(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 6, Issue 2 , Page No: 289-295
March-April 2023

IJMSCR

Genetic Factors Associated With Medical Cannabis Treatment: Efficacy And Safety

Chilita Assamakorn
[1]Mahidol University International Demonstration School,
Salaya, Phutthamonthon, Nakhon Pathom, Thailand 73170

***Corresponding Author:**
Chilita Assamakorn
Mahidol University International Demonstration School,
Salaya, Phutthamonthon, Nakhon Pathom, Thailand 73170

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

The use of cannabis for medicinal purposes is increasing globally. Numerous medical professionals express the need for additional scientific evidence concerning the use of medical cannabis. Patients frequently inquire about clinicians regarding their safety and efficacy. Around 50-70 per cent of the variance in cannabis use and use disorders is due to heritable factors. For cannabis use, the remaining variance can be broken down into familial and person-specific environmental factors, whereas for use disorders, only the latter factor. Numerous candidate gene studies have identified the role of common variation in cannabis involvement susceptibility, but replication has been complex. No genome-wide association study has been adequately powered to identify significant loci. Despite this, research employing polygenic techniques and integrating genetic variation with neural phenotypes and measures of environmental risks, such as childhood adversity, is yielding promising new leads. The small effect sizes associated with cannabis involvement variants will only be reliably identified in significantly larger samples. Furthermore, given the unusual route taken by medical cannabis to legalization, we advocate for changes in public policy to reflect the patient-reported efficacy of cannabis from real-world studies, even though regulatory bodies have not traditionally utilized real-world evidence.

Keywords: Medical Cannabis, endocannabinoid system, cannabinoids, marijuana

Introduction

A*Cannabis Sativa* L, also known as marijuana or hemp, is considered as a herbaceous plant about 28 million years ago [1]. It belongs to the Cannabaceae family, a small family of flowering plants [2]. Cannabis has been widely cultivated in many countries around the world since it is one of the major sources for a lot of products, such as medical uses [3]. Cannabis has been used for medicinal purposes a long time ago [4]. It has been used to treat a lot of diseases, depression, nausea, glaucoma, and Alzheimer's disease [5, 6]. Due to this, it becomes valuable for being able to cure a lot of illnesses [6]. There is an argument between the medical properties that cannabis can be used, and drugs that can make people get addicted. However, cannabis is still one of the modern-day medicines [7]. The number of diseases that cannabis can treat is constantly increasing each day. Some cases of patients with poor prognosis of glioma or epilepsy use cannabis, and their symptoms have gotten better [8]. Nevertheless, the effect of using cannabis is still imponderable as the knowledge of people to this kind of herbaceous plant is still not enough [9]. Due to this problem, the answer to many questions that people have can be answered by the pharmacogenetics [10]. The knowledge about proteins and molecules involved in the transport, action, and metabolism of cannabinoids in the human organism helps people to predict candidate genes which variations are responsible for the presence of the treatment and the

side effects of medical cannabis [11]. It can be divided into receptor genes—*CNR1*, *CNR2*, *TRPV1*, and *GPR55*, transporters—*ABCB1*, *ABCG2*, *SLC6A*, biotransformation, biosynthesis, and bioactivation proteins encoded by *CYP3A4*, *CYP2C19*, *CYP2C9*, *CYP2A6*, *CYP1A1*, *COMT*, *FAAH*, *COX2*, *ABHD6*, *ABHD12* genes, and also *MAPK14* [11, 12]. The purpose of this study is to know and understand how genetic factors can be associated with medical cannabis treatment.

