WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Background and Current Research on Cannabis Plant and Its Effects on the Body

Mr.Shubham Ramdhan Dabhade, Mr.PrashantIngle, Dr. Shivshankar D. Mhaske

Satyajeet College of Pharmacy, Mehkar

Abstract:-

One of the earliest plants to be cultivated, Cannabis sativa L. is a member of the Cannabaceae family and was first used for food, medicine, and fiber. The plant, which is widely found in both temperate and tropical climates, is referred to by a number of names, such as hemp and marijuana, which have different legal statuses and chemical makeups. While marijuana refers to high-THC strains used for recreational purposes, hemp refers to strains with low levels of the psychoactive chemical delta-9 tetrahydrocannabinol (THC), usually less than 0.3%. Many of the more than 750 bioactive substances found in cannabis, such as terpenes, flavonoids, fatty acids, and cannabinoids (such as THC, cannabidiol [CBD], and cannabigerol [CBG]), contribute to its potential for therapeutic use. Cannabis has been used medicinally to treat a variety of illnesses, such as multiple sclerosis, epilepsy, chronic pain, cancer symptoms, and neurodegenerative diseases. Through the cannabinoid receptors CB1 and CB2, the endocannabinoid system (ECS) is the primary mediator of its pharmacological actions. THC's psychotropic and neuromodulatory effects are caused by CB1 receptors, which are mostly found in the central nervous system. Immune cells have the majority of CB2 receptors, which are linked to anti-inflammatory reactions. Transient receptor potential (TRP) channels, opioids, and serotonin (5-HT1A) are among the additional receptor systems that cannabis interacts with, suggesting a complicated multi-target mechanism of action. The "entourage effect" refers to the synergistic action of cannabis ingredients, whereby terpene and cannabinoid mixtures produce better therapeutic results than single substances.Cannabis is still the most often used illegal substance worldwide, despite its potential medical benefits. It is linked to hazards such psychological disorders and cognitive impairment, especially in teenagers. To fully understand its advantages and disadvantages, improve treatment formulations, and guide public health policy, more study is necessary.

Introduction:-

Cannabis sativa L. (C. sativa) is a flowering shrub plant that grows quickly and reaches a height of 1-2 meters. It is a member of the Cannabaceae family and the Cannabis genus. Originating in Central Asia, C. sativa, sometimes referred to as hemp, cannabis, or marijuana, is widely found in temperate and tropical regions. [1] Plants such as Cannabis sativa or Cannabis indica, or a collection of their bioactive chemicals, are collectively referred to as cannabis [2]. For thousands of years, people have utilized plant components and concoctions for both medicinal and recreational purposes. [3]In the late 19th and early 20th centuries, it was known as “Devil’s lettuce” for its psychoactive effects and thus prohibited in many countries.[4] One of the world's earliest plants to be cultivated is Cannabis sativa L. Humans first utilized it as a textile fabric and as roughage for animal feed, and later on, they turned to it for use in food and medicine [5]. Cannabinoids are bioactive substances found in the plant [6]. Although hemp has been used medicinally in Europe since the 13th century, its anticonvulsant, analgesic, and antiemetic qualities were not established until the 19th century [7]. Russia and Italy were the two largest hemp-growing nations in Europe by the end of the 1950s, both in terms of the amount of acreage utilized and the caliber of the final products produced [8].

However, many nations stopped cultivating the plant and using its seeds and flowers for food production after it was discovered that 9-THC from hemp produces psychotropic effects. This was due to a greater awareness of the plant's negative effects on the human body. Due to its minimal soil and hydrological requirements, hemp has become more and more popular over the years. It can be cultivated on nearly any soil, regardless of climate, and doesn't require specific fertilizers. Because of these benefits, hemp is starting to represent sustainable agriculture. Numerous disorders have been reported to benefit from the use of non-narcotic hemp cultivars [9].Notwithstanding the plant's therapeutic value, it is crucial to remember that, according to estimates from the World Health Organization (WHO), cannabis is the most often grown, trafficked, and abused illegal substance, used by about 147 million people [10]. In many nations, marijuana use can even overtake tobacco use as the most common illegal substance among adults and adolescents [11]. Teenagers' use of marijuana tends to rise progressively [12]. Adolescent cannabis usage has been linked to psychiatric symptoms such psychosis, mania, and suicidality as well as poor cognitive function [13].It's critical to distinguish between marijuana and hemp when discussing the impact of the cannabis plant on health and wellness. The term hemp is used to refer to therapeutic ingredients, fibers, and seeds [15], whereas the name marijuana is primarily used to refer to the plant's recreational uses [14]. The distinction between these phrases may also be botanical in nature, since hemp is the fibrous part of the plant, whereas marijuana refers to the flowering tops, seeds, stems, and leaves of C. sativa [16]. Furthermore, according to pharmacological definitions, hemp is a cannabis plant that has a total delta-9 tetrahydrocannabinol (THC) content of less than 0.3% (w/w), whereas marijuana has a THC content of more than 0.3% (w/w) [17].Because of the complexity of the molecules, there is a considerable chance that components of different cannabis products will combine. The psychoactive compounds 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most well-known, well-known, and responsible for the pharmacological activity of the Cannabis sp., out of the more than 100 cannabinoids that have

