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Cannabis/ Marijuana for Healthcare

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With profound gratitude, the editors dedicate this book to their beloved parents for their unwavering support and for creating a fulfilling life.

Preface

The current and future healthcare primarily emphasizes the standard guideline-based mental and physical healthcare maintenance, significant enhancement of the quality of life, and deterrence of early and premature morbidity and mortality. Achieving the above global healthcare goals requires novel, affordable, practical, and applicable pharmacological and/or non-pharmacological interventions that must be developed urgently. The discovery and development of new prophylactic and/or therapeutic drugs is a protracted process and can be an exceedingly expensive and unproductive corporate venture and scientific effort. Unfortunately, prospective medicines are excluded at the preclinical stages, and subsequently, these natural products/synthetic compounds have not been further elucidated for other potential cosmeceuticals, nutraceuticals, and therapeutic value. Thus, the private and public global healthcare industries and organizations appreciate the imperative demand for additional potent, cost-effective, and efficient scientific beneficial interventions.

Cannabis (synonym = dope, grass, marijuana, pot, weed) is a botanical used for centuries worldwide. Cannabis has been predominantly utilized for commercial, ritual, recreational, and healthcare purposes. However, at the beginning of the last century, the psychotropic effects of cannabis/marijuana were considered to be detrimental to society, and therefore it was banned. Based on modern scientific advancements in the understanding of cannabis/cannabinoids, the interaction of cannabinoids with the human system/brain, the potential of cannabinoids' medicinal use for treating a variety of ailments is increasingly attracting the attention of researchers, policymakers, and entrepreneurs. In recent years, the substantial prominence on the application and abuse/use of Cannabis has increased exponentially worldwide. However, there is a lacuna in the cohesive information on the use of Cannabis in healthcare.

Thus, our current book on *Cannabis/Marijuana for Healthcare* delivers an admirable appraisal of scientific knowledge provided by eminent and established scientists and educational experts addressing the importance of the present and forthcoming healthcare. The subject matter of the present book deals with the critical evaluation of cannabis/marijuana for healthcare (medicinal, nutritional, skincare). Further, the traditional healthcare and cultural uses of cannabis/marijuana in

different parts of the world also constitute an important part of the book. Due to the rapidly increasing commercial activity of cannabis-derived products for medicinal, nutritional, and recreational purposes, researchers/innovators have started protecting their inventions through patents. Hence, a unique feature of the present book is chapter "A Complete Patent Analysis of Cannabis/Marijuana in Drug Delivery and Disease Conditions", providing a complete patenting history and in-depth analysis along with the future growth trajectory of cannabis/marijuana-derived cannabinoids for healthcare.

Understanding the mechanism of interactions of cannabinoids (endocannabinoid/phytocannabinoids) with cannabinoid receptors is very important. While chapter "Neuropharmacological Approaches to Modulate Cannabinoid Neurotransmission" describes the neurotransmission and metabolic pathways for cannabinoids at the molecular level, chapter "Cannabinoids in Cancer: Cross-Talk Between Cannabinoids and miRNAs" details the interactions of cannabinoids with miRNA specifically for cancer interventions. Chapter "Cannabis as a Potent Therapeutic Agent for Pharmaceutical Drugs: Recent Advancement in Drug Discovery and Human Healthcare" provides a comprehensive review of the recent advancements of research on the use of Cannabis in drug discovery and therapeutical applications. Interestingly, chapter "Cannabinoid-Based Innovative Prophylactic and Therapeutic Interventions for Neuropathic Pain and Migraine" reviews the prophylactic and therapeutic use of cannabinoids for treating neuropathic pain and migraine.

Legal aspects of cannabis/marijuana may vary from country to country and even state to state within a country like the USA, India, etc. Chapter "The Legality of Use and Consumption of Cannabis (Marijuana) in the United States of America" describes the detailed legal aspects and the prospects of cannabis/marijuana production and applications for healthcare and recreational purposes. Chapter "Cannabis in Healthcare: Ethnobotanical and Pharmaceutical Perspectives and Legal Status in Turkey and the Middle East" reviews the ethnobotanical and pharmaceutical perspective and legal aspects of Cannabis in Turkey and the Middle East. While research exploring the application of cannabinoids for treating various ailments is increasingly gaining momentum, the safety aspects of these drugs, used for medical or recreational purposes, must also be understood for any possible short- and long-term side/adverse effects. Chapter "Understanding the Pharmacokinetics, Safety Profile, and Scope of the Concerned Issue to Evade the Consumption of Cannabis/Marijuana", quite aptly, provides the details about the pharmacokinetics, safety profile, and issues related to the consumption of cannabis/marijuana.

Human development happens by building on the knowledge and experiences of previous/former generations passed on to present and future generations. Hence traditional, cultural, and time-tested knowledge and past experiences are beneficial for further development and cannot be ignored. However, there must be a validation applying modern research and development practices and tools. Chapters "Traditional Uses of Cannabis in the Middle East and the Pathway to Cannabis-Based Healthcare in Israel", "Traditional and Modern Health Uses of *Cannabis sativa* L. in Africa and Its Phytochemical and Pharmacological Profile", and "Traditional Claims

on Cannabis: An Indian and Global Scenario" trace the traditional roots of the use of Cannabis in Israel/Middle East, Africa, and India, respectively. Further, the traditional applications of Cannabis are also compared with modern-day uses of the same. Chapter "Cannabis (*Bhanga*) in Classical Text of Ayurveda: An Evidence-Based Rationale" deals with validating the unbroken tradition of using cannabis-based formulations, derived mainly from cannabis dried leaves called Vijaya or Bhang, for treating a plethora of indications, as described in ancient Indian Ayurvedic medical pharmacopeia/scriptures, using evidence-based rationale.

Apart from using for therapeutic applications, Cannabis-derived products are also found quite useful for cosmeceutical and nutraceutical purposes. Chapter "Cannabis-Based Cosmetic Products and Their Uses" provides details about the cosmetic applications of Cannabis-derived non-psychotropic products like cannabidiol. Chapters "Cannabis as a Unique and Valuable Nutraceutical Formulation for the Current and Future Global Wellbeing" and "Traditional, Cultural, and Nutraceutical Aspects of Cannabis in India" deal with nutritional aspects of Cannabis, mainly its seeds. While chapter "Cannabis as a Unique and Valuable Nutraceutical Formulation for the Current and Future Global Wellbeing" focuses on the present and future global well-being, chapter "Traditional, Cultural, and Nutraceutical Aspects of Cannabis in India" discusses the traditional nutraceutical aspects, mainly from the Indian perspective.

The editors, through this book, aim to provide a unique combination of modern scientific-based and traditional usage of cannabis/marijuana for comprehensive healthcare in various parts of the world. Another salient aspect of the present book is a complete mapping and region- and sector-wise critical analysis of cannabis/marijuana patents and future directions for the benefit of researchers and businesses/entrepreneurs interested in the rapidly advancing area of Cannabis. The editors sincerely hope that this unique compendium of review articles will be useful as a reference book for advanced students, researchers, academics, business houses, and all individuals interested in medicinal, nutritional, traditional, legal, and commercial aspects of cannabis usage.

Disclaimer: The main purpose of this book is to make readers aware of Cannabis, based on the rationale of scientific research. The editors/authors do not wish to promote and should not be construed promoting the use/misuse/abuse of any psychoactive substances, including Cannabis/Marijuana/Bhang.

Taichung, Taiwan — Dinesh Chandra Agrawal
Pune, Maharashtra, India — Rajiv Kumar
Auburn, AL, USA — Muralikrishnan Dhanasekaran
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The editors also thank and appreciate their respective families (Manju, Somya, Neha, and Mihir—Family Agrawal; Anu, Sharmishtha, Amit, Swati, and Atanu—Family Rajiv Kumar; Madhu and Rishi—Family Dhanasekaran) for the encouragement and wholehearted support during the progress of the book. Editor Dr. Rajiv Kumar wishes to gratefully acknowledge his grandfather (Late) Mr. Radhakishan Chaturvedi, who got him interested in the fascinating area of Cannabis sharing his vast knowledge and experience about the medicinal aspects of Cannabis leaves (*Bhang*).

The editors express profound gratitude towards "The Infinite Being," "Lord Shiva, the Adiyogi" for providing guidance, strength, and skill to accomplish the arduous task of handling this book.

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About the Editors

Dinesh Chandra Agrawal, PhD, is a professor in the Department of Environmental Engineering and Management and the Department of Applied Chemistry, Chaoyang University of Technology (CYUT), Taiwan. In 2013, he superannuated as a chief scientist and professor of biological sciences after serving for more than 31 years in the Council of Scientific and Industrial Research (CSIR), Ministry of Science and Technology, Govt. of India. He has about 40 years of research experience in plant biotechnology of diverse species, including medicinal plants and mushrooms, and has more than 200 publications, including six books (four by Springer Nature). Professor Agrawal was awarded several prestigious fellowships, including the Alexander von Humboldt Fellowship (Germany), Visiting Scientist to Mississippi State University (USA), British Council Scholar (UK), and European Research Fellow (UK). Since 2016, Professor Agrawal has been serving as associate editor-in-chief of the *International Journal of Applied Science and Engineering* (Scopus).

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Muralikrishnan Dhanasekaran is a professor at Harrison School of Pharmacy, Auburn University, USA. He obtained his Ph.D. from the Indian Institute of Chemical Biology, Kolkata, India, and then received his postdoctoral training from renowned scientists Dr. Manuchair Ebadi (University of North Dakota) and Dr. Bala Manyam (Scott & White Clinic/Texas A&M, USA). Dr. Dhanasekaran's research areas are pharmacology, neuroscience, toxicology, dietary, natural products, and the development of drugs/compounds targeting Alzheimer's and Parkinson's disease. Dr. Dhanasekaran completed the New Investigator Research Grant from Alzheimer's Association, several Auburn University grants, and several other research projects from a pharmaceutical company. Dr. Dhanasekaran has guided 16 students (as a mentor) and currently has 5 graduate students under his leadership, and he has

trained more than 50 undergraduate students in his lab. Dr. Dhanasekaran has received several teaching awards from Auburn University. He has published more than 200 scientific abstracts, 103 peer-reviewed publications, 2 books, and several book chapters.

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A Complete Patent Analysis of Cannabis/Marijuana in Drug Delivery and Disease Conditions

Mandar Vaidya, Abhishek Choudhury, Charles Brumlik, Dinesh Chandra Agrawal, and Rajiv Kumar

Abstract The cannabis plant has more than 100 cannabinoid molecules, plus many other classes of phytochemicals, including flavonoids and terpenes, which may contribute to the entourage effects of the plant extract. Cannabis plant extract and these cannabinoids are used primarily for medical and recreational purposes. There seems a trend towards deregulation and regulatory approvals for the use of cannabis in the medical industry. In this chapter, a complete patent perspective and detailed analysis of medical cannabis and its derivatives are evaluated, focusing on medical use and various delivery mechanisms. We find an increasing trend for cannabis research in therapeutic and recreational applications. The major medical applications for cannabis are for pain management and the treatment of nervous system disorders. Nanotechnology drug delivery formulations improve the bioavailability and absorption of cannabis, e.g., nanoparticles, nano-emulsions, liposomes. The United States (US) is the most active country for inventors. Over one-third of Chinese patent filings focus on natural medicine. Most major US and European pharmaceutical companies are actively involved in the research-driven cannabis businesses, growing rapidly.

Keywords Bio-absorption · Bioavailability · CBD · Cannabinoids · Drug delivery · Marijuana · Medical cannabis · THC

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Abbreviations

ACE2	Angiotensin-Converting Enzyme 2
AIDS	Acquired immunodeficiency syndrome
ARDS	Acute respiratory distress syndrome
BBB	Blood Brain Barrier
CB1	Cannabinoid Receptor 1
CB2	Cannabinoid Receptor 2
CBC	Cannabichromene
CBD	Cannabidiol
CBG	Cannabigerol
CBN	Cannabinol
CJI	Confined Impingement Jet
CNS	Central Nervous System
ERK	Extracellular Signal-Regulated Kinase
FDA	US Food and Drug Administration
GPR	G Protein-Coupled Receptor
gRNA	Guide RNA
HER2	Human Epidermal Growth Factor Receptor-2
MHC	Major Histocompatibility Complex
MIVM	Multi-Inlet Vortex Mixing
PCT	Patent Co-operation Treaty
POC	Proof of Concept
PPAR	Peroxisome Proliferator-Activated Receptor
PrPres	protease-resistant prion protein
PTSD	Post-Traumatic Stress Disorder
TEER	Trans-Endothelial Electrical Resistance
THC	Tetrahydrocannabinol or delta-9-tetrahydrocannabinol
THCV	Tetrahydrocannabivarin
TRP	Transient Receptor Potential
TRPV	Transient Receptor Potential Vanilloid
TTF	Tumor-Treating Fields
UK	United Kingdom
US	United States
USSR	Union of Soviet Socialist Republics
VR1	Vanilloid Receptor Type 1

1 Introduction

Cannabis, one of the oldest plants humans have been using (Russo 2005, Chaturvedi and Agrawal 2021), is on the way to regain its lost glory owing to the pioneering research in the area of cannabis and its medicinal uses (Gaoni and Mechoulam 1964;

Mechoulam et al. 1990; Devane et al. 1992; Matsuda et al. 1990; Munro et al. 1993; Bragança et al. 2020). The spurt in R&D, specifically in the last two decades, coupled with increasing acceptance, both at the public and the policy-makers level, led to a significant increase in protecting the innovations through patenting. The patents focus on the rapidly growing area of cannabis-derived products for health care (medical, nutraceutical, and skincare) as well as recreational applications. These activities also led to the rapid and enormous growth in the business opportunities for cannabis/marijuana-derived products. For example, according to a recent report (Wyse and Luria 2021), the global medical cannabis market is expected to grow from USD 13.4 billion in 2019 to USD 66.3 billion by 2025, with a very healthy compound annual growth rate (CAGR) of 22.9%. The North American Medical Marijuana Index, founded in 2015, listed 49 companies with a total market capitalization of USD 32 billion. As of January 28, 2020, the market cap of major global marijuana-related companies was USD 40.88 billion (Wyse and Luria 2021).

It is of paramount interest for rapidly growing innovation-driven businesses to have a clear patenting strategy to support sustained growth. Surprisingly, few reports review or provide an in-depth analysis of patent literature of this field. Although several main research papers, reviews, and books on cannabis/marijuana are available and are referenced here to facilitate further study (Labigalini et al. 1999; Wright et al. 2003; Hanuš and Mechoulam 2005; Russo 2005; Pertwee 2006; Montoya and Weiss 2019; Tikka and D'Souza 2019; Finn 2020; Ambastha et al. 2020; Chaturvedi and Agrawal 2021), now we review the complete patent literature published on medicinal cannabis. This chapter deals with the analysis of cannabis/marijuana-related patents from the first patent published in 1907 until the end of 2020. Data sets pertained to country of origin (location of the inventors), therapeutic applications, and drug delivery systems/materials.

2 Methodology

A keyword-based patent search for cannabis and similar concepts retrieved over 15,000 patent families (unique inventions) published from 1907 through December 31, 2020. However, more than 95% were published in the last 20 years, and about 5% were published between 1907 and 2000. Other than the meteoric growth of Chinese patenting, cannabis far outpaces the average global growth in patenting.

The patent search was conducted using the GridLogics patent search and analytics tool Patseer (https://patseer.com). The keywords searched in the Title, Abstract, and Claims were: marijuana or cannabi* or tetrahydrocannabino* or CBD AND Publication Date: [1700-01-01 TO 2020-12-31]. The patents listed can easily be retrieved through Google patents (https://patents.google.com/) using a two-letter country code followed by the Patent number. The country codes for few main patenting countries are US for the United States of America; CN for China; WO for PCT Applications; EP for European Applications; JP for Japan; IN for India.

A patent family may comprise one or more patents/patent applications originating from a single original (priority) application. Therefore, the analysis of the patent family reflects the accurate number of inventions because generally, there is only one invention per patent family. In comparison, an analysis using a raw number of patent publications inevitably involves double or multiple counting because one patent family may contain several patent publications if the applicant files for the same invention in more than one country.

Hence analysis by the patent family gives more accurate results regarding the level of inventive activity taking place. Therefore, the patent family we considered for the analysis was prioritized as follows:

- English document—Mainly US Patent, European Union Patent or Patent Co-operation Treaty Application (PCT).
- Non-English versions were considered when there was a non-English patent family. The translation was used from the European Patent Office's Espacenet database (https://worldwide.espacenet.com).

Our study divided the cannabis-related patent research into three parts:

- All cannabis-related patents published before 2001.
- All cannabis-related patents published from 2001 to 2020.
- Cannabis-related patents for healthcare applications published during 2001–2020.

3 Patents Published Before 2001

This section provides a quick snapshot of patenting activity related to cannabis published before the year 2001 (1907-December 31, 2000).

3.1 Filing Trend

More than 800 patent application families were published for cannabis-related inventions from 1907 through 2000. The patent filing activity increased from 1970 onwards, coinciding with the isolation and identification of THC and CBD (Gaoni and Mechoulam 1964). More than 80% of these 800 patent applications were filed in just three decades, i.e., 1971–1980, 1981–1990, 1991–2000. A sharp rise in patent filing with a growth rate of more than 40% is seen in the decade of 1991–2000. The share of patent filings in the 1991–2000 decade is approximately 50% of all the patents filed from 1907 to 2000. Of all the patents filed between 1907 and 2000, ca. 50% of these patent applications were granted patents. This corresponds with the typical patent acceptance rate (e.g., 52% in the US).

3.2 Country of Origin

The patents and published patent applications for cannabis originated from more than 25 countries from 1907 through 2000. The US is the major country of origin since 40% of patents were first filed in the US. China holds a 12% share, followed by Japan with a 9% share. The Soviet Union (USSR), Great Britain, Germany, France, Israel, Switzerland, and the Republic of Korea are also among the top ten countries with major inventions related to the cultivation, extraction, and usage of cannabis.

3.3 Industries/Application Areas

The major topics of these early patents included the following categories:

1. Cultivation
2. Manufacturing and Extraction
3. Characterization
4. Application Areas

3.3.1 Cultivation/Farming

The patents and published patent applications in this category discuss the various methods for selecting cannabis plants for compounds, their cultivation, and processing devices for cannabis products.

3.3.2 Manufacturing and Extraction of the Cannabis Compounds

The patents and published patent applications filed in this category discuss the various methods of manufacturing cannabis and its derivatives such as esters, cannabinol protein conjugates, cannabinoid precursors, and methods of extraction/isolation/separation of cannabis-derived products.

3.3.3 Characterization/Testing of Cannabis

The patents and published patent applications filed in this category discuss various techniques and methods used to characterize and analyze the cannabis samples. The methods include immunoassays, test kits for the detection of cannabinoids, etc. Other detection/testing methods, such as identifying the presence of cannabis in the human body or the biological fluids, are also discussed. Some interesting inventions are related to identifying the country of origin of cannabis.

3.3.4 Application Areas of Cannabis Compounds

There are multiple healthcare-related applications for cannabis that are discussed in the patents and published patent applications. Other main application areas for cannabis are related to agriculture, food and beverage, and biotechnology.

The patents and applications filed in this category discuss the following major application areas:

Healthcare and Pharmaceuticals

There are several patents and patent applications that discuss the applicability of cannabis in the medical industry. Cannabis can be mainly used for the following applications in the healthcare area.

- Anti-inflammatory agent
  - Treatment of Pain
  - Treatment of Arthritis
- Analgesic agent
- Immunomodulator
  - Treatment of immune diseases
- Antiemetic agent

Various routes of administration for cannabis are discussed:

- oral
- transdermal
- subcutaneous
- nasal spray or mucosal
- inhalation

Agriculture

The patents and published patent applications filed in this category describe the use of cannabis and cannabis-derived compounds as biocides, pest repellants or attractants, or plant growth regulators in agriculture/farming.

Biotechnology

The patents in this category mainly discuss the new tetrahydrocannabinolic acid synthase gene production and developing monoclonal antibody-forming cell lines by bonding to THC and its derivatives.

Food and Beverage

The patents and applications filed in this category mainly discuss natural healthcare food, energy drinks, fruit juices made from cannabis, immune-correcting food substances, tea formulation, etc.

4 Patents Published During 2001–2020

This section provides a quick overview of the recent cannabis-related patents published during the last two decades (2001–2020).

4.1 Filing Trend

There have been around 14,000 patent applications published for cannabis-related inventions in the last 20 years (2001–2020). There is an exponential growth in the patent filings from 2012 to 2016. The patent filing activity increased by 52% from 2012 to 2016. The compound annual growth rate for the patent filings from 2012 to 2016 is 25–26%. This coincides with the increasing legalization of cannabis/marijuana for the annual patent filing, even for recreational purposes in various member states in the US, Canada, and Europe. Figure 1 depicts the patent application filing trend from 2001 till 2020. As mentioned above, there was a significant increase in patent filing from 2012 onwards. It must be mentioned that ca. 22% of all the patent applications published in the last two decades are granted patents. This is generally

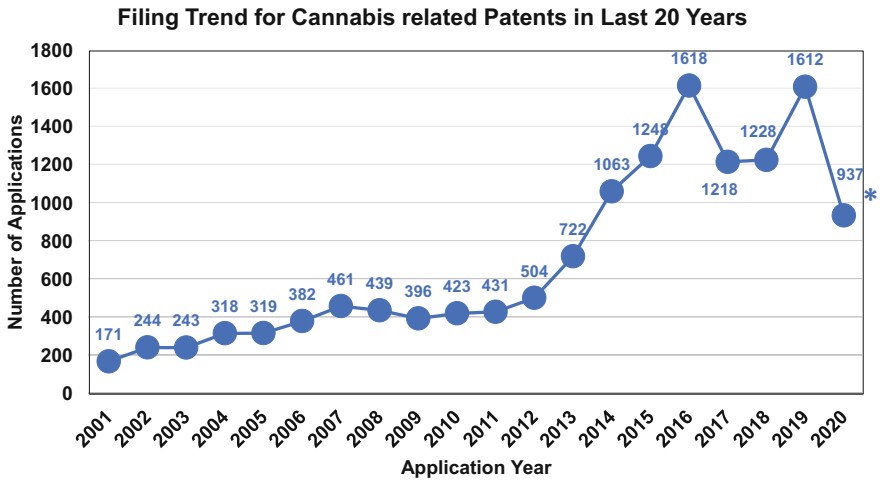

Fig. 1 Cannabis-related patent filing trend in last 20 years

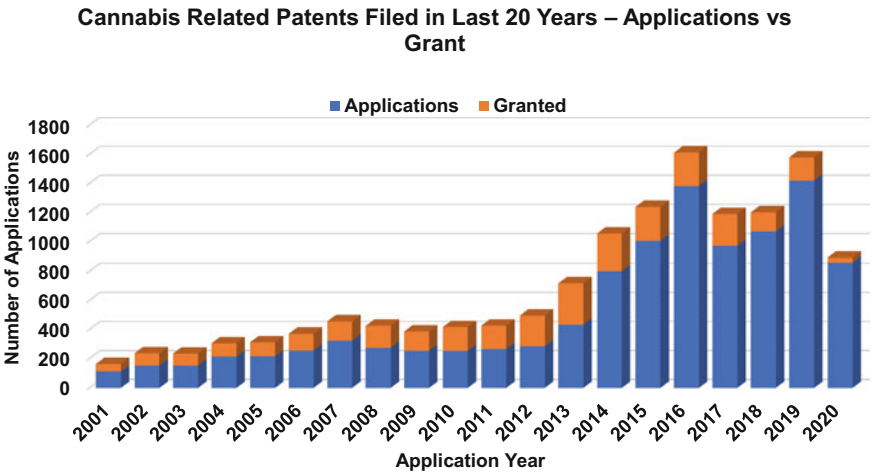

Fig. 2 The trend of cannabis-related patent applications vs. grants in the last 20 years (2001–2020)

due to rejection by the patent office or failure of the inventor or their assignee to continue pursuing the patent application. It should also be noted that the patent applications are typically not published until 18 months following the earliest filing date. Hence, the filing trend for 2019 and 2020 is incomplete since the patent applications filed in the second half of 2019 and 2020 are yet to be published. This secrecy of almost all applications filed in 2020 accounts and the reliance on only published applications accounts for the significant dip in 2020 numbers shown in Fig. 1. In Fig. 2, the distribution of granted patents and published patent applications is shown where the number of granted vs. published applications are plotted for each of the last 20 years (2001–2020).

4.2 Country of Origin

The patents and published patent applications for cannabis published in the last 20 years originated from more than 50 countries. In contrast to the earlier scenario (patents published before 2000), China surpassed the US as the major country of origin with a 47% share, followed by the US with a 32% share. Major European countries such as Germany, France, and the United Kingdom (UK) are among the top ten countries (Fig. 3). Apart from China, other countries like Japan and Korea are among the top ten countries of origin, while India is at the 11th spot.

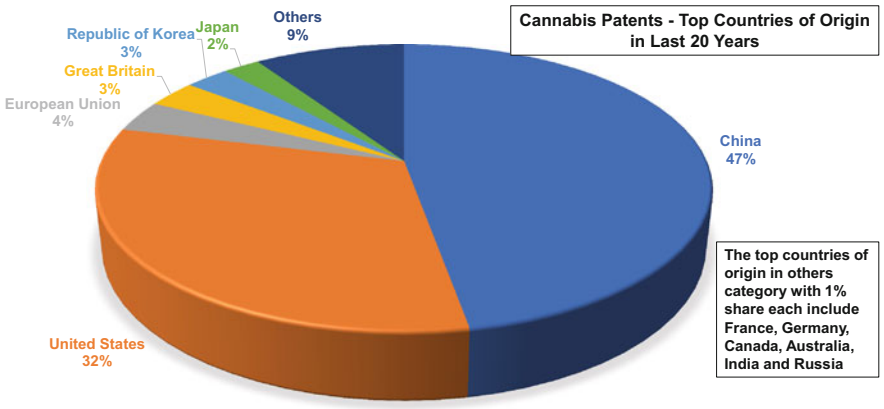

Fig. 3 Top countries of origin for cannabis-related patents in the last 20 years

4.3 Industries/Application Areas

The major topics of the inventions include cannabis cultivation, extraction, manufacturing, characterization, and various applications.

According to the various stages of the cannabis lifecycle, the patents are categorized as follows:

1. Cultivation
2. Manufacturing and Extraction
3. Characterization
4. Application Areas

4.3.1 Cultivation

The patents and published patent applications in this category discuss the inventions related to cannabis cultivation methods, plant growth, instruments, and machinery used.

A representative list of inventions in this category include:

- Soilless cultivation (e.g., hydroponics)
- Treatment of plants, e.g., for preventing decay of wood, for tingeing flowers or wood, for prolonging the longevity of plants
  - Electric or magnetic treatment of plants for promoting growth
  - Plant growth regulators for boosting plant growth
- Methods of fertilizing, sowing, or planting
- Greenhouse technologies for cultivation and growth

  - Cooling systems such as devices for heating, ventilating, regulating temperature, or watering, in greenhouses
  - Air-conditioning systems for cultivation
  - Lighting with special arrangements for promoting plant growth

4.3.2 Manufacturing and Extraction of the Cannabis Compounds

The patents and published patent applications in this category discuss manufacturing and processing cannabis compounds and their derivatives.

A representative list of inventions in this category include:

- Preparation methods of cannabis compounds
- Extraction methods of THC from the cannabis
- Methods for separation, extraction, and purification of compounds or CBD oil
  - Devices used in the separation, extraction, and purification of cannabis compounds
  - Dewaxing and decoloring of extract
- Preservation methods of cannabis compounds

4.3.3 Characterization/Testing of Cannabis

The patents and published patent applications filed in this category discuss the various techniques and methods used for characterization/testing the presence of cannabis in the human body or the biological fluids.

The techniques discussed include:

- Immunological testing, e.g., immunoassays
- Chromatography, e.g., ion exchange, column chromatography
- Investigating or analyzing materials by the use of optical means, i.e., using infrared, visible, or ultra-violet light:
  - Fluorescence
  - Phosphorescence
  - Raman scattering
- Optical detectors
- Mass spectrophotometer

4.3.4 Application Areas of Cannabis Compounds

There are multiple healthcare-related applications for cannabis discussed in the patents and published patent applications. Other application areas for cannabis are found in agriculture, food and beverage, and biotechnology.

The patents and published patent applications filed in this category discuss the following major industries:

Healthcare and Pharmaceuticals

The major industry where cannabis is used is healthcare and pharmaceuticals.

The inventions in the patents and published patent applications discuss the usage of cannabis for the treatment of the following ailments:

- Rheumatoid arthritis
- Neoplasm (i.e., a tumor)
- Dermatological disorders
  - Skincare preparations
  - Anti-aging preparations
- Neurodegenerative disorders of the CNS
  - Alzheimer's disease
  - Dementia
- Constipation and GI tract
- Bacterial infections
- Epilepsy and convulsion

The healthcare and pharmaceutical application of cannabis are detailed in Sect. 5.

Food and Beverage

The patent filing related to cannabis in the food and beverage industry has increased in the last 20 years than before 2000.

The patents and published patent applications filed related to the application of cannabis in the food and beverage industry discuss the food composition, function of food ingredients, or processes for food or foodstuffs.

A representative list of inventions in this category include:

- Food ingredients prepared by plant extracts
- Modifying nutritive qualities of foods
  - Using plant extracts based nutritive food additives
- Non-alcoholic composition
- Coffee, tea, and their substitutes (manufacture, preparation, and infusion)
- Foods, ingredients, or supplements having a functional effect on health systems such as
  - Digestive tract
  - Immune system

  - Cardiovascular system
  - Blood cholesterol
  - Glycemic control and diabetes
- Food ingredients used as promoters of weight control and weight loss
- Composition of animal feed

Agriculture

Some patents and published patent applications have been filed under the application of cannabis in the agriculture and farming industry. The major usage of cannabis in the agriculture industry discussed in the patents and published patent applications include the composition of:

- Biocides
- Pest repellants or attractants
- Plant growth regulators
- Organic fertilizers

Biotechnology

The patents and published applications filed in this category discuss the following topics:

- Method for increasing cannabis yield via gene editing
  - Selecting a gene involved in the flowering pathways of a particular Cannabis species
  - Synthesizing or designing a Guide RNA (gRNA) expression cassette corresponding to a targeted cleavage locus along the Cannabis genome
  - Transforming Cannabis plant cells to insert new genetic material
  - Culturing Cannabis plant cells
  - Selecting Cannabis cells that express desired mutations in the target region
  - Regenerating a plant from transformed plant cells, plant cell nucleus, or plant tissue
- Method of producing a Cannabis cultivar containing its genetic material
  - Cannabis cultivars with a THC content of 0.2% by dry weight
- Nucleic acid molecules from cannabis to produce cannabinoid compounds
  - Nucleic acid molecules from cannabis have been isolated and characterized, and encoded polypeptides have cannabichromenic acid synthase activity
  - The expression or over-expression of the nucleic acids alters levels of cannabinoid compounds
  - The polypeptides may be used in vivo or in vitro to produce cannabinoid compounds

5 Patents Published in the Healthcare Domain From 2001 to 2020

5.1 Filing Trend

More than 6000 patents and patent applications have been published for cannabis-related inventions used in healthcare applications in the last 20 years (2001–2020). There has been an exponential growth in patent filings since 2013. Of all the patent applications published in the last 20 years, about 18% are granted patents (Figs. 4,5).