Medical Cannabis

About 10,000 years ago, agricultural farming started, and Cannabis sativa L. is one of the earliest known cultivated plants [3]. This plant is a multi-propose crop with various agricultural and industrial applications, ranging from production of paper, wood, including fiber, to the use in medicinal purposes [13]. The first-ever report was published in 1843, it already revealed the chance of cannabis as a medicinal plant and the extracts of the plant that can be used to treat patients suffering from some disease, tetanus, hydrophobia, and cholera [6, 14]. However, in 1869, the first chemical identified was oxy-cannabis, isolated cannabinoid (1896), and fully identified in 1940 was cannabidiol (CBD) followed by tetrahydrocannabinol (THC) and cannabigerol (CBG) in 1964, and cannabichromene (CBC) in 1966 [1]. Identification of THC later led to an understanding of the endocannabinoid system followed by the discovery of the first cannabinoid receptor (CB1) in 1988 [15]. CB1 receptor acts as a homeostatic regulator of neurotransmitters for pain relief mechanisms, but the same mode of action was responsible for intoxicating effects from cannabinoids' excessive use [16]. Thus, the understanding of mode of action of CB1 receptor raised concerns about the adverse effects of cannabis use [17]. Consequently, the plant was removed from the medicinal category and recategorized exclusively to the category of drug-type plants [18]. Complexity of the cannabinoid pathway, as well as individual genetic predispositions in the population, can lead to various body responses on the cannabinoids treatment [18]. It has been considered that long-term use of cannabis may be a risk factor for psychosis and neurocognitive disorders. Short-term application may result in an increase in non-serious adverse events [18].

The patient's response to cannabinoid treatment may have a genetic background, which depends on genes polymorphism involved in the action, metabolism, and the transport of these substances in the organism [11]. Based on the cannabinoid distribution and activity mechanism as well as proteins involved in their biotransformation, a set of candidate genes can be chosen which variants may determine the therapeutic effect and also the occurrence of possible side effects and adverse reactions [11]. It can be divided into the following groups and contain genes encoding receptors—*CNR1*, *CNR2*, *TRPV1*, *GPR55*, *OPRM1*, and *GABRA2;* transporters and action—*ABCB1*, *ABCG2*, *SLC6A4*, and *COMT*; enzymes involved in the metabolism of cannabinoids—*CYPs* and *UGTs*; biosynthesis, and bioactivation of endocannabinoids: *FAAH*, *MAGL*, *COX2*, *ABHD6*, and *ABHD12*; and cannabinoid-related cellular processes: *MAPK14* [19].

Aspects of genetics and marijuana usage

The research identified 96 genetic variants associated with different cannabis doses. Eighteen of these genetic variants fulfilled the genome-wide significance criteria of p 5–8 and are all freely available [20]. No genetic variants under consideration in this study were reported in several studies [21]. Hence meta-analyses were not possible [13]. However, several of the genetic changes revealed in this study are located in genes that have been linked to mental health in previous research, including ANKFN1, INTS7, PI4K2B, CSMD1, CST7, ACSS1, and SCN9A [11, 22].

With the legalisation of cannabis, more research has been conducted on the substance's virtues and downsides [23]. However, few genome-wide association studies (GWASs) have been conducted to find genetic links between cannabis use and its effects [24]. This review was able to qualitatively analyse data from GWASs with borderline genome-wide significance to identify SNPs that may be replicable in future studies [21]. Six articles providing independent GWAS results were identified, one primarily concerned with a GWAS meta-analysis [15]. Only people of European or African American ancestry were included in the included studies, highlighting the necessity for genetic research in ethnically diverse populations [25]. However, no two studies identified the same

Volume 6, Issue 2; March-April 2023; Page No 289-295
© 2023 IJMSCR. All Rights Reserved

