurology 2018; 17(9): 749-59.
16. Brunt TM and Bossong MG: The neuropharmacology of cannabinoid receptor ligands in central signaling pathways. European Journal of Neuroscience 2020.
17. Lu D and Potter DE: Cannabinoids and the cannabinoid receptors: An overview. Handbook of Cannabis and Related Pathologies 2017; 553-63.
18. Moussa-Tooks AB, Hetrick WP and Green JT: Differential effects of two early life stress paradigms on cerebellar-dependent delay eyeblink conditioning. Neurobiology of Stress 2020; 13: 100242.
19. Gao Y, Vasilyev DV, Goncalves MB, Howell FV, Hobbs C, Reisenberg M, Shen R, Zhang MY, Strassle BW, Lu P and Mark L: Loss of retrograde endocannabinoid signaling and reduced adult neurogenesis in diacylglycerol lipase knockout mice. Journal of Neuroscience 2010; 30(6): 2017-24.
20. Ratano P, Palmery M, Trezza V and Campolongo P: Cannabinoid modulation of memory consolidation in rats: beyond the role of cannabinoid receptor subtype 1. Frontiers in Pharmacology 2017; 8: 200.
21. Martínez-Pinilla E, Rico AJ, Rivas-Santisteban R, Lillo J, Roda E, Navarro G, Lanciego JL and Franco R: Expression of GPR55 and either cannabinoid CB 1 or CB 2 heteroreceptor complexes in the caudate, putamen and accumbens nuclei of control, parkinsonian, and dyskinetic non-human primates. Brain Structure and Function 2020; 225(7): 2153-64.
22. Covey DP, Mateo Y, Sulzer D, Cheer JF and Lovinger DM: Endocannabinoid modulation of dopamine neurotransmission. Neuropharmacology 2017; 124: 52-61.