5.2 Country of Origin

The patents and published patent applications for cannabis published in the last 20 years for the healthcare applications originated from more than 50 countries. China is the major contributor, with a 50% share of patents first filed in China, followed by the US with a 33% share. Thus China and the US are dominating the healthcare applications for cannabis-related inventions. Other countries filings cannabis patents include the UK, Republic of Korea, Japan, Germany, France, while India occupies tenth place (Fig. 6).

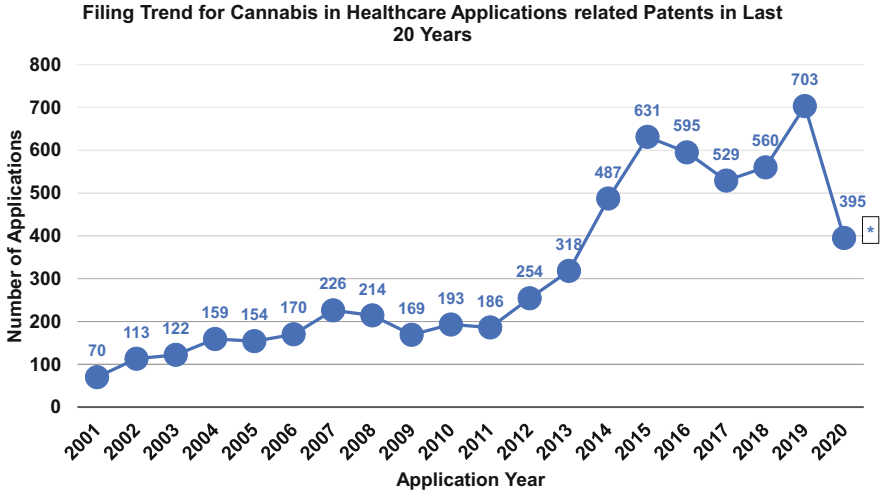

Fig. 4 Cannabis in healthcare-related patent filing trend in the last 20 years

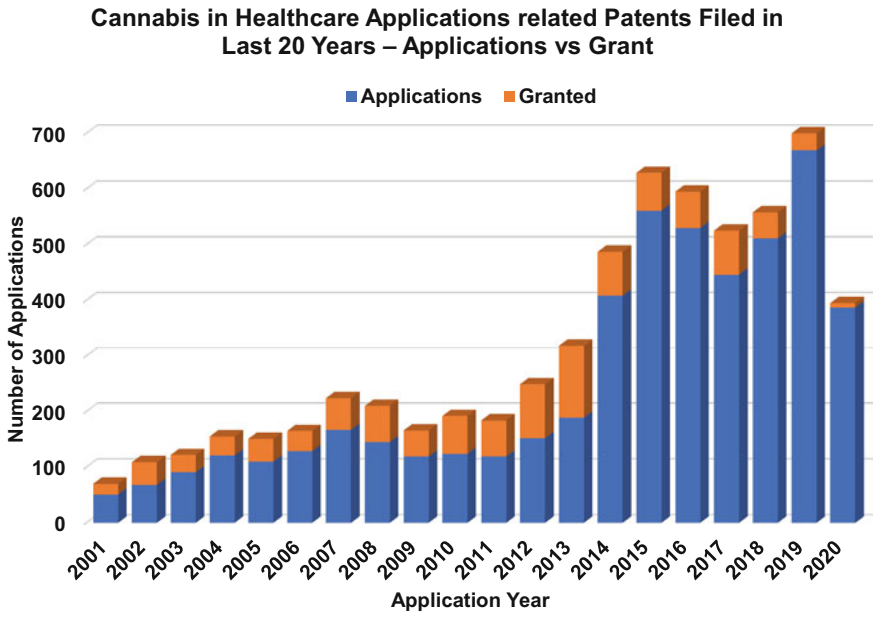

Fig. 5 The trend of patent applications vs. grants for cannabis in healthcare

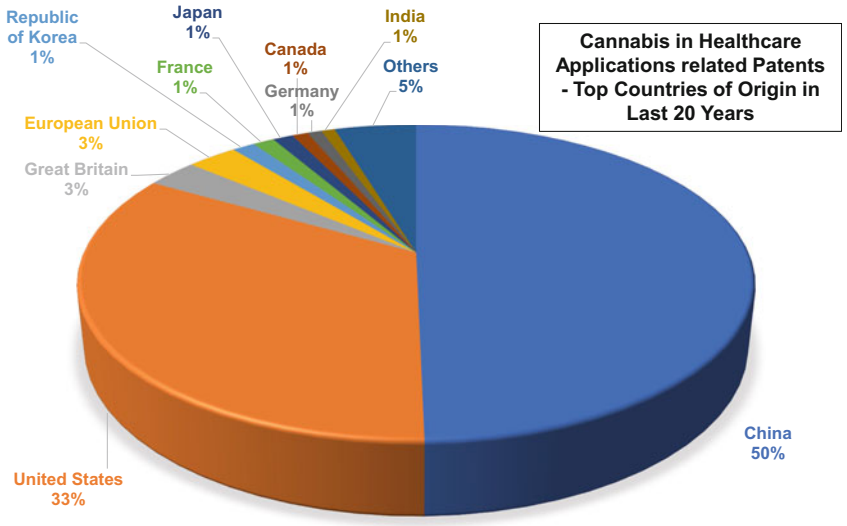

Fig. 6 Top countries of origin for cannabis in healthcare applications related patents in the last 20 years

5.3 Major Companies Filing for Patents

Among the top five major pharmaceutical companies filing for patents on pharmaceutical formulations of cannabis are Sanofi, GW Pharma Ltd., Merck, and Roche, based in Europe, and Pfizer, in third place is based in the US (Fig. 7).

Israel is ninth among the top ten companies. Yissum Research development is the technology transfer company of the Hebrew University of Jerusalem. They hold a substantial number of patents related to pharmaceutical formulations of cannabis to treat various diseased conditions.

5.4 Patent Technical Categorization

Cannabis has applicability in the healthcare industry for the treatment of various ailments/indications.

The patents and patent applications that discuss the use of cannabis formulations for healthcare applications are mainly categorized based on two criteria:

1. Dosage form or drug delivery mechanism (Cannabis or its derivatives)
2. Disease conditions/indications used in cannabis formulations

5.4.1 Dosage Form/Delivery Mechanism

There are various dosage forms/delivery mechanisms available for any drug administered in the body. The categories of major dosage forms/delivery mechanisms are depicted in Fig. 8.

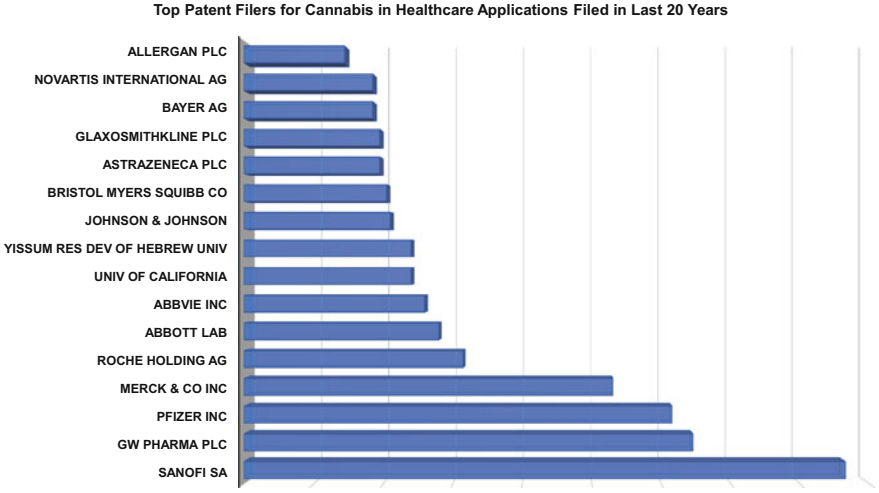

Fig. 7 **Major** companies patenting cannabis in healthcare applications (2001–2020)

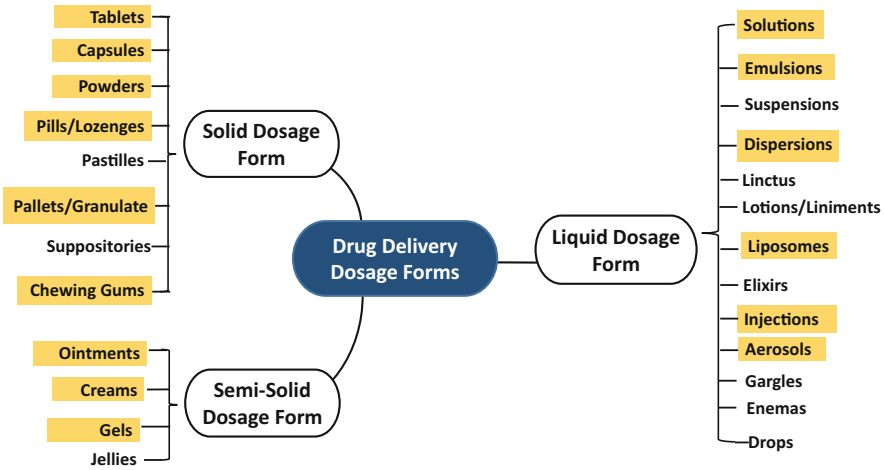

Fig. 8 Major dosage forms/delivery mechanisms for administration of a drug in the body

The yellow highlighted dosage forms/delivery mechanisms exhibited in Fig. 8 are the most cited dosage forms/delivery mechanisms for administering cannabis into the human body.

The most cited dosage forms/delivery mechanisms (shown as yellow highlights in this figure) for the administration of cannabis into the human body are discussed below.

Pills, Lozenges or Tablets

The cannabis is delivered in pills, lozenges, or tablets to overcome the disadvantages of cannabis characteristics such as reducing the unpleasant taste, increased bioavailability, improved release properties, etc. The drug is typically absorbed in the buccal cavity through the mucosal layer. The tablets are delivered through an oral route, and the trend is seen in the use of the nanoparticle-based delivery system, self-emulsifying agents, and chewable tablets. In addition, sugar-based chewable tablets are becoming popular for drug delivery. The tablet formulations of cannabis are used for pain management, sleep disorders, mood relaxation, etc.

Emerson et al. (2020) discussed that a nanoparticle-based cannabinoid-controlled release tablet formulation is prepared by mixing the cannabinoid with silica or ceramic, or solid lipid nanoparticles and a surfactant. The other additives may include microcrystalline cellulose, lubricant, and terpenoid to form a dry powder. The dry powder is compressed to form the tablets. Bruun et al. (2020a) reported a chewable cannabis tablet having self-emulsifying agents and sugar particles for better taste. Upon oral administration, the self-emulsifying system forms an emulsion to deliver one or more cannabinoids to a mucosal surface when hydrated with saliva. This chewable cannabis tablet shows reduced dissolution time in the oral

cavity while still achieving significant cannabinoid plasma levels. Similarly, several other orally administrable tablets using cannabinoids and various sweeteners, nanomaterials, edible materials like citric acid, ethylcellulose, etc. are also reported for enhancing salivation and improving the delivery system (Capaldi and Cumming 2020; Ross and Gin 2019).

Emulsions/Dispersion

The emulsion formulations of cannabis are advantageous because they provide good solubility, storage stability, and increased bioavailability of cannabis. The colonic route of administration is preferred for the delivery of the emulsion formulation of cannabis. The nano-emulsion formulation of cannabis is recently trending with greater improvement in the stability of cannabis molecules and prolonged storage time. Another novel drug delivery system discussed in the emulsion formulation is CBD self-emulsifying drug delivery system for fast drug dissolution. These formulations are used to treat diseases of the gastrointestinal tract as well as prevention of pain.

The CBD-based formulation comprising CBD, vegetable oil, and an oil-in-water emulsifier is developed where the vegetable oil can encapsulate CBD molecules, thereby effectively avoiding the contact of CBD molecules with emulsifiers and possible oxidizing substances (such as air) in the environment. As a result, the final emulsion formulation greatly improves the stability of CBD molecules and prolongs storage time. (Xiao et al. 2020). Several other emulsion- and nano-emulsion-based formulations of cannabinoids claim improved bioavailability and storage stability (Qin et al. 2020; Luan et al. 2019a, b, c, d; Zhang et al. 2020). In addition, various excipients, including gum Arabic, monoglycerides, polyglycerides, sorbitan esters, cyclodextrin, and phospholipid, can be used to control particle size and better dispersibility.

Capsules

The capsule formulations of cannabis are increasingly describing microcapsule, microencapsulation, and dual-chambered liquid-gel capsule formulations that have shown good drug stability, improved bioavailability. The major mode of delivery is the oral route. The absorption mechanism is through the gastrointestinal tract, while sometimes through the sublingual or buccal route for greater bioavailability. The capsule formulation of cannabis is claimed to manage diabetes with improved glycometabolism in human bodies. Another use of capsule formulations is for appetite stimulation and weight gain in patients suffering from symptomatic HIV infection.

Farber (2020) of Healthy Option Consulting developed a dual-chambered liquid-gel capsule with the first chamber containing a sublingual cannabis composition and the second chamber containing an ingestible cannabis composition. The first

chamber is released in the mouth under the patient's tongue for sublingual absorption. The second chamber dissolves or breaks inside the patient's stomach or small intestine to release the oral cannabis composition into the digestive tract. Sun (2017) from Harbin Huimeijia Biology Tech Co Ltd. reported preparing a CBD soft capsule by mixing CBD, vitamin E, and edible plant oil to improve glycometabolism in human bodies. Zhang et al. (2019a) of Seebio Biotech Shanghai Co Ltd. developed a water-soluble CBD microcapsule prepared by performing specific micro micelle processing on the capsule walls, thereby improving the bioavailability and action effect, improving the anti-oxidation ability, and making the active ingredient last longer and more stable. Additionally, Plasse (2004) described THC or its synthetic analogue called dronabinol in an amount sufficient to cause an increase in weight of the patient-administered as an oral soft gelatin capsule.

Particulate Form—Powders

The emerging trend in the particulate form of cannabis is in micro or nano-sized particles to improve the drug's dissolution rate and bioavailability. The particulate form of cannabis is typically administered through an oral route. The prepared particulate form could be in final formulations such as tablets, suspensions, creams, liposomes or nano-emulsions, etc. The particulate form of cannabis usually affects treating pain, anxiety & stress, seizures, malaise, inflammation, mood disorders, and insomnia.

Dai et al. (2020) of Yunnan Hanmeng Pharma Co Ltd. discussed CBD nanopowder compositions containing nano-sized CBD, surfactants, polymer auxiliary materials, and optional antioxidants. The composition improved the dissolution rate of the CBD and thereby enhanced its bioavailability in vivo. Likewise, Priestley (2020) from Princeton University claimed preparation of encapsulated nanoparticles of CBD by confined impingement jet (CIJ) mixing or multi-inlet vortex mixing (MIVM) that are stabilized by a cellulosic amphiphilic polymer. These CBD nanoparticles are stable in an aqueous environment and can be used in the formulation of various products for oral ingestion, including powders for tablets, in creams, or beverage formulations. Further, Sloat et al. (2020) of Disruption Lab Inc. developed a lipid-based nanoparticle formulation in dry powder form comprising CBD, phosphatidylcholine, sterol, and medium-chain triglyceride. The formulation is finally administered via oral route in the liposomes and/or an oil-in-water nano-emulsion form.

Agglomerates/Granulates

The granulated dosage form of cannabis is typically used for immediate release dosage form for faster absorption. These are generally significantly larger particles than the powders above and are typically not pressed into a sold form. It is administered through the oral route and is commonly used to treat pain, nausea,

sleep apnea, stress disorders, inflammation, depression, anxiety, epilepsy, schizophrenia, migraines, arthritis, weight loss, poor appetite, etc.

Haswani et al. (2017) developed an immediate release cannabinoid-based granulated dosage form used as abuse-deterrent. The core-shell particles of cannabinoids are prepared by mixing them with a wax, a sugar sphere, a microcrystalline cellulose sphere, or a gelling polymer. The cannabinoid in combination with cyclobenzaprine shows a muscle relaxant effect. In contrast, Nowak et al. (2020) of Glatt GmbH discussed an oral composition for the immediate-release formulation of cannabinoids mixed with a granulating liquid such as emulsion, suspension, or a hydroalcoholic mixture. The immediate-release formulation treats pain, nausea, sleep apnea, stress disorders, inflammation, depression, anxiety, epilepsy, schizophrenia, migraines, arthritis, weight loss, and poor appetite.

Liposomes

The liposome dosage form is the fairly recent drug delivery system used to improved dissolution, taste, and enhanced bioavailability and absorption of cannabis. The liposomes containing CBD packaged in nano-vehicle systems help transport it to a selectively targeted part, effectively showing high absorption properties. The liposome formulations discussed in the patents are typically administered through oral or intravenous administration. The most cited applications of liposomal forms of cannabis include treating epilepsy and cancers. Also, it is used in alleviating pain or reducing undesirable side effects associated with radiation therapy or chemotherapy in disorders such as cancer, pulmonary disease, or a condition that causes violent tremors.

The nanosome formulation in the liposome delivery is a new delivery form for cannabis delivery in the treatment of emesis. It is beneficial for chemotherapy or surgery-induced nausea and vomiting.

Lai (2020) has researched a nano-CBD liposome system prepared by dissolving CBD in an ethanol solvent to make the dispersal phase, mix lecithin and olive oil through homogeneous stirring, and completely dissolve it in oil to make a liposome carrier. Then, added the liposome carrier to the CBD dispersal phase and processed it to form a liposome suspension-water solution. Further, the mixture of liposome suspension-water solution was homogenized by injecting through 30 Mpa high-pressure homogenizers to obtain a nano-CBD liposome system. The CBD liposome formulation is claimed to have high absorption and an increase in bioavailability.

Liu et al. (2019) from Yunnan Lyuxin Biology Pharmacy Co Ltd. developed a CBD liposome preparation comprising phospholipid, cholesterol, CBD, and buffer salt solution. The preparation method includes - dissolving the phospholipid, cholesterol, and the CBD in an organic solvent, evaporating a mixture on a rotary evaporator to remove the solvent, and enabling residues to form a phospholipid film on the inner wall of a container. Further adding a certain pH (potential of hydrogen) buffer solution to mix mixture, rotatably evaporate the mix, and enable the phospholipid film to fall off, followed by ultrasonic treatment in an ice-water

bath and filter sterilizing and freeze-drying mixture to obtain the CBD liposome. This CBD liposome preparation is claimed to have a high entrapment rate and good water solubility and can be used in cosmetics and medicines. Winnicki (2015) reported that an alginate liposomal cannabinoid suspension was used to encapsulate a cannabinoid or its analogue within the membrane of the micelles or liposomes. A solvent solution containing the cannabinoid extract was used to stabilize the colloidal suspension. Sydney et al. (2020) from Fordoz Pharma Corp developed a nanosome formulation of the cannabis as intravenous administration is stable and ready-to-use liposomes in the treatment of emesis and is particularly useful for chemotherapy or surgery-induced nausea and vomiting.

Ointments (Base Formulation)—Gel and Cream

The ointment base form is used to prepare gel or cream formulations. The cannabis gel or cream formulation has a good moisturizing effect and improved skin penetration to treat skin diseases. The gel or cream formulation of cannabis is suitable for the transdermal route by absorption through the skin for the skin disorders such as inflammatory dermatosis or to relieve pain. Some inventions discuss using cannabis gel as gynecological gels to treat vaginitis and cervicitis, including bacterial vaginitis, trichomonas vaginitis, mixed vaginitis, gonococcal infection, and chronic cervix Inflammation. The water in oil-based ointments is popular in the cannabis gel or cream formulation.

Shen (2020) developed an oil-soluble CBD gel prepared by mixing a moisturizer, an emollient, a solubilizer, a rheologic modifier, water-soluble CBD, EDTA-2Na, flavors, and a preservative. The composition has shown high water solubility. The CBD in this gel formulation can bind or insert cell membranes to change membranes' fluidity and other physiological properties and effectively inhibit bacteria growth. Liang et al. (2020) discussed that CBD cream is an emulsifiable water-in-oil cream, a uniform semi-solid external preparation prepared by dissolving or dispersing the drug in an oil phase emulsion liquid matrix and the water phase. As the cream spreads uniformly and finely, it can dissolve and disperse fat-soluble drugs uniformly. The formulation has shown improved skin absorption by accumulating in different layers of the skin. In addition, the formulation provides good skin moistening and moisturizing effects, and it can inhibit the local inflammatory reaction such as inflammatory dermatosis. Khubani (2020) from Hempvana LLC developed a topical gel formulation with improved pain relief efficacy and moisturizing properties consisting of *Cannabis sativa* oil combined with a topical analgesic.

Solutions

The solutions or liquid formulations of cannabis can be used to enhance the solubility of the drug. The cannabis-derived solution-based formulations are typically administered through the oral route, ophthalmic formulation through the eye, or

aerosol solution for inhalation through the nose. The oral formulations are claimed to treat a plethora of indications such as (1) pain disorder and side effects associated with chemotherapy, (2) pain, nausea, and vomiting associated with Acquired immunodeficiency syndrome (AIDS) or hepatitis, (3) neuropathic pain, anorexia neurodegenerative diseases, hypoxia, including stroke or trauma, paralytic symptoms associated with multiple sclerosis or traumatic transverse disorder, dystonic dyskinesia, bronchial asthma, epileptic seizures or generalized epilepsy, withdrawal symptoms associated with alcohol dependence, benzodiazepine dependence, and opiate dependence, Parkinson's disease, dementia, Alzheimer's disease, arthritis, glaucoma, migraine, Crohn's disease, tremor, attention deficit disorder, Irritable Bowel Syndrome and Dysmenorrhea. In addition, the ophthalmic formulations of cannabis are used to treat glaucoma. Touitou and Natsheh (2020) from Yissum Research Development Co of the Hebrew University developed a water-free liquid formulation of the cannabinoid-phospholipid mixture prepared by first mixing the solid form of cannabinoid with a solid form of a phospholipid, addition of solvents/diluents, only then the cannabinoid(s) and phospholipids are associated in a liquid form. The liquid formulation can be finally filled in the soft gelatin capsules.

Levine and Cohen (2020) from Izun Pharma Inc. discusses a cannabinoid bound to plasma protein where cannabinoid extract is combined with an aqueous solution or suspension comprising plasma protein to form a protein-bound cannabinoid. This oral formulation claimed to treat diseases such as a pain disorder associated with chemotherapy, pain disorders and "wasting" syndrome associated with AIDS, nausea, and vomiting associated with AIDS or hepatitis, as well as a side effect of chemotherapy, neuropathic pain, anorexia or cachexia, neurodegenerative diseases, hypoxia, including stroke or trauma, paralytic symptoms associated with multiple sclerosis or traumatic transverse disorder, dystonic dyskinesia, bronchial asthma, epileptic seizures or generalized epilepsy, withdrawal symptoms associated with alcohol dependence, benzodiazepine dependence, and opiate dependence, Parkinson's disease, dementia, Alzheimer's disease, arthritis, glaucoma, migraine, Crohn's disease, tremor, attention deficit disorder, Irritable Bowel Syndrome and Dysmenorrhea. Davies et al. (2008) of Insys Therapeutics Inc. developed an aqueous cannabinoid formulation of dronabinol in a mixture of buffer solution and organic co-solvents such as ethanol, propylene glycol, and polyethylene glycol. The dronabinol aqueous solution can treat a human patient with glaucoma (Kottayil et al. 2008). In addition, Vectura Ltd. created an aerosol formulation containing a cannabinoid, a hydrofluorocarbon propellant, and an optional amount of an alcohol co-solvent in a pressurized metered-dose inhaler.

Chewing Gum—Gummies

The chewing gums and gummies are popular orally administered cannabis formulations that show improved unpleasant sensory sensation and maximize the cannabinoid release from the chewing gum for the desired medical effect. The cannabis chewing gums are absorbed in the body through the sublingual or mucosal

mechanism. The typical applications of cannabis chewing gum formulations include pain alleviation, relaxation, or counteracting side effects concerning cancer treatment and nausea.

Neergaard and Ogbonna (2019) of Nordiccan developed a medical chewing gum of cannabinoids used in pain alleviation treatment. The chewing gum comprised base granules prepared using polymers such as polyvinyl acetate and vinyl laurate-vinyl acetate copolymer. Microcrystalline cellulose is used as the carrier for cannabinoid chewing gum preparation. This formulation has shown improved taste masking, prolonged-release compared to chewable tablets. Hess (2020) developed a sub-lingual delivery of cannabinoids through bubble gum formulation consists of decarboxylate of CO2 activated hash oil, cannabinoids, confectioner's or powdered sugar, gum base, corn syrup, and food-grade glycerin. The mixture of ingredients is microwaved and then agitated. Sugar is added to the mixture, and it is pulled and twisted until it becomes gum-like preparation. It is finally converted to bubble gum through rolling, freezing, and cutting to the defined shape. The sublingual delivery can aid in controlling dosage and the psychosomatic and physiological effects typical to cannabis-infused edible products. Bruun et al. (2020b) discussed that chewing gum for mucosal delivery of cannabinoids is prepared by water-soluble chewing gum ingredients mixed into the water-insoluble gum base. The gum base consists of natural resins such as polyterpene resins, resins based on gum rosin, wood rosin, or tall oil resin; elastomers such as styrene-butadiene copolymers, polyisobutylene, isobutylene-isoprene copolymers, polyethylene, polyurethane, and plasticizers such as polyvinyl acetate elastomer. The chewing gum formulations show improved sensory characteristics and high drug release quickly.

Aerosols/Inhalation

The aerosol formulation of cannabis increases the stability of the drug. It is used in conditions like nausea and vomiting associated with chemotherapy, muscle spasticity, pain, anorexia associated with AIDS wasting syndrome, epilepsy, glaucoma, bronchial asthma, and mood disorders. The aerosol formulation is typically administered through the nasal route using a metered-dose inhaler.

Woolfe et al. (2008) of Norton Healthcare Inc. developed an aerosol formulation of a cannabinoid consisting of propellant and an adequate cough suppressant for the metered-dose inhaler. The cough suppressant is a medium-chain triglyceride or propylene glycol diester, while a propellant is 1,1,1,2-tetrafluoroethane. The administration of aerosol compositions comprising the cannabinoid and propellant into the lungs of patients caused coughing. The cough suppressant acts to reduce the cough. Additional carriers used in the aerosol formulation include ethanol, methanol, and/or essential oils. Davies et al. (2008) at Vectura Ltd. created an aerosol formulation containing a cannabinoid, a hydrofluorocarbon propellant, and an optional amount of an alcohol co-solvent in a pressurized metered-dose inhaler. Cannabis can also be

administered through cigarette smoking for recreational or medicinal application. Robertson (2019) developed a liquid formulation of the CBD, a natural base of glycerol derivatives and natural flavoring agents added into a delivery system such as a personal vaporizer or E-cigarette, heated to vaporization point, then inhaled for recreational use or medicinal needs. Tan et al. (2019) of Hanyi Biological Tech Beijing Co Ltd. developed a cannabinoid inhalation administration comprising heating and vaporizing and/or atomizing a composition containing cannabinoids and a drug carrier (preferably PEG6000), filtering and cooling, and inhaling. The drug carrier has a melting point close to that of the cannabinoid with a difference of ±0–20°C. The delivery method showed high drug absorption and bioavailability.

5.4.2 Disease Conditions

The patents and published applications related to cannabis discuss the following pharmacological usages to treat various diseased conditions (Fig. 9).

Alimentary Tract or the Digestive System

The cannabis formulations act as antiemetics used to treat digestive system disorders such as nausea, vomiting, motion sickness caused by radiotherapy, chemotherapy, or others.

Javid and Whittle (2019) at GW Pharma Ltd. developed a cannabinoid acid composition consisting of a cannabinoid and its acid forms to treat nausea, vomiting, emesis, motion sickness. The formulation is administered in gels, liquids, sprays, aerosols, inhalers, vaporizers, enemas, rectal suppositories, etc. The route of administration is specifically mentioned as intraperitoneal. Still, it could be oral, buccal, sublingual, or any other suitable route e.g. the respiratory tract, nasal tract, and distal rectum.

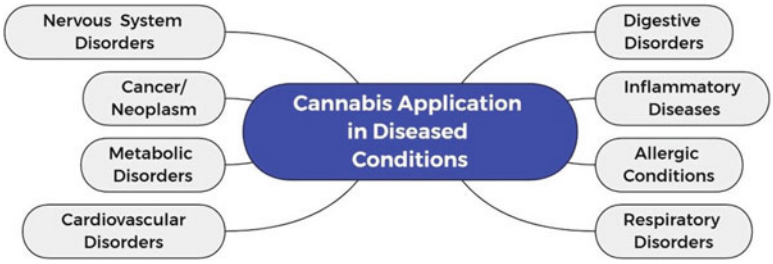

Fig. 9 Major cannabis applications in disease conditions

Respiratory System

Cannabis formulations can be used in the treatment of respiratory system disorders such as bronchiolitis obliterans and asthma. The formulations are commonly administered via nasal route using metered-dose inhalers.

Yeshurun (2020) from Mor Research Applic Ltd. developed an inhalation formulation of CBD combined with immunosuppressant cyclosporine administered intra-nasally through a vaporizer or a humidifier for treating or preventing bronchiolitis obliterans. Medina and Tamayo (2002) from Medina Gallo Floripes and team discussed the use of cannabis sativa extract to treat migraines and asthma. For recent developments related to cannabis and covid-19, please refer to sect. 5.4.2.9.

Nervous System

Cannabis effectively treats various disorders of CNS such as epilepsy & seizures, Parkinson's, mania or schizophrenia, depression, Alzheimer's, dementia, multiple sclerosis, anxiety, etc. The dosage forms discussed to administer the cannabis formulation in treating CNS disorders include injection, aqueous solution or suspension, transdermal patch, tablets or capsules, etc. The cannabis formulations to treat CNS disorders are administered through oral, intraperitoneal injections and transdermal routes.

Decleves et al. (2020) of INSERM (Institut National De La Santé Et De La Rech Médicale), University of Paris, Assist Publique-Hôpitaux De Paris (APHP) collaboratively developed a method for modulating blood-brain barrier (BBB) by administering CBD that acts as modulator of transient receptor potential vanilloid-2 (TRPV2). The CBD administration induces proliferation, migration, tubulogenesis and increases the trans-endothelial electrical resistance (TEER) in human brain endothelial cells. The modulation of TRPV2 helps in modulating the human BBB. The formulation is claimed to treat many brain-related disorders, including neuroinflammation, traumatic brain injury, or ischemic stroke. Whalley et al. (2020) at GW Pharma Ltd. discussed a CBD composition used with an agonist of 5-HT2B receptors such as amphetamine or amphetamine derivative to treat epilepsy. The combination of the drugs claimed to demonstrate a significant reduction in seizures and reduced dosage of either of the drugs. The dosage form is administered as an intraperitoneal injection. Robson and Chabry (2009) from GW Pharma Ltd. also developed a CBD formulation to treat a transmissible neurodegenerative disorder, particularly a prion disease. CBD was found to inhibit the formation of protease-resistant prion protein (PrPres) in cells and exhibited neuroprotective activity against PrPres -induced neurotoxicity. The prion diseases are characterized by loss of motor control, dementia, paralysis, wasting, and eventually death. Levine and Cohen (2020) at Izun Pharma Inc. discusses a cannabinoid bound to plasma protein where cannabinoid extract is combined with an aqueous solution or suspension comprising plasma protein to form a protein-bound cannabinoid. This oral formulation claimed to treat diseases such as a pain disorder associated with chemotherapy,

pain disorders and "wasting" syndrome associated with AIDS, nausea, and vomiting associated with AIDS or hepatitis, as well as a side effect of chemotherapy, neuropathic pain, anorexia or cachexia, neurodegenerative diseases, hypoxia, including stroke or trauma, paralytic symptoms associated with multiple sclerosis or traumatic transverse disorder, dystonic dyskinesia, bronchial asthma, epileptic seizures or generalized epilepsy, withdrawal symptoms associated with alcohol dependence, benzodiazepine dependence, and opiate dependence, Parkinson's disease, dementia, Alzheimer's disease, arthritis, glaucoma, migraine, Crohn's disease, tremor, attention deficit disorder, Irritable Bowel Syndrome and Dysmenorrhea.