been found thus far [18]. The plant produces these cannabinoids in an acidic form, which need to be decarboxylated, primarily by a high temperature. Other cannabinoids, including cannabigerol (CBG), cannabichromene (CBC), cannabidivarin
(CBDV), and cannabinol (CBN), are also present in the plant. But the Cannabis sp. is made up of more than only cannabinoids. Sugars, steroids, fatty acids, noncannabinoid phenols, flavonoids, phenylpropanoids, alkanes, and nitrogenous compounds are among the more than 600 compounds that have been reported thus far, including more than 150 distinct terpenes, including monoterpenes, sesquiterpenes, and di- and triterpenes [19].According to estimates, 38 million people worldwide are infected with HIV [20], 170 million with hepatitis C virus [21], 10–20 million with human T-lymphotropic virus type 1 (HTLV-1 [22]), and an estimated 161 million have contracted the coronoavirus SARS-Cov2 [23]. These figures are in addition to problematic cannabis use. Numerous negative physiological, psychological, social, and economic effects are linked to cannabis use.Numerous reviews and publications have focused on the psychological effects of marijuana use, including school dropout, low academic performance, and antisocial and other behaviors in young people. Nearly every physiological and biochemical system is affected by cannabis usage, including the immunological, hepatic, renal, endocrine, reproductive, and central neurological systems, as well as genetics and overall health [24].Cannabis has chemicals that can be used to treat pain and lessen the negative effects of certain medical treatments. One of the most significant cannabis chemicals, cannabidiol, for instance, soothes a variety of chronic and nonchronic pains and can be used to treat anxiety, nausea, inflammation, and febrile convulsions [25]. According to recent research, these substances can effectively treat breast and other types of cancer as well as modulate or alleviate the symptoms of rheumatism, migraine, multiple sclerosis (MS), and schizophrenia [26]. Another significant cannabis-derived pharmaceutical is Marinol®, which is administered as an anti-nausea and appetite suppressant for patients receiving chemotherapy, experiencing radiation-induced nausea, or experiencing neurotoxicity as a result of AIDS. It has been demonstrated that the benefits of cannabis and its cannabinoids are effective in reducing some of the symptoms associated with AIDS [27].Cannabis sativa L., a plant that has been grown since ancient times, primarily for its fibers and oil but also for its medicinal qualities, is one of the plants that is being examined more frequently because of the promising multidirectional biological activity of its ingredients [1]. The plant has a large number of physiologically active chemicals [28], which makes it particularly intriguing as a source of molecules that have been identified as medicinal as well as compounds that are being studied for their medical qualities [29]. Components of Cannabis sativa L. that exhibit antioxidant qualities are of special interest because they may be able to reduce oxidative stress, which is linked to the onset of many illnesses [30].