SNP. SNPs were associated with cannabis use disorder, cannabis initiation, age of commencement of cannabis use, DSM-IV cannabis dependence criteria count, and lifetime cannabis use in several gene regions [25]. Based on a review using the Q-genie and GRADE tools, no research or result was deemed poor. In addition, because GWAS require thousands of participants to have enough statistical power, all studies met this condition [25]. As noted, most genes discovered in the included studies had no known function or biological plausibility, and none were associated with cannabis use in any other way [26]. Several genes have been linked to mental health disorders, including *ANKFN1*, *INTS7*, *PI4K2B*, *CSMD1*, *CST7*, *ACSS1*, and *SCNN1*, are protein-coding genes associated with nicotine addiction and quitting smoking [26]. INTS7 is a component of the integrator complex, responsible for the transcription of the short nuclear RNAs U1 and U2 and associated with bipolar temperament [11]. ADHD, logical memory and abnormal neural migration are linked with PI4K2B. Bipolar disorder, disinhibited behaviour, schizophrenia, cognitive tests, chronic bronchitis, and chronic bronchitis have all been connected to CSMD1 [11]. CST7 and alcohol use are connected to myocardial infarction. ACSS1 catalyses the formation of acetyl-CoA and has been associated with cognitive test performance and alcohol use [11]. SCN9A controls the voltage-dependent sodium ion permeability of excitable membranes and is implicated in pain processes, including the onset of inflammatory pain [27]. Since cannabis is known to harm learning, memory, chronic bronchitis, and a recognised relationship with mental illness and a potential role in pain management, these areas may have significance in cannabis use despite having no apparent biological connection [28, 29].

Genetic associations have been discovered between schizophrenia, bipolar disorder, ADHD, depression, and autism spectrum disorder, with a strong genetic correlation between schizophrenia and bipolar disorder and moderate genetic correlations between ADHD and depression, ADHD and autism spectrum disorder, and ADHD and depression [30, 31]. A new GWAS meta-analysis adds to the evidence for shared genetic correlations across neuropsychiatric illnesses by showing that an increased risk of cannabis use disorder is genetically linked to an increased risk of smoking, alcohol use, nicotine dependence, and mental disorders (e.g., ADHD, schizophrenia, major depression) [6]. Moreover, it is essential to note that genes identified in this review as being associated with cannabis use or CUD have also been linked to other neuropsychiatric disorders, such as nicotine dependence, ADHD, bipolar disorder, schizophrenia, and alcohol consumption, suggesting that the genetic risk for the development of these disorders may not be independent [32]. Specific genetic correlations between neuropsychiatric diseases, including cannabis use disorder, may indicate genuine pleiotropy or demonstrate that various mental disorders, including CUD, are not entirely independent [33]. Therefore, it is crucial to investigate the biological and psychological factors that influence the development of neuropsychiatric disorders.

Multiple factors, including genetics, personality and mood characteristics, psychological state, behaviour, neurocognitive ability, and demography, influence neuropsychiatric illnesses [34]. Non-specific to CUD, the prenatal environment, including prenatal nutrition, maternal stress, and maternal drug use, might influence brain development and child behaviour [35]. Potential mechanisms by which the prenatal environment can influence brain development include genetic selection, epigenetic modification, mediation of brain-immune communications, abnormal metabolism pathways, synthetic mediation of hormones and the hypothalamic-pituitary-adrenal axis, and mediation of the microbiota-gut-brain axis [36, 37].

Mechanism of endogenous cannabis

The endocannabinoid system (ECS) is a homeostatic biological system that controls the activity of numerous excitatory and inhibitory neurotransmitter systems, including glutamatergic, serotoninergic, dopaminergic, noradrenaline, acetylcholine, and gamma-aminobutyric acid (GABA) systems [38]. The ECS is composed of the CB1 and CB2 subtypes of the G protein-coupled receptor (GPCR), the endocannabinoid lipid-based ligands 2-arachidonoylglycerol (2-AG) and anandamide (AEA), as well as the enzymes and metabolic processes involved in their synthesis and metabolism [34]. The CB1 receptor consists of 472 amino acids, is encoded by the cannabinoid receptor 1 (CNR1) gene, and is expressed primarily in the brain and

Volume 6, Issue 2; March-April 2023; Page No 289-295
© 2023 IJMSCR. All Rights Reserved

central nervous system, as well as the liver and pancreas [34]. The CB1 receptor of the ECS, in addition to being a receptor for the endogenous cannabinoids 2-AG and AEA, also mediates the effects of cannabis [34]. A single-nucleotide polymorphism (SNP) is a genetic variation at a single nucleotide in which the genetic base differs from the typical base observed in other members of the same species. Genetic variety in the CNR1 gene may result in population-level variations in the receptor's structure and function, influencing CB1 signalling and cannabis's effects [32]. Several SNPs within the CNR1 gene have been identified in the last several decades, and their influence on drug use patterns and effects has been studied [22].