Stratemeyer-Trinczek and Lecky (2020) is researching a CBD formulation administered through a transdermal patch to alleviate anxiety, depression, pain, inflammation, epilepsy, Parkinson's disease, etc. The formulation consists of a carrier agent dimethyl sulfoxide mixed with the CBD. Mukunda et al. (2019) from India Globalization Capital Inc. developed a formulation containing THC, melatonin, and curcumin to treat CNS disorders such as amyloidosis, protein folding diseases, tauopathy, specifically Alzheimer's Disease, Parkinson's Disease, etc. Haas et al. (2013) of Deva Holding AS discussed a single-unit oral formulation of fingolimod or its pharmaceutically acceptable salts combined with nabiximols mainly composed of CBD type compound or its derivative and THC type compound or its derivative in the treatment of multiple sclerosis. Adler (2020) is researching a CBD formulation that reduces cortisol levels and treats various ailments consisting of other therapeutic compounds such as hydroxytyrosol (olive oil), phospholipids, and carotenoids. The formulation is used to treat multiple ailments, including anxiety, depression, post-traumatic stress disorder ("PTSD"), stress, insomnia, and drug addiction.

Inflammatory Diseases

Cannabis formulations are also used to treat inflammatory diseases such as rheumatoid arthritis, pain management, gout, etc. The use of cannabis in pain management is discussed in many patents and published patent applications. The dosage forms discussed to administer the cannabis formulation in treating inflammatory diseases include ointment, gel, cream, an aqueous or non-aqueous liquid formulation, or capsule form. The cannabis formulations are commonly administered via the transdermal route or an oral route.

Wong et al. (2020) from Inmed Pharma Inc. developed a topical cannabinoid formulation helpful in treating pain consisting of anti-inflammatory agents, steroids, or terpenoids. The drug carriers are also selected from the group consisting of Labrasol™, Transcutol™, lecithin, lysolecithin, isopropyl palmitate, and isopropyl myristate. Cannabinoids exert their effects by interacting with receptors present on the surface of cells. For example, certain cannabinoids modulate the CB1 endocannabinoid receptors and modulate the pathways leading to nociception. In addition, the cannabinoids can interact with Transient Receptor Potential (TRP) channel proteins, TRPV1–4, TRPA1, and TRPM8, to influence nociception. Wang

et al. (2020) of Yunnan Lyuxin BioPharma Co Ltd. discussed an anti-inflammatory ointment containing cannabis flavone consisting of paraffin wax, Vaseline, beeswax, cannabis flavone, wintergreen oil, and penetration enhancer emulsifying agent, moisturizer, essence, and preservative. The composition demonstrates inhibition effects on arthritis pain, gout, and rheumatoid arthritis. The rash has a good inflammation elimination effect on inflammation caused by bacteria and viruses and has the effects of resisting allergy, bacteria, and viruses. Mills et al. (2019) at Cannpal Animal Therapeutics Ltd. developed an oral liquid formulation comprising THC and CBD to control the patient's heart rate and treat pain, inflammation, and/or anxiety.

Metabolic Disorders

The cannabis formulation has shown how to treat metabolic disorders such as weight reduction (obesity) and diabetic management, including prevention of renal failure, neuronal damage due to diabetes, etc. The typical dosage forms of cannabis used in treating metabolic disorders are gel, tablets, capsules, etc. The commonly used routes for cannabis administration are sublingual, buccal, oral, rectal, nasal, and pulmonary systems. Glas (2020) of CBM Labs developed a pharmaceutical composition comprising tetrahydrocannabivarin (THCV) to prevent and treat overweight associated with obesity. THCV and THC, when used in combination, demonstrate synergistic effects to induce weight loss with a reduction in appetite. Zhang et al. (2019b) at Hanyi Bio-Tech Company Ltd. discussed a CBD composition to prevent diabetes, containing cannabinoids combined with one or more hypoglycemic agents. The pharmaceutical composition can effectively decrease blood sugar and significantly mitigate an adverse reaction induced by hypoglycemic agents such as metformin or sulfonylurea secretagogues.

Berry et al. (2008) at Yissum Research Development Co of the Hebrew University is researching a cannabinoid formulation for alleviating neuronal damage due to hyperglycemia or treating neuronal damage in a diabetic subject consisting of THC and synthetic cannabinoid agonist HU-210, which is (+)-1,1-dimethylheptyl analogue of 7-hydroxy-de/to-6-THC. The HU-210 claimed to attenuate neural oxidative stress, b.rain function impairment, neural apoptosis, proliferation arrest, and differentiation without affecting glycemic control. Guy et al. (2013) from GW Pharma Ltd. developed a formulation of CBD alone or in combination with another cannabinoid or the THCV alone or combined with another cannabinoid are used as part of a regime to manage or treat type I or II diabetes, obesity, dyslipidemia related metabolic disorders, and cardiovascular disease. The cannabinoids, CBD and THCV, act via the peroxisome proliferator-activated receptor-gamma (PPAR'y). The agonists of the PPARy isoform improve insulin sensitivity and are often used to manage type II diabetes.

Cancer/Neoplasm

The cannabis formulation has shown anti-cancer activity and can treat various body parts such as breast cancer, lung cancer, colorectal cancer, glioma, skin melanoma, etc. The cannabis formulation for cancer treatment is usually administered through tablets, injections, or capsule dosage form. The typical routes include oral, transdermal, rectal or intravenous, intramuscular, subcutaneous, intrauterine dura mater, or intracerebroventricular injection. The sublingual absorption of orally delivered cannabis formulation is discussed in some inventions. The cannabis formulations, in combination with other cancer treatments, showed synergistic effects and better efficacy.

The combination of THC and CBD for use in the treatment of breast cancer or to treat, prevent or reduce the risk of cancer metastasizing can also be used to prevent or treat cancer of the lymph nodes of the lungs. For example, Sanchez et al. (2014) of GW Pharma Ltd. and Otsuka Pharma Co Ltd. collaboratively developed an oral composition of THC to treat aggressive breast cancer characterized by overexpression of the HER2 (human epidermal growth factor 2, ErbB-2) gene. In addition, the composition may also include a monoclonal antibody such as trastuzumab for a synergistic effect.

Javid et al. (2018) at GW Pharma Ltd. and Otsuka Pharma Co Ltd. collaboratively filed a patent about using phytocannabinoids such as CBD or the combination of CBG with CBD or CBD THCV that are used in the treatment of ovarian carcinoma. Fisher et al. (2019) from Diverse Biotech Inc. discussed that an oral cannabinoid preparation for cancer treatment is administered by placing an aliquot of the composition sublingually to minimize the first-pass metabolism by the liver. It inhibits cancer progression by reducing proliferation or destroying the neoplastic or pre-neoplastic cells, inhibiting metastasis, or decreasing the size of a tumor. The cannabinoid preparation can be administered in conjunction with one or more other cancer therapies such as chemotherapies, immunotherapies, tumor-treating fields (TTF, e.g., OPTUNE system), radiation therapies (XRT), and other therapies (e.g., hormones, autologous bone marrow transplants, stem cell reinfusion). The cannabinoid preparation is helpful to treat a patient with colon cancer, rectal cancer, pancreatic cancer, multiple myeloma, or glioblastoma multiforme in conjunction with an additional therapy appropriate for particular cancer. Lee et al. (2019) of Kaiyou Biotech Co Ltd. and the University of Korea researched a formulation of cannabinoid extract for preventing or treating colorectal cancer by induction of apoptosis of colon cancer cell lines. The cannabinoid acts by binding to cannabinoid receptors (CB1, CB2). When it binds to a receptor, it makes Ceramide (family waxy lipid molecules found in high concentrations within the cell membrane of eukaryotic cells), which induces autophagy and cell death through Endoplasmic Reticulum stress and can also induce cell cycle arrest through Extracellular signal-regulated kinase (ERK). ERK are molecules involved in the regulation of meiosis, mitosis, and postmitotic functions in differentiated cells. All modes of administration can be expected, for example, oral, rectal or intravenous, intramuscular, subcutaneous, intrauterine dura mater, or by intracerebroventricular injection.

Jefferies et al. (2020) from Pascal Biosciences Inc. developed a cannabinoid preparation used to enhance the immunogenicity of tumor or infected cells by increasing the expression of major histocompatibility complex (MHC) class I surface molecules. The cannabinoid compounds and structural analogues can increase MHC class I expression on tumor cells grown in cell culture, enabling detection and destruction by cytotoxic T-lymphocyte cells. The cannabinoid preparation demonstrates activity such as enhancing an immune response against cancer in subjects treated concurrently with immune-activating agents such as checkpoint inhibitors, coactivating receptor agonists, and cancer vaccines. When administered in combination, such compositions may enhance immune-oncology and anti-infectious disease agents. Daniela et al. (2018) at GW Pharma Ltd. also discussed a composition containing a combination of the phytocannabinoids THC and CBD and temozolomide, which demonstrated efficacy in treating glioma tumors in the brain's glial cells. The cannabinoids in the formulation induce proliferation, growth arrest, or apoptosis in many cells, including neurons, lymphocytes, and various transformed neural and non-neural cells, inducing apoptosis of glioma cells in culture and regression of malignant gliomas in vivo. Luan et al. (2019a, b, c, d) are researching the formulation of cannabis in combination with artemisinin compounds to treat skin melanoma. The combination of cannabinoid and artemisinin shows a synergistic inhibitory effect on tumors, particularly inhibiting skin melanoma growth.

Allergic Conditions

Cannabis is also used against allergic conditions such as urticaria, itching, etc. The cannabis formulation is administered through a topical route for various skin-related allergic conditions.

Li et al. (2019) of Yunnan Feijiuxiao Tech Co Ltd. developed a CBD formulation to treat urticaria by mixing CBD, *Ligusticum chuanxiong Hort* extract, *Scutellaria baicalensis* extract, *Cortex dictamni* extract, polyoxyethylene castor oil, span-80, sorbitol, peppermint oil, and potassium sorbate. The formulation claimed to suppress itching for acute and chronic urticaria quickly, does not cause skin allergy, and has no toxic side effects. In addition, the formulation demonstrated a synergistic effect when using the combination of cannabinoids with other given plant extracts and claimed to have improved efficacy and stability.

Cardiovascular System

Cannabis is claimed to have various applications for treating several cardiovascular diseases such as ischemic or atherosclerotic diseases, e.g., angina pectoris, coronary disorders, myocardial infarction, cerebrovascular insufficiency, renal arteriosclerosis, etc. The cannabis formulation for cardiovascular system disorders is typically administered through tablets, injection, or capsule form. The typical routes of administration include oral, buccal, sublingual, or intravenous delivery. The

absorption of cannabis formulation mainly occurs through the gastrointestinal tract or sublingual mechanism. Luan et al. (2019a, b, c, d) are researching a pharmaceutical injection formulation that combines *Cannabis sativa* flower and leaf extract and breviscapine to treat ischemic cerebral apoplexy sequelae. The composition promotes blood circulation to remove blood stasis, enhances dredging collaterals, and improves brain tissue damage repair. Lu and Zhang (2019) at Xiamen Zsbio Tech Co Ltd. discussed a cannabinoid formulation containing CBD extract to treat cardiovascular and cerebrovascular diseases. The composition regulates the body's cytokines and effectively treats cardiovascular and cerebrovascular diseases.

Smeeding and Sherwood (2020) discussed a formulation with a combination of statin and a cannabinoid to treat hypercholesterolemia and atherosclerosis that has shown an improved effect over existing statin formulations. CBD's mechanism is through activation of TRPV1 channels, inhibition of uptake and metabolism of the endocannabinoid anandamide, inhibition of adenosine uptake, antagonism of GPR55, and agonism of PPARy and 5-HT1A receptors, and increase of intracellular calcium ions. In addition, the statins are metabolized by different CYP enzymes; CBD can displace CYP3A4-metabolized statins and slow their metabolism, resulting in increased bioavailability.

Cannabis and Covid-19

The recent COVID-19 pandemic has resulted in millions of deaths worldwide, forced to close international borders, and caused the collapse of many economies. This contagious respiratory disease can cause fever, fatigue, severe breathing problems, and can be fatal.

Some studies are claiming that cannabis affects the treatment of Covid-19.

One of the primary biological events that occur in patients with severe acute respiratory distress cases from COVID-19 is something called a "cytokine storm." A cytokine storm is where the body experiences a drastic increase in proinflammatory cytokines. These cytokines are a category of proteins, and the cytokines involved in a cytokine storm led to a rise in inflammation.

Multiple studies published in scientific journals have demonstrated that cannabis could reduce multiple cytokines and pathways related to inflammation and fibrosis and stop the cytokine storm. Thus, it would suppress inflammation, prevent lung fibrosis that occurred by Covid-19, and put the patients in remission (Simpson 2021; Rees 2021).

Two of the cytokines that *Cannabis sativa* reduced were TNFa and IL-6, which are thought to be the main targets when trying to block a COVID-19 cytokine storm and acute respiratory distress syndrome (Simpson 2021; Rees 2021).

Some study shows that *Cannabis sativa* extracts down-regulate angiotensin-converting enzyme 2 (ACE2) expression in target COVID-19 tissues. According to the researchers, high levels of ACE2 expression in oral epithelial tissues suggest that the oral cavity could be highly susceptible to SARS-CoV-2 infection and thus an important target for prevention strategies (Simpson 2021; Rees 2021).

An Israel-based company, STERO Biotechs, is supporting a clinical study to evaluate the safety and efficacy of STERO's CBD solution for treating patient cytokine storms in severe stages of COVID-19.

- The clinical trial has already received Helsinki Committee approval and plans to include 20 patients as a Proof of Concept (POC), using STERO's CBD-based treatment.
- The study aims to help severely affected COVID-19 patients with respiratory failure stemming from acute respiratory distress syndrome (ARDS). The treatment cycle could be 14–28 days with a subsequent follow-up period of the same length.
- After the success of this Proof of Concept, STERO plans to expand and scale to a Phase 2a multicentre study with 40 additional patients, under FDA clinical trial guidelines and regulations.

Though there are some reports about the use of cannabis in Covid-19, WHO and the US Food and Drug Administration (FDA) warned several CBD producers and vendors not to claim their product usage for mitigating the symptoms of or treating COVID-19 (Sagiv 2021).

6 Conclusion

The patent filing trend for cannabis continues to increase, with the US and China as major patenting countries. Medical cannabis legalization is the primary reason for high patent filings from the US. In the case of China, most patent filings (more than 75%) are related to the natural medicinal use of cannabis for the treatment of various disorders when used in combination with other plant extracts/natural medicines. The trending technologies in cannabis formulations focus on improving the solubility, absorption, and bioavailability of cannabis in the human body. Cannabis is commonly used to treat various central nervous system (CNS) disorders and pain management. It is also found that cannabis affects the treatment or management of other severe disorders such as cancer, cardiovascular disorders, diabetes, and respiratory disorders. Cannabis is used in food and beverages to provide nutrient benefits and weight loss. More recently, there have been reports on the effect of cannabis in the treatment of Covid-19.

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Neuropharmacological Approaches to Modulate Cannabinoid Neurotransmission

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Abstract The endocannabinoid system was discovered and named because of the extended historical use of Cannabis throughout history for fiber, medicinal, and psychoactive reasons by many different cultures. Millions of people worldwide today use Cannabis. Synthetic cannabinoid agonists that were designed and created eventually helped scientists discover the cannabinoid receptors of the endocannabinoid system. From there on, the endocannabinoid system became seriously studied and researched in multiple scientific fields. The major biosynthetic pathways of the endocannabinoid system produce anandamide and 2-arachidonoylglycerol (2-AG).

Fatty-Acid amide hydrolase (FAAH) is the main degrading/metabolizing enzyme of anandamide, and monoglyceride lipase (MGL) is the main degrading enzyme for 2-AG. Cannabinoid-1 (CB_1) receptors are primarily concentrated in the central nervous system (CNS), while Cannabinoid-2 (CB_2) receptors are mainly found in the peripheral nervous system (PNS). The endocannabinoid system acts in a retrograde manner. Once an action potential is generated from the nervous system, endocannabinoids are synthesized post-synaptically and travel retrogradely to act on the presynaptic cannabinoid receptors. Once the endogenous ligand bind, the receptors cause depolarization-induced suppression of inhibition (DSI) in the synaptic knob, blocking calcium (Ca^{2+}) from entering and forcing potassium (K^+) to exit the cell, and this restores the neurons to their resting membrane potential (RMP). The endocannabinoid system plays a role in many significant body functions, like

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memory, gastrointestinal motility, and pain management. Thus, this is an important system to study due to the pharmacological benefits that can come from it.

Keywords Cannabinoids · Endocannabinoids · Neurotransmission · Physiological · Receptors · Signaling

Abbreviations

2-AG	2-arachidonoylglycerol
Abh4	α/β hydrolase 4
AEA	Anandamide
AG-L	Diacylglycerol lipase
CBD	Cannabidiol
CNS	Central Nervous System
DAG	Diacylglycerol
DSI	Depolarization-Induced Suppression of Inhibition
FAAH	Fatty-Acid Amide Hydrolase
GP-NAE	Glycerophospho-N-acylethanolamine
HPA	Hypothalamic-pituitary-adrenal (HPA)
LPA	Lysophosphatidic acid
lyso-NAPE	*N*-acyl-lyso-phosphatidylethanolamine
MGL	Monoglyceride Lipase
N-acyl-PlsEt	*N*-acyl-plasmenylethanolamine
NAE	*N*-acylethanolamines
NAPE	*N*-Acylphosphatidylethanolamine
NAPE-PLD	*N*-acyl phosphatidylethanolamine-specific phospholipase D
pAEA	phosphoanandamide
PNS	Peripheral Nervous System
RMP	Resting membrane potential
sPLA	Secretory phospholipases
THC	Delta-9-tetrahydrocannabinol

1 Introduction

Medicinal effects of the *Cannabis sativa* plant have been known since the Ancient Greeks and were consistently documented throughout history by ancient Indian, Chinese, and European historians and medical authors (Freund et al. 2003). There is archaeological proof that the Chinese domesticated Cannabis in two ways. They isolated and bred plants with high delta-9-tetrahydrocannabinol (THC) content and removed male versions of plants because they have lower THC concentrations than female plants, suggesting that even ancient civilizations used Cannabis for its

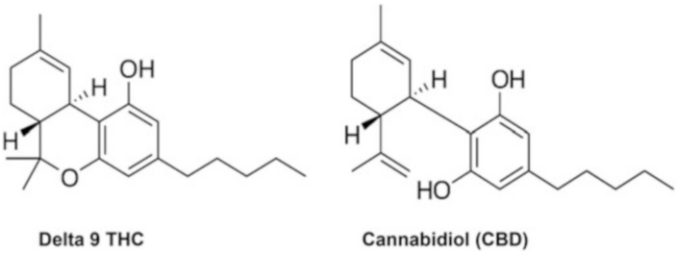

Fig. 1 Structures of delta 9-THC and Cannabidiol

psychotropic effects. They also bred and isolated cannabis plants to make clothing and ropes or food fibers (Crocq 2020). Many other historical references to Cannabis are found in ancient Greek literature by Homer and Herodotus, Roman literature by Pliny the Elder and Dioscorides, and ancient Egyptian writings. The tradition of documenting the use of Cannabis for its psychoactive and anti-inflammatory properties continued throughout history in Western Europe and the Middle East. Then in the late nineteenth century, as science advanced, the study of the cannabis plant for its medicinal properties began to grow, and societies throughout history wrote about Cannabis for its medicinal and psychoactive effects (Crocq 2020).

Today, there are an estimated 200 million cannabis users worldwide and 14.6 million young European consumers (age 15–34); it is estimated that more than 13 million are dependent on Cannabis today (Degenhardt and Hall 2012). The plant, when ingested, produces effects in humans such as euphoria, relaxation, and hypothermia. It is now known that the primary psychoactive ingredient in the *Cannabis sativa* plant is delta-9-tetrahydrocannabinol, also known as delta-9-THC, and the main anti-inflammatory and relaxing agent in Cannabis is Cannabidiol, also known as CBD (Fig. 1). There are between 80 and 100 different cannabinoids and over 400 chemicals present in any given plant. Most have not been extensively investigated to determine the pharmacological and toxicological effects they may produce (Atakan 2012). Many of these cannabinoids are present in much smaller quantities than THC and CBD in commercially sold Cannabis, and their physiologic actions are currently not as well understood as those of THC and CBD.

The research into Cannabis and its medicinal properties was hindered due to its extreme insolubility in water, making it difficult for investigators to determine its mode of action. In more recent years, two things proved to be major steps forward in cannabis research. The first was that scientists who were studying Cannabis for potential therapeutic applications started to create synthetic analogs, such as WIN 55,212–2 (a CB_1 agonist) and JWH-133 (a CB_2 agonist) (Fig. 2) that produced the same effects as Cannabis but more selectively (An et al. 2020). Second, with the development of these two compounds and subsequent analogs, scientists could use synthetic analogs to directly study cannabinoid receptors and their existence using radioligand binding techniques. Both advances demonstrated that even though cannabinoids are highly insoluble, they interact with selective receptors in the

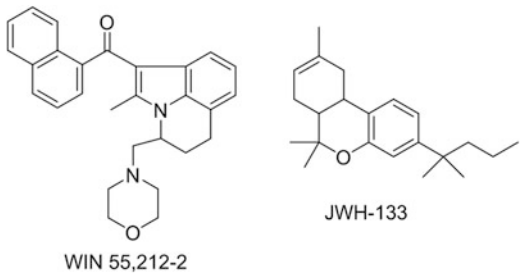

Fig. 2 Structures of the synthetic cannabinoids

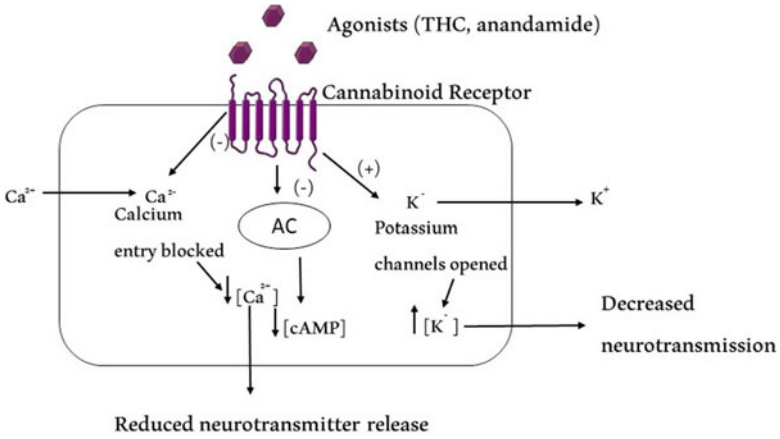

Fig. 3 Cannabinoids acting on the receptors

brain and not with cell membranes. The first receptor discovered is now referred to as the CB_1 receptor (Freund et al. 2003).

The discovery of endogenous cannabinoids represented the next significant advance in cannabinoid research, along with the cloning of cannabinoid receptors. The CB_1 receptor physiologically controlled locomotion, ocular pressure, pain perception, memory, feeding, and anxiety (Barna et al. 2004). Cannabinoids also affect the production of hormones in the gonads, pituitary, and thyroid and control aspects of the hypothalamic-pituitary-adrenal (HPA) axis, which plays critical roles in the body's response to stress and basal homeostasis (Barna et al. 2004). The CB_1 receptor affects many intracellular pathways, such as adenyl cyclase activity, inhibition of voltage-activated calcium channels, and activation of potassium channels (Fig. 3).

CB_1 receptors are present throughout the central nervous system (CNS) in peripheral organs and tissues. The presence of these receptors throughout the CNS has been related to the cannabis plant's ability to produce neurochemical effects, such as euphoria. Delta-9-THC, the main psychoactive ingredient in Cannabis, is a ligand for CB_1 receptors, which is problematic because of its connection with a potential addiction. CB_1 receptors are also being studied as therapeutic targets for

anti-obesity and chemotherapeutic medications. CB_1 antagonists reduce hunger, food consumption, and consequently body weight. CB_1 antagonists are also being studied in the treatment of cravings for alcoholics and drug addicts (Mackie 2006). After the discovery and cloning of CB_1 receptors, the question of how cannabinoids produced effects in tissues outside the CNS remained unsolved until the discovery of the CB_2 receptor. The CB_2 receptor is expressed in immune tissues, which leads scientists to believe it plays a role in immunosignaling. It also plays a role in modulating the inflammatory responses of the body (Freund et al. 2003). Due to the extensive roles that both the CB_1 and CB_2 receptors play in the body, they are being studied as major targets for therapeutic interventions. CB_2 receptors specifically are being targeted to treat neuropathic pain and related conditions and neurodegenerative diseases such as Alzheimer's disease (Bie et al. 2018). There are other pharmacological and toxicological effects produced by cannabinoids that have not yet been explained by the CB_1 and CB_2 receptors, which leads scientists to believe that there are other undiscovered cannabinoid receptors in the body. Due to the wide range of effects produced by the cannabinoids, potential therapeutic interventions with cannabinoid drug products must carefully consider all of the potential physiologic outcomes of cannabinoid receptor interactions (Bie et al. 2018).

2 The Endogenous Cannabinoid System

2.1 Biosynthetic Pathways

2.1.1 Anandamide (AEA) Biosynthesis

Anandamide was initially thought to be synthesized by the condensation reaction between ethanolamine and arachidonic acid. Therefore, the enzyme that catalyzed this reaction was coined "anandamide synthase", but additional studies revealed that the enzyme was Fatty Acid Anandamide Hydrolase (FAAH), which more commonly breaks down anandamide into ethanolamine and arachidonic acid by hydrolysis, working in the reverse direction (Fig. 4). This enzymatic pathway for biosynthesis is not very feasible inside the human body because it takes a much larger concentration of ethanolamine and arachidonic acid than is present *in vivo* to make this reaction occur (Freund et al. 2003). Other biosynthetic pathways of anandamide are more relevant because they have been found to occur *in vivo*. The first discovered, simplest, and most well understood biosynthetic pathway is the hydrolysis of *N*-Acylphosphatidylethanolamine (NAPE) by *N*-acyl phosphatidylethanolamine-specific phospholipase D (NAPE-PLD); this is known as the NAPE-PLD pathway (Fig. 4). Phosphatidylethanolamines are membrane phospholipids that are characteristic of nervous tissue. After being cleaved, membrane-bound calcium (Ca^{2+}) dependent *N*-acyl transferase (Ca-NAT) creates *N*-Acylphosphatidylethanolamines (NAPEs) from the cleaved phosphatidylethanolamines. NAPE-PLD then hydrolyzes the NAPEs to form anandamide (AEA) among

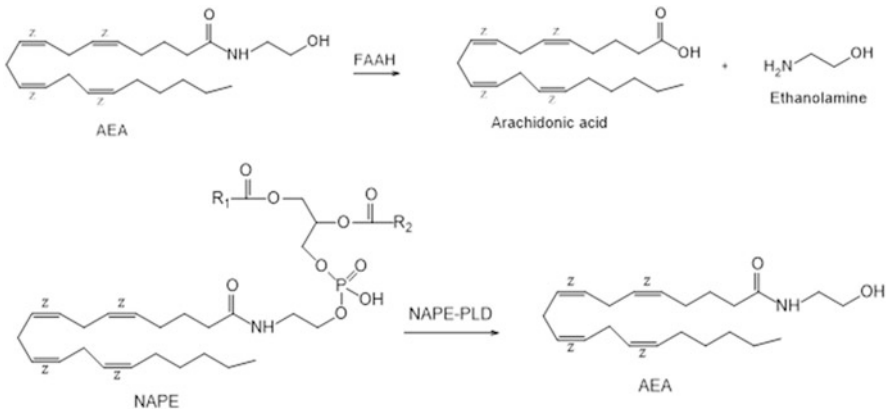

Fig. 4 Biosynthesis of anandamide (AEA)

other *N*-acylethanolamines (NAEs). NAPE-PLD production is stimulated by rising Ca^{2+} levels as well as the activation of the CB_1 receptors (Lu and Mackie 2016).

Although they are distinct pathways, AEA and NAPE are formed at the same time. Both reaction pathways synthesizing AEA and NAPE are initiated by rising Ca^{2+} levels or by activating neurotransmitter receptors (Freund et al. 2003). Neurotransmitter receptors that have been found to activate NAPE biosynthetic pathways are the CB_1, CB_2, and specific dopamine receptors such as D_2. These receptors appear to act cooperatively in the endocannabinoid system (Zhang et al. 2011). For example, the stimulation of D_2 receptors enhances CB_1 receptor activation indirectly by enhancing its downstream effects (Benbadis et al. 2014).

The remaining three reactions are all NAPE-PLD independent, and they are multi-step pathways. The most well-understood of these NAPE-PLD independent biosynthetic pathways of anandamide involves NAPE-PLC cleaving the phosphodiester bond of NAPE to create phosphoanandamide (pAEA) (Fig. 5). This phosphoanandamide is subsequently dephosphorylated by certain phosphatases to create anandamide. This pathway has been well-studied in immune cells, and its presence in the brain and nervous tissue is indicated by collected evidence (Liu et al. 2006). This is probably the more common and better understood multi-step biosynthetic pathway of anandamide. The other two potential pathways of AEA formation start with the same basic reaction: the hydrolysis of NAPE into *N*-acyl-lyso-phosphatidylethanolamine (lyso-NAPE) catalyzed by secretory phospholipases (sPLAs) IB, IIA, and V as well as α/β hydrolase 4 (Abh4) enzymes. The Abh4-GDE1 pathway takes this lyso-NAPE, and Abh4 further catalyzes a reaction that turns the Lyso-NAPE into Glycerophospho-N-acylethanolamine (GP-NAE) (Fig. 5). GP-NAE is then hydrolyzed again, making glycerol-3-phosphate (G3P) and AEA, which is catalyzed by Glycerophosphodiesterase 1 (GDE1). The difference between this pathway and the final pathway is the starting molecule. Instead of starting with NAPE like the rest of the pathways, this pathway begins with *N*-acyl-plasmenylethanolamine (*N*-acyl-PlsEt), which is another biochemical known as a

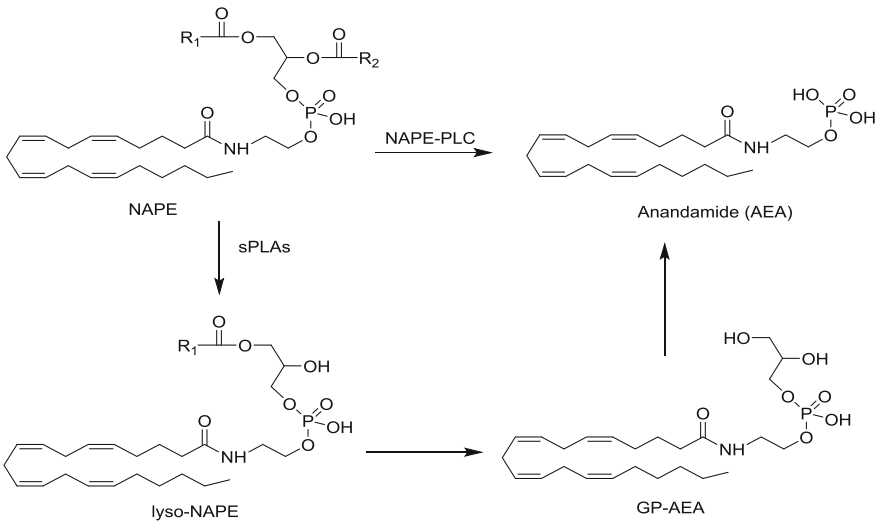

Fig. 5 Biosynthesis of AEA from NAPE

plasmalogen phospholipid commonly found in the brain and nervous tissue. This *N*-acyl-PlsEt can go through a one-step, NAPE-PLD pathway as described in the first reaction pathway above, or it can go through the Abh4-Lyso-PLD-type enzymes pathway. The hydrolysis of *N*-acyl-PlsEt to AEA is catalyzed by the Lyso-PLD-type enzymes and releases alkenyl-type lysophosphatidic acid (LPA) and AEA (Tsuboi et al. 2013).