Background on the Cannabis Plant:-

Numerous trichomes, which resemble protuberances and cover the plant's leaves and stems, are a defining trait of cannabis. There are two types of trichomes in Cannabis sativa L.: glandular (secretory) and non-glandular. Many physiologically active substances, including terpenoids (which give hemp its scent) and phytocannabinoids (which shield the plant from pests and herbivores), are biosynthesised and/or released within the secretory trichomes. Furthermore, more than 750 compounds with a wide range of biological activities have been found in hemp, such as terpenoids (140 compounds), flavonoids (23 chemical individuals), and cannabinoids (86 compounds) [51]. The specific chemical individuals' contents are closely linked to the type of hemp. This variance is most noticeable in 9-THC concentration, which varies according to the plants' intended purpose. Insignificant levels of the psychoactive cannabinoid, which is present in high concentrations in the so-called "medical varieties," are detected in Cannabis sativa L. cultivars used for primarily industrial reasons (such as those related to the textile industry or the production of biomaterials for construction). This is related to the fact that many nations prohibit the growth of cultivars with high levels of 9-THC; only medical and scientific uses are permitted [52]. Variable amounts of phytocannabinoids, such as cannabidiol and cannabigerol, which do not have psychoactive effects, are another manifestation of variations in phytocannabinoid contents brought on by the various intended applications of cannabis cultivars [53]. It is important to note that the flowers and leaves of inflorescences that are harvested from the top portions of the plant have the highest concentrations of CBG within a single plant; these contents are roughly ten times higher than those found in fan leaves [52]. In addition to the substantial amounts of terpenoid and cannabinoid, hemp contains fatty acids (e.g., -linolenic acid, oleic acid, and linoleic acid), carbohydrates (mono-, di-, and polysaccharides, and amino sugars), flavonoids (e.g., terpinolene, quercitrin, kaempferol), phytosterols, vitamins, simple alcohols, esters, and organic acids (Figure 1). It's interesting to know that hemp seed oil contains 33 different types of fatty acids, with unsaturated acids being the most prevalent. Linoleic (LA), α-linolenic (ALA), oleic (OA), γ-linolenic (GLA), stearidonic (SDA), and cis-vaccenic acids are all present in the oil in significant amounts [54]. been found in hemp seed oil, with unsaturated acids being the group that is obviously most prevalent. Linoleic (LA), -linolenic (ALA), oleic (OA), -linolenic (GLA), stearidonic (SDA), and cis-vaccenic acids are all abundant in the oil. [54] A class of 21-carbon terpenophenolic chemicals is known as phytocannabinoids [55]. As of right now, phytocannabinoids are a class of terpenophenolic substances with 21 carbons [55]. To date, cannabis has yielded about 120 phytocannabinoids, including two compounds: (−)-trans-Δ9-tetrahydrocannabinol (Δ9-THC...). Two compounds, ()trans-9-tetrahydrocannabinol (9-THC) and ()-trans-8-tetrahydrocannabinol (8-THC), are among the more than 120 phytocannabinoids that have been identified from cannabis. These compounds bind to cannabinoid receptors to create the distinctive psychoactive effect [56]. Cannabigerol and its derivatives are another group of phytocannabinoids that include 16 of them [57].Hemp contains cannabinol (CBN), cannabidiol (CBD), cannabichromene (CBC), 9-tetrahydrocannabivarin (THCV), cannabivarin (CBV), and cannabidivarin (CBDV) in addition to thephytocannabinoids mentioned above [58]. Despite having lesser concentrations in Cannabis sativa L., other phytocannabinoids, including cannabinodiol (CBND), cannabielsion (CBE), cannabicyclol (CBL), and cannabitriol (CBT), have also been the focus of research in recent decades [23]. and (−)-trans-Δ8-tetrahydrocannabinol (Δ8-THC), which bind to cannabinoid receptors to provide the distinctive psychotropic effect [56]. Cannabigerol and its derivatives are another group of phytocannabinoids that include 16 of them [57]. Hemp contains cannabinol (CBN), cannabidiol (CBD), canna bichromene (CBC), Δ9-tetrahydrocannabivarin (THCV), cannabivarin (CBV), and canna bidivarin (CBDV) in addition to the phytocannabinoids mentioned above [58].Despite having lesser concentrations in Cannabis sativa L., other phytocannabinoids, including cannabinodiol (CBND), cannabielsion (CBE), cannabicyclol (CBL), and cannabitriol (CBT), have also been the focus of research in recent decades [59]. Like endocannabinoids, phytocannabinoids are thought to influence the human body by interacting with Gprotein-coupled membrane receptors, such as cannabinoid receptors (CB1 and CB2), to which members of the group exhibit varying degrees of affinity [58]. Additionally, several phytocannabinoids have recently been found to have molecular targets

outside of the endocannabinoid system. It has been demonstrated that plant cannabinoids interact with nuclear receptors, ligand-gated ion channels, transient receptor potential (TRP) channels, opioid or serotonin receptors, and other G proteincoupled receptors (GPR55 or GPR18 receptors) [60].

Fig. Cannabis Sativa L

release and immune cell movement to produce anti-inflammatory and analgesic effects. [68].
• CBD has a modest affinity for CB1 and CB2 receptors but indirectly affects their activity, whereas THC is a partial agonist at both receptors [66].

2. Neurotransmitter Modulation

THC and CBD affect a number of non-cannabinoid receptor systems: • THC interacts with serotonin 5-HT1A receptors, which contributes to its anxiolytic effects, and mu-opioid receptors, which enhance pain relief [67]. Conversely, CBD increases the concentration and effect of an endogenous cannabinoid by inhibiting the FAAH enzyme, which stops it from breaking down
[65].

3. Signaling Pathways Within Cells

Activation of cannabinoid receptors affects the MAPK and PI3K-AKT pathways and suppresses cyclic AMP levels. These cascades alter inflammation, neuronal plasticity, and cell survival [69].