23. Temel ŞG: The Expression of Vanilloid Receptor Subtype-1 (VR1) in Gonadotropin-Releasing Hormone in Rat Brain. SDÜ Tıp Fakültesi Dergisi 2020; 27(3): 331-6.
24. Palazzo E, Rossi F and Maione S: "Role of TRPV1 receptors in descending modulation of pain," Molecular and Cellular Endocrinology 2008; 286: 79–83.
25. de Lago E, de Miguel R, Lastres-Becker I, Ramos JA and Fernandez-Ruiz J: Involvement of vanilloid-like receptors in the effects of anandamide on motor behavior and nigrostriatal dopaminergic activity: *in-vivo* and *in-vitro* evidence. Brain Research 2004; 1007; 152–159.
26. Consroe P and Sandyk R: Potential role of cannabinoids for therapy of neurological disorders. Marijuana Cannabinoids 2019; 459-524.
27. Volkow ND, Swanson JM, Evins AE, DeLisi LE, Meier MH, Gonzalez R, Bloomfield MA, Curran HV and Baler R: Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. JAMA Psychiatry 2016; 73(3): 292-7.
28. Deusch E, Kress HG and Kraft B: The procoagulatory effects of delta-9-tetrahydrocannabinol in human platelets. Anesth Analg 2004; 99: 1127-1130.
29. Aran A, Cassuto H, Lubotzky A, Wattad N and Hazan E: Brief report: cannabidiol-rich cannabis in children with autism spectrum disorder and severe behavioral problems a retrospective feasibility study. Journal of Autism and Developmental Disorders 2019; 49(3): 1284-8.
30. Iannotti FA, Di Marzo V and Petrosino S: Endocannabinoids and endocannabinoid-related mediators: Targets, metabolism and role in neurological disorders. Progress in Lipid Research 2016; 62: 107-28.
31. Shrader SH, Tong YG, Duff MB, Freedman JH and Song ZH: Involvement of dopamine receptor in the actions of non-psychoactive phytocannabinoids. Biochemical and Biophysical Research Communications 2020; 533(4): 1366-70.
32. Bartoli F, Riboldi I, Bachi B, Calabrese A, Moretti F, Crocamo C and Carrà G: Efficacy of Cannabidiol for Δ-9-Tetrahydrocannabinol-Induced Psychotic Symptoms, Schizophrenia, and Cannabis Use Disorders: A Narrative Review. Journal of Clinical Medicine 2021; 10(6): 1303.
33. Leweke FM, Piomelli D and Pahlisch F: Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Translational Psychiatry 2012; 2(3): 94.
34. Freundt-Revilla J, Kegler K, Baumgärtner W and Tipold A: Spatial distribution of cannabinoid receptor type 1 (CB1) in normal canine central and peripheral nervous system. PLoS One 2017; 12(7): 0181064.
35. Navarrete F, García-Gutiérrez MS, Aracil-Fernández A, Lanciego JL and Manzanares J: Cannabinoid CB1 and CB2 receptors, and monoacylglycerol lipase gene expression alterations in the basal ganglia of patients with Parkinson's disease. Neurotherapeuti 2018; 15(2): 459-69.
36. Kirson D, Oleata CS, Parsons LH, Ciccocioppo R and Roberto M: CB 1 and ethanol effects on glutamatergic transmission in the central amygdala of male and female MSP and Wistar rats. Addict Biology 2018; 23(2): 676-88.
37. Harlan BA, Becker HC, Woodward JJ and Riegel AC: Opposing actions of CRF-R1 and CB1 receptors on VTA-GABAergic plasticity following chronic exposure to ethanol. Neuropsychopharmacol 2018; 43(10): 2064-74.
38. da Cruz JF, Busquets-Garcia A, Zhao Z, Varilh M, Lavanco G, Bellocchio L, Robin L, Cannich A, Julio-Kalajzić F, Leste-Lasserre T and Maître M: Specific hippocampal interneurons shape consolidation of recognition memory. Cell Reports 2020; 32(7): 108046.
39. Magid L, Heymann S, Elgali M, Avram L, Cohen Y, Liraz-Zaltsman S, Mechoulam R and Shohami E: Role of CB2 receptor in the recovery of mice after traumatic brain injury. Journal of Neurotrauma 2019; 36(11): 1836-46.
40. Reyes-Resina I, Navarro G, Aguinaga D, Canela EI, Schoeder CT, Załuski M, Kieć-Kononowicz K, Saura CA, Müller CE and Franco R: Molecular and functional interaction between GPR18 and cannabinoid CB2 G-protein-coupled receptors. Relevance in neurodegenerative diseases. Biochemical Pharmacology 2018; 157: 169-79.
41. Howes J and Osgood P: The effect of delta9-tetrahydrocannabinol on the uptake and release of 14C-dopamine from crude striatal synaptosoma; preparations. Neuropharmacology 1974; 13: 1109–1114.
42. Chetia S and Borah G: Δ 9-Tetrahydrocannabinol toxicity and validation of cannabidiol on brain dopamine levels: an assessment on cannabis duplicity. Natural Products and Bioprospecting 2020; 1-2.
43. Bloomfield MAP, Ashok AH and Volkow ND: The effects of Δ9-tetrahydrocannabinol on the dopamine system. Nature 2016; 539: 369–377.
44. Cooray R, Gupta V and Suphioglu C: Current aspects of the endocannabinoid system and targeted THC and CBD phytocannabinoids as potential therapeutics for Parkinson's and Alzheimer's diseases: a review. Molecular Neurobiology 2020; 57(11): 4878-90.
45. Kicman A, Pędzińska-Betiuk A and Kozłowska H: The potential of cannabinoids and inhibitors of endocannabinoid degradation in respiratory diseases. European Journal of Pharmacology 2021; 174560.
46. Buhmann C, Mainka T, Ebersbach G and Gandor F: Evidence for the use of cannabinoids in Parkinson's disease. J of Neural Transmission 2019; 126(7): 913-24.
47. Meschler JP, Howlett AC and Madras BK: Cannabinoid receptor agonist and antagonist effects on motor function in normal and 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP)-treated non-human primates. Psychopharmacology (Berl) 2001; 156: 79–85.
48. Tchekalarova J, da Conceição Machado K, Júnior AL, Cavalcante AA, Momchilova A, Tzoneva R. Pharmacological characterization of the cannabinoid receptor 2 agonist, β-caryophyllene on seizure models in mice. Seizure 2018; 57: 22-6.
49. Johnston TH, Lee J, Gomez-Ramirez J, Fox SH and Brotchie JM: A simple rodent assay for the *in-vivo* identification of agents with potential to reduce levodopa-induced dyskinesia in Parkinson's disease. Experimental Neurology 2005; 191(2): 243-50.
50. Brugnatelli V, Turco F, Freo U and Zanette G: Irritable bowel syndrome: manipulating the endocannabinoid system as first-line treatment. Frontiers in neuroscience. 2020; 14: 371.
51. Behl T, Kaur G, Bungau S, Jhanji R, Kumar A, Mehta V, Zengin G, Brata R and Fratila O: Distinctive Evidence Involved in the Role of Endocannabinoid Signalling in Parkinson's Disease: A Perspective on Associated Therapeutic Interventions. International Journal of Molecular Sciences 2020; 21(17): 6235.
52. Komeili G, Haghparast E and Sheibani V: Marijuana improved motor impairments and changes in synaptic plasticity-related molecules in the striatum in 6-OHDA-treated rats. Behavioural Brain Research 2021; 410: 113342.
53. Behl T, Kaur G, Bungau S, Jhanji R, Kumar A, Mehta V, Zengin G, Brata R and Fratila O: Distinctive Evidence Involved in the Role of Endocannabinoid Signalling in Parkinson's Disease: A Perspective on Associated

Therapeutic Interventions. International Journal of Molecular Sciences 2020; 21(17): 6235.
54. More SV and Choi DK: Promising cannabinoid-based therapies for Parkinson's disease: motor symptoms to neuroprotection. Molecular Neurodegeneration 2015; 10(1): 1-26.
55. Vallée A, Vallée JN and Lecarpentier Y: Potential role of cannabidiol in Parkinson's disease by targeting the WNT/β-catenin pathway, oxidative stress and inflammation. Aging (Albany NY 2021; 13(7): 10796.
56. Rojo-Bustamante E, Abellanas MA, Clavero P, Thiolat ML, Li Q, Luquin MR, Bezard E and Aymerich MS: The expression of cannabinoid type 1 receptor and 2-arachidonoyl glycerol synthesizing/degrading enzymes is altered in basal ganglia during the active phase of levodopa-induced dyskinesia. Neurobiology of Disease 2018; 118: 64-75.
57. Van Waes V, Beverley J, Siman H, Tseng KY and Steiner H: CB1 cannabinoid receptor expression in the striatum: association with corticostriatal circuits and developmental regulation. Frontiers in Pharmacology 2012; 3: 21.
58. Antonazzo M, Gomez-Urquijo SM, Ugedo L and Morera-Herreras T: Dopaminergic denervation impairs cortical motor and associative/limbic information processing through the basal ganglia and its modulation by the CB1 receptor. Neurobiology of Disease 2021; 148: 105214.

How to cite this article:
Chhakchhuak DZ, Tabassum GSS and Raj A: Review on activity of cannabis treatment on Parkinson's disease. Int J Pharm Sci & Res 2022; 13(6): 2221-29. doi: 10.13040/IJPSR.0975-8232.13(6).2221-29.