2.1.2 2-Arachidonoylglycerol (2-AG) Biosynthesis

2-AG biosynthesis is much simpler than the synthesis of AEA. Two different, two-step pathways start with a phosphatidylinositol molecule present in cells as a membrane phospholipid, and one additional pathway beginning with arachidonoyl-LPA. The first pathway is a PLCβ-mediated hydrolysis reaction that cleaves the phosphatidylinositol molecules and forms a diacylglycerol (DAG) (Fig. 6). DAG is then hydrolyzed by diacylglycerol lipase (DAGL) to form 2-AG (Lu and Mackie 2016). This pathway is engaged by stimulating PLC-activating receptors such as Orexin A, group I metabotropic glutamate, and M_1 or M_3 muscarinic receptors. Two isoforms of DAGL play a role in the biosynthesis of 2-AG in the PLC-mediated pathway: DAGLα and DAGLβ. DAGLα is the dominant form that produces 2-AG in adult CNS and evidence shows that inhibiting DAGLα leads to lower 2-AG production. Evidence suggests that DAGLβ also plays an important role in 2-AG formation in certain situations, especially during an immune response.

The second biosynthetic pathway for 2-AG is mediated by phospholipase A (PLA). The phosphatidylinositol is transformed into a lysophospholipid by PLA,

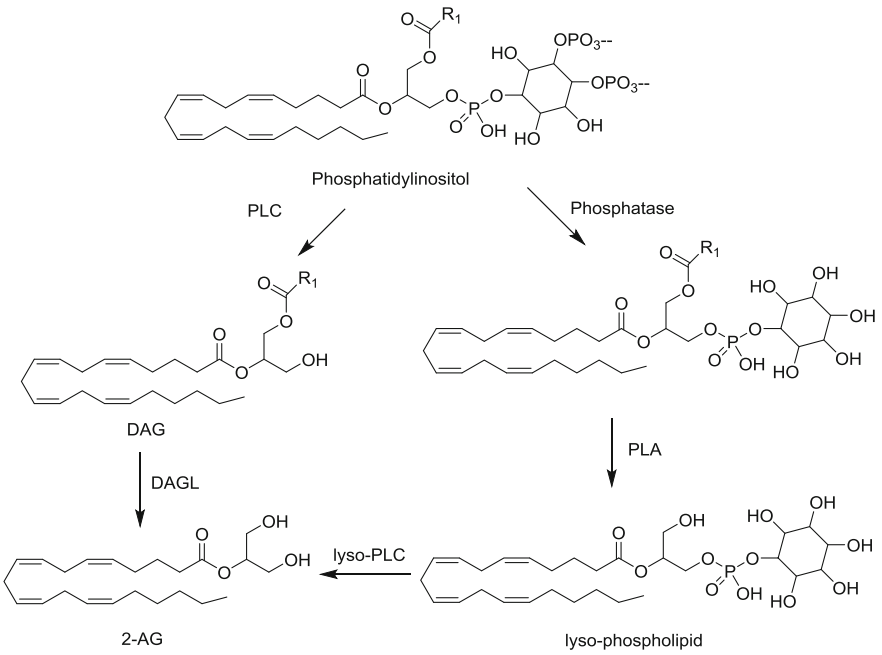

Fig. 6 Biosynthesis of 2-AG

and then the lysophospholipid is hydrolyzed at the phosphate ester bond to form 2-AG by lyso-PLC. The third pathway starts with arachidonyl-LPA. LPA hydrolysis then occurs through the catalyzation of LPA phosphatase. This hydrolysis reaction forms 2-AG. The importance in the CNS of the latter two of the three pathways discussed here has not yet been established (Murataeva et al. 2014).

2.1.3 Other Endogenous Cannabinoids Synthesized

A few other endogenous compounds are analogs of anandamide and are produced similar to anandamide in smaller quantities. These are eicosatrienoyl ethanolamide and docosatetraenoyl ethanolamide (Fig. 7). These interact with receptors in identical ways to anandamide due to their structural similarities. Noladin ether and virodhamine are newly discovered brain lipids that interact with the CB_1 receptors (Fig. 7). Noladin ether produces cannabinoid-like effects such as antinociception and sedation. Virodhamine was a weak agonist of the CB_1 receptor producing some cannabinoid-like effects, but a possible cause for this is virodhamine's instability in solution; it rapidly converts to anandamide which could cause the CB_1 agonist properties of virodhamine. The importance of these molecules is still being investigated, and for now, they are another form of regulation in the endocannabinoid system (Freund et al. 2003).

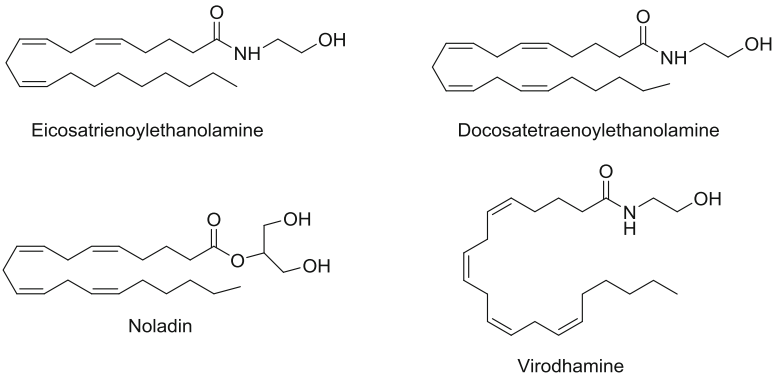

Fig. 7 Other endogenous eicosanoid cannabinoids

2.2 Termination of Endocannabinoid Effects: Transport and Degradation

2.2.1 Anandamide Transport

Even though it is a lipid that could potentially diffuse through cell membranes, Anandamide undergoes facilitated diffusion in the form of carrier-mediated transport. Carrier-mediated transport allows for quick delivery of lipid molecules to specific parts of the cell, which explains why anandamide undergoes carrier-mediated transport versus just passively diffusing across the membrane. Other evidence that it undergoes carrier-mediated transport is that transporting anandamide across the cell membrane requires no additional energy nor Na^+ concentration. Anandamide transport is also independent of its hydrolysis by fatty acid amide hydrolase (FAAH), as evidenced by anandamide transport rates remaining unchanged in the presence of FAAH inhibitors (Freund et al. 2003).

2.2.2 2-AG Transport

2-AG inhibits anandamide transport, indicating that the two compounds compete for the same transport system. AM404 (an anandamide analog) is also an inhibitor of 2-AG transport. This evidence suggests that the carrier-mediated transport system utilized by anandamide is the same transport system that 2-AG uses (Freund et al. 2003).

2.2.3 Anandamide Hydrolysis

Anandamide is primarily hydrolyzed by FAAH (described earlier). The hydrolysis of anandamide produces arachidonic acid and ethanolamine. FAAH is a major target

of inhibition for pharmacological studies because of the positive effects that anandamide produces in the body. FAAH is largely distributed throughout the CNS, and because of this, many types of inhibitors are being developed to try and control where FAAH is inhibited and by how much.

2.2.4 Monoglyceride Lipase (MGL) Hydrolyzes 2-AG

MGL breaks down 2-AG into fatty acid and glycerol. FAAH also breaks down 2-AG, but at a rate slower than MGL. This was determined by analyzing 2-AG hydrolysis in systems lacking FAAH and seeing that the rate of 2-AG hydrolysis was unaffected.

3 Cellular Distribution of Neuronal Cannabinoid Receptors

3.1 Characteristic Differences in CB1 Receptor Distribution in the Brain

CB1 receptors are the most densely expressed G protein-coupled receptors in the brain and are mainly concentrated in the cortex, hippocampus, amygdala, basal ganglia, and cerebellum (Mackie 2005). Although they are present throughout the body, the CB1 receptors are primarily located in the brain. The location and concentration of the CB_1 receptors in the CNS help explain the wide array and specific effects produced by endocannabinoids and cannabinoids that bind to CB_1 receptors such as THC. Although the location of these receptors can help explain some of the effects produced by cannabinoids, many other factors play a role in the functions of the central nervous system besides cannabinoids and the location of their receptors alone; however, presently, most of these are poorly understood (Arria et al. 2015).

3.2 Selective Expression of CB1 Cannabinoid Receptors by Identified Cell Types of Complex Networks

The presence of CB_1 receptors in the cortex is the highest in the cingulate and frontal cortices. In the cingulate cortex, the presence of receptors may explain the analgesic effect that cannabinoids produce in the body. The analgesic effects can also be partly explained by the concentration of the receptors in the limbic system (Milligan et al. 2020). The amygdala plays an essential role in both memory, and emotional responses, especially fear and anxiety, which may explain the anxiolytic effects of marijuana. This can be somewhat misleading because paranoia also originates from

the amygdala, another possible effect of cannabinoids (DeLisi 2008). The frontal cortex and hippocampus affect higher learning, memory, and perception. The presence of CB_1 receptors in this region may explain the impact cannabinoids have on higher learning and memory (Arria et al. 2015; Schoeler and Bhattacharyya 2013). The CB_1 receptors in the cerebellum and basal ganglia could explain the decreased motor activity when cannabinoids are consumed (Freund et al. 2003). There is a low concentration of CB_1 receptors in the parts of the brainstem associated with cardiovascular and respiratory function. This possibly explains why even extremely high concentrations of cannabinoids are not toxic to humans (Herkenham et al. 1990).

Interestingly in autoradiographic assays of the CNS, to determine the location and concentration of CB_1 receptors, it was found that some places in the CNS that were associated with effects that cannabinoids produce, did not have a high concentration of receptors but had very tight G protein-coupling (Freund et al. 2003). For example, CB_1 receptors are not highly concentrated in the hypothalamus, yet the hypothalamus is affected by cannabinoids and produces the hypothermia and hunger seen when cannabinoids are consumed in humans (Wenger and Moldrich 2002). The spinal cord and brain stem are other examples of tissues with lower concentrations of CB_1 receptors yet produce significant responses when exposed to cannabinoids such as blood pressure changes and anti-emetic effects associated with the brain stem being affected, and analgesia and anti-hypernociceptive effects associated with the spinal cord (Malinowska et al. 2012; Manzanares et al. 2006).

4 Physiological and Pharmacological Indication for the Presynaptic Localization of CB1 Cannabinoid Receptors in the Brain

Depolarization-induced suppression of inhibition (DSI) occurs when cannabinoids bind to CB_1 receptors. The axon is depolarized by rising intracellular Ca^{2+} levels, which causes the resting membrane potential to increase from -70 mV to anywhere from -30 mV to 0 mV (Diana and Marty 2004). This signals postsynaptic endocannabinoid biosynthesis, and the endocannabinoids produced travel backward (retrogradely) to the presynaptic CB_1 receptors. The activation of CB_1 receptors through the binding of endocannabinoids blocks Ca^{2+} from entering the cell and releasing neurotransmitters. Furthermore, the CB_1 receptor activation inhibits adenyl cyclase and, therefore, blocks cAMP production, which is also involved in neurotransmitter release. It also opens K^+ channels so that K^+ leaves the cell, which eventually returns the resting membrane potential to its original state at -70 mV. This depolarization stops excitatory and inhibitory neurotransmitters, such as glutamate and GABA, from being released (Alger 2013). The above process effectively allows for neurons to control their own synaptic input using a retrograde pathway. It is retrograde because endocannabinoids are released post-synaptically and travel

against the normal current of neurotransmitters to bind to the CB_1 receptors pre-synaptically. This process is known as retrograde synaptic signaling (Freund et al. 2003). This process was important in discovering and confirming the presynaptic distribution of CB_1 receptors (Fig. 2).

4.1 Anatomical Evidence for Presynaptic Cannabinoid Receptors

The development of specific antibodies that bind to CB_1 receptors was crucial in discovering and confirming that CB_1 receptors were indeed located pre-synaptically. More specific antibodies are preferred due to the notoriety surrounding the non-specificity of antibody binding sites (Grimsey et al. 2008). These antibodies were analyzed microscopically and found on axons based on the thin structure and a high number of varicosities in the structures that the antibodies were bound to (Katona et al. 1999). Many different examples were found where the structures that the antibodies were binding with matched the description and characterization of axons in different parts of the brain (Freund et al. 2003).

4.2 Physiological and Pharmacological Evidence for Presynaptic Cannabinoid Receptors

4.2.1 Hippocampus, Amygdala, and Cortices

In the hippocampus, cannabinoids decrease the function and number of $GABA_A$ inhibitory postsynaptic currents (IPSCs). The evidence for CB_1 receptors being the modulators of this is derived from studies where CB_1 agonists were found to strengthen this effect and antagonists were found to block this effect completely (Hájos et al. 2000). These actions lead to neurotransmitter vesicles not being released nearly as frequently, giving rise to the idea that CB_1 receptors in the hippocampus act pre-synaptically (Freund et al. 2003). Similar results were found in the amygdala, prefrontal cortex, and neocortex. In these areas of the brain, a novel cannabinoid receptor distinct from CB_1 mediates glutamate release. This is evidenced by the fact that CB_1 agonists do not bind well in the absence of CB_1 receptors, yet a CB_1 antagonist binds to this new receptor very well in the absence of CB_1 receptors. Another indicator that a novel receptor exists is CB_1 receptors appear to be only minimally on glutamatergic neurons, yet cannabinoids still regulate glutamate release (Marsicano and Lutz 1999). The CB_1 receptor's activation blocks the release of acetylcholine, as evidenced by cannabinoid receptor agonists blocking the release of acetylcholine and cannabinoid receptor antagonists preventing this effect (Kathmann et al. 2001). Norepinephrine is also inhibited by CB_1 activation, as evidenced in a similar way to previously mentioned neurotransmitters. The

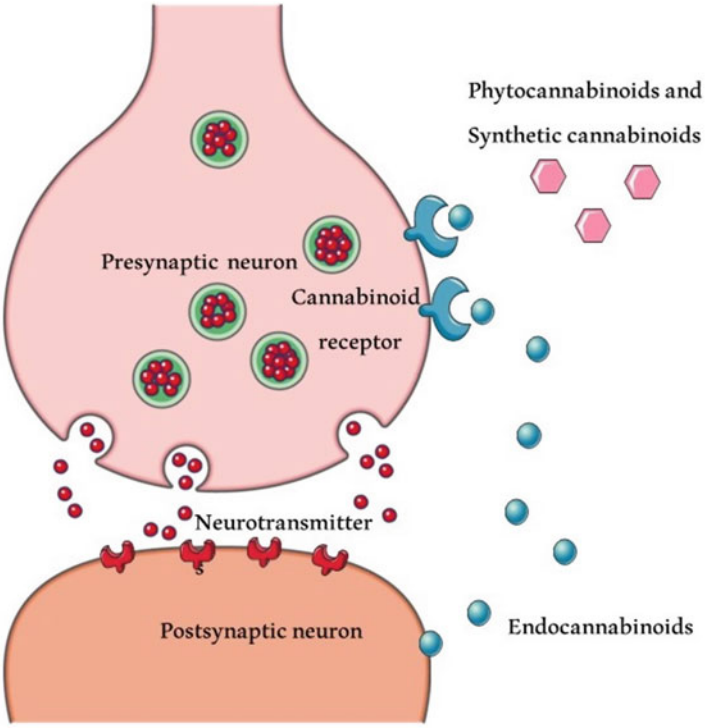

Fig. 8 Presynaptic location of cannabinoid receptors

interesting thing is that, depending on the species, norepinephrine regulation by CB_1 receptors depends on location in the brain. For example, humans and Guinea pigs exhibit norepinephrine regulation in the hippocampus and cortex, but rat hippocampal tissue does not. This is intriguing considering the high conservation of the endocannabinoid system (Steffens et al. 2004). Cannabinoids somewhat inhibit serotonin release, but to a lesser degree than acetylcholine and GABA. In addition, some results have been inconclusive, and the existence of serotonergic cells with CB_1 receptors has yet to be found (Nakazi et al. 2000). Cannabinoids and cannabinoid agonists inhibit the release of cholecystokinin as well, and antagonists prevent CCK from being blocked. Interestingly this effect does not appear to be ubiquitous to these three regions in the brain. This is more evidence of the presynaptic location of CB_1 receptors (Fig. 8).

4.2.2 Basal Ganglia

Experiments similar to those performed in the hippocampus and cortex to determine the location of CB_1 receptors. Experiments were also performed on cells from the basal ganglia with similar results. GABA is inhibited through presynaptic activation

of CB_1 receptors (Wallmichrath and Szabo 2002). Similar to the hippocampus, glutamate release is probably mediated by a novel cannabinoid receptor, but there is also a lower concentration of CB_1 receptors in the basal ganglia when compared to the hippocampus and cortex, so this could be a possible confounding factor (Gerdeman et al. 2002; Robbe et al. 2001).

4.2.3 Cerebellum

GABA inhibition by CB_1 receptors acting pre-synaptically was also demonstrated (Kreitzer and Regehr 2001). The very large number of CB_1 receptors in the cerebellum makes the effects of GABA blockage more intense. The cerebellum, similar to other parts of the brain, inhibits the release of glutamate when exposed to cannabinoids, but, also like other parts of the brain, the evidence points to the involvement of a unique and different cannabinoid receptor in this action rather than the CB_1 receptors (Matsuda et al. 1993). All evidence points to a presynaptic action by CB_1 receptors (Takahashi and Linden 2000).

4.2.4 Nociceptive Pathways

In the spinal cord and supraspinal area, GABA and glycine release is inhibited by cannabinoids. However, whether CB_1 receptors are mediating this action remains unclear. This area needs more research to determine if GABA blockage is associated with CB_1 receptors (St. Marie and Leo 2021). It is known that the regulation of glutamate plays a role in nociceptive effects produce by cannabinoids. Similar to other CNS organs, glutamate is probably not regulated by CB_1 receptors. Interestingly, not all the cell and tissue types exhibit the glutamate inhibition seen throughout the other CNS tissues (St. Marie and Leo 2021). There is evidence that the presence of anandamide inhibits the release of the neuropeptides Substance P and CGRP. This is probably due to action by CB_1 receptors and contributes to the analgesic and anti-inflammatory effects that anandamide produces (Richardson et al. 1998).

4.2.5 Postsynaptic CB1 Receptors?

There is evidence that postsynaptic CB_1 receptors do exist and have different functions. Currently, no evidence suggests that CB_1 receptors are present in the postsynaptic membrane, but the possibility cannot be ruled out at this point (Busquets-Garcia et al. 2018). Mitochondrial CB_1 ($mtCB_1$) is present in presynaptic and somatodendritic compartments in GABA and glutamate signaling cells. The presence within the cell post-synaptically could indicate that these receptors act intracellularly rather than intercellularly (Bénard et al. 2012). There is also evidence that CB_1 receptors are present on astrocytes to increase Ca^{2+} within the cell

(Busquets-Garcia et al. 2018). The activation of these receptors on astrocytes releases gliotransmitters which act on nearby neurons (Navarrete and Araque 2010).

5 Physiological Roles of Endocannabinoids

Endocannabinoids are critical modulators of the CNS and affect many different functions throughout the body. The endocannabinoid system regulates cell reproduction, apoptosis, and differentiation of cell types in many tissues throughout the body, such as the brain, adipose tissue, and blood (Galve-Roperh et al. 2013). In the CNS, endocannabinoids affect pain perception, regulation of body heat, motor function, learning, memory, sleep, emotions, behavior (especially stress), appetite, reproductive process, and visual perception (Pertwee 2015). On a smaller scale, endocannabinoids also control the release and secretion of dopamine, GABA, glutamate, and other neurohormones (van der Stelt and Di Marzo 2003); (Meccariello et al. 2014). The endocannabinoid system also plays a role in the heart and blood by regulating platelets, blood pressure, vasodilation, and even heart rate (Watkins et al. 2010). The digestive tract is also affected by the endocannabinoid system through its effects on peristalsis in the intestines (Fasano et al. 2009). The endocannabinoid system also controls inflammation by affecting adipose and muscle tissue. The pancreas and liver are also regulated by the endocannabinoid system, specifically the function of these organs in the homeostasis of glucose and lipids (Fasano et al. 2009). There are also many steps involved in reproduction, from the production of sex hormones to gametes' actions in fertilization, controlled by the endocannabinoid system (Fasano et al. 2009). Overall, the endocannabinoid system has many physiological roles, and it is spread throughout the body rather than being limited to the CNS.

6 Conclusion

The molecular signaling systems in neuroscience have become increasingly important to understand. Research must be performed so that the physiological and pathological roles of the endocannabinoid system can be elucidated. The worldwide in-depth research in this field has, in a brief period, created effective and selective drugs targeting the endocannabinoid system that have provided innovative ways to potentially treat significant diseases such as cancer, pain, neurodegenerative diseases, anxiety, and addiction. This approach can be a new initiation for the modern age that learns from the ancient use of Cannabis as a therapeutic approach.

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Cannabinoids in Cancer: Cross-talk Between Cannabinoids and miRNAs

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Abstract At present, the pharmacological applications of exogenous cannabinoids have been validated, and an increasing number of studies have shown their role in cancer pathogenesis and treatment. Both exogenous and endogenous cannabinoids exhibit their effects through cannabinoid receptors, which then modulate several signaling pathways vital in controlling cell proliferation and survival. Recent studies have shown that microRNAs (miRNAs) play vital roles in critical biological processes, including gene expression and chromatin regulation. Deregulation of miRNAs contributes to the dysfunction of many vital cellular processes, leading to cancer growth, progression, and chemoresistance. The present chapter highlights the recent findings concerning the implications of cannabinoids in cancer, miRNAs in cancer, and the cross-talk between cannabinoids and miRNAs in cancer pathogenesis and treatment.

Keywords Cannabis · Cannabinoids · THC · CBD · Cancer · miRNA

Abbreviations

Δ9-THC	Delta-9-tetrahydrocannabinol
2-AG	2- Arachidonoylglycerol
CB	Cannabinoid Receptor
CBD	Cannabidiol

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eCBS	Endocannabinoid system
GPR55	G protein-coupled receptor 55
HCC	Hepatocellular carcinoma
miRNA	microRNA
TRPV	Transient receptor potential channels of the vanilloid subtype

1 Cannabinoids and Cannabinoid Receptors

1.1 Natural and Synthetic Cannabinoids

Cannabinoids, the active compounds extracted from *Cannabis sativa,* interact with cannabinoid receptors by mimicking their endogenous counterparts, endocannabinoids. The most well-studied exogenous cannabinoids are phytocannabinoids; cannabidiol (CBD), and delta-9-tetrahydrocannabinol (Δ9-THC) (Dinu et al. 2020). Additional phytocannabinoids exist as well, such as delta-8-tetrahydrocannabinol (Δ8-THC), cannabigerol (CBG), and cannabicyclol (Morales et al. 2017) (Fig. 1). Synthetic cannabinoids or cannabimimetics are synthesized in the laboratory and are functionally similar to THC. These cannabimimetics have been developed as therapeutic agents to treat nausea and vomiting caused by cancer chemotherapy, weight loss, and poor appetite in patients with AIDS. Other identified synthetic compounds include HU-210, CP 47,497, JWH-018, JWH-073, and JWH-250 (Elsohly et al. 2014) (Fig. 1). The two major endocannabinoids, which are the endogenous lipids naturally found in mammalians, are anandamide and 2-arachidonoylglycerol (2-AG) (Alexander et al. 2009; Smith et al. 2010) (Fig. 1).

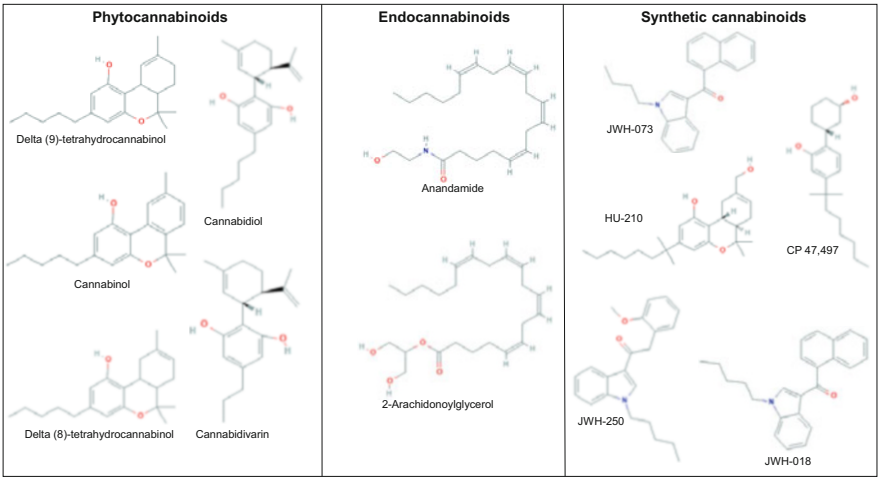

Fig. 1 Natural and synthetic cannabinoids and their chemical structures

1.2 Cannabinoid Receptors and Their Mechanisms

The active cannabinoids mediate their activity by binding to the cannabinoid receptors (CBs). CBs belong to the G-protein receptor family, and at present, two types have been identified: CB1 and CB2 (Zou and Kumar 2018). Although cannabinoids bind to other receptors besides CB1 and CB2, those receptors are, at present, not yet well studied (Basavarajappa 2007). CB1 is present in the central nervous system, specifically the amygdala, cerebellum, cortex, hypothalamus, and the hippocampus in humans (Mechoulam and Parker 2013), as well as other tissues of the body, including the tongue, intestine, spleen, heart, adrenal gland, ovaries, endometrium, and testes (Sathynathan et al. 2021). This receptor plays a role in regulating mood, sleep, memory, appetite, and pain. CB2 is mainly present in the immune system, specifically in lymphocytes, lymph nodes, macrophages, and the spleen (Pyszniak et al. 2016) and is responsible for the anti-inflammatory effects (Nikan et al. 2016). An orphan G protein-coupled receptor 55, GPR55, assumed to be the third cannabinoid receptor CB3, is found in the brain and endothelial tissues such as those in the intestine and lymphatic vessels (Breivogel et al. 2001). The activation of these receptors promote their interaction with G-proteins of the Gi/o family resulting in inhibiting adenylyl cyclase function, thereby reducing cellular cAMP levels. Specifically, CB1 activation stimulates cellular signal transduction via Gi/o pathway leading to a decrease in cAMP levels in neuronal cells, while CB2 only couples strongly to Gi (Glass and Northup 1999) (Basavarajappa 2007).

2 Cannabinoid System and Cancer

Differential expression of CB1 and CB2 receptors in different cancer tissues has been described. CB1 expression was detected in 28% of human breast cancer tumor tissue, predominately in HER2-type breast tumors (Rahman et al. 2019). CB1 is also upregulated in various breast cancer cell lines such as MCF-7, T-47D, MDA-MB-231, TSA-E1, MDA-MB-468 as detected by RT-PCR and Western blot (Guindon and Hohmann 2011). Caffarel et al. looked at CB2 expression in *ERBB2*-positive human breast tumors. They found that CB2 immunoreactivity was identified in 72% of the breast tumor tissue, and CB2 receptors were found in 91% of the *ERBB2*-positive tumor tissue (Caffarel et al. 2010).

The expression of CB1 and CB2 receptors has also been evaluated in prostate cancer tissues and cell lines. It was reported that CB1 expression is upregulated in prostate cancer tissue (Czifra et al. 2009). The severity and outcome of prostate cancer are related to the increase in expression of the CB1 receptor (Chung et al. 2009). Various prostate cancer cell lines such as PC-3, DU-145, LNCaP, CWR22Rv1, CA-HPV-10, and human prostate cancer tissues were also shown to express CB1 and CB2 receptors by RT-PCR and Western blot (Guindon and Hohmann 2011).

Furthermore, increased CB1 and CB2 receptors expression was also seen in pancreatic cancer cells, mantle cell lymphoma, B cell non-Hodgkin lymphoma (Wasik et al. 2011), and human melanomas and melanoma cell lines (Blazquez et al. 2006). In colorectal cancer human specimens, only CB2 receptor is expressed while CB1 receptor was mainly expressed in the human normal colonic epithelium (Cianchi et al. 2008).

2.1 Cannabinoids in Cancer Pathogenesis

Multiple studies have evaluated the effects of cannabinoids on tumors both in cancer pathogenesis and in cancer treatment. In some studies, the use of cannabinoids generated an increased risk of cancer and promoted cancer progression, while in others use of cannabinoids proved an effective treatment of cancer. In recent studies, cannabinoids have been shown to exhibit immunomodulatory properties with the ability to suppress the antitumor response of the immune system (McKallip et al. 2005). More research is necessary to determine if cannabinoids can be used as an effective cancer treatment. In cancer development, cannabis can induce cancer mechanisms, promoting cell proliferation and metastasis. Additionally, cannabinoids can directly influence the tumor and increase susceptibility to infections by affecting the immune system, increasing the risk of infection, and promoting tumor growth (McKallip et al. 2005).

For example, there is evidence of an increased risk of head, neck, and lung cancers using cannabinoids (McKallip et al. 2005) (Fig. 2). Δ9-THC can impair the function of macrophages and the proliferation of T-cells, and the production of antibodies in B-cells through CB2 receptors. Additionally, Δ9-THC has been shown to alter the activity of cytokines, specifically those critical to the immune response. It has a two-fold effect of both making the body more susceptible to various infections and suppressing the immune response to tumors (Eisenstein and Meissler 2015).

In many cancers, the activation of CB1 and CB2 receptors by various ligands increases the activity of cancerous cells. The increased expression of CB1 and CB2 has led to cell proliferation and the development of certain cancers. Specifically, in skin cancer, an increase in activation of CB1 and CB2 led to increased cancer activity. The UV radiation from sunlight directly activates the CB1 and CB2 receptors, inducing tumor mechanisms – the essential processes to the survival of the tumor, such as the main hallmarks of cancer cells, specifically sustained proliferative signaling, evading cell death, evading growth suppressors, and activating invasion and metastasis mechanisms. Evidence of resistance to skin cancers caused by UV radiation is shown in mice with a decreased expression of both the CB1 and CB2 receptors. However, increased expression of these cannabinoid receptors in other cancers promoted apoptosis and inhibited cell proliferation (Zheng et al. 2008) (Fig. 2).