4. Pharmacokinetics and Distribution

THC is highly lipophilic, allowing rapid distribution to fatty tissues such as the brain.

- When inhaled, it reaches peak plasma levels within minutes; when ingested, onset is delayed due to first-pass metabolism in the liver, where it is converted to 11-hydroxy-THC, a more potent psychoactive metabolite [65].
- THC and its metabolites are stored in adipose tissue and released gradually, contributing to prolonged effects [70].

5. Anti-inflammatory and immunomodulatory effects

By activating CB2 and PPAR-γ receptors, cannabinoids reduce the release of pro inflammatory cytokines such TNF-α and IL-6.
• A rise in anti-inflammatory markers including IL-10 expression [71]. In chronic inflammatory conditions such multiple sclerosis and rheumatoid arthritis, these effects are noteworthy [70].

6. The Encouragement Effect

Terpenes and flavonoids are among the more than 500 bioactive substances found in cannabis that alter the effects of cannabinoids; this is referred to as the "entourage effect" [72]. Myrcene, for instance, might increase THC's ability to pass across the blood-brain barrier.

7. Pharmacokinetics and Delivery Methods

The effects of cannabis vary significantly by delivery method and metabolism:

- Inhalation (Smoking/Vaping):

Onset: 5–10 minutes.

Peak plasma THC levels within 10–15 minutes.

Bioavailability: ~10–35% due to combustion losses.

Effects typically last 2–4 hours [73].

- OralIngestion (Edibles):

Onset: 30–90 minutes.

Peak effects: 2–4 hours post-ingestion.

Bioavailability: Lower (~6–10%) due to first-pass hepatic metabolism.

Duration: 6–8 hours, longer with high-fat foods [74].

- Topical/Transdermal:

Offers localized effects without significant psychoactivity; bioavailability remains under investigation [75].

Medicinal Properties of Cannabis

General Overview of Medicinal Properties of Cannabis and Their Mode of Action

A substantial body of scientific literature supports the medicinal potential of cannabis, highlighting its diverse pharmacological properties such as anti-inflammatory [31], anti-diabetic [32], neuroprotective [33], anti-cancer [34], antioxidant [35], antimicrobial [36], antiviral [37], and antifungal activities [38]. Cannabis has demonstrated therapeutic efficacy in managing a range of health conditions, including epilepsy, Alzheimer's disease, Parkinson's disease, post-traumatic stress disorder (PTSD), skin disorders, and cancer, along with cancer-associated symptoms such as appetite loss, chronic pain, and nausea [39].The therapeutic effects of cannabis are attributed to its rich phytochemical profile, which varies in effectiveness based on factors such as concentration, stability, volatility, pharmacological activity, physicochemical characteristics, and interactions between compounds [40]. Multiple classification systems exist for cannabis chemotypes; one such system identifies five chemotypes according to their dominant terpenes: (i) myrcene, (ii) α- and βpinene, (iii) caryophyllene and limonene, (iv) caryophyllene alone, and (v) terpinolene [41].It is essential to recognize that the active constituents of many plant extracts, including cannabis, can interact synergistically or antagonistically [42]. Synergy refers to a scenario where the combined effect of two or more compounds exceeds the sum of their individual effects [43]. Such synergistic interactions among phytocannabinoids and other cannabis-derived phytochemicals contribute significantly to its wide-ranging therapeutic applications. However, many of these interactions remain unexplored or insufficiently studied. In some cases, antagonistic effects may occur. For instance, two bicyclic monoterpenes, α-pinene and β-pinene, have been shown to inhibit acetylcholinesterase activity in the brain, which may enhance memory and mitigate the cognitive impairment caused by THC intoxication [44].Synergistic mechanisms involving phytocannabinoids and terpenoids have potential therapeutic relevance in the treatment of conditions like allodynia, itch, and other superficial pain disorders affecting the skin and peripheral sensory nerves [45]. Known mechanisms of synergy include multi-target actions, pharmacokinetic modifications, and the modulation of adverse effects [46]. Additionally, cannabisderivedphytocannabinoids and terpenes may play a role in the treatment of diabetes and its complications [47].These interactions collectively contribute to what is known as the "entourage effect," wherein the presence of multiple cannabis compounds enhances the efficacy of the active agent beyond what is observed with isolated constituents [48]. First introduced by Ben-Shabat et al. in 1998 [48], this concept remains a focal point for ongoing research, as many potential synergistic combinations of cannabis components have yet to be thoroughly investigated. Experimental studies continue to demonstrate that cannabis extracts often exhibit superior medicinal properties compared to individual isolated compounds, supporting the existence of the entourage effect [49]. A comprehensive understanding of this effect could lead to the classification of interactions between phytocannabinoids, terpenoids, and phenylpropanoids as synergistic in nature [50].