A recent study discovered that rs1049353 T-allele carriers report much less state satiety in response to THC consumption than CC individuals, probably indicating more potent subjective effects resulting in a desire for more cannabis [39]. In contrast, an analysis of sociodemographic data indicates that the CC genotype is more widespread among cannabis users and that the C-allele confers a greater likelihood of becoming a cannabis user [33]. The Profile of Mood States (POMS) scale was utilised to assess emotional impacts on mood pre-and post-cannabis smoking, and it was discovered that C carriers of the rs1049353 polymorphism display higher anger and hostility after cannabis exposure [33]. The rs1049353 polymorphism's predominant C allele has been associated with cannabis dependency symptoms [33]. This connection, however, was not maintained after correction, and neither allele has been associated with cannabis use disorder [33].

Endocannabinoid Candidate Gene Studies

The psychotropic component of cannabis, tetrahydrocannabinol (THC), was discovered in 1964, its binding sites were not identified until the 1980s and 1990s [40]. These discoveries and the ongoing characterisation of the endocannabinoid system have provided the blueprint for contemporary research into the mechanisms by which cannabis influences the body and the diverse roles of the endocannabinoid system in a variety of behavioural and neural phenotypes, such as anxiety, obesity, inflammation, stress recovery, and brain maturation [41]. Additionally, this study sparked other candidate gene studies investigating whether genetic variation within the endocannabinoid system confers susceptibility to cannabis initiation, use, and CUD [38]. Candidate gene association studies of cannabis involvement have primarily focused on variation within the cannabinoid type 1 receptor (CB1) gene (CNR1) due to evidence indicating that the psychoactive effects of cannabis are achieved primarily through THC-CB1 binding and linkage analysis associating the genomic region in which CB1 resides with cannabis use disorder [25]. Nevertheless, despite these intriguing findings, research on CNR1 polymorphisms has generated conflicting relationships with cannabis involvement characteristics [42]. For example, nominally significant connections for the CNR1 Single Nucleotide Polymorphism (SNP) rs806380 (in which the A allele has been linked to increased cannabis dependency) have been reported; however, these are in contrast to reports of no association [7]. A meta-analysis of 3 CNR1 polymorphisms in known data revealed that only the AAT repeat polymorphisms in CNR1 were putatively linked with illegal drug dependency in the general population. Whether these inconclusive results are due to methodological differences (e.g., the control population being exposed to cannabis, e.g., or a mixture of individuals who have never initiated cannabis use and those who have but have not developed cannabis dependence symptoms, e.g.), small studies providing imprecise estimates for minor effects, or are simply false positives, remains unknown [23, 43].

Genetic variation within the Fatty Acid Amide Hydrolase (FAAH) gene, specifically the functional SNP rs324420, has been investigated for its association with marijuana-related traits. FAAH is a membrane-bound enzyme that degrades endocannabinoids (particularly anandamide) [36, 44]. The A allele at rs324420 is related to decreased FAAH expression and, presumably, increased AEA function and AEA-CB1 binding. Although the research on FAAH and marijuana-related traits is substantially smaller than that on CNR1, it has yielded more consistent results [45, 46]. Indeed, evidence suggests that the C allele at rs324420 may confer susceptibility to cannabis dependence, possibly via multiple mechanisms, including increased withdrawal symptoms, greater reward-related brain activation to marijuana cues, and increased positive responsiveness (i.e., increased

Volume 6, Issue 2; March-April 2023; Page No 289-295
© 2023 IJMSCR. All Rights Reserved

happiness and decreased heart rate) following acute marijuana use [5, 11]. It should be noted, however, that there is little genetic research examining the relationship between FAAH and cannabis, and what there is has mostly been done on small sample sizes [47, 48].