Some cannabinoids also have been shown to promote metastasis and tumor generation. Increased activity of the endocannabinoid system is often linked to

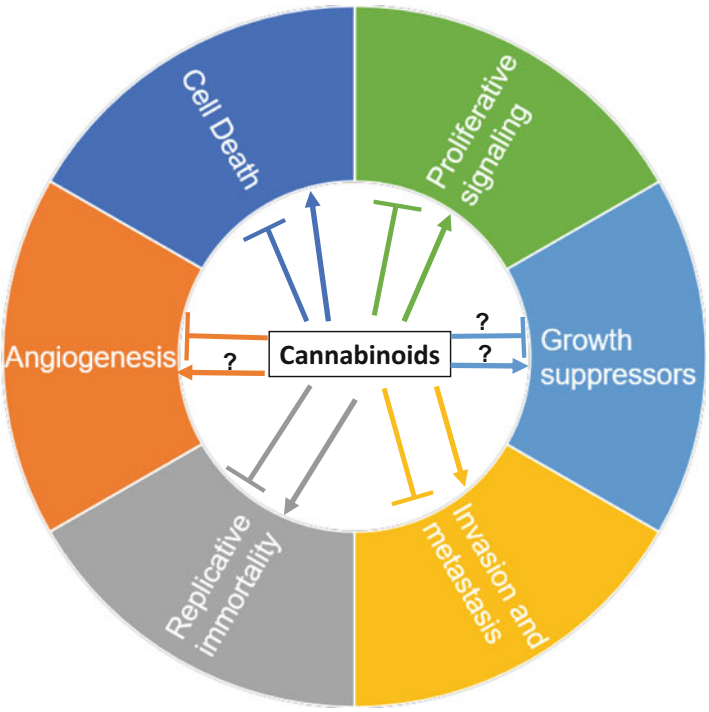

Fig. 2 Cannabinoids in cancer (The role of cannabinoids in inducing (↑) or inhibiting (⍰) the hallmarks of cancer)

tumor aggressiveness in many cancers (Laezza et al. 2020). In tumors such as many breast, lymphomas, leukemia, prostate, and pancreatic cancers, the upregulation of one or both of the cannabinoid receptors indicates a more severe cancer (Velasco et al. 2016). Many studies show the endocannabinoid system increasing tumor activity and severity of the disease due to increased cell proliferation and promotion of metastasis. The overactivation of the endocannabinoid system in many cancers leads to an upregulation of essential tumor mechanisms, such as sustained proliferative signaling, evading cell death, evading growth suppressors, and activating invasion and metastasis mechanisms (Sledzinski et al. 2018) (Fig. 2).

Current evidence indicates that the endocannabinoid system plays a dual role in cancer development and suppression (Velasco et al. 2016). In some cancers, the overexpression of CB1 and CB2 leads to more aggressive tumors with increased cell proliferation and metastasis. Conversely, in other cancers, the upregulation of these receptors induces cell apoptosis and inhibits cell proliferation (Daris et al. 2019) (Fig. 2).

The effects of activation or suppression of the endocannabinoid system are both context and cancer-specific; therefore, more research is necessary to determine the differential role of cannabinoids in cancer development and suppression.

2.2 Cannabinoids in Cancer Therapy

Researchers began paying attention to the medicinal properties of cannabis, specifically for its role in the mitigation of pain. They found that two compounds, in particular, THC and CBD, could be an effective treatment for both cancer-related pain and inflammation (Pellati et al. 2018) and for multiple other symptoms and co-morbidities that accompany cancer and cancer treatment (Abbott et al. 2020b). CBD's ability to act on monoamine receptors as both an agonist and an antagonist can modulate symptoms such as loss of appetite, pain, anxiety, nausea, and vomiting (Pellati et al. 2018) reacting to the disequilibrium in the body. The effect of CBD varies depending on the type and location of the symptoms, as CBD can bind to various protein complexes. Additionally, CBD is typically preferred over THC due to its non-psychoactive properties. That is why such an extensive research effort has been made regarding CBD to treat various symptoms.

Recent studies have expanded on CBD specifically for the treatment of cancer along with mitigation of the symptoms that accompany treatments such as chemotherapy. Additionally, researchers have investigated the indirect role of CBD in cancer via blocking inflammatory pathways involved in tumor progression as multiple cancers develop in the wake of infection, inflammation, and irritation. Inflammatory cells largely regulate the development of tumors as they promote cell growth and division, cell survival, and migration throughout the body (Pellati et al. 2018). Thus, modulating such activities becomes a viable course of combatting tumorigenesis. CBD's effect on inflammation has been shown to suppress the proliferation of tumors in several cancers. In aggressive tumors, CB receptors are often overexpressed; however, more recent studies have shown that when cannabinoids are introduced to the tumor, the activation of CB receptors has an anti-tumorigenic effect. Specifically, by targeting components of the endocannabinoid system (ECS), such as CB1 and CB2 receptors, cannabinoids block the mechanism for proliferation, promote apoptosis, inhibit angiogenesis, and block the ability of tumors to metastasize (Daris et al. 2019) (Fig. 2). With the introduction of cannabinoids, CB1 and CB2 are activated and begin to produce ceramide. This sphingolipid promotes apoptosis by inducing the endoplasmic reticulum (ER) stress-related signaling pathway (Sledzinski et al. 2018).

However, many researchers worry about the psychoactive side effects of cannabinoids. Though they have a strong potential for cancer treatment, the prolonged use of some cannabinoids, such as THC, can impact cognitive functions, specifically in developing and adolescent brains (Daris et al. 2019). Further research has shown that cannabinoids lacking psychoactive properties still display anti-cancer activity. CBD and CBG act independently of the classic CB receptors, CB1 and CB2. They interact with other receptors (GPR55, TRPV1, TRPM8) as antagonists (Sledzinski et al. 2018) and can induce apoptosis directly and indirectly through the CB2 receptor. Additionally, research has shown that CBD inhibits cancer cell growth and proliferation in specific cancers such as leukemia, colorectal, neuroblastoma, breast, glioblastoma, lung, melanoma, or prostate cancer (Sledzinski et al. 2018).

It is now clear that cannabinoids may interact with tumors through alternative pathways independent of the ECS. In these alternative pathways, receptors can interact with multiple cannabinoids, specifically non-psychoactive, and induce anti-cancer mechanisms. For example, by specifically binding to GPR55, non-psychoactive cannabinoids can bind to and affect this receptor. GPR55 plays a role in both angiogenesis and neuropathic pain as well as in the inflammatory processes. This receptor protein has proven to be a possible target in different cancers as it modulates pathways that are often deregulated. GPR55 is a non-CB1/CB2 receptor that binds cannabidiol and other non-psychoactive cannabinoids and therefore is recognized as the third cannabinoid receptor, CB3 (Yang et al. 2016a). CBD acts as an antagonist, inhibiting the overexpression of GPR55 in cancerous cells. GPR55 upregulates phosphorylated extracellular signal-related kinase (ERK), which induces cell proliferation. Research has strongly indicated that the antagonistic relationship between non-psychoactive cannabinoids and the GPR55 protein promotes anti-cancer activity, such as decreased the expression of proteins involved in angiogenesis (Pellati et al. 2018).

Another alternative pathway, indirectly taking place via inflammatory process, occurs between the transient receptor protein of vanilloid types 1 and 2 (TRPV1, TRPV2) and cannabinoids (Pellati et al. 2018). This receptor has shown the ability to bind to both endocannabinoids and phytocannabinoids. TRP receptors are involved in regulating temperature perception and receive signals for thermal pain and noxious stimuli (Tominaga 2007). In addition, they function in several biological processes—most importantly in cell proliferation. Both TRPV1 and TRPV2 are expressed throughout the body but are most prevalent in the central nervous system. However, they differ in the activities they induce (Pellati et al. 2018). TRPV1 is heat-activated, and once stimulated, it opens, allowing calcium and magnesium ions to flow into the cell. TRPV2 is activated by mechanosensory or osmosensory activity in the body rather than thermally activated. However, both share an affinity for CBD and other cannabinoids. Studies have determined that both TRPV1 and TRPV2 play a role in inflammatory and chronic pain. Thus, the activation or inhibition of these specific receptors is the source of the pain relief caused by CBD. Additionally, these receptors' overexpression and increased activation enhance cancer progression in some tissues (Peralvarez-Marin et al. 2013). Thus, to utilize this alternative pathway for cancer treatment, the type of cancer must be considered. Cancers such as glioma, prostate, hepatocellular carcinoma (HCC), and urothelial require an antagonistic relationship between the CBD and the TRPV receptor. In contrast, other cancers such as bladder, skin, and hepatocellular carcinoma depend on an agonistic interaction. Furthermore, the interaction of CBD, TRPV1, and CB2 has inhibited multidrug resistance (MDR) proteins. A specific study showed that the binding of CBD to TRPV2 increased the cytotoxic properties of multiple drugs as it increased the uptake of the drugs (Neumann-Raizel et al. 2019). Finally, CBD can also inhibit the glioma cancer stem cells' proliferation by forcing the stem cells to differentiate by increasing pro-differentiation factor ID2 while decreasing the expression of metastatic factor ID1 (Nabissi et al. 2012).

In addition to GPR55 and TPRV, cannabinoids can bind to orphan receptors and peroxisome proliferator-activated receptors (PPARs) (Davis 2016). However, it has been shown that the effects and benefits of CBD in cancer treatments are limited by the complexity of the biological interactions between the components.

While many studies have shown that CBD and other related cannabinoids are an effective method of managing inflammation and other cancer-related pain, researchers are cautious about encouraging cancer treatment with cannabinoids. It is mainly because the interaction of the cannabinoids with tumors is cancer-specific and that some tumors can use the binding of cannabinoids as a survival mechanism (Davis 2016). Newer studies show that CBD can have vast antitumor effects on cancers, especially those related to cell proliferation, angiogenesis, and apoptosis (Daris et al. 2019) (Fig. 2). Depending on tissue type and context, the differential effect in cancer must be investigated to more clearly understand the effects of cannabinoids in cancer.

3 Role of miRNAs in Cannabinoid Mediated Cancer Development and Therapy

MicroRNAs (miRNAs) are non-coding single-stranded RNAs frequently associated with 5′ or 3′ regions of genes and are about 20 nucleotides long (Dinu et al. 2020). It has been demonstrated that miRNAs are involved in a wide variety of physiological processes, including cell proliferation and differentiation, development, apoptosis, metabolism, angiogenesis, immunity, and homeostasis (Li et al. 2009) (Fig. 3). MiRNAs post-transcriptionally regulate mRNA through the RNA-induced silencing complex. Therefore, misregulation of miRNAs contributes to the dysfunction of vital cellular processes and has been linked to several diseases, especially cancer. Furthermore, deregulation of miRNAs alters the therapeutic response of cancer cells to anti-cancer drugs (Winter et al. 2009; Chen et al. 2014). For example, miRNA-21 is shown to promote resistance to Doxorubicin and Trastuzumab through downregulation of PTEN in breast cancer cells (De Mattos-Arruda et al. 2015). In ovarian cancer cells, miRNA-106a and miRNA-93 promoted Cisplatin's resistance by targeting genes such as the pro-apoptotic PDCD4 and PTEN, a tumor suppressor gene (Si et al. 2019). Numerous studies also implicate irregular miRNA expression patterns in most, if not all, human malignancies.

3.1 miRNAs in Cancer Pathogenesis

Several miRNAs exhibit oncogenic-like or tumor-suppressor-like activities by regulating oncogenic signaling pathways and tumor suppressor genes (Fig. 3). Global miRNA processing changes can also lead to malignant transformation (Kumar et al.

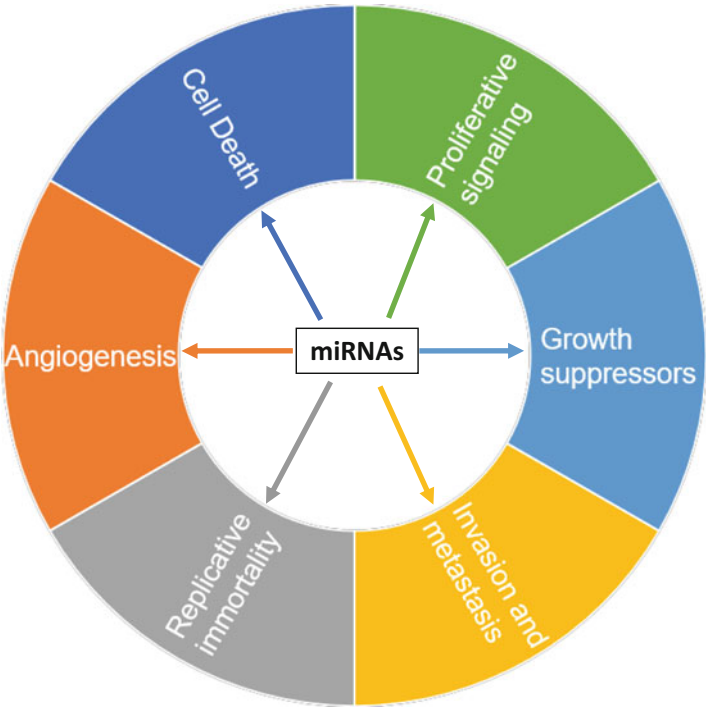

Fig. 3 Role of miRNAs in hallmarks of cancer

2008) and induce the classical hallmarks of cancer pathogenesis – self-sufficiency in growth, insensitivity to anti-growth signals, apoptosis evasion, infinite replicative potential, angiogenesis, and invasion and metastases (Negrini et al. 2009; Hanahan and Weinberg 2011) (Fig. 3).

Tumor cells activate different pathways to avoid external growth factor signals' regulation and maintain cell proliferation and survival. miRNAs can extensively modulate these pathways. For example, RAS proteins modulate many major proliferation pathways in the mammalian cells, and their deregulation has critical consequences in tumor development. RAS oncogenic signaling is associated with reduced levels of the let-7 miRNA family, a post-transcriptional RAS regulator that is inversely correlated with RAS expression in several cancers (Johnson et al. 2007). Let-7 downregulation has also been found in several cancers, including lung cancer (Eder and Scherr 2005). The transcription factor AP-1, which functions downstream of the RAS pathway, plays a crucial role in cancer by inducing the transcription of oncogenic miRNA-21. Overexpression of miRNA-21 enhances tumorigenesis, and the genetic deletion of miRNA-21 partially protects against tumor formation. miRNA-21 is often upregulated in tumors and drives tumorigenesis through inhibition of negative regulators of the RAS pathway (Hatley et al. 2010). For example, miRNA-21 exerts its oncogenic effect by targeting programmed cell death protein

4 (PDCD4), which negatively controls AP-1 activity in response to the RAS pathway (Talotta et al. 2009).

Another important hallmark of cancer cells is insensitivity to anti-growth signals, and miRNAs play an important role in cancer cell's ability to escape from inhibitory growth signals. For example, the E2F family transcription factors play an important role in controlling cell cycle progression by regulating the expression of genes required for DNA synthesis. The activity of E2F transcription factors is controlled by a series of miRNAs, including miRNA-17-5p, miRNA-20a, miRNA-106b, and miRNA-330-3p (O'Donnell et al. 2005; Petrocca et al. 2008). The levels of miRNA-106a and miRNA-17-5p were inversely correlated with E2F1 levels in colon cancer (Diaz et al. 2008). In another example, miRNA-330-3p, which acts as a tumor suppressor, negatively regulates E2F1 expression in prostate cancer (Lee et al. 2009).

Changes in the expression of miRNA can also affect the ability of cancer cells to resist apoptosis. p53 promotes tumor suppression by controlling the expression of several target genes involved in cell cycle arrest and apoptosis. miRNAs, such as miRNA-34a/b/c, miRNA-29, miRNA-15a, and miRNA-16, are known transcriptional targets of p53 (Boominathan 2010). miRNA-34a functions as a potent suppressor of cell proliferation by modulating CDK4/6 and CyclinD1/E2 signals and promoting apoptosis (He et al. 2007) (Fig. 1). Notably, the cancer-associated genomic region 1p36, lost or rearranged in many cancers, contains the candidate tumor suppressor miRNA-34a. Similarly, pro-apoptotic miRNA-15a and miRNA-16-1, which repress anti-apoptotic Bcl2 protein, are clustered on human chromosome 13q14, which is often lost or downregulated in human cancers, including leukemia (Calin et al. 2008). These examples suggest that the downregulation of tumor-suppressive miRNAs in cancer cells confers resistance to apoptosis.

Cancer cells show nearly unlimited replication, unlike normal cells that can pass through only a limited number of cell division cycles. The telomeres are crucial for this replication limit. Most human cancers express a specialized enzyme called telomerase, which can add telomeric repeats to the end of the chromosomes. Telomerase was found to be a direct target of regulation by miRNAs such as miRNA-138 (Mitomo et al. 2008). Downregulation of miRNA-138 is associated with overexpression of human telomerase in thyroid carcinoma cells.

Cancer cells can turn on an angiogenic switch to produce large amounts of angiogenic factors, such as vascular endothelial growth factor (VEGF), to promote neovascularization. miRNA-126 is an essential regulator of angiogenesis (Wang et al. 2008), and its expression was found to be enriched in endothelial cells during angiogenesis to repress sprouty-related EVH1 domain-containing protein 1 (SPRED1) and Phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2), which are negative regulators of the VEGF pathway (Wang et al. 2008). The miRNA-17-92 cluster (miRNA-17, miRNA-18a, miRNA-19a, miRNA-20a, miRNA-19b, and miRNA-92a) targets hypoxia-inducible factor-1α (HIF-1α), which is a critical regulator of angiogenesis (Taguchi et al. 2008) (Fig. 1). The miRNA-17-92 cluster is overexpressed in lung cancer (Taguchi et al. 2008).

The metastatic process involves detaching tumor cells from the primary tumor and spreading them to distant organs via blood or lymph. Upregulation of miRNA-10b has been shown to promote invasion and metastasis. HOXD10 is a homeobox transcription factor that maintains an epithelial phenotype by repressing RhoC, a G-protein involved in metastasis. However, HOXD10 is a target of miRNA-10b and is expressed at low levels in metastatic tumors (Ma et al. 2007). Moreover, Twist, a metastasis-promoting transcription factor, induces miRNA-10b expression to downregulate HOXD10 expression to promote metastasis by RhoC (Ma et al. 2007). Collectively, all these data support that miRNAs play crucial roles in cancer pathogenesis by modulating oncogenic signaling pathways and tumor suppressor genes.

3.2 miRNAs in Chemoresistance

Chemotherapy is widely used to treat various cancers as surgery and radiation are often ineffective in treating metastasized cancers that spread to different body parts. Unfortunately, long-term chemotherapy often fails due to the resistance of cancer cells to anti-cancer drugs. Several mechanisms contribute to chemoresistance, including cancer pathogenic mechanisms such as drug-insensitive proliferation and apoptosis and increased drug metabolism/elimination. Accumulating evidence demonstrates that miRNAs play a role in chemoresistance by modulating the expression of their target genes involved in proliferation, apoptosis, drug metabolism, or drug elimination to confer chemoresistance (Wei et al. 2019; Raziq et al. 2020).

For example, the expression of miRNA-221 is upregulated in tamoxifen-resistant human epidermal growth factor receptor 2 (HER2)-positive human breast cancer tissues compared with HER2-negative tissue samples (Miller et al. 2008). In MCF-7 human breast cancer cells, ectopic expression of miRNA-221 led to increased resistance toward tamoxifen. It decreased expression of the cell cycle inhibitor p27 (Miller et al. 2008), suggesting that miRNA-221 confers resistance to chemotherapy in breast cancer cells by regulating the proteins involved in the cell cycle and proliferation. Additionally, miRNA-15b and miRNA-16, which were found to be downregulated in SGC7901/VCR human gastric cancer cells, displayed enhanced resistance to vincristine by increasing the expression of anti-apoptotic protein Bcl-2 (Xia et al. 2008). In contrast, overexpression of miRNA-15b and miRNA-16 led to reduced Bcl-2 protein levels. It sensitized SGC7901/VCR cells to vincristine-induced apoptosis, suggesting that these miRNAs could play a role in developing chemoresistance in gastric cancer cells by modulating the proteins involved in programmed cell death (Xia et al. 2008).

3.3 miRNAs in Cancer Therapy

While dysregulation in miRNA expression can cause several cancers, different strategies utilizing the ability of miRNAs to act as tumor suppressors or oncogenes, known as oncomiRs, and the ability to target miRNAs through miRNA mimics and molecules are being developed (Cheng et al. 2015). These miRNA-targeted therapeutics can be a prospect for the development of treatment avenues towards various types of cancers. For example, miRNA mimics, which imitate the function of an endogenous miRNA, can be chemically altered to enable it to be more stable and allow targeted delivery to tumors. A miRNA-34 mimic is currently under testing in Phase I clinical trial (NCT01829971) towards its effect on several cancers such as pancreatic, lung, and liver cancer. In *in vivo* models of non-small cell lung cancer, this miRNA mimic has exhibited significant tumor growth inhibition, and the tumors expressed lower levels of miRNA-34 regulated proteins such as the MET proto-oncogene and the anti-apoptotic Bcl-2 (Trang et al. 2011). In an *in vivo* model of pancreatic cancer, systemic delivery of this miRNA resulted in tumor growth downregulation, an increase in tumor cell apoptosis, and a decrease in $CD44^+$, indicative of a reduction in metastasis of the cancer cells (Pramanik et al. 2011). In a prostate cancer mouse model, miRNA-34 also decreased tumor growth by repression of $CD44^+$ (Liu et al. 2011).

Another miRNA being studied towards cancer therapeutics is miRNA-200c. In an *in vivo* mouse model of lung cancer, systemic administration of this miRNA resulted in longer survival due to increased sensitivity of the tumor to radiation treatment (Cortez et al. 2014). This miRNA was also reported to target genes involved in oxidative stress response, such as NF-E2-related factor 2 (NRF2), leading to increased levels of reactive oxygen species, which then causes the cancer cells to undergo apoptosis (Lin 2019).

In another study involving an ovarian cancer mouse model, administration of a miRNA-506 mimic resulted in tumor deterioration (Yang et al. 2013). Lastly, a significant decrease in tumor volume and growth was observed after ectopic expression of the miRNA-15/16 cluster in a leukemic cell line model, MEG-01 (Calin et al. 2008).

4 Cross-Talk Between Cannabinoid System and miRNAs

The anti-cancer activities of cannabinoids have been extensively studied, and clinical trials for the treatment of several cancers with cannabinoids have been reported (Pellati et al. 2018). Cannabinoids inhibit growth, induce apoptosis, have anti-metastatic and antiangiogenic activities in multiple cancer cell lines, and inhibit tumor growth in *in vivo* mouse models (Daris et al. 2019) (Fig. 2). Cannabinoids are active in the tumor microenvironment, and the effects of cannabinoids are complex, and the responses can also be CB receptor-dependent or independent. Additionally,

Table 1 The interplay of Cannabinoids and miRNAs in cancer

Hallmark of Cancer	Cannabinoid or Cannabinoid Receptor	miRNA
↑ cell death	CBD THC	↓ Hsa-let-7a (Alharris et al. 2019) ↓ miRNA-421 (Huang et al. 2013)
↑ proliferative signaling ⍰ proliferative signaling	THC GPR55 (CB3) WIN	↓ miRNA-374b (Yang et al. 2016b) ↓ miRNA-675-5p (He et al. 2015) ↓ miRNA-27a (Sreevalsan and Safe 2013)
⍰ angiogenesis	CBD	⍰ miRNA-155 (Juknat et al. 2019) ⍰ miRNA-17-92 (Taguchi et al. 2008)
↑ invasion and metastasis ⍰ invasion and metastasis	CB1	↑ miRNA-1273 g-3p (Li et al. 2018) ⍰ miRNA-146a (Wang et al. 2019)
⍰ replicative immortality	CBD	↑Has-miRNA-1972 (Alharris et al. 2019) ↑miRNA-34a (Juknat et al. 2019)

↑-increase, ↓-downregulation, ⍰- inhibition.

the effects of the CB1 and CB2 receptors on epigenetic processes have also been validated, and one of the major players is changes in miRNA expression (Dinu et al. 2020). Recent studies have proven the existence of specific links between cannabinoid activity and the response of the CB1, CB2, and CB3 receptors by modulating the expression of miRNAs (Table 1). Therefore, the activity of cannabinoids in cancer cells may also be due, in part, to the downregulation or upregulation of miRNAs by cannabinoids in these cells (Table 1).

For example, the role of cannabinoids in mediating miRNA expression in cancer was studied in neuroblastoma cell lines, SH SY5Y, and IMR-32 (Alharris et al. 2019). The result of this study suggests that CBD-mediated apoptosis in neuroblastoma cells is regulated by miRNAs, as CBD administration in neuroblastoma cell lines altered the expression of miRNA, specifically, by down-regulating hsa-let-7a and upregulating hsa-miRNA-1972 (Table 1). Hsa-let-7a has been shown to regulate glycolysis in various cancers (Nguyen and Zhu 2015). In addition, SIRT2, which was downregulated by hsa-miRNA-1972, is a potent regulator of glycolysis. Therefore, the alterations caused by CBD in miRNA may be responsible for changes in cell metabolism and can alter the expression of miRNAs that are associated with essential signaling pathways linked to hallmarks of cancer such as apoptosis and invasion, as well as metabolic functions in neuroblastoma cells (Alharris et al. 2019).

In another study, WIN, a synthetic cannabinoid, and a CB1 agonist, decreased the expression of specificity protein transcription factors Sp1, 3, and 4 in the human SW480 colon carcinoma cell line. Sp1, Sp3, and Sp4 are highly expressed in cancer cells and are an adverse prognostic factor for patient survival (Hedrick et al. 2016). This study demonstrated that this synthetic cannabinoid has anti-cancer activity by significantly inhibiting cell proliferation. The WIN-mediated decrease in expression

of the specificity proteins Sp1, Sp3, and Sp4, was due to downregulation of miRNA-27a and induction of miRNA-27a-regulated ZBTB10, a specificity protein repressor (Sreevalsan and Safe 2013) (Table 1).

Another study showing a connection between miRNA-27a and CB1 and CB2 receptors is from Liu et al. In this study, treatment of MDA-MB-453 breast cancer cell line with betulinic acid resulted in downregulation of miRNA-27a, then leading to inhibition of tumor growth and apoptosis induction. Furthermore, this study showed that the downregulation of miRNA-27a after the treatment with betulinic acid in a breast cancer cell line was CB1 and CB2 receptor-dependent, as betulinic acid can directly bind to both receptors was confirmed to be a CB receptor agonist (Liu et al. 2012).

Aside from cannabinoids modulating miRNA expression, miRNAs can also be target genes of cannabinoid receptors; therefore, the activity of cannabinoid receptors can be modulated by specific miRNAs contributing to either cancer development or inhibition of cancer. For example, in an *in vitro* model of colorectal cancer, LoVo cells, a colon cancer cell line, miRNA-1273 g-3p was shown to promote cell proliferation, migration, and invasion. In this study, the CB1 receptor was identified as a direct target gene of miRNA-1273 g-3p. This study showed that miR-1273 g-3p promotes LoVo cell proliferation, migration, and invasion by directly targeting the CB1 receptor, as an abrogation of the CB1 receptor restored the phenotypes LoVo cells, transfected with a miRNA-1273 g-3p inhibitor (Li et al. 2018) (Table 1).

On the other hand, an example that miRNAs can also be target genes of cannabinoid receptors leading to anti-cancer activity is from a study by He et al. In this study, the role of miRNA on GPR55, which is proposed to be the third cannabinoid receptor, was seen in non-small cell lung cancer (NSCLC). In NSCLC, the expression levels of miRNA-675-5p were found to be reduced compared to normal tissues. The expression of this miRNA in patients with NSCLC had a negative correlation with the lymphatic metastasis TNM stage. In an *in vivo* model, downregulation of miRNA-675-5p resulted in increased cell growth and proliferation and tumor cell migration. After further exploration of the target genes of miRNA-675-5p, GPR55 exhibited the most complementary structure with miRNA-675-5p. It was, therefore, a functional target of this miRNA, which was further confirmed in an *in vitro* model, the A549 human lung cancer cells. This study shows that the miRNA-675-5p has anti-oncogenic activity in NSCLC, and this activity involves regulating its target gene GPR55 (He et al. 2015) (Table 1).

Recent studies have shown the involvement and link of CB1 and CB2 receptors in physiological processes such as immune and inflammatory response and redox activity. The effects of cannabinoids on miRNA expression are also shown to be responsible for the modulation of the immune and inflammatory systems (Li et al. 2013). Currently, there is only a limited number of studies regarding the interaction of cannabinoids, miRNA, and cancer. However, more studies have explored the relationship between cannabinoids, miRNA, and inflammation. This avenue should be considered as numerous cancer causes, and risk factors are linked with some form of chronic inflammation. Inflammation plays a vital part at various stages of tumorigenesis, such as initiation, malignant transformation, invasion, and metastasis.

Inflammatory responses also impact cancer treatment response, and the immune cells that invade the tumors are involved in substantial cross-talk with cancer cells (Grivennikov et al. 2010).

For example, a study by Juknat and et al. reported the beneficial influence of cannabinoids on immune response such as neuroprotection and immunosuppression by modulation of miRNAs. In this study, they utilized endotoxins to stimulate immortalized mouse microglia (BV2) cells and looked at the role of the phytocannabinoids, THC, and CBD on the expression of miRNAs. The results they gathered indicated a link between the effects of cannabinoids on inflammatory signaling pathways. Induction of inflammation in these microglia cells upregulated the expression of pro-inflammatory miRNAs associated with Toll-like receptor and NF-κB signaling, including miRNA-21, miRNA-146a, and miRNA-155. At the same time, CBD inhibited inflammation-stimulated expression of miRNA-146a and miRNA-155. Furthermore, CBD upregulated miRNA-34a. miRNA-155 and miRNA-34a are considered redox-sensitive miRNAs and are involved in immune response, cell cycle regulation, as well as cellular stress, and redox homeostasis (Juknat et al. 2019) (Table 1). Although these occurrences involve normal microglia cells, such a mechanism can also be possible and should be explored in cancer cells. miRNA-21 is known to play a role in cancer. Its overexpression is linked to enhanced tumorigenesis by participating in cell proliferation, differentiation, and apoptosis and is closely related to tumor growth, invasion, and metastasis (Huang et al. 2013). Additionally, enhanced miRNA levels are a marker of immune cell activation (Feng and Tsao 2016).

miRNA-155, like miRNA-21, is often overexpressed in malignant tumors and plays a role in cancer therapy resistance (Bayraktar and Van Roosbroeck 2018). miRNA-146a plays a role in regulating innate immunity, antiviral pathways, and inflammatory response (Li et al. 2010). Similarly, miRNA-146a was shown to be involved in cancer initiation, and tumor progression in several human malignancies, with the most studied being HCC, wherein increased miRNA-146a levels are associated with the development and progression of HCC (Wang et al. 2019). Another study showing the involvement of cannabinoids and miRNAs in immune response was reported by Yang et al. (2016b). In this study, RNA sequencing was applied to look at the transcriptomes and transcript variants differentially regulated in normal lymph node cells and $CD4^+$ T cells of 6-week-old C57BL/6 J mice after intraperitoneal injection of THC. They reported a decrease in expression of miRNA-17, miRNA-92, miRNA-421, and miRNA-374b after THC activation in lymph node cells and $CD4^+$ T cells (Yang et al. 2016b). The miRNA-17-92 cluster is involved in tumorigenesis by playing a role in cell cycle, proliferation, and apoptosis (Mogilyansky and Rigoutsos 2013), and the miRNA-374b/421 cluster plays a regulatory role in cell growth and differentiation (Bian et al. 2019).

Changes in the expression and regulation of these miRNAs can therefore play a role in cancer development. Therefore, the link to how cannabinoids affect miRNAs involved in cancer development during inflammation should also be further explored.