Medicinal Properties of Cannabis sativa L. (central node)

1. Pain Relief (Analgesic)
2. Anti-inflammatory
3. Anti-nausea (Antiemetic)
4. Appetite Stimulation
5. Seizure Control (Anticonvulsant)
6. Anxiety Relief (Anxiolytic)
7. Sleep Aid
8. Neuroprotective Effects
9. Muscle Spasm Relief (Antispasmodic)

Adverse Effects and Risks:-

Cannabis use poses several health risks:

- CognitiveandPsychiatricEffects: Regular use, particularly beginning in adolescence, has been linked to impairments in memory, attention, and executive function. It also increases the risk of psychiatric disorders like anxiety, depression, and schizophrenia in genetically susceptible individuals
- [73].
- Dependency and Withdrawal: Cannabis use disorder (CUD) affects around 9– 10% of users. Dependence can result in withdrawal symptoms like irritability, sleep disturbances, and appetite changes [74].
- Respiratory Health: Smoking cannabis may lead to airway inflammation and chronic bronchitis. The link with lung cancer remains unclear due to confounding factors like tobacco use [75].
- Cardiovascular Risks: THC can cause transient increases in heart rate and blood pressure, which may elevate the risk of cardiac events, particularly in older adults or those with pre-existing conditions [76].
- ReproductiveandPrenatalImpact: Prenatal cannabis exposure is associated with lower birth weights and may affect fetal brain development [77].

(CBD)—have garnered the most research interest. These compounds interact with a broad range of molecular targets, especially within the endocannabinoid system, which is integral to maintaining physiological balance, immune responses, and neurological function.THC, through its interaction with CB1 receptors, is responsible for the psychoactive properties of cannabis, yet also contributes to therapeutic effects such as analgesia, antiemesis, and relief from muscle spasticity. In contrast, CBD, a non-psychoactive cannabinoid, exhibits anti-inflammatory, anxiolytic, and neuroprotective activities. It exerts these effects not only by modulating endocannabinoid tone but also through interactions with other molecular targets, including serotonin receptors and ion channels. This broad receptor activity accounts for the wide array of physiological and psychological effects attributed to cannabis, which supports its clinical application in treating conditions ranging from epilepsy and multiple sclerosis to symptoms associated with cancer and psychiatric disorders.Despite its therapeutic promise, cannabis also poses certain risks, particularly among adolescents. Early and frequent cannabis use during neurodevelopmental stages has been associated with cognitive impairment, increased risk of psychosis, and social difficulties. This dichotomy between potential benefit and harm highlights the need for a balanced, evidence-driven approach to cannabis use, grounded in scientific rigor and public health
considerations.Furthermore, distinctions between high-THC "marijuana" strains and low-THC "hemp" cultivars emphasize the need for accurate chemical characterization to ensure the safety and efficacy of medical cannabis products. A particularly noteworthy concept in cannabis pharmacology is the "entourage effect"—the theory that combined activity of cannabinoids, terpenes, and other phytochemicals may enhance therapeutic effects while reducing adverse outcomes. This challenges the conventional reductionist model of pharmaceutical development and supports the potential value of full-spectrum cannabis extracts in clinical settings.In conclusion, Cannabis sativa represents a plant of significant therapeutic promise and complex pharmacodynamics. Its future utility in medicine depends on responsible application, guided by comprehensive scientific research, robust regulatory oversight, and policies that ensure equitable and informed access. Harnessing the full spectrum of its bioactive compounds while minimizing potential harms will be essential in
integrating cannabis into modern healthcare.