Conclusion

Cannabinoid chemicals with potential medical, pharmacological, and neurological uses have been the subject of increased scientific study since cannabis became legal. Recent advances in sequencing methods have prompted a paradigm change in cannabis research toward the genetic genomics of fibre-and drug-producing plants. Due to the exponential expansion of genomic data and the rapid development of artificial intelligence (AI)-based data analysis technologies, it is now possible to investigate cannabis plants at the genetic and molecular levels. Integrated omics studies that combine genomic and expression data with metabolite profiles are now shedding light on the genetic control of the cannabis biosynthesis pathway. In particular, by elucidating the relationship between the expression of cannabinoid genes and the THC: CBD ratio and cannabinoid concentration. The knowledge might be taken further to genetically edit cannabis with pathways tuned for optimal metabolite production and composition. Advanced biotechnology approaches might be expanded for the recombinant synthesis of cannabis in metabolically modified hosts, such as yeasts or bacteria. The recombinant synthesis of THC in yeast is problematic due to unstable THCA and CBGA expression and significant levels of byproducts. In the future, however, combining genetic technologies to get higher expression rates will increase cannabis yields in a way that makes sense from an economic point of view.

References

1. M. Zagožen, A. Čerenak, and S. Kreft, "Cannabigerol and cannabichromene in Cannabis sativa L," Acta Pharmaceutica, vol. 71, no. 3, pp. 355-364, 2021.
2. J. McPartland, "Cannabis: the plant, its evolution, and its genetics—with an emphasis on Italy," Rendiconti Lincei. Scienze Fisiche e Naturali, vol. 31, no. 4, pp. 939-948, 2020.
3. D. Adhikary et al., "Medical cannabis and industrial hemp tissue culture: present status and future potential," Frontiers in plant science, vol. 12, p. 627240, 2021.
4. H. P. V. Rupasinghe, A. Davis, S. K. Kumar, B. Murray, and V. D. Zheljazkov, "Industrial hemp (Cannabis sativa subsp. sativa) as an emerging source for value-added functional food ingredients and nutraceuticals," Molecules, vol. 25, no. 18, p. 4078, 2020.
5. K. Weston-Green, "The united chemicals of cannabis: beneficial effects of cannabis phytochemicals on the brain and cognition," in Recent advances in cannabinoid research: IntechOpen, 2018.
6. J. Sarris, J. Sinclair, D. Karamacoska, M. Davidson, and J. Firth, "Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review," BMC psychiatry, vol. 20, no. 1, pp. 1-14, 2020.
7. G. Abate, D. Uberti, and S. Tambaro, "Potential and Limits of Cannabinoids in Alzheimer's Disease Therapy," (in eng), Biology (Basel), vol. 10, no. 6, Jun 17 2021, doi: 10.3390/biology10060542.
8. M. Haney, "Cannabis use and the endocannabinoid system: a clinical perspective," American Journal of Psychiatry, vol. 179, no. 1, pp. 21-25, 2022.
9. O. Michael, O. Uzoamaka, G. Adaugo, E. N. S. Ohadugha, and A. Chikere, "Cannabis as Medicine: Pros and Cons."
10. C. Citti et al., "Pitfalls in the analysis of phytocannabinoids in cannabis inflorescence," Analytical and Bioanalytical Chemistry, vol. 412, no. 17, pp. 4009-4022, 2020.
11. S. Hryhorowicz, M. Walczak, O. Zakerska-Banaszak, R. Słomski, and M. Skrzypczak-Zielińska, "Pharmacogenetics of cannabinoids," European journal of drug metabolism and pharmacokinetics, vol. 43, no. 1, pp. 1-12, 2018.
12. R. Melzer, P. F. McCabe, and S. Schilling, "Evolution, genetics and biochemistry of plant cannabinoid synthesis: a challenge for biotechnology in the years ahead," Current Opinion in Biotechnology, vol. 75, p. 102684, 2022.
13. J. Gertsch, "The intricate influence of the placebo effect on medical cannabis and cannabinoids,"

Volume 6, Issue 2; March-April 2023; Page No 289-295

© 2023 IJMSCR. All Rights Reserved

Medical Cannabis and Cannabinoids, vol. 1, no. 1, pp. 60-64, 2018.
14. A. Aran, H. Cassuto, and A. Lubotzky, "Cannabidiol based medical cannabis in children with autism-a retrospective feasibility study (P3. 318)," ed: AAN Enterprises, 2018.
15. F. M. Leweke et al., "Role of the endocannabinoid system in the pathophysiology of schizophrenia: implications for pharmacological intervention," CNS drugs, vol. 32, no. 7, pp. 605-619, 2018.
16. J. Tam, L. Hinden, A. Drori, S. Udi, S. Azar, and S. Baraghithy, "The therapeutic potential of targeting the peripheral endocannabinoid/CB1 receptor system," European journal of internal medicine, vol. 49, pp. 23-29, 2018.
17. H.-C. Lu and K. Mackie, "Review of the endocannabinoid system," Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, vol. 6, no. 6, pp. 607-615, 2021.
18. A.-M. Smolyakova, A. Zagzoog, A. L. Brandt, T. Black, K. Mohamed, and R. B. Laprairie, "The endocannabinoid system and synthetic cannabinoids in preclinical models of seizure and epilepsy," Journal of Clinical Neurophysiology, vol. 37, no. 1, pp. 15-27, 2020.
19. A. M. Gregus and M. W. Buczynski, "Druggable targets in endocannabinoid signaling," Druggable Lipid Signaling Pathways, pp. 177-201, 2020.
20. S. Soundararajan et al., "FAAH and CNR1 Polymorphisms in the Endocannabinoid System and Alcohol-Related Sleep Quality," Frontiers in psychiatry, vol. 12, p. 712178, 2021.
21. J. Lazary et al., "Genetic analyses of the endocannabinoid pathway in association with affective phenotypic variants," Neuroscience Letters, vol. 744, p. 135600, 2021.
22. A. Singh, A. Bilichak, and I. Kovalchuk, "The genetics of Cannabis—genomic variations of key synthases and their effect on cannabinoid content," Genome, vol. 64, no. 4, pp. 490-501, 2021.
23. M. F. Fantauzzi et al., "Expression of endocannabinoid system components in human airway epithelial cells: impact of sex and chronic respiratory disease status," ERJ open research, vol. 6, no. 4, 2020.
24. D. Bahceci, "Preclinical validation of endocannabinoid system drug targets for the treatment of Dravet syndrome," 2020.
25. L. Elkrief et al., "Endocannabinoid gene× gene interaction association to alcohol use disorder in two adolescent cohorts," Frontiers in psychiatry, p. 369, 2021.
26. M. Colizzi, S. Cao, J. S. Womersley, and P. Conrod, "Endocannabinoid Gene× Gene Interaction Association to Alcohol Use Disorder in Two Adolescent Cohorts," The Endocannabinoid System: Filling the Translational Gap between Neuroscience and Psychiatry, 2022.
27. D. P. Finn, S. Haroutounian, A. G. Hohmann, E. Krane, N. Soliman, and A. S. C. Rice, "Cannabinoids, the endocannabinoid system, and pain: a review of preclinical studies," Pain, vol. 162, pp. S5-S25, 2021.
28. R. Greco et al., "The endocannabinoid system and related lipids as potential targets for the treatment of migraine-related pain," Headache: The Journal of Head and Face Pain, vol. 62, no. 3, pp. 227-240, 2022.
29. J. Park, "The Potential Ergogenic Effects of CBD and How the ECS Combats Performance Deficits from Overtraining."
30. N. Brunkhorst-Kanaan et al., "Sphingolipid and endocannabinoid profiles in adult attention deficit hyperactivity disorder," Biomedicines, vol. 9, no. 9, p. 1173, 2021.
31. M. De Pol and N. J. Kolla, "Endocannabinoid markers in autism spectrum disorder: A scoping review of human studies," Psychiatry Research, vol. 306, p. 114256, 2021.
32. A. Ahmadalipour et al., "The first evidence of an association between a polymorphism in the endocannabinoid-degrading enzyme FAAH (FAAH rs2295633) with attention deficit hyperactivity disorder," Genomics, vol. 112, no. 2, pp. 1330-1334, 2020.
33. D. Navarro et al., "Molecular Alterations of the Endocannabinoid System in Psychiatric Disorders," International Journal of Molecular Sciences, vol. 23, no. 9, p. 4764, 2022.
34. M. Ahmed, L. M. Best, C. F. Pereira, I. Boileau, and S. Kloiber, "Effects of Endocannabinoid System Modulation on Social Behaviour: A Systematic Review of Animal Studies,"