5 Future Directions

As mentioned above, several studies have explored the effects of cannabinoids in cancer pathology and treatment, and they showed conflicting results. In some studies, the use of cannabinoids generated an increased risk of cancer and promoted cancer progression, while in others, the use of cannabinoids proved an effective cancer treatment. Therefore, further research is necessary to determine if cannabinoids can regulate all six aspects of the hallmarks of cancer and the specific effects of each hallmark of cancer.

The activation or suppression of the endocannabinoid system is both context and cancer-specific. However, more research is necessary to determine the differential role of cannabinoids in cancer development and suppression. It is also necessary to discern a clear role of cannabinoids and the CB1 and CB2 receptors and their tumorigenic and anti-tumorigenic activities. Further experimentation is also needed to determine the cell-type or tissue-type dependency of cannabinoids and if there are any receptor dependencies in its activity.

It has also been shown and validated that there are multiple alternative pathways through which cannabinoids can affect cancer cells, not only through the cannabinoid receptors but also through other non-cannabinoid receptors such as GPR55 and TRPV1, and TRPV2. Further experimentation is essential to determine their specific mechanisms and the complex mechanisms of both the cannabinoid receptors and non-cannabinoid receptors.

Most importantly, cannabinoids can modulate miRNA expression. Additionally, miRNAs can also be target genes of cannabinoid receptors contributing to either cancer development or inhibition of cancer (Table 1).

Although little information is available regarding the interaction of cannabinoids, miRNA, and cancer, there is potential for the cross-talk between cannabinoids and miRNAs in cancer development or inhibition. The ability of cannabinoids to regulate miRNAs and vice versa, wherein miRNAs regulate cannabinoid receptors, can serve a critical role in moderating cancer development and inhibition and should be further explored (Fig. 4).

6 Conclusion

The palliative effects of cannabinoids in cancer-associated symptoms have been well established. Additionally, studies have shown that cannabinoids and CB receptor agonists play a role in multiple signaling pathways involved in the known hallmarks of cancer. It is important to note that these effects are highly dependent on the cell type and the type of cannabinoid (McKallip et al. 2005; Daris et al. 2019). Cannabinoids have also been shown to have immunosuppressive properties that could augment tumor cell proliferation and hasten cancer progression in patients. This further cements that biological response to cannabinoids depends on cellular context.

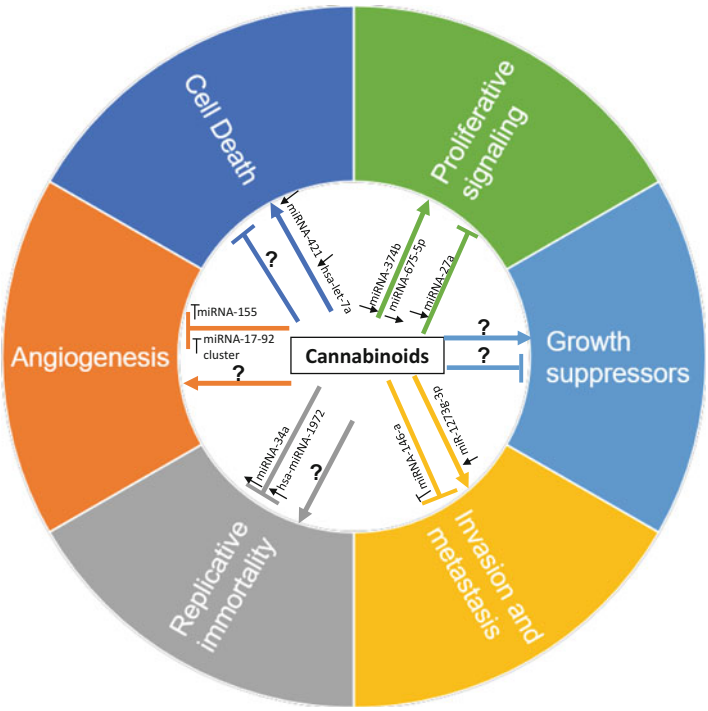

Fig. 4 Cross-talk between cannabinoids and miRNAs in cancer

miRNAs can function as either tumor suppressors or oncogenes, whose loss or overexpression plays a role in all hallmarks of cancer (Dinu et al. 2020; Li et al. 2009). The cannabinoid-mediated changes leading to cancer suppression or progression likely involve a change in miRNAs expression that play an important role in driving the effects of cannabinoids and cannabinoid receptor agonists (Dinu et al. 2020). Therefore, further research is necessary to define the exact molecular cross-talk between cannabinoids and miRNAs.

Additionally, concomitant administration of a cannabinoid or a cannabinoid receptor modulator and a clinical drug can also affect not only the metabolism of both substances (Salamat et al. 2020; Abbott et al. 2020a) but also exert a combinatorial effect on miRNA expression. A multi-discipline approach may be needed to determine the overall effects of combination treatments, including *in silico, in vitro,* and *in vivo* models. It is important to consider that both cannabinoid metabolism and miRNA profile can be differentially expressed in different species, such as in rodents and primates, therefore humanized animal models can be valuable to address this concern (Salamat et al. 2021; Mor et al. 2011). Besides *in vivo* and *in vitro* models, *in silico* prediction can also be helpful in the identification of specific miRNA and cannabinoid/cannabinoid receptor interactions (Qu et al. 2019).

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Cannabis as a Potent Therapeutic Agent for Pharmaceutical Drugs: Recent Advancement in Drug Discovery and Human Healthcare

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Abstract Cannabis has been well known for centuries due to its medicinal properties. In recent decades, the inclination of researchers towards its important phytoconstituents as a potential therapeutic alternative has been propounded due to the discovery of its major active constituent, i.e., Δ^9-tetrahydrocannabinol (Δ9-THC). Besides this, the presence of other phytoproducts, including cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC), etc., also contribute towards its medicinal importance. Interestingly, due to the effectiveness of cannabis against various pathological conditions, its use for medicinal purposes has been revolutionized worldwide. Despite these facts, it has become obligatory to explore synergistic interactions and mode of action of its phytoconstituents involving various biological pathways. Current advancements have allowed medical practitioners to better understand cannabis-derived products as a pharmacological choice in several conditions, including pain treatment, stress, anxiety, neurodegenerative disorders, and cancer. However, there exists a lacuna in the literature regarding its beneficial doses. Since medicinal exploration and the legalization of cannabis depend upon various factors, the present review deals with the important phytocannabinoids, their biogenesis, types of drugs obtained, mode of action, therapeutic implications, and new approaches for supporting this plant as a critical therapeutic agent for pharmaceutical drugs. Overall, this may provide an insight into the role of cannabis as a potent

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candidate for future drug discovery and generate efficient products for human welfare.

Keywords Cannabis · Cannabinoids · Pain management · Phytocannabinoid · Therapeutic

Abbreviations

2-AG	2-Arachidonoylglycerol
AD	Alzheimer's Disease
AEA	N-Arachidonoyl ethanolamine
AIDS	Acquired immunodeficiency syndrome
BCE	Before Common Era
CB1	Cannabinoid Receptor Type 1
CB2	Cannabinoid Receptor Type 2
CBC	Cannabichromene
CBD	Cannabidiol
CBD	Cannabinodiol
CBDA	Cannabidiolic acid
CBDV	Cannabidivarin
CBG	Cannabigerol
CBGA	Cannabigerolic acid
CBN	Cannabinol
CBs	Cannabinoids
CNS	Central Nervous System
FDA	Food and Drug Administration
MS	Multiple Sclerosis
PD	Parkinson's Disease
THC	Tetrahydrocannabinol
THCA	Tetrahydrocannabinolic acid
THCV	Tetrahydrocannabivarin
TS	Tourette's Syndrome
TSC	Tuberous Sclerosis Complex

1 Introduction

In recent years, the terms "cannabis" or "marijuana" have been considered interchangeably; however, the latter is associated with important phytoconstituents derived from the plant *Cannabis sativa* L. belonging to the Cannabaceae family. It is originally a native plant of Western and Central Asia and has been extensively cultivated in Asia, Europe, and other continents. Its medicinal uses are also well

documented in the Indian Ayurvedic system as early as 900 BC. Also, this plant has been encouraged for both inducing pleasures and pain alleviation since its discovery. This is evident from the details that preparations obtained from resins/flowers of cannabis have been well explored to treat malaria, fever, constipation, menstrual disorders, gout, pain, and rheumatism in China (Brill 1981). Similarly, Arabs have used it for identical medicinal uses (Machado Rocha et al. 2008). In western countries, cannabis was commonly used as a pain remedy before the introduction of aspirin (Russo 2007). Therefore, for many centuries, *Cannabis sativa,* including other subspecies *viz., C. indica, C. ruderalis,* have been inspected to treat various ailments, including epilepsy, cancer, glaucoma, nausea, and neuropathy, etc. Hence, with progressive global liberalization and awareness regarding the effectiveness of cannabis and its pharmaceutical derivatives, healthcare providers' understanding has advanced concomitantly.

Interestingly, the pharmacological action of this plant is found to be at higher nerve centers. It is capable of producing hallucinations and is also used as an intoxicant. The nature of its efficiency depends on the environmental conditions and the individual's response to its consumption. Due to its psycho-pharmaceutical activities, the use of cannabis has been well appreciated by the medical system throughout the last century. As a psychotropic drug, cannabis is used as a beverage. The common name (s) of cannabis in different countries/locations include Bhang (India), Gaanja (India), Hashish, Marihuana (Spain, Hungary, Russia, United States), Marijuana (France), Xian ma, Huo ma (China), Hind kinnabi (Turkey), Taima (Japan), Marihuana (Germany) Til (Arab countries), Hemp, Indian hemp (United Kingdom).

Cannabis is a storehouse of many phytoconstituents/chemicals belonging to different classes (ElSohly and Slade 2005), including terpenoids, flavonoids, cannabinoids, and sugars, nitrogenous compounds, phenols, fatty acids, glycoproteins, esters, steroids pigments, etc. Interestingly, female *Cannabis sativa* is considered the main source of most chemical constituents obtained from this plant. Hundreds of female plants are classified based on the chemical composition of fatty compounds, also known as phytocannabinoids. The identification of overall 568 compounds has been carried out, of which 120 belong to phytocannabinoids whose site of synthesis is mainly secretory cells in trichomes. Moreover, phytocannabinoids possess a dibenzopyran ring and a hydrophobic alkyl chain and are further distributed as subclasses *viz.,* Δ9-tetrahydrocannabinol (THC) cannabidiol (CBD), cannabigerol (CBG), cannabidivarin (CBSV), cannabinodiol (CBND), Δ9-tetrahydrocannabivarin (THCV). Among these, the most abundant phytocannabinoids are THC and CBD, obtained from the dried cannabis plant, and the cannabis formulations are known to possess high proportions of cannabidiol.

Owing to the above facts, the medicines and formulations based on *Cannabis sativa* have been extensively explored to cure patients worldwide. However, the scientific confirmation regarding the medicinal potential of such herbal drugs/products and their targeted pathways is scanty. In the present era, the peculiar "cannabis type" used in medical treatments is attributed to the popular name of "strain," which

further depends upon its taste, aromatic properties, and the amount of the major phytocannabinoids such as THC and CBD (Hanuš et al. 2016).

Both are naturally occurring phytoconstituents and decarboxylated forms of Tetrahydrocannabinolic acid (THCA) and Cannabidiolic acid CBDA, respectively. Based on their content, the *C. sativa* strains are either considered as "high in THC," which can be sativa originated or indica-originated with "high CBD," thus forming the basis of its therapeutic potency (De Meijer 2014).

Unfortunately, plant-derived cannabis products are still not monitored as compared to other traditional medicines. Though synthetic forms of cannabis are accessible by prescription, cannabis plants and their products contain a varied amount of THC and CBD, thus leading to unpredictable exposure effects. Consequently, there remains a substantial degree of equipoise between the benefits and harms of cannabis use as medicine which needs to be addressed. Therefore, the present dwells upon a better understanding of cannabis as a potent therapeutic agent. Also, it evaluates the equilibrium of health benefits of cannabis via either plant-based or derived, or synthetic drugs for various medical pathologies. Furthermore, different aspects, including biogenesis, properties of cannabis products, role in therapeutic conditions, and advancements in obtaining desired cannabis products crucial for establishing cannabis as a valuable pharmaceutical agent in future drug discovery, have been summarized.

2 Brief History of Cannabis Use

The exploitation of cannabis and its phytoconstituents as an herbal medicine has been done for several thousand years. The Chinese Emperor Shen Nung reported the use of cannabis as medicine in the twenty-eighth century BCE (Chwistek 2019). Cannabis and its bioactive constituents were initially utilized in the Northern and Central Asian regions for therapeutic use in the form of hashish, flower buds, marijuana, and resin. The scientific interest in cannabis has proliferated after the identification of Δ9-THC from more than 60 cannabis constituents (Mechoulam and Parker 2013).

According to the National Institute of Health PubMed database, 22,497 articles (as of June 2020) are listed, out of which 903 are associated with cancer, and the list is still increasing. As discussed above, more than 500 compounds have been reported from several Cannabis species (Hanuš et al. 2016). Because of the psychoactive effects, the cannabis plant and its products are placed in the class of controlled drug substances. Cannabinol (CBN), cannabinodiol (CBND), and Δ9-THC are the major bioactive compounds of *C. sativa,* documented in the controlled substances act (CSA). Although accepted as a therapeutically important agent, cannabis gained little interest in the scientific fraternity because it is placed under controlled drug substances (Abrams 2016; Pavlovic et al. 2018). From the past few decades, cannabis has experienced resurgence because of the documentation of its bioactive

chemicals, and some cannabinoids (CBs) have been approved for human trials (Owens 2015; Bonini et al. 2018; Lal et al. 2021).

In 1986, dronabinol was permitted to treat nausea and vomiting induced by chemotherapy in cancer patients. Later, it was used in AIDS (Acquired immunodeficiency syndrome) patients to treat weight loss. Food and Drug Administration (FDA) also approved Epidiolex (CBD) for severe epileptic conditions, Lennox-Gastaut syndrome, and Dravet syndrome. In Europe and Canada, oromucosal spray, Nabiximols, was approved for different clinical conditions, for instance, neuropathic pain, spasticity, and multiple sclerosis. CBs showed various pharmacological activities for several diseases, including cancer (Blasco-Benito et al. 2018; Chanda et al. 2019; Dariš et al. 2019). It has been reported that the oral administration of Δ8-tetrahydrocannabinol (Δ8-THC) and CBN-derived agents from cannabis reduces tumor growth in mouse models. Since then, many studies on animal cell lines have established the remarkable potential of CBs as therapeutic agents (Velasco et al. 2016; Reddy et al. 2019). The first study of CBs on humans to assess the anti-tumor activity was reported in 2006 (Guzmán et al. 2006). Presently, Epidioloex containing CBD is prescribed as an adjuvant for glioma treatment (Vemuri and Makriyannis 2015). Therefore, these studies further opened the way for testing cannabis-derived drugs/products such as cannabinoids to investigate their therapeutic potential.

3 Biogenesis of Cannabis

In nature, the phytocannabinoid distribution is limited but varies greatly. These phytoconstituents are present in flowering plants, fungi, and liverworts (Nagashima and Asakawa 2011; Hanuš et al. 2016; Zhou et al. 2020). Phytocannabinoids were first isolated from *Cannabis sativa* L., a plant with a long and controversial history of use and abuse (Russo 2007, 2011). Cannabis mainly produces alkyl-type cannabinoids that carry a monoterpene isoprenyl moiety (C10) and a pentyl side chain (C5) (Hanuš et al. 2016).

The biosynthesis of cannabinoids starts from cannabigerolic acid (CBGA). Olivetolic acid is the main precursor for the synthesis of CBGA that forms resorcinol core. The resorcinol core is enclosed by carbon skeletons of different lengths responsible for the structural characteristics of these bioactive compounds. Most of the CBs are synthesized from CBGA (a vital precursor). The synthesis of CBs includes various enzymatic reactions. For instance, synthases convert CBGA into Δ9-THCA and cannabidiolic acid (CBDA) (De Backer et al. 2012; Lal et al. 2021). Further, Δ9-THC undergoes oxidation and photochemical reactions that ultimately form CBND and CBN, respectively (ElSohly and Slade 2005). Likewise, CBD and CBG are produced via photochemical reactions of CBDA and CBGA. The biosynthesis of cannabigerolic acid and cannabinoids is depicted in Figs. 1 and 2. It has

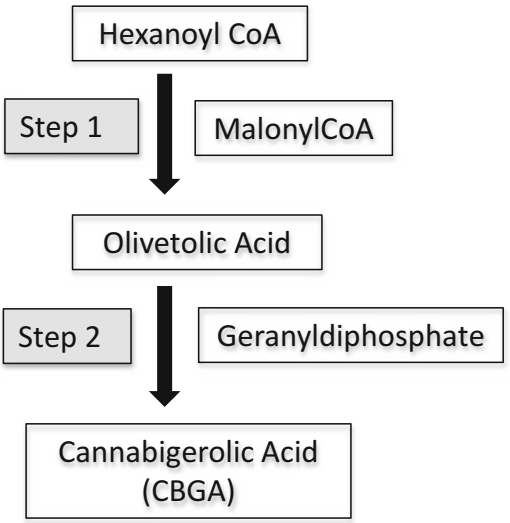

Fig. 1 Biosynthesis of cannabigerolic acid (CBGA). Enzymes involved in Step 1: Tetraketide synthase and Olivetolic acid cyclase; Enzymes involved in Step 2: Olivetolate geranyl transferase

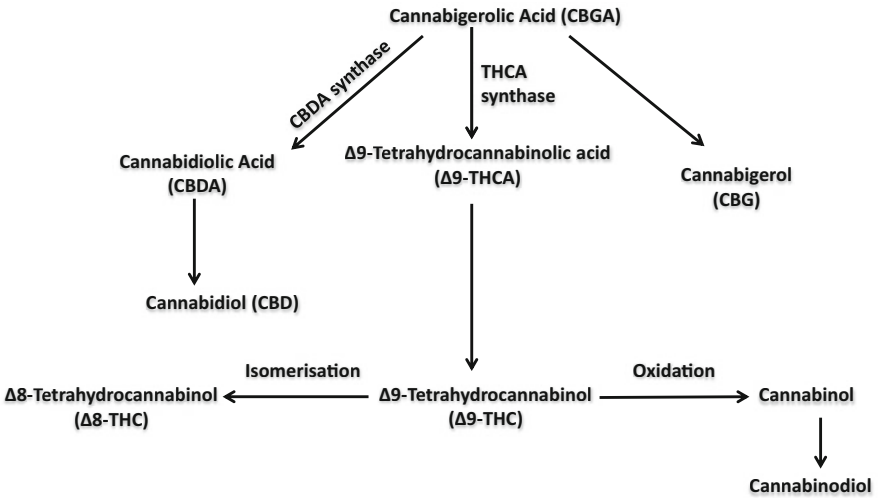

Fig. 2 Biosynthesis of important phytocannabinoids

been reported that binding affinity towards CB1 (cannabinoid receptor type 1) and CB2 (cannabinoid receptor type 2) receptors is increased when dried cannabis extract containing phytocannabinoids is subjected to heat or sunlight (Hazekamp et al. 2013).

4 Classification of Cannabis Phytoconstituents

In the past few decades, scientists have inclined their studies towards significant investigation regarding the safe, efficient, and clinical effectiveness of cannabis and its products in various trials related to humans. These observations have also been utilized for the treatment of various types of symptoms associated with cancer. Since cannabis-derived drugs/products can also attenuate several conditions such as memory, appetite, mood, and pain (Russo and Hohmann 2013; Gonçalves et al. 2019). Thus, researchers and clinicians have evaluated the potential of this plant for medicinal use in treating various disorders. Therefore, to have insight into the possible role of cannabis as a strong therapeutic agent, it is necessary to explore different aspects of cannabis products and their properties that can be exploited for human welfare.

Cannabis possesses cannabinoids that are majorly responsible for its therapeutic/medicinal properties and are further broadly classified into three classes: (1) phytocannabinoids, (2) endocannabinoids, (3) synthetic cannabinoids.

4.1 Phytocannabinoids

Phytocannabinoids belong to a class of compounds that are "naturally derived" from plants and can interact with cannabinoid receptors. In the past years, studies have indicated the presence of terpenophenolics which are constituents of *C. sativa,* other phytoconstituents viz., Δ9-THC, and its natural derivatives as Δ8-THC, Δ9-THC. Among these, Δ9-THC is the key chemical constituent of cannabis and shows instability in its pure form (Hanuš et al. 2016). It is an exciting candidate for drug discovery due to its low toxicity when compared to other compounds.

The structural diversity in the naturally occurring phytocannabinoids might be due to differences in the isoprenyl residues, resorcinyl core, and the side-chain (Raikos et al. 2014). Therefore, phytocannabinoids occur in nine basic topological arrangements: cannabicyclol-type, cannabifuran-type, cannabielsoin-type, cannabichromene-type compounds (Stern and Lambert 2007). The raw extracts of cannabis consist of a resorcinyl core that undergoes carboxylation and is decarboxylated on heating at higher temperatures. Such compounds are called acidic phytocannabinoids, which are attracting attention in the field of drug discovery. Interestingly, native extracts of cannabis constitute various phytocompounds, including terpenes, flavonoids, phytocannabinoids, and fatty acids (Lal et al. 2021).

4.2 Endocannabinoids

These compounds represent an important class of cannabinoids that act as endogenous ligands. N-arachidonoyl ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) are two well-explored endocannabinoids derived from arachidonic acid (Sugiura et al. 1995). Both have modulated many biological processes, such as cellular growth and cell proliferation in humans. This has been well established via evaluating their anti-carcinogenic potency in diverse cancer cell lines (Morals and Jagrovic 2019). However, these compounds' molecular mode of action is regulated by different factors, including the site of action and the type of cancer. Interestingly, researchers have also observed their protection against apoptosis in cells. Even the synthetic analogues of endocannabinoids have efficiently reduced malignancy caused by breast cancer stem cells, indicating their critical role in drug preparations obtained from cannabis (Luca et al. 2009; Quintana et al. 2016; Mohammadpour et al. 2017).

4.3 Synthetic Cannabinoids

Synthetic cannabinoids are a diversified class of compounds developed for utilization as therapeutic agents. The advantage of these compounds is that they are the "pure" forms of phytoconstituents in contrast to raw extracts of cannabis and thus can bind to the selective receptor for efficient pharmacological action (Hanlon et al. 2016). The ubiquitous acceptance of synthetic cannabinoids among patients agrees to their effective and proficient effects (Castaneto et al. 2014). Such compounds have also been observed to possess enhanced therapeutic and pharmacological profiles than naturally occurring psychoactive Δ9-THC in numerous anticancer and analgesic disorders, thus qualifying them as important therapeutic agents (Guzman 2003; Gunderson et al. 2012).

5 Properties of Cannabis Products

5.1 Synergistic Interactions

The literature survey reveals that compounds such as THC can act as a psychoactive agent, whereas CBD can play a non-psychoactive constituent in cannabis. To obtain the medicinal effect, "synergistic interactions" of these products have been studied for whole cannabis extract, which is more effective than individual administration in *in vivo* models (Blasco-Benito et al. 2018; Nallathambi et al. 2018). Such synergistically derived relationships can occur among diverse cannabinoids known as "intra-entourage" or between terpenes and cannabinoids termed "inter-entourage"

interactions. Interestingly, the term "entourage" is used to explain such an amalgamation of mutual interactions of the compounds. Recently, synergistic combinations of terpenes and cannabinoids have also been reported to exhibit cytotoxicity against colorectal cancer cell lines, an important achievement for drug discovery (Nallathambi et al. 2018). Therefore, to obtain effective therapeutic effects, optimization of cannabis-derived compounds alone and in combination is essential.

5.2 Targets of Action: Cannabinoid Receptors and Signaling

To improve the medicinal application of cannabis preparations, it is important to understand the mode of action of cannabis products and their target sites, respectively. The endocannabinoid system comprises cannabinoid receptor type 1 (CB1), cannabinoid receptor type 2 (CB2), endogenous endocannabinoids ligands, and endocannabinoid metabolism enzymes (Howlett and Abood 2017). THC, along with synthetic compounds and endocannabinoids, have been observed to play a role in the activation of G-protein-coupled cannabinoid receptor 1 (CB1) and endocannabinoid receptor 2 (CB 2) (Pertwee et al. 2010). Maccarrone et al. (2015) reported the synaptic effects of cannabinoids in different cells and tissues. Recent studies have also suggested that binding agonists to the receptor 1 and 2 results in functional selectivity that can activate or inhibit CB1 and CB2 signaling pathways downstream (Di Marzo 2018; Navarro et al. 2020). Moreover, alterations in the endocannabinoid ligand availability, receptor activity/expression, or metabolic enzyme activity of endocannabinoids have been reported to be associated with various pathological conditions (Koltai et al. 2019). These facts are also visible from a large amount of information on the CB receptors and their signal transduction pathway.

5.3 Importance of Cannabinergic Compounds

Ccannabinergic compounds can modulate the endocannabinoid system irrespective of their chemical structure or pharmacological potency. This group constitutes CB1 or CB2 receptor binding ligands (agonist/antagonist), substrates/inhibitors of endocannabinoid transporters (Goutopoulos and Makriyannis 2002). Many studies have been focused on determining structure-activity interactions between synthesized cannabinergic compounds that are phytocannabinoid derivatives and their receptors (Lu et al. 2005; Vemuri and Makriyannis 2015; Silva et al. 2017). In turn, this has formed the basis for evaluating their biological activities and pharmacokinetic properties (Kulkarni et al. 2016). Moreover, such inferences are important for developing novel medicinal applications involving cannabis to curb many deleterious effects, including pain disorders, and generate anti-inflammatory therapeutics (Lu et al. 2006; Aggarwal 2013).

6 Cannabis-Based Drugs

6.1 Cannabis-Inspired Drugs

Marinol® was the first approved drug with high dronabinol content, which is synthetically similar to THC (Table 1). It was clinically tested for the stimulation of appetite and as an antiemetic. Marinol antiemetic efficiency was reported maximum in patients who received cytotoxic therapy for Hodgkin's and non-Hodgkin's lymphomas.

6.2 Cannabis-Derived Drugs

Epidiolex® is the second registered drug having a high content of plant-derived CBD (Table 1). In 2018, U.S. Food and Drug Administration (FDA) approved Epidiolex as a cannabis-derived drug. Nowadays, it is used to treat Dravet syndrome and Lennox-Gastaut (types of epilepsy) (Sekar and Pack 2019). Other one molecule drugs were used to treat diverse medical conditions such as appetite stimulation, cancer-associated pain relief, nausea, and vomiting related to cancer chemotherapy (Table 1). More recently FDA permitted Epidiolex for the treatment of 'Tuberous

Table 1 Important drugs derived from cannabis

Drug name	Mode of administration	Cannabis element	Intended Indication	Approval
EPIDIOLEX® by GW pharmaceuticals	Oral solution	CBD	Approved for treating Lennox Gastaut syndrome and Dravet syndrome in patients	FDA, USA
MARINOL® by GW pharmaceuticals	Oral capsule	Synthetic THC	Approved for treating stimulation of appetite; antiemetic associated with cancer chemotherapy and anorexia related to weight loss in patients suffering from AIDS	FDA, USA
SYNDROS® by Benuvia therapeutics Inc	Oral solution	Dronabinol (synthetic THC)	Approved for treating anorexia; nausea and vomiting associated with cancer chemotherapy	FDA, USA
CESAMET® by Valeant pharma Int	Oral capsule	Nabilone (synthetic cannabinoid similar to THC)	Approved for treating nausea and vomiting induced by cancer chemotherapy	FDA, USA
SATIVEX® by GW pharmaceuticals	Oromucosal spray	Plant-derived CBD, THC, and terpenes	Approved for treating pain management	Europe and Canada

Sclerosis Complex (TSC), which is a rare genetic disease that causes non-cancerous (benign) tumors in patients 1 year of age and older (Felberbaum 2018).

6.3 Combinatorial Drugs from Cannabis

Sativex, a drug developed by GW Pharmaceuticals (USA), contains both CBD and THC, and some terpenes, is preferred for pain relief (Table 1). Patients having moderate to severe spasticity with multiple sclerosis (MS) can be treated with Sativex. Moreover, it was found to be effective for the treatment of other medical conditions. For instance, treatment with Sativex noticeably improved the frequency and severity of motor and vocal tics post-treatment in treatment-resistant Tourette syndrome patients (Namdar et al. 2020). FDA has not yet approved Sativex, but it is registered for commercial distribution in Canada and Europe.

7 Therapeutic Implications

7.1 Pain Management

Pain management is a problem that has increasingly attracted the attention of several countries that have now started considering cannabis for curing acute or chronic pain. Recent years have observed an enhanced number of clinical studies related to this particular area. In a study, adults consuming opioids and cannabis for pain management were efficiently relieved of symptoms including pain, nausea, anxiety, insomnia, depression, and stress signifying cannabis as a potent candidate for pain and pain-related disorders (Bigand et al. 2019). Similarly, a study of endometriosis concluded that females using cannabis and hemp/CBD oil assessed such compounds in the category of the most effective therapeutic agents in reducing pain (Armour et al. 2019). Since current medical treatments cannot offer adequate pain relief without severe side effects, cannabis has been explored as an effective alternative concerning rheumatic patients. However, it has also been reported that the side effects of medicinal use of natural compounds in these patients should be based on the beneficial effects and cannabis-related adverse effects including, appetite changes, psychomotor effects, mood effects, dizziness, should be taken care of (Fitzcharles et al. 2019). This study reported that the older adults using cannabis showed a considerable decrease in prescription drugs, thus establishing cannabis as another medical option for curbing such symptoms (Palace and Reingold 2019). This effect can be attributed to CBD, which can eliminate psychoactive effects and thus improve the safety profile in chronic pain management. The use of cannabis and cannabinoid has also been reported to treat cancer pain, including breast cancer, cervical cancer, and lymphoma (Abrams and Guzman 2015). It has been observed that THC can act as an effective agent for reducing cancer-related pain. However, the

consumption of cannabis is still limited due to its adverse side effects (Shin et al. 2019). Interestingly, cannabinoids have also been associated with fibromyalgia treatment, including tiredness, lumbar pain, and mood changes. Researchers have also reported the correlation linking deficiencies in the endocannabinoid system and fibromyalgia and found that the use of cannabis products led to the improvement of pain in fibromyalgia patients (Habib and Artul 2018; Habib and Avisar 2018; van de Donk et al. 2019).

In a nutshell, pain management is the most studied therapeutic effect of cannabis. Overall, studies have supported that cannabis-based drugs/medicines efficiently restrict the painful spasms and neuropathic pains associated with diabetes and multiple sclerosis. Also, cannabis and its phytoconstituents can further be exploited to cure cancer, chronic pain, and other disorders, and their use showed positive results in such deleterious conditions.

7.2 Epilepsy/Seizures

It is a disorder related to the Central Nervous System (CNS). The brain activity becomes abnormal, resulting in episodes of involuntary movement involving a part or entire body. Several studies have focused on using isolated CBD as a medicinal potential for curing epilepsy during the last few years. As evident from earlier studies, patients treated with CBD showed significant improvement in seizures throughout the study (Mechoulam and Carlini 1978). Even administration of 200–300 mg of CBD improved seizures in adult patients (Cunha et al. 1980). Moreover, insufficient clinical and preclinical data have triggered the requirement for efficient and effective therapies for epilepsy based on CBD treatment. Owing to this, recent research has been directed towards clinical trials that have investigated the additive impacts of purified CBD in children and adults (Devinsky et al. 2017; Szaflarski et al. 2018). In continuation to these observations, Devinsky et al. (2016) studied efficacy and safety parameters on patients receiving the cannabis-based drug, Epidiolex. They reported that CBD administration orally at concentrations reaching up to 20 mg/kg/day resulted in limitation of convulsive seizure frequency significantly. Similarly, a study involving CBD treatment in double-blind, placebo-controlled clinical trials led to a better reduction in the number of seizures frequency among children and adults with Lennox–Gastaut Syndrome (Thiele et al. 2018).