References:-

1. Bonini SA, Premoli M, Tambaro S, Kumar A, Maccarinelli G, Memo M, et al. Cannabis sativa: A comprehensive ethnopharmacological review of a medicinal plant with a long history. J Ethnopharmacol. 2018;227:300–15.
2. Jett J, Stone E, Warren G, Cummings KM. Cannabis use, lung cancer, and related issues. J Thorac Oncol. 2018;13:480–7.
3. Page RL 2nd, Allen LA, Kloner RA, Carriker CR, Martel C, Morris AA, et al. Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement From the American Heart Association. Circulation. 2020;142:e131–52.
4. Napoletano F, Schifano F, Corkery JM, Guirguis A, Arillotta D, Zangani C, et al. The psychonauts' world of cognitive enhancers. Front Psychiatry.
5. 2020;11:546796.
6. Pellati F, Borgonetti V, Brighenti V, Biagi M, Benvenuti S, Corsi L. Cannabis sativa L. and non-psychoactive cannabinoids: Their chemistry and role against oxidative stress, inflammation and cancer. Biomed Res Int. 2018;2018:1691428.
7. Karas JA, Wong LJ, Paulin OKA, Mazeh AC, Hussein MH, Li J, et al. The antimicrobial activity of cannabinoids. Antibiotics. 2020;9:406.
8. Baker D, Pryce G, Giovannoni G, Thompson AJ. The therapeutic potential of Cannabis. Lancet Neurol. 2003;2:291–8.
9. Da Porto C, Decorti D, Natolino A. Potential oil yield, fatty acid composition, and oxidation stability of the hempseed oil from four Cannabis sativa L. cultivars. J Diet Suppl. 2014;12:1–10.
10. Farinon B, Molinari R, Costantini L, Merendino N. The seed of industrial hemp (Cannabis sativa L.): Nutritional quality and potential functionality for human health and nutrition. Nutrients. 2020;12:1935.
11. Alves VL, Gonçalves JL, Aguiar J, Teixeira HM, Câmara JS. The synthetic cannabinoids phenomenon: From structure to toxicological properties. A review. Crit Rev Toxicol. 2020;50:359–82.
12. Winters KC, Waldron H, Hops H, Ozechowski T, Montano A. Brief interventions for cannabis using adolescents. Child AdolescPsychiatr Clin N Am. 2023;32:127–40.
13. Riggs P, Hinckley JD, Ross JM. Addressing cannabis use during adolescence. Child AdolescPsychiatr Clin N Am. 2023;32:xiii–xv.
14. Johnson-Ferguson L, Di Forti M. From heavy cannabis use to psychosis: Is it time to take action? Ir J Psychol Med. 2023;40:13–8.
15. Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: A clinical review. JAMA.
16. 2015;313:2474–83.
17. Johnson R. Hemp as an agricultural commodity. Washington, DC: Congressional Research Service; 2013.
18. Hasan MA, Hussain MH, Chowdhury AS, Dhar SB, Abedin M, Fima IN. Computational identification of potential microRNAs and their targets from expressed sequence tags of marijuana (Cannabis sativa). Meta Gene. 2016;10:45–55.
19. Acosta A, Li L, Weaver M, Capote R, Perr J, Almirall J. Validation of a combined Fast blue BB and 4-Aminophenol colorimetric test for indication of Hemp-type and Marijuana-type cannabis. Forensic Chem.
20. 2022;31:100448.
21. Ferber SG, Namdar D, Hen-Shoval D, Eger G, Koltai H, Shoval G, et al. The "entourage effect": Terpenes coupled with cannabinoids for the treatment of mood disorders and anxiety disorders. CurrNeuropharmacol. 2020;18:87–96.
22. Namdar D, Voet H, Ajjampura V, Nadarajan S, Mayzlish-Gati E, Mazuz M, et al. Terpenoids and phytocannabinoids co-produced in Cannabis sativa strains show specific interaction for cell cytotoxic activity. Molecules. 2019;24:3031.
23. Centers for Disease Control and Prevention. Global HIV and TB [Internet]. 2021 [cited 2021 Feb 21]. Available from: https://www.cdc.gov/globalhivtb/ index.html
24. Centers for Disease Control and Prevention. Global viral hepatitis: Millions of people are affected [Internet]. 2021 [cited 2021 Feb 21].
25. Available from: https://www.cdc.gov/hepatitis/global/
26. National Organization for Rare Disorders. Rare Disease Database: HTLV Type I and Type II [Internet]. 2021 [cited 2021 Feb 21]. Available from: https://rarediseases.org/rare-diseases/htlv-type-i-and-type-ii/
27. Johns Hopkins University of Medicine. Coronavirus Resource Center
28. [Internet]. [cited 2021 May 23]. Available from: https://coronavirus.jhu.edu/
29. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014;370:2219–27.
30. Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French JA, Hill C, et al. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia. 2014;55:791–802.
31. Russo EB. Cannabis therapeutics and the future of neurology. Front IntegrNeurosci. 2018;12:51.
32. Ellis RJ, Topero W, Vaida F, van den Brande G, Gonzales J, Gouaux B, et al. Smoked medicinal cannabis for neuropathic pain in HIV: A randomized, crossover clinical trial. Neuropsychopharmacology. 2008;34:672–80.
33. Hartsel JA, Eades J, Hickory B, Makriyannis A. Chapter 53—Cannabis sativa and hemp. In: Gupta RC, editor. Nutraceuticals. Boston, MA: Academic Press; 2016. p. 735–54. ISBN: 978-0-12-802147.
34. Stasiłowicz A, Tomala A, Podolak I, Cielecka-Piontek J. Cannabis sativa L. as a natural drug meeting the criteria of a multitarget approach to treatment. Int J Mol Sci. 2021;22:778.
35. García-Valverde MT, de Medina VS, Codesido V, Hidalgo-García J, FerreiroVera C. Exploring the mysteries of cannabis through gas chromatography.
36. In: Mutelet F, editor. Recent Advances in Gas Chromatography. London, UK: IntechOpen; 2020. ISBN: 978-1-83962-603-6.
37. Carvalho ACAD, Souza GAD, Marqui SVD, Guiguer ÉL, Araújo AC, Rubira CJ, et al. Cannabis and cannabinoids on the inflammatory bowel diseases:
38. Going beyond misuse. Int J Mol Sci. 2020;21:2940.