Volume 6, Issue 2; March-April 2023; Page No 289-295
© 2023 IJMSCR. All Rights Reserved

Neuroscience & Biobehavioral Reviews, p. 104680, 2022.
35. K. Butler and B. Le Foll, "Novel therapeutic and drug development strategies for tobacco use disorder: endocannabinoid modulation," Expert Opinion on Drug Discovery, vol. 15, no. 9, pp. 1065-1080, 2020.
36. R. Meccariello et al., "The epigenetics of the endocannabinoid system," International Journal of Molecular Sciences, vol. 21, no. 3, p. 1113, 2020.
37. A. Veerappa, G. Pendyala, and C. Guda, "A systems omics-based approach to decode substance use disorders and neuroadaptations," Neuroscience & Biobehavioral Reviews, vol. 130, pp. 61-80, 2021.
38. S. Pietropaolo and G. Marsicano, "The role of the endocannabinoid system as a therapeutic target for autism spectrum disorder: Lessons from behavioral studies on mouse models," Neuroscience & Biobehavioral Reviews, 2021.
39. E. Cosker et al., "The effect of interactions between genetics and cannabis use on neurocognition. A review," Progress in Neuro-Psychopharmacology and Biological Psychiatry, vol. 82, pp. 95-106, 2018.
40. S. Pietropaolo, L. Bellocchio, I. Bouzón-Arnáiz, and B. K. Yee, "The role of the endocannabinoid system in autism spectrum disorders: evidence from mouse studies," Progress in Molecular Biology and Translational Science, vol. 173, pp. 183-208, 2020.
41. M. Bioque et al., "Gene-environment interaction between an endocannabinoid system genetic polymorphism and cannabis use in first episode of psychosis," European Neuropsychopharmacology, vol. 29, no. 6, pp. 786-794, 2019.
42. M. Colizzi, R. Bortoletto, R. Costa, S. Bhattacharyya, and M. Balestrieri, "The Autism–Psychosis Continuum Conundrum: Exploring the Role of the Endocannabinoid System," International Journal of Environmental Research and Public Health, vol. 19, no. 9, p. 5616, 2022.
43. I. Gallego-Landin, A. García-Baos, A. Castro-Zavala, and O. Valverde, "Reviewing the Role of the Endocannabinoid System in the Pathophysiology of Depression," Frontiers in pharmacology, vol. 12, 2021.
44. R. Schrott et al., "Cannabis use is associated with potentially heritable widespread changes in autism candidate gene DLGAP2 DNA methylation in sperm," Epigenetics, vol. 15, no. 1-2, pp. 161-173, 2020.
45. L. Li et al., "Identification of key candidate genes and pathways in glioblastoma by integrated bioinformatical analysis," Experimental and Therapeutic Medicine, vol. 18, no. 5, pp. 3439-3449, 2019.
46. Z. Dai et al., "Using literature-based discovery to identify candidate genes for the interaction between myocardial infarction and depression," BMC Medical Genetics, vol. 20, no. 1, pp. 1-10, 2019.
47. T. Kearney-Ramos et al., "The relationship between circulating endogenous cannabinoids and the effects of smoked cannabis," Cannabis and Cannabinoid Research, 2022.
48. T. Chen, "3-year outcomes of cannabis use patterns: evidence from a longitudinal survey," 2019.

Volume 6, Issue 2; March-April 2023; Page No 289-295
© 2023 IJMSCR. All Rights Reserved