Interestingly, evaluation of cannabis products has also been done in context to refractory epilepsy, which depicted a significant reduction in (50%) frequency of seizures while incorporating CBD – enriched extracts of cannabis at doses of 2–5 mg/kg/day (Hausman-Kedem et al. 2018). Similar results were obtained in analyzing Dravet syndrome with doses ranging from 7–16 mg/kg/day (McCoy et al. 2018). Moreover, a study of medicinal cannabis on children and adolescents with intractable epilepsy resulted in an efficient reduction in seizure frequency that ranged between 100% and 25% reduction (Tzadok et al. 2016).

Therefore, CBD-enriched cannabis and its medicinal incorporation are shaping a promising anticonvulsant choice with an encouraging safety profile for patients. However, the risks, the legality of cannabis consumption, and consistent formulation via strict methodology must be followed for a proper implication of its extensive use. Hence, a synergistic approach involving phytocannabinoids and other phytocompounds, *viz.* flavonoids and terpenoids, attains the desired target.

7.3 Neurodegenerative Disorders

7.3.1 Parkinson's Disease

Parkinson's disease (PD) is the most common neurodegenerative disorder characterized by tremor, rigidity, postural instability, and bradykinesia. These symptoms arise because of the loss of dopaminergic neurons in the substantia nigra. PD has multifaceted etiologies related to other clinical motor symptoms and showed differences in pathology (Mhyre et al. 2012). Research studies on PD have suggested that pathways associated with immunology are crucial in the pathophysiology (Zipp and Aktas 2006). The clinical effect of cannabis on motor and non-motor indications of PD may be regulated by the serotonergic, dopaminergic, neuroprotective, and adrenergic effects of cannabinoids (Stampanoni Bassi et al. 2017). CBD and THC are the two main phytoconstituents in cannabis, mainly responsible for the pharmacological properties (Babayeva et al. 2016; Lafaye et al. 2017). CBD has shown anxiolytic, hypnotic, neuroprotective, neuromodulatory, and antipsychotic effects (Suryadevara et al. 2017; Cooray et al. 2020; Patricio et al. 2020). THC is responsible for the psychotropic effects of cannabis, and it operates via two types of receptors, i.e., CB1 and CB2. The CB1 receptor is localized in the central nervous system (CNS) and is expressed in basal ganglia, mainly in PD (Gonçalves et al. 2019). Owing to their localization, CB1 receptors control both cognitive and motor movement. The CB2 receptors are expressed highly in lymphoid organs, peripheral t cells, and CNS (Patel et al. 2019; Tansey and Romero-Ramos 2019). The CB2 receptors have been shown to modulate microglia's activation, playing an important role in neuroprotection (Nunez et al. 2008). Moreover, clinical studies have shown that cannabinoids check the neuronal damage in rodents by their antioxidant activity (Nunez et al. 2008). In an experimental model, Peres et al. (2016) reported that CBD's anti-inflammatory and antioxidant actions would reduce reserpine-induced motor impairment. In some studies, it has been reported that the patients who consumed cannabis showed improved PD symptoms such as bradykinesia, tremor, rigidity, problems with sleep, and pain (Balash et al. 2017; Kindred et al. 2017; Shohet et al. 2017).

7.3.2 Alzheimer's Disease

Alzheimer's disease (AD) is a chronic neurodegenerative disorder that arises when neurons in the brain degenerate and die. Pain commonly occurs in older patients with neurodegenerative diseases, including AD. Alzheimer's disease is mainly caused due to the deposition of amyloid-β protein in specific brain locations leading to neuroinflammatory responses (Esposito et al. 2006). These events lead to neuronal cell death, associated with functional synapses loss and altering neurotransmitter signals (Wang et al. 2017). Numerous research studies have suggested the beneficial effects of cannabinoids for reducing pain and toxic protein from the brain and reinstate cognitive malfunctions of AD (Cheng et al. 2014). Furthermore, endocannabinoid signaling has largely been shown to control the various pathological processes in neurodegenerative disorders, such as mitochondrial dysfunction, misfolding of protein, neuroinflammation, and oxidative stress. Recently, nabilone, a synthetic cannabinoid, has been used for treating patients suffering from AD by using the pain assessment in the advanced dementia scale (https://clinicaltrials.gov/ct2/show/NCT03247244). Clinical evidence showed that dronabinol might be beneficial in treating behavioral and psychological symptoms of dementia (Gonçalves et al. 2019).

7.3.3 Tourette's Syndrome

Tourette's syndrome (TS) is a neuropsychiatric disorder present in approximately 1% of the population and is characterized by multiple motor and at least one vocal tic (Robertson et al. 2009). The main role of the central endocannabinoid system (ECS) is inhibitory modulation of all-important neurotransmitter systems in the brain. In TS, there is significant evidence for an association of the dopaminergic system. Many patients with TS were reported using cannabis illegally to improve their tics or comorbid psychiatric disorders (Szejko et al. 2018). Based on several clinical studies, it has been found that medicine derived from cannabis may be novel and promising for the treatment of TS patients. Numerous studies explored the effectiveness and acceptability of various cannabis-derived medicines for curing patients with TS, including THC (dronabinol), nabiximols (Sativex®), and medicinal cannabis (https://clinicaltrials.gov/ct2/show/NCT03247244).

7.4 Sleep and Anxiety Disorders

Although the therapeutic utilization of cannabis and its products is confusing for treating insomnia, some researchers have supported its use on patients suffering from sleeping disorders in the past few years. Interestingly, THC and CBD have been associated with the induction of sleeping due to their psychoactive and

non-psychoactive actions, which promotes a probable interaction of both cannabis components (Belendiuk et al. 2015). A study carried out by Nicholson et al. (2004) indicated that both THC and CBD could provide better balance in sleep promotion due to their different activities. Further, a literature survey reveals that cannabis is efficient in insomnia treatment since its phytoproducts also play an important role in inducing effects under sleep deprivation (Tringale and Jensen 2011). However, if cannabis is associated with contradictory less sleep, that can be attributed to the concentration of cannabinoids, dose, and its route of administration, respectively (Babson et al. 2017). Reports regarding the enhanced consumption of cannabis products in people with anxiety issues have prompted researchers to study a possible reason. The answer lies in the relaxation experienced after cannabis use further promotes its use by such patients. THC behaves differently under two conditions: anxiogenic agents at high doses and anxiolytic agents at low doses. Besides, CBD also plays a vital role in behaving as an anxiolytic compound at oral administration, thus attenuating the anxiogenic effects. It was supported by a study in which patients suffering from social anxiety disorder experienced less anxiety when they were administered CBD (Bergamaschi et al. 2011). Overall, such explanations strongly recommend the medicinal use of cannabis for stress and anxiety disorders which further forms a strong base as an incredible research subject.

To date, cannabis use has been focused on deleterious diseases, including Huntington's or Parkinson's and inflammatory bowel diseases, which still lack sufficient evidence related to cannabis's role. Similarly, anxiety-related conditions, such as depressive disorders, post-traumatic stress, and chronic pain, have not been extensively studied in clinical trials. However, patients suffering from such circumstances have reported cumulative benefits from cannabinoids.

8 Recent Approaches for Enhancing the Quality of Cannabis Products

Since the critical review of *Cannabis sativa* and its therapeutic constituents has profusely signified its role in human welfare, promoting the quality of natural or synthetic cannabis products has become important. Although substantive production of such pharmaceutical drugs/products seems to be perfect on a small scale still there is need for substantial efforts to achieve the required targets (De Meijer 2014). Recent studies have shown vital steps required for attaining the desired results (Fig. 3). In the first step, comprehensive profiling regarding the chemical constituents of the *C. sativa* is carried out. The second approach revolves around determining suitable mixtures of phytoconstituents for curative treatments since synergistic interaction plays a crucial role in therapeutic potential, as already discussed above. The advantage of knowing synergistic interaction leads to the development of suitable strains of cannabis to produce the proper combinations of compounds that are nowadays labeled and then assigned further for medical use against many

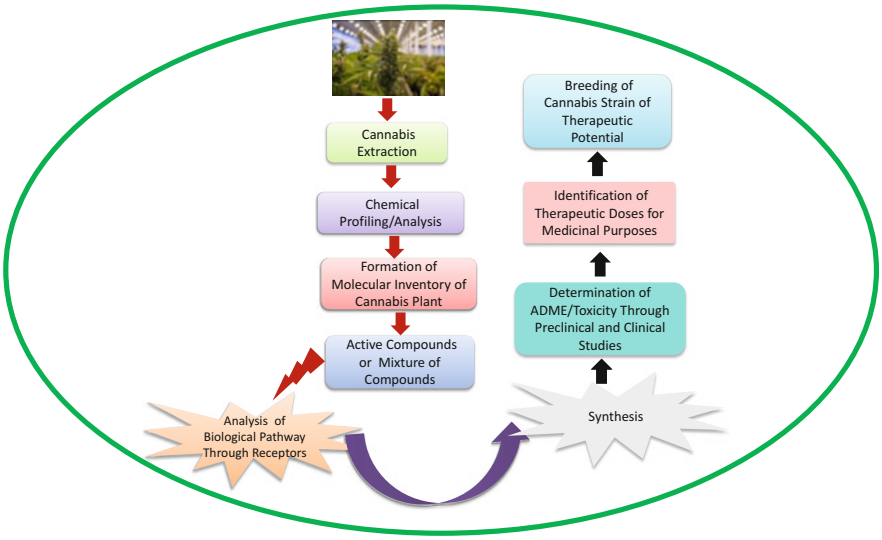

Fig. 3 Schematic representation of steps involved in the use of cannabis for therapeutic application

diseases. Thirdly, the compounds are purified from cannabis, or their synthetic analogs are also synthesized. This, in turn, promotes the effective utilization of phytoconstituents capable of mimicking the designated biological activity. In addition to this, another vital approach that is being explored is to characterize various biological pathways in humans, especially at cellular and tissue levels which in turn help medical practitioners for drug innovations. All these concepts are affirmed by data resources, including the Therapeutic Targets Database, which is maintained in accordance with the target and drug entries complementing the pathways associated and hence has supported drug discovery and design concerning judicious use of cannabis products (Yang et al. 2016).

Interestingly, the success of cannabis-based drug development lies in the basis that pharmaceutical products should target specific receptors without exhibiting any significant toxicity in a cell. Compared to other drugs, CBD has been associated with superior efficacy and a better side-effect profile (Russo 2019). However, fundamental specifications must be studied concerning other cannabis compounds except for CBD and THC, which are currently used to cure many adverse effects (Iffland and Grotenhermen 2017). Moreover, more clinical trials are now in progress, with a larger number of participants in chronic cannabis compound administration (Iffland and Grotenhermen 2017).

Therefore, such processes revolving around the preclinical trials followed by human testing are required to establish drug efficacy under cost-effective conditions. Hence, extensive *in vitro* to *in vivo* studies in cell assays and animal model systems must be followed by human *in vivo* experiments required to identify most potential cannabis products or a mixture of these products for human consumption. Overall

such advancement is used to determine the action of new cannabis compounds either individually or in a mixture to attain maximum safety margin.

Considering the above facts, it can be presumed that the key to successfully exploring the therapeutic properties of cannabis is to find proper synergistic mixtures of its active compounds. Therefore, along with in vitro assays, in silico molecular structure-based studies such as pharmacokinetics, pharmacodynamics, molecular modelling are being considered (Koltai et al. 2019). Peculiarly, the drug-to-drug interactions responsible for efficacy should be considered for final human doses of cannabis molecules. This further leads to replicate the desired amount of individual cannabis compounds present in the mixed preparations for *in vivo* environment. This strategy, in turn, can act as a powerful tool for the early drug discovery stage. Amidst all the recent advancements, it can be attributed that for the medicinal implementation of cannabis use, absorption, distribution, metabolism, elimination, and toxicity must be profiled and characterized for final therapeutic doses for human administration (Vlot et al. 2017).

9 Conclusion

Cannabis and its products, i.e., natural or synthetic, have shown tremendous potential in curbing many deleterious diseases. This is indicated by several studies and observations that have been conducted at *in-vitro* and *in-vivo* levels and also implying human trials. However, this plant's efficient and successful utilization and its phytoconstituents depend upon many factors, including signaling pathway and target of action. Extensive research related to clinical disorders, including pain, epilepsy, anxiety, Parkinson's disease, has established the therapeutic role of cannabis in curbing them. However, there is still a prerequisite to explore the effects of most of the chemical constituents of cannabis concerning their efficacy, doses, the responsiveness of patients, administration method, and the respective adverse effects. Owing to its promising nature, the scientific community is motivated to explore novel therapeutic possibilities of cannabis. This approach still forms a firm foundation for cannabis synergy and botanical drug development using its single component or cannabis extract. Despite these facts, the legalization of cannabis for research purposes is still a huge barrier that should be overcome. In most cases, this aspect causes a restriction in the regulated and controlled use of cannabis in the pharmaceutical industry.

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Cannabinoid-Based Innovative Prophylactic and Therapeutic Interventions for Neuropathic Pain and Migraine

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Abstract The application of medical marijuana is becoming increasingly widespread in the USA due, in part, to legalization in several states. The US federal government continues to categorize all forms of marijuana as illicit; however, the government has mainly not intervened with the applications of medical marijuana that have been deemed legitimate under state laws. Provided that peripheral neuropathy, neuropathic pain, and migraine are complicated conditions challenging to treat, this chapter reviews the effectiveness, roles, and consequences of medical marijuana in treating peripheral neuropathy and migraine. Furthermore, the study of the cannabinoid-mediated mechanisms in treating peripheral neuropathy and migraine is discussed.

Keywords Cannabis · Medical uses · Migraine · Neuropathy · Pain · Receptors

Abbreviations

AEA	N-Arachidonoylethanolamine (Anandamide)
2-AG	2-Arachidonoylsn-glycerol
CB1	Cannabinoid type 1 receptor

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CB2	Cannabinoid type 2 receptor
CGRP	Calcitonin gene-related peptide
DSE	Depolarization-induced suppression of excitation
DSI	Depolarization-induced suppression of inhibition
FAAH	Fatty acid amide hydrolase
THC	Δ-9-tetrahydrocannabinol

1 Introduction

Pain is arguably one of the most impactful sensations due to its ability to inhibit the quality of life. Its discrepant nature makes it challenging to study; therefore, one may not understand another's pain. There are genetic variants of pain. One example is the alleles of the SCN9A gene, which can determine the experience and intensity of the pain (Koenig et al. 2015). Additionally, the psychosocial aspects of pain, such as the previous circumstances of a patient's life, can affect their responses to pain stimuli (Johnson and Faraone 2013; Johnson and Flores Mosri 2016). In the United States, chronic pain affects a staggering 40% of adults with an estimated total cost of $635 billion (Simon 2012). Neuropathic pain is an incapacitating form of chronic pain resulting from damage to the central or peripheral nervous systems during physical trauma, immune disease, or infection. These traumas can stem from various afflictions, including vehicular accidents, surgery, and conditions such as cancer, diabetes, and immune disorders (Lozeron and Kubis 2015). Neuropathic pain is triggered by damage to spinal or sensory nerves, which can cause them to send erroneous pain messages to the body's higher centers (Kremer et al. 2016). It is characterized by spontaneous pain, mechanical allodynia, thermal allodynia, hyperalgesia, and comorbid psychosocial conditions such as depression, anxiety, sleep, and social disturbances (Casey and Vaughan 2018). Due to the many and varied causes of neuropathic pain, more research and treatment development remains significant.

Cannabis sativa, referred to as hemp, is an annual, dioecious plant originating in agricultural communities in Asia. It is an abrasive, bush-like plant that can grow up to 3 meters tall in mild and tropical weather with palmate leaves decorated with green flowers (Manzanares et al. 2006). Cannabis has been utilized throughout history for various purposes, including paper and textiles and recreation and medicinal applications. Its pharmacological properties vary depending on quantity, quality, strain, culture, and preservation conditions. The extracts of the dried green flowers, buds, and leaves are known as cannabis or marijuana. Moreover, Hashish is a resin that the female plant eludes (Manzanares et al. 2006). This contentious plant continues to ignite political, societal, and scientific debate due to its remedial and psychoactive capabilities. In 1964, Mechoulam and associates discovered the main psychoactive component of *Cannabis Sativa* (Gaoni and Mechoulam 1964). It is referred to as Δ-9-tetrahydrocannabinol (D9-THC), which was later found to affects the N-arachidonoylethanolamine (AEA) and 2-arachidonoyl glycerol (2-AG) endocannabinoid ligands and the Cannabinoid type 1 and 2 (CB1 and CB2) receptors (Bonini et al. 2018).

Cannabinoid receptors are $G_{i/o}$- protein-coupled receptors anchored in the cell membrane and consist of 7 folded transmembrane helices. The CB_2 receptor is predominantly situated in the immune system, while the CB_1 receptor is located in the brain, spinal and peripheral nervous tissue, endothelial cells, and uterus (Pertwee 1997). Endogenous cannabinoids also referred to as endocannabinoids, are a family of bioactive lipids that activate the cannabinoid receptors to facilitate neural transmission. They assist in pain perception, mood, appetite regulation, and memory. Studies show that noxious stimuli increase endocannabinoid release supporting the hypothesis that they are involved in pain modulation (Walker et al. 2002). Additionally, exogenic synthetic or natural cannabinoid compounds can mimic endocannabinoid effects (Manzanares et al. 2006.

With the rise in demand for chronic pain management paired with the concern of the opioid epidemic, physicians struggle to find a solution for the treatment of chronic pain. There is a current increase in interest in the potential utilization of cannabis due to a moderation of political and societal viewpoints in the United States. Although the plant has been used for centuries, its therapeutic potential has only recently been investigated using more evidence-based strategies. At present, more research is required to define the potential of cannabis in treating human diseases. (Bridgeman and Abazia 2017).

2 History of Cannabis and Pain

Cannabis has been used throughout the world for hundreds of years. Evidence suggests that cannabis was utilized over 5000 years ago in the region that is now Romania (Holland 2010). Additionally, a Chinese encyclopedia originating in approximately 2900 BC providing agricultural and medicinal information titled The Shennong Ben Cao Jing is the oldest written record of cannabis use in medicine. In this publication, cannabis was reportedly used to treat constipation, rheumatic pain, female reproductive tract disorders, and malaria (Touw 1981). It was also used as an anesthetic in surgical procedures when combined with wine (Li 1973). The Chinese typically use cannabis seeds that contain low delta-9-tetrahydrocannabinol levels (Li 1973). Later, around 1000 BC in India, three methods were used to prepare the female plant's flowers with variable levels of strength (Touw 1981). The most potent strain was used for analgesic, hypnotic, tranquilizing, antispasmodic, and anti-inflammatory properties (Aldrich 1997). Cannabis was not introduced into western medicine until the early nineteenth century. During this time in Europe and the United States, cannabis' exploration revolved around its analgesic and hypnotic effects (Grinspoon and Bakalar 1993).

Civilizations throughout history have documented the various ailments that utilized cannabis as a treatment for, including joint pain and muscle spasms (Russo 2007). Though it has been used for different medicinal treatments, the proposed scientific rationale for its efficacy was not recorded. To this day, scientists continue to investigate which medical conditions may respond to cannabis treatment.

Cannabis research has been stunted due to governmental restrictions and opposing societal and political views (Savage et al. 2016). Cannabis was deemed a Schedule I Drug (drugs with no medicinal use but high abuse potential) by the United States Controlled Substances Act in 1976 (Anonymous 2021). California became the first state in the US to legalize botanical cannabis for therapeutic use in1996 (Anonymous 2021). In 2015, it was estimated that 8.3% (22.2 million people) of the American population (ages 12 and over) utilized cannabis for medicinal or recreational purposes (CBHSQ 2016). In a Gallup poll in October 2016, 60% of the American population surveyed indicated that cannabis should be legalized (Swift 2016). Additionally, a poll done at Quinnipiac University found that 54% of American voters would encourage the legalization of cannabis without further constraints, and 81% indicated they favored the legalization of medicinal cannabis (Bridgeman and Abazia 2017). By March 2017, 28 states and the district of Columbia legally allowed cannabis for medicinal purposes, and 8 of the states, including the district of Columbia, have even legalized recreational cannabis utilization (Anonymous 2021).

Pain relief is the most commonly documented therapeutic use for cannabis. All conditions are coherent in integrating chronic pain as one of the disorders in which cannabis may be used as a pharmacotherapy tool (Bestrashniy and Winters 2015; Ilgen et al. 2013; O'rens et al. 2017). With a broader acceptance of cannabis use, more patients ask their healthcare providers if cannabis is a potentially effective treatment for their various conditions. Currently, two strands of cannabis are approved by the United States Food and Drug Administration (FDA).

3 Cannabinoids and their Receptors Involved in Pain Signaling

Cells in injured tissue produce endocannabinoids which are derivatives of arachidonic acid. The endocannabinoids activate cannabinoid receptors (also targeted by Δ-9-tetrahydrocannabinol) to regulate the conduction of pain signaling by alleviating sensitization and inflammation (Rice 2001). CB_1 receptors present in nociceptive sensory neurons and non-nociceptive sensory neurons of the dorsal root and trigeminal ganglion, macrophages, mast cells, and epidermal keratinocytes, moderate neurotransmitter release into the central nervous system (Price et al. 2003; Sugawara et al. 2013). Though minimal CB_2 receptors are located in the brain, spinal cord, and dorsal root ganglion, they increase peripheral nerve damage, control neuroimmune connections, and obstruct inflammatory hyperalgesia (Guindon and Hohmann 2009) (Fig. 1).

Upon injury, tissues' biochemical pathways produce endocannabinoids, anandamide, and 2-arachidonoylsn-glycerol (2-AG). These pathways activate CB receptors to suppress sensitization and inflammation (Fig. 2).

Anandamide (AEA), derived from the Sanskrit word "Ananda, "translated to "bliss," is an autocrine and paracrine messenger utilized in response to inflammation

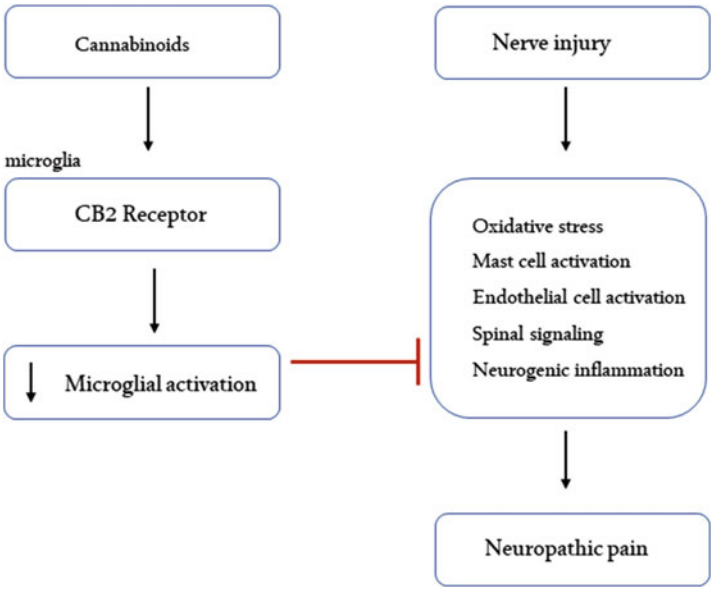

Fig. 1 Cannabinoids acting as agonists for CB_2 receptors decrease microglial activation and inhibits inflammatory responses thereby decreasing neuropathic pain

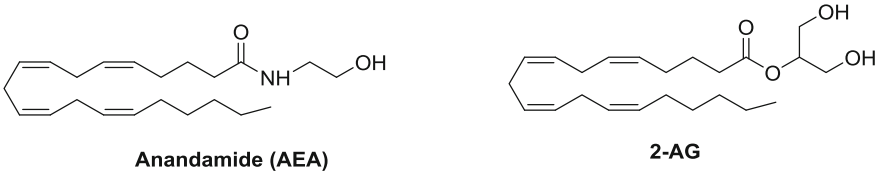

Fig. 2 Cannabinoids produced during injury

and nerve injury. When released from the postsynaptic terminal, it interacts with presynaptic cannabinoid receptors and is quickly removed from the presynaptic space via a high-affinity transport system in neurons and astrocytes. Anandamide is metabolized (Fig. 3) into arachidonic acid and ethanolamine by fatty acid amide hydrolase (FAAH) or proalgesic prostanoids by COX-2 (Massaro et al. 2015; Piomelli et al. 2007). Anandamide is essential for memory, higher thought processes, and movement control (Manzanares et al. 2006). The enzyme FAAH is produced at high levels in somatodendritic regions of neurons that are postsynaptic to the CB_1-positive axon terminals in areas of the brain such as the cerebellum, hippocampus, and neocortex. Therefore, CB_1 receptors and FAAH are anatomically close and their actions complemented (Elphick and Egertová 2001).

The endogenous cannabinoid 2-AG is formed by the catalytic hydrolysis of phospholipid phosphatidylinositol-4,5-biphosphate, creating intra and extracellular messengers. Acute stress plays a significant role in the descending modulation of

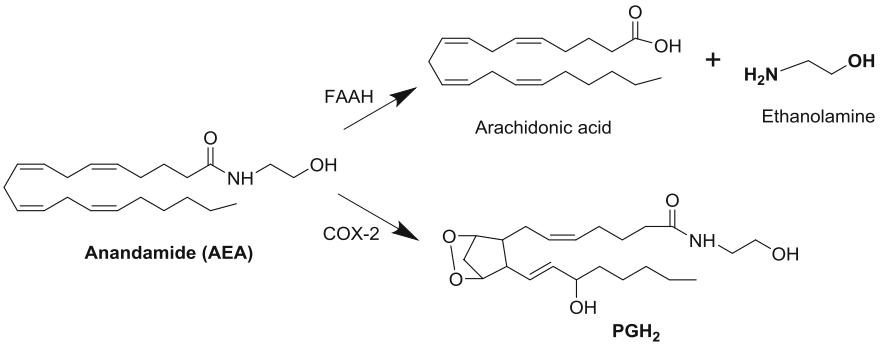

Fig. 3 Metabolism of anandamide (AEA)

pain (Hohmann et al. 2005). Different sections of the brain contain other neurons, nerve cells, and levels of 2-AG. The biosynthesis of these crucial components is controlled separately (Porter and Felder 2001). In conjunction, anandamide and 2-AG provide the first response to nociceptive signaling after the tissue has been injured, supporting a theory that understanding the processes and operations of endogenous cannabinoids may support the efficacy of exogenous cannabinoids in pain regulation (Hill et al. 2017).

Endogenous cannabinoids activated CB_1 receptors coupled to $G_{i/o}$-proteins. This action causes the inhibition of adenylate cyclase, decreases the conduction of Ca^{2+}, increases the conductance of K^+, and increases mitogen-activated protein kinase activity (Howlett 2004). CB_1 receptors are presynaptic, which demonstrates that cannabinoids modulate neurotransmitter release from axon terminals. Cannabinoids also affect synaptic function via inhibition of the release of neurotransmitters (such as L-glutamate, GABA, noradrenaline, dopamine, serotonin, and acetylcholine) and cause depolarization that creates inhibition of electrical activity (Katona et al. 2000). Hence, endocannabinoids regulate depolarization-induced suppression of inhibition (DSI) or excitation (DSE), though it is contingent upon the environment of the presynaptic terminal (Kreitzer and Regehr 2001). CB_1 receptor antagonists can block depolarization-induced suppression of inhibition and depolarization-induced suppression of excitation. Endocannabinoids are crucial for fast alterations of synaptic transmission in the central nervous system via a retrograde signaling pathway (Manzanares et al. 2006). This path can influence local synapses through inhibitory effects on excitatory and inhibitory neurotransmitter release, crucial in controlling neural circuitry. Cannabinoid receptor activation produces an inhibitory effect on GABAergic synaptic transmission, while depolarization of the postsynaptic neurons inhibits GABA release, thereby creating depolarization-induced suppression of inhibition (Manzanares et al. 2006).

As mentioned above, the primary psychoactive component of cannabis is a component called Δ-9-tetrahydrocannabinol (THC), which works via activating the CB_1 receptors in the central nervous system. According to Pertwee and the team, the cannabinoid that has ignited the most scientific interest is CBD, which does

not contain any psychoactive components (Pertwee et al. 2010). CBD has a high therapeutic potential in epilepsy, anxiety, psychosis, inflammation, and neuroprotective outcomes without producing a significant activity on the CB_1 and CB_2 receptors (Bridgeman and Abazia 2017). Medicinal applications of CBD are emerging in treating chronic and neuropathic pain, diabetes, cancer, and neurodegenerative diseases.

Animal studies have demonstrated that high doses of CBD inhibit the psychoactive effects of THC. In contrast, human clinical studies propose that oral and oromucosal CBD administration can "prolong or intensify" the effects of THC (Bridgeman and Abazia 2017). Preliminary clinical trials indicate that a dose of oral 150-600 mg CBD per day may provide symptomatic relief for conditions such as epilepsy, insomnia, and anxiety disorders. The high dose may also cause sedation (Zhornitsky and Potvin 2012). A systematic review of control trials investigating cannabinoids in the treatment of non-cancer pain was conducted by Lynch and Campbell (2011). The trials included smoking cannabis, oromucosal administration of cannabis-based medicine, nabilone, dronabinol, and a novel THC equivalent. The ailments treated included neuropathic pain, fibromyalgia, rheumatoid arthritis, and other mixed chronic pains. A total of 15 out of 18 studies determined a significant analgesic effect of cannabinoids compared to the placebo, and the cannabinoids were typically well tolerated by the patients. The adverse effects were mainly mild to moderate in severity. The study indicates that cannabinoids are a safe and moderately effective therapy for neuropathic pain, fibromyalgia, and rheumatoid arthritis (Lynch and Campbell 2011).

4 The Emerging Role of Cannabinoids in Migraine

Migraine is a disorder characterized as a headache with nausea and other sensory-related symptoms (Pavlovic et al. 2014). Migraines affect individuals in different degrees and can often affect the performance of activities of daily life. Owing to its high incidence and debilitating nature, the mechanisms contributing to migraine headaches have been intensely studied over several decades. Still, much remains to be discovered about the underlying pathology of this disease. The current theory states that migraine pain is caused by decreasing the tolerance of nociceptive signal processing in response to the release of pro-inflammatory mediators. The initial migraine attack is thought to be due to a link between environmental and hormonal triggers (Pavlovic et al. 2014). These triggers can lead to pathophysiological changes because of sterile neurogenic inflammation in meninges and activation of trigeminal sensory nerves involving mediators such as calcitonin gene-related peptide (CGRP) (Gouveia-Figueira et al. 2017; Pietrobon and Moskowitz 2013).

Although several therapies with different mechanisms of action are available for treating migraine disorders, including serotonergic agonists (triptans) and CGRP antagonists, there remains a need for more effective treatments with fewer adverse effects regarding migraine pathology. The cannabis plant has many different

characteristics that have been shown to alleviate some of migraine symptoms. These characteristics include anticonvulsive, analgesic, antiemetic, and anti-inflammatory effects (Rosenberg et al. 2015; Parker et al. 2011; Nagarkatti et al. 2009). Many CB1 receptors in the brain are functionally related to CB2 receptors, a type 2 cannabinoid receptor (Chakrabarti et al. 2015). The treatment would target blocking peripheral and central nociceptive traffic. Due to the enteral nervous system also being affected by migraines, the cannabinoid inhibition of CB1 receptors enteric and afferent neurons may be beneficial (Marco et al. 2012). The CB2 receptors are targeted towards the peripheral organs and are restricted towards the immune system (Chakrabarti et al. 2015). These receptors respond to the pro-inflammatory responses and target them (Leimuranta et al. 2018). Chronic migraines cause inflammation and increased inflammatory cytokines in the blood (Leimuranta et al. 2018). Cannabinoids at CB2 receptors could reduce the number of cytokines being produced, thereby reducing the inflammatory response. Cannabinoid treatment has been shown to produce relief in many patients with migraines. The plant's effectiveness and patient satisfaction suggest a therapeutic role for the cannabinoids as a treatment for migraines.

5 Cannabis Therapeutics and the Future

Cannabis treatments for health conditions have increased throughout western medicine. There has been success in treating epilepsy, rheumatic pains, and tetanus (Gonen and Amital 2020; Perucca 2017; Russo 2018). Cannabis and epilepsy have been tested, and there has been a link to cannabis helping seizures. The endocannabinoid system mediates the seizure threshold (Wallace et al. 2003). The anticonvulsant activity of cannabis is linked to the reduction of seizures. Cannabis's effects on central and peripheral systems have helped reduce pain associated with migraines. Cancer patients who have developed opioid resistance have reportedly experienced reduced pain after using cannabis treatments (Johnson et al. 2010). Nabiximols, a drug-treated to relieve pain caused by multiple sclerosis, has been granted regulatory approval (Rog et al. 2005). Cannabis therapies for numerous other conditions have been researched in recent years. The findings to date show that cannabis is a treatment that can have beneficial effects for specific health conditions. Cannabis contains many components that provide many benefits on different symptoms from diseases like Alzheimer's and Parkinson's. For Alzheimer's disease, the symptoms that can benefit from cannabinoid treatment include agitation, anxiety, psychosis, insomnia, anorexia, aggression, depression, and neuroprotection (Russo and Marcu 2017). For these symptoms, different components of the plant appear to help with different symptoms. An approach that includes nutrition, lifestyle, and cannabinoids as treatment may prove to be more preventative while also providing better treatments; the combined approach includes aerobic activity and probiotic diets and supplantation with cannabis extracts (Russo 2018; Fallon and Enig 2001; Russo and Marcu 2017).

6 Future Perspective

The recent progression in cannabinoid research has been promising and, in many instances, positive. The treatment of pain with cannabinoids has proven to be very helpful for many individuals. Acting upon the findings of cannabinoid efficacy and building on these discoveries will advance the future of cannabinoids in the healthcare field. Clinical trials, studies, and research will help identify areas where there is documented efficacy and aid in the development of novel agents with fewer side effects. Better efficacy and fewer side effects will enhance treatment options and help reduce opioid use and addiction, and the use of other drugs. The impact of cannabinoids on the peripheral and central nervous system pathways has shown to be a positive and effective treatment. However, further assessments of cannabinoid safety and efficacy remain to be completed.

7 Conclusion

Cannabis therapeutics and availability have increased in healthcare, and therefore healthcare providers should be informed about the drug's safety and potential efficacy. Cannabis has been around for centuries, and through the decade's laws have changed regarding the recreational and medical use of cannabis-derived products. Though there have been constant changes within recent times, there has been an emergence of cannabis for medicinal applications. Studies and research are ongoing to understand the overall efficacy and safety profile of cannabis and cannabis-derived drug products. With the discovery of the endocannabinoids as regulators of the nociception, cannabis medicines have been increasingly explored and found to be effective as therapies for demonstrated their efficacy for pain relief. And patient use is continuing, with the exploration of the use of cannabinoids for other health conditions. While cannabis appears to be an effective treatment for various diseases and symptoms, cannabis contains multiple active substances, and research continues to discover how these different cannabinoids may affect patients. As this discovery progresses, healthcare providers need to continue learning and being educated about cannabinoids to apply this information safely and effectively in the therapeutic setting.

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The Legality of Use and Consumption of Cannabis (Marijuana) in the United States of America

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Abstract In the United States of America (USA), the procurement, possession, and consumption of Cannabis and its associated products have remained prohibited at the federal level from the time of issuing the Controlled Substance Act (CSA) in the year of 1970. However, since the end of the twentieth Century, the legalization of cannabis use has become more open-minded and liberal. Under the current United States law, Cannabis is categorized as a Schedule I substance, classifying it as a substance likely to possess the excessive capacity for dependence and abuse with no documented legitimate medical use. However, based on the recent scientific reports on the use/abuse, various states have passed to authorize and legalize Cannabis for medical and recreational use. More recently, the federal government's Hemp Farming Act of 2018 has removed hemp (Cannabis with less than 0.3% delta-9-tetrahydrocannabinol (THC) from Schedule I controlled substances. However, since cannabis legality varies among the states and the federal government, it is crucial to know the amount authorized to possess, whether it may be shipped, and who is permitted to use it. The present chapter dwells on the current state/region-wise legality aspects of Cannabis in the USA.

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Abbreviations

AIDS	Acquired immunodeficiency syndrome
CBD	Cannabidiol
CNS	Central Nervous System
CSA	Controlled Substance Act
DEA	Drug Enforcement Administration
FDA	Food and Drug Administration
HIV	Human immunodeficiency virus
NIDA	National Institute on Drug Abuse
THC	Delta-9-tetrahydrocannabinol
US	United States
USA	United States of America
USDA	United States Department of Agriculture

1 Introduction

Cannabis is a flowering plant belonging to the Cannabaceae family. Generally, the term cannabis refers to three plant species (*Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*). The botanical products obtained from the cannabis plants are referred to as "weed", "pot", "marijuana", "ganja", "stinkweed", "mary jane", and "dope". Cannabis has a long history of human consumption as well as use for commercial purposes. Historical research indicates that the Cannabis or hemp plant was initially grown in Central Asia about 11,700 years ago before the plant was established in Africa, Europe, and eventually the Americas. The history of Cannabis as a crop in America dates back to the early colonists, who grew Cannabis for commercial purposes, including textiles, paper, sails, nets, and rope. Also, the Cannabis seeds were used for consumption as food and oil (Anonymous 2019). Traditionally, the psychoactive botanical was also consumed for recreational, spiritual, and even medicinal purposes (Maule 2015).

In the modern era, Cannabis or Cannabis-derived products are the most commonly consumed substance of abuse in the United States of America (USA). Nearly 94 million individuals in the USA have used Cannabis or Cannabis-derived products. The individual users have admitted to consuming Cannabis or Cannabis-derived products at least once in their lifetime. Based on the World report on Cannabis by the United Nations, 158.8 million individuals globally consume this botanical representing about 3.8% of the world's population (Anonymous 2021a).

Cannabis products are primarily consumed by smoking, vaporizing, or mixing with various food (National Institute on Drug Abuse, NIDA 2019). The main

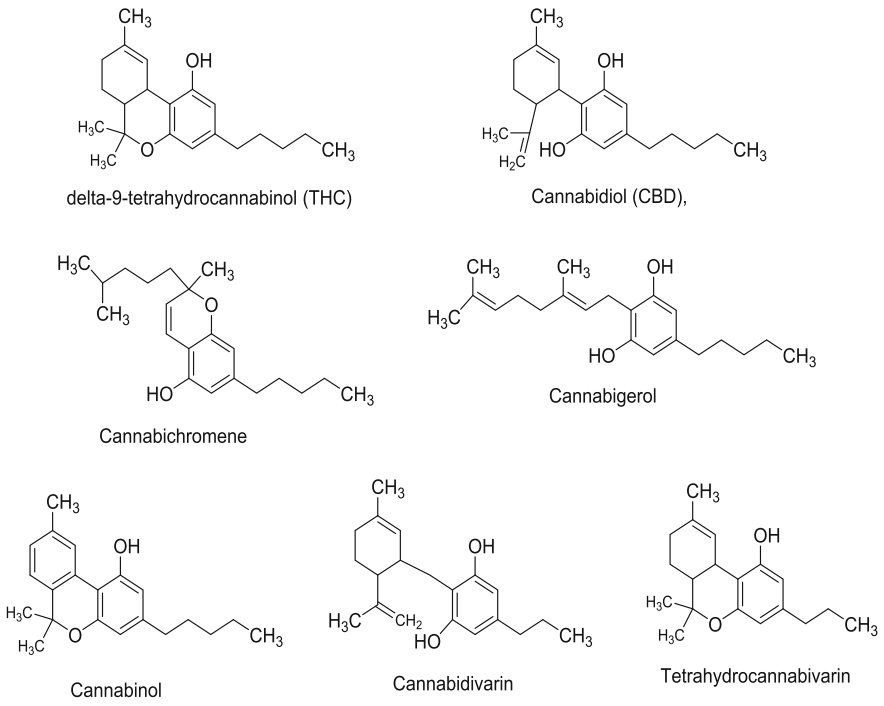

Fig. 1 Chemical structures of some important cannabinoids

psychoactive element of Cannabis is delta-9-tetrahydrocannabinol (THC) (Fig. 1). However, other bioactives present in the plants, including cannabidiol (CBD), cannabichromene, cannabigerol, cannabinol, cannabidivarin, and tetrahydrocannabivarin (Fig. 1), may also affect the central nervous system (CNS) and modify the actions of THC ("entourage effects").

Interestingly, legislation permitting the medical use of Cannabis restricts its use to a few indications, including human immunodeficiency virus (HIV) /acquired immunodeficiency syndrome (AIDS), cachexia, spasticity in multiple sclerosis, neuropathic pain, epilepsy/seizure, and nausea or vomiting associated with chemotherapy. Even though Cannabis has demonstrated some medicinal or therapeutic potential, the substantial and rigorous scientific literature is not always present to validate the use of this botanical. The link between legalization and prevalence remains unclear. Though the states in the USA where cannabis consumption is legal to have greater usage ratios than states where use is not legal, higher rates of use were commonly observed even prior to legalization. Currently, several states in the USA have legalized cannabis use for both medical and recreational purposes, raising public health concerns about the effects of cannabis use on driving abilities, the accidental consumption of cannabis products by children, the correlation between Cannabis and opioid use, and whether there will be an upsurge in the health problems related to

Table 1 Milestones of Cannabis/marijuana/hemp laws for production and usage in the USA

Time	Status of Cannabis/marijuana production and usage
Seventeenth Century	US government encouraged the production of hemp for ropes, sails, and clothing
Nineteenth Century	Marijuana became a popular ingredient in many medicinal products and was sold openly in pharmacies in the USA
By 1931	29 states in the US outlawed marijuana due to fear of Mexican immigrants excessively scaling up production and potential problems associated with marijuana
1937	US Government passed Marijuana Tax Act criminalizing marijuana.
2018	USA passed the Hemp Farming Act to remove hemp (Cannabis with less than 0.3% THC) from Schedule I controlled substances
2020	UN Commission on Narcotic Drugs (UNCND) reclassified Cannabis out of the most dangerous category of drugs

cannabis use, such as dependency/addiction, psychosis, and pulmonary ailments (Wilkinson et al. 2016).

In the USA, the procurement, possession, and consumption of Cannabis and its associated products have remained prohibited at the federal level from issuing the Controlled Substance Act (CSA) in the year 1970. Before this, in 1937, the US government enacted Marijuana Tax Act, which heavily taxed hemp cultivation, resulting in abandoning the crop in the USA. For several decades, US federal law did not differentiate among cannabis plants producing specific quantities of the two most important cannabinoids, THC or CBD. However, extensive research showed that not all cannabis plants induce mind-altering (psychotropic) compounds. There exist cannabis plants producing a high quantity of non-psychotropic compound CBD and negligible amounts of THC. These plants are safe and have tremendous potential for various industrial uses. Thus, backed by scientific evidence and considering growing public interest and vast potential of cannabis products for medicinal and various industrial purposes, the US Farm Bill 2018 was passed by the federal government in December 2018. In this farm law, hemp (defined as Cannabis with less than 0.3% THC) has been removed from Schedule I controlled substances (Table 1). However, it is important to know that this law does not create a free system to grow, sale or use hemp. There are certain restrictions in the law. First, THC content cannabis plants should be $<0.3\%$ of dry weight basis. Second, there exists a significant, shared state-federal regulatory power over hemp cultivation and production under the control of USDA. Third, the law outlines actions that are considered violations of federal hemp law (such as cultivating or producing Cannabis with >0.3 percent THC without appropriate approvals and license) (Hudak 2018).

In the present chapter, we explore the state/region-wise legality of the use and consumption of Cannabis in the United States of America. Major milestones of Cannabis/marijuana/hemp laws 167 for production and usage in the USA (Anonymous 2020) are given in Table 1.

2 Legal vs. Illegal Use of Cannabis in the Various States in the USA

The legality of cannabis use is not uniform among the federal and state governments in the USA (Table 2). While, Cannabis for medical use is legalized in 36 states, 4 territories, and the District of Columbia, at the federal level, its use even for medical purposes remains prohibited (Anonymous 2021b). Currently, several states have initiated legislation to decriminalize recreational use. Conceptually, the basic consequence of state legalization abolishes felony punishment or imprisonment for possessing or utilizing a minor quantity of cannabis products. Many other states continue to criminalize cannabis use or possession but do not imprison violators but impose more benign penalties such as civil fines. However, even these states may enforce a prison penalty for repetitive violations related to cannabis possession. Medically legalized marijuana/cannabis is defined as the use of cannabis products by patients with specified medical conditions under recommendations from qualifying physicians. The term "medical marijuana" implies therapeutic usage of Cannabis instead of recreational or leisure use. For medical purposes, Cannabis is available in

Table 2 The current legal status of Cannabis under the laws of the states/regions of the USA

States/regions that have legalized Cannabis only for therapeutic/medical purposes and *not for adult use* or recreational uses	States/regions that have allowed utilizing Cannabis for medical purposes and recreational use but *only by adults*. These states have decriminalized cannabis products	States/regions that have *not yet legalized* Cannabis for medicinal or recreational purposes
Alabama	Alaska	Georgia
Arkansas	Arizona	Idaho
Connecticut	California	Indiana
Delaware	Colorado	Kansas
Florida	Illinois	Kentucky
Hawaii	Maine	Mississippi
Iowa	Massachusetts	Nebraska
Louisiana	Michigan	North Carolina
Maryland	Montana	South Carolina
Minnesota	Nevada	Tennessee
Missouri	New Jersey	Texas
New Hampshire	New Mexico	Wisconsin
North Dakota	New York	Wyoming
Ohio	Oregon	
Oklahoma	South Dakota	
Pennsylvania	Vermont	
Rhode Island	Virginia	
Utah	Washington	
West Virginia	Guam	

different dosage forms and present in different concentrations of cannabinoids, in which the amount of tetrahydrocannabinol is predominant.

3 The Rationale and Justification for Legalization

Anglo-Americans and Europeans have recognized the therapeutic potential of Cannabis since the 1830s. Over that period, Sir William Brooke O'Shaughnessy, an Irish doctor researching in India, reported that cannabis extracts could relieve cholera symptoms (abdominal pain, nausea, and vomiting). In the late nineteenth Century, Americans and Europeans procured cannabis extracts from the drug stores or pharmacies and medical practitioners to treat gastric pains, migraines, inflammation, insomnia, and other pathological conditions. However, only anecdotal user reports of the efficacy of cannabis products by cannabis users to treat various medical illnesses or disorders do not prove efficacy or justify its legalization. Some recent scientific investigations have supported the assertions that cannabis products may effectively treat certain disease conditions and that these products are relatively safe. Additionally, the fact sheet on the drug by the United States Drug Enforcement Administration (DEA) imparts that "No fatality from an overdose of cannabis has been turned up" (Little 2018).

It is an interesting historical fact that the use of cannabis products was not always forbidden. The effects and frequency of cannabis consumption have been extensively studied. Several studies have established the frequency of at least day-to-day, weekly, and monthly cannabis usage. The results indicate that cannabis usage remained significantly higher in United States 'legal' states, 11.3%, 18.2%, 25.0%, respectively, than 'illegal' states, 7.4%, 11.6%, 16.8%, respectively; $p < 0.001$. In the USA, in 'legal' states, users commonly utilized significantly higher Cannabis concentrates, vaped-oils, edibles, and drinks, and consume mostly a dried herb either daily or weekly compared to individuals in 'illegal' states in the USA (Goodman et al. 2020). Additionally, the enormous program deviation across time and among states would seem to give scientists or researchers abundant prospects to quantitatively evaluate the outcome of marijuana/cannabis legalization policies on an array of health and social outcomes (Pacula and Smart 2017).

4 Regulating Agency for the Use of Cannabis in the USA

Cannabis legalization is spreading across the United States and the world. The state and national regulatory authorities are working to maintain control over various elements (Borodovsky et al. 2021). Under the CSA, Cannabis is classified as a Schedule I substance (Anonymous 21b), which means it has a high risk of abuse or addiction and has no FDA-approved medical purpose in the United States. The federal government carefully regulates Schedule I controlled substances. States,

territories, districts, and Indian tribes that have legalized Cannabis in the United States have the following cannabis regulatory bodies.

1. Drug Enforcement Administration (DEA)
2. Food and Drug Administration (FDA)
3. United States Department of Agriculture (USDA, hemp)
4. Cannabis Justice Office (grantmaking office, projected under Marijuana Opportunity Reinvestment and Expungement Act of 2019)

The Controlled Substances Act (CSA), which detailed the legal and regulatory framework for cannabis use in the United States of America under federal law, was enacted in part to carry out the Single Law's commitments (Mead 2019). Under the CSA, elements are classified into five schedules (I-V), based upon their medicinal value and ability to consequence in abuse, recreation, dependence, and addiction (Yeh 2012).

Under the CSA, "*the term 'marihuana means all parts of the plant Cannabis sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination*" (Mead 2019). Thus, cannabinoids (> 100) found in the cannabis plant are also classified in Schedule I by definition, not due to a scientific analysis of their abuse potential (Brenneisen 2007).

In the USA, substances in Schedule 1 are considered to have a high potential for abuse, hence are not allowed even for medical use. However, there is no such restriction for substances in Schedule II for medical purposes. Substances in Schedules III–V has less potential for abuse and are allowed for medical use (DEA 2021). However, the concept of accepted medical use is still not precisely defined by CSA in any schedule. However, the United States Drug Enforcement Administration (DEA) has developed criteria that must be met to establish access (Harris 2014).

The following indicates the laws by state, depending on age-based use of Cannabis and possession limits in the United States of America (Anonymous 2021b).

4.1 Alabama

A person under the age of 19 is not allowed to buy or use medical Cannabis with more than 3% of THC in the Cotton State, Yellowhammer State (Alabama). Concerning the medical usage, not more than 70 regular dosages, as defined by a medical doctor, may not go above 50 mg of THC except to a larger extent is

considered medically required. Recreational use of Cannabis is not allowed in the state of Alabama.

4.2 Alaska

There are no specific age restrictions for medical use, and if under age 21, not allowed to buy, acquire, or utilize recreationally. The possession limit is no more than 1 ounce (One ounce = ~ 28.35 g).

4.3 Arizona

There are no specific age restrictions in the Grand Canyon State (Arizona), and limits are no more than 2.5 ounces for medical use. Cannabis for recreational use is not allowed for a person under the age of 21. However, for persons over the age of 21, the limit is no more than 1 ounce (with a limit of 5 g marijuana concentrate).

4.4 Arkansas

If a person is under age 21, not permitted to smoke medical marijuana in the Natural State (Arkansas), and over age 21, the quantity is no more than 2.5 ounces for medical use. Arkansas does not currently allow the usage of Cannabis as a recreational drug.

4.5 California

There are no specific age restrictions in the Golden State (California) for medical purposes, and restrictions are not more than 8 ounces unless a more significant amount is medically needed. For recreational, if under age 21, not permitted. Moreover, for the rest, the limit is no more than 28.5 g of Cannabis, not in the type of concentrated Cannabis and no more than 8.0 g of concentrated Cannabis.

4.6 Colorado

If under age 18, not allowed to smoke medical marijuana in the Centennial State (Colorado), the limit is no more than 2 ounces except a larger amount is medically

necessary for the therapeutic purpose. Recreationally, if under age 21, not authorized, and for the rest, the limit is no more than 2 ounces.

4.7 Connecticut

If under age 21, only for medical use, cannot smoke medical marijuana. The limit is not specific but not to surpass an extent reasonably needed to ensure uninterrupted availability for 1 month. Connecticut (Nutmeg State, Constitution State) does not currently allow Cannabis as a recreational drug.

4.8 Delaware

For medical use, if under age 18, patients may use only medical marijuana oil in the First State, Diamond State (Delaware) and specifically for specified unbearable conditions and symptoms with the limit of not more than 6 ounces. Delaware does not currently allow the usage of Cannabis as a recreational drug.

4.9 Florida

There are no specific age restrictions in the Sunshine State (Florida) for medical use. The limit is a 70-day supply or 4 ounces in a form for smoking unless a more significant amount is medically needed. Florida does not currently allow the usage of Cannabis as a recreational drug.

4.10 Georgia

There are no specific age limitations in the Peach State, Empire State of the South (Georgia). The limits are no more than 20 fluid ounces of specific cannabis product that comprises 5% THC for medical use. Georgia does not currently allow the usage of Cannabis as a recreational drug.

4.11 Hawaii

There are no specific age limitations in the Aloha State (Hawaii), and the restriction is no more than 4 ounces for therapeutic purposes. Hawaii does not currently allow the usage of Cannabis as a recreational drug.

4.12 Illinois

For medical use, if under age 18, patients may use for seizures or as required by administrative rule in the Prairie State, Land of Lincoln (Illinois). For persons under the age of 21, use for recreational purposes is not permitted. However, for a medical cause, they are allowed no more than 2.5 ounces of cannabis-based products. For persons above 21 years of age, the limit is 30 ounces of cannabis flower, 500 mg of THC in the cannabis-based product, and 5 g of Cannabis concentrates.

4.13 Indiana

There are no specific age limitations in Hoosier State (Indiana). However, the restriction is for cannabis product that comprises no more than 0.3 percentage THC for medical use. Indiana does not currently allow the usage of Cannabis as a recreational drug.

4.14 Iowa

There are no specific age limitations in the Hawkeye State, Corn State (Iowa) for medical use. The limit is no more than 4.5 g in 90 days unless a more significant amount is considered therapeutically required. Iowa does not currently allow the usage of Cannabis as a recreational drug.

4.15 Kansas

There are no specific age limitations in the Sunflower State, Jayhawker State state (Kansas). However, a particular cannabis product that comprises no more than 5 percent THC comparative to the cannabidiol concentration in the preparation can be used medically. Kansas does not currently allow the usage of Cannabis as a recreational drug.

4.16 Kentucky

There are no specific age limitations in the Bluegrass State (Kentucky) for therapeutic use. However, a cannabis product from industrial hemp can be used after a physician's written order is approved as an FDA prescription. Kentucky does not currently allow the usage of Cannabis as a recreational drug.

4.17 Louisiana

There are no specific age limitations in the Pelican State, Creole State, Sugar State (Louisiana) for medical use. However, THC levels should be diminished to the lowest possible acceptable medicinal concentrations accessible. Louisiana does not currently allow the usage of Cannabis as a recreational drug.

4.18 Maine

There are no specific age limitations in the Pine Tree State (Maine). However, the limit is up to 2.5 ounces. For recreational use, if the age is under 21, not permitted to use, the rest limit is up to 2.5 ounces.

4.19 Maryland

There are no specific age limitations in the Free State, Old Line State (Maryland) for therapeutic use. However, no more than a 30-day supply except to a greater extent is considered medically crucial. Maryland does not currently allow the usage of Cannabis as a recreational drug.

4.20 Massachusetts

There are no specific age limitations in the Bay State, Old Colony State (Massachusetts) for medicinal use, but no more than a 60-day supply, up to 10 ounces or as defined by the cannabis control commission. For recreational purposes, if under age 21, not authorized to acquire or use, and for the rest, not more than 1 ounce; within the person's primary residence, not more than 10 ounces.

4.21 Michigan

There are no specific age limitations in the Wolverine State, Great Lake State (Michigan) for medicinal use, although no more than 2.5 ounces. For recreational purposes, if under age 21, not permitted to use. For others, no more than 2.5 ounces within the person's residence, no more than 10 ounces.

4.22 Minnesota

There are no specific age limitations in the North Star State, Gopher State, Land of 10,000 Lakes, Land of Sky-Blue Waters (Minnesota) for medicinal use, though no more than a 30-day supply. Minnesota does not currently allow the usage of Cannabis as a recreational drug.

4.23 Mississippi

There are no specific age limitations in the Magnolia State (Mississippi) for therapeutic usage, even though no more than 2.5 ounces. Mississippi does not currently allow the use of Cannabis as a recreational drug.

4.24 Missouri

Specific medicinal-based use limitations are there for patients under the age of 18. These patients may not acquire or occupy marijuana in Show Me State (Missouri). Furthermore, at least a 60-day supply, though qualifying patients who can grow marijuana may acquire up to a 90-day supply. Missouri does not currently allow the usage of Cannabis as a recreational drug.

4.25 Montana

Certain medicinal-based use restrictions exist for patients under 18 in Treasure State, Big Sky Country (Montana). These patients are permitted marijuana-infused products up to 1 ounce. Persons under age 21 are not allowed to use Cannabis for recreational purposes. For others, the limit is 1 ounce with 8 g of marijuana concentrate or 800 mg of THC content in the edible marijuana products in solid form.

4.26 Nevada

There are no age restrictions for therapeutic usage in Silver, Sagebrush, and Battle Born State (Nevada). However, the limit is 2.5 ounces in 14 days unless a more significant amount is deemed medically necessary. For recreational purposes, if under age 21, not allowed to acquire or use. For the rest, the limit is 1 ounce.

4.27 New Hampshire

There are no specific age restrictions in the Granite State (New Hampshire) for therapeutic use, even though no more than 2 ounces. New Hampshire does not currently allow the usage of Cannabis as a recreational drug.

4.28 New Jersey

There are no particular age limitations in the Garden State (New Jersey) for medicinal use. At the same time, no more than 3 ounces in 30 days except to a more significant extent is medically necessary. If under age 21, recreational use is not permitted currently.

4.29 New Mexico

A 3-month supply as possession limit is allowed in the Land of Enchantment, Sunshine State (New Mexico) for medicinal use. About the recreational use, if a person is under age 21, not permitted. For the rest, the limit is 2 ounces of Cannabis, 16 g of a cannabis extract, and 800 mg of edible Cannabis outside the residence.

4.30 New York

For therapeutic purposes in the Empire State (New York), no more than a 60-day supply of the dosage of Cannabis is recommended by a medical practitioner. Moreover, a patient can keep no more than 5 pounds of Cannabis in their residence. For recreational use, persons under the age of 21, not allowed to use Cannabis. For others, the limit is 3 ounces of Cannabis, 24 g of Cannabis concentrate. Within a person's private residence, the limit is 5 pounds of Cannabis.

4.31 North Carolina

There are no specific age restrictions in the Tar Heel State, Old North State (North Carolina) for therapeutic use. While specified and some cannabis product, which comprises not more than 0.9 percent THC can be used for medical purposes. North Carolina does not currently allow the usage of Cannabis as a recreational drug.

4.32 North Dakota

For medical purposes in the Flickertail State, Sioux State, Peace Garden State (North Dakota), patients under 19 can utilize "pediatric medical marijuana". Pediatric medical marijuana includes not more than 6% THC, and the possession limit is no more than 3 ounces, except an amount up to 7.5 ounces is medically required. North Dakota does not currently allow the usage of Cannabis as a recreational drug.

4.33 Ohio

There are no particular age restrictions in the Buckeye State (Ohio) for therapeutic use, although the limitation is for possession is not more than a 90-day supply. Ohio does not currently allow the usage of Cannabis as a recreational drug.

4.34 Oklahoma

There are no specific age limitations in the Sooner State (Oklahoma) for medicinal utilization. However, the limit for possession is 72 ounces of edible Cannabis and 3 ounces of Cannabis on the person. This limit is 8 ounces of marijuana and 1 ounce of Cannabis concentrated within the residence. Oklahoma does not currently allow the usage of Cannabis as a recreational drug.

4.35 Oregon

If a person is under 18, they are not permitted to produce medical Cannabis in the Beaver State (Oregon). However, for medical use, one can use no more than 24 ounces of Cannabis. For recreational purposes, if the age is under 21, not authorized to purchase, acquire, or use. For others, the limit is 8 ounces of usable

Cannabis, 16 ounces of cannabinoid products in solid, 72 ounces of cannabinoid products in liquid form, and 16 ounces of cannabinoid concentrate.

4.36 Pennsylvania

No particular age restrictions are required in the Keystone State (Pennsylvania) for medicinal use, though no more than a 30-day supply is possession limit. This state does not currently allow the usage of Cannabis as a recreational drug.

4.37 Rhode Island

Though there are no specific age limitations in the Ocean State, Little Rhody (Rhode Island), for medicinal use, possession is limited to 2.5 ounces of wet Cannabis as defined by the departments of health and business regulation. Rhode Island does not currently allow the usage of Cannabis as a recreational drug.

4.38 South Carolina

There are no specific age restrictions in the Palmetto State (South Carolina) for therapeutic use, and this applies only for the specified cannabis product containing $<0.9\%$ THC. South Carolina does not currently allow the usage of Cannabis as a recreational drug.

4.39 South Dakota

There are no specific age restrictions in The Mount Rushmore State (South Dakota) for medicinal usage, and this applies for all cannabis products no more than 3 ounces. For recreational purposes, if the age under is 21, not permitted to acquire and use Cannabis. For the rest, the limit is 1 ounce consisting of a maximum of 8 g cannabis concentrate.

4.40 Tennessee

There are no specific age limitations in the Volunteer State (Tennessee) for therapeutic usage, and this applies only for the specified cannabis product that contains

less than 0.9 percent THC. Tennessee does not currently allow the use of Cannabis as a recreational drug.

4.41 Texas

There are no specific age limitations in the Lone Star State (Texas) for medicinal use, and this applies only for specified cannabis products containing no more than 1% THC. Texas does not currently allow the usage of Cannabis as a recreational drug.

4.42 Utah

For medical usage in the Beehive State (Utah), if under 18, they may only be eligible for a provisional patient card. The possession limit is an amount enough for 30 days of treatment. The upper limit of unprocessed Cannabis is 113 g comprising not more than 20 g of THC. Utah does not currently allow the usage of Cannabis as a recreational drug.

4.43 Vermont

There are no specific age restrictions in the Green Mountain State (Vermont) for medical treatment, yet no more than 2 ounces is allowed. Moreover, persons under 21 are not permitted for recreational use, while the limit is 1 ounce for others.

4.44 Virginia

There are no specific age limitations in the state of The Old Dominion, Mother of Presidents (Virginia) for medicinal treatment. People can use more than one cannabis product, CBD oil, etc., with a limit of 4 ounces of botanical Cannabis per 30-day period. For recreational use, persons below 21 of age are not permitted to consume Cannabis. For above 21, the limit is 1 ounce of Cannabis.

4.45 Washington

For medical use in the Evergreen State, Chinook State (Washington), if under 18, possession limits are 48 ounces of cannabis-infused product (solid) comprising

3 ounces of useable cannabis. The upper limit for cannabis-infused products (liquid) is 216 ounces or 21 g of marijuana concentrate. There could be exceptions in the case of medical necessity. For recreational use, people below 