39. Kim Y, Kim W, Kim S-H, Sim K-S, Kim K-H, Cho K-H, et al. Protective effects of hemp (Cannabis sativa) root extracts against insulin-deficient diabetes mellitus in mice. Molecules. 2023;28:3814.
40. Borgonetti V, Biagi M, Galeotti N, Manetti F, Governa P. Investigation on the neuroprotective effect of a cannabidiol-enriched non-psychotropic Cannabis sativa L. extract in an in vitro model of excitotoxicity. Fitoterapia.
41. 2022;163:105315.
42. Seltzer ES, Watters AK, MacKenzie DJ, Granat LM, Zhang D. Cannabidiol
43. (CBD) as a promising anti-cancer drug. Cancers. 2020;12:3203.
44. Russo F, Tolomeo F, Vandelli MA, Biagini G, Paris R, Fulvio F, et al.
45. Kynurenine and kynurenic acid: Two human neuromodulators found in
46. Cannabis sativa L. J Pharm Biomed Anal. 2022;211:114636.
47. Barak T, Sharon E, Steinberg D, Feldman M, Sionov RV, Shalish M. Antibacterial effect of cannabidiol against the cariogenic Streptococcus mutans bacterium: An in vitro study. Int J Mol Sci. 2022;23:15878.
48. Milloy MJ, Marshall B, Kerr T, Richardson L, Hogg R, Guillemi S, et al. High-intensity cannabis use associated with lower plasma human immunodeficiency virus-1 RNA viral load among recently infected people who use injection drugs. Drug Alcohol Rev. 2015;34:135–40.
49. Glodowska M. Cannabis sativa L. and its antimicrobial properties—A review. Pulawy, Poland: Institute of Soil Science and Plant Cultivation— State Research Institute; 2016.
50. Pattnaik F, Nanda S, Mohanty S, Dalai AK, Kumar V, Ponnusamy SK, et al.
51. Cannabis: Chemistry, extraction and therapeutic applications. Chemosphere. 2022;289:133012.
52. Mullins M. Defining recent cannabis use analytically. Clin Toxicol. 2023;61:324–5.
53. Shapira A, Berman P, Futoran K, Guberman O, Meiri D. Tandem mass spectrometric quantification of 93 terpenoids in cannabis using static headspace injections. Anal Chem. 2019;91:11425–32.
54. Hochma E, Yarmolinsky L, Khalfin B, Nisnevitch M, Ben-Shabat S, Nakonechny F. Antimicrobial effect of phytochemicals from edible plants. Processes. 2021;9:2089.
55. Greco WR, Faessel H, Levasseur L. The search for cytotoxic synergy between anticancer agents: A case of Dorothy and the ruby slippers? J Natl Cancer Inst. 1996;88:699–700.
56. Miyazawa M, Yamafuji C. Inhibition of acetylcholinesterase activity by bicyclic monoterpenoids. J Agric Food Chem. 2005;53:1765–8.
57. Schlosburg JE, O'Neal ST, Conrad DH, Lichtman AH. CB1 receptors mediate rimonabant-induced pruritic responses in mice: Investigation of locus of action. Psychopharmacology. 2011;216:323–31.
58. Wagner H, Ulrich-Merzenich G. Synergy research: Approaching a new generation of phytopharmaceuticals. Phytomedicine. 2009;16:97–110.
59. Ghasemi-Gojani E, Kovalchuk I, Kovalchuk O. Cannabinoids and terpenes for diabetes mellitus and its complications: From mechanisms to new therapies. Trends Endocrinol Metab. 2022;33:828–49.
60. Ben-Shabat S, Fride E, Sheskin T, Tamiri T, Rhee MH, Vogel Z, et al. An entourage effect: Inactive endogenous fatty acid glycerol esters enhance 2arachidonoyl-glycerol cannabinoid activity. Eur J Pharmacol. 1998;353:23–
61. 31.
62. Russo EB. Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol.
63. 2011;163:1344–64.
64. Koltai H, Poulin P, Namdar D. Promoting cannabis products to pharmaceutical drugs. Eur J Pharm Sci. 2019;132:118–20.
65. Hartsel JA, Eades J, Hickory B, Makriyannis A. Chapter 53—Cannabis Sativa and Hemp. In: Gupta RC, editor. Nutraceuticals. Boston, MA:
66. Academic Press; 2016. p. 735–54. ISBN: 978-0-12-802147-7.
67. Bernstein N, Gorelick J, Koch S. Interplay between chemistry and morphology in medical cannabis (Cannabis sativa L.). Ind Crops Prod. 2019;129:185–94.
68. Schilling S, Melzer R, McCabe PF. Cannabis sativa. Curr Biol. 2020;30:R8–9.
69. Brenneisen R. Chemistry and analysis of phytocannabinoids and other cannabis constituents. In: ElSohly MA, editor. Marijuana and the Cannabinoids. Totowa, NJ: Humana Press; 2007. p. 17–49. (Forensic
70. Science and Medicine). ISBN: 978-1-59259-947-9.
71. Nigro E, Formato M, Crescente G, Daniele A. Cancer initiation, progression and resistance: Are phytocannabinoids from Cannabis sativa
72. L. promising compounds? Molecules. 2021;26:2668.
73. Tagen M, Klumpers LE. Review of delta-8-tetrahydrocannabinol (Δ8THC): Comparative pharmacology with Δ9-THC. Br J Pharmacol.
74. 2022;179:3915–33.
75. Filipiuc LE, Ababei DC, Alexa-Stratulat T, Pricope CV, Bild V, Stefancescu R, et al. Major phytocannabinoids and their related compounds: Should we only search for drugs that act on cannabinoid receptors? Pharmaceutics. 2021;13:1823.
76. Lu D, Potter DE. Chapter 58—Cannabinoids and the cannabinoid receptors: An overview. In: Preedy VR, editor. Handbook of Cannabis and Related Pathologies. San Diego, CA: Academic Press; 2017. p. 553–63. ISBN: 978-0-12-800756-3.
77. Prandi C, Blangetti M, Namdar D, Koltai H. Structure-activity relationship of cannabis-derived compounds for the treatment of neuronal activityrelated diseases. Molecules. 2018;23:E1526.
78. Morales P, Hurst DP, Reggio PH. Molecular targets of the phytocannabinoids: A complex picture. Prog Chem Org Nat Prod. 2017;103:103–31.
79. Flores-Sanchez IJ, Verpoorte R. Secondary metabolism in cannabis. Phytochem Rev. 2008;7:615–639.

80. Grant S, Houben A, Vyskot B, Siroky J, Pan W-H, Macas J, et al. Genetics of sex determination in flowering plants. Dev Genet. 1994;15:214–230.
81. McPartland JM, Clarke RC, Watson DP. Hemp Diseases and Pests:
82. Management and Biological Control—An Advanced Treatise. Wallingford, UK:
83. CABI; 2000.
84. Solymosi K, Köfalvi A. Cannabis: A Treasure Trove or Pandora's Box? Mini Rev Med Chem. 2017;17:1223–1291.
85. Klumpers LE, Thacker DL. A Brief Background on Cannabis: From Plant to Medical Indications. 2019.
86. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids. 2008.
87. Blessing EM, et al. Cannabidiol as a potential treatment for anxiety disorders. 2015.
88. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the CNS. 2018.
89. Howlett AC, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. 2002.
90. Hernandez FA, Chandra SB. The Current State and Potential Direction of Cannabis Research. 2016.
91. Atwood BK, Mackie K. CB2: a cannabinoid receptor with an identity crisis. 2010.
92. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. 2011.
93. Pryce G, Baker D. Cannabis pharmacology and cognitive effects: A mechanistic review. 2022.
94. Sexton M, Cuttler C, Mischley L. Clinical considerations for cannabis withdrawal and oral delivery pharmacokinetics. 2023.
95. Laviolette SR, Grace AA. Cannabis respiratory risks and advancements in delivery systems. 2021.
96. Russo EB. Cardiovascular considerations and drug interactions of cannabinoids. 2021.
97. Lambert N, Karanges E, McGregor I. Prenatal cannabis exposure:
98. Neurodevelopmental and perinatal effects. 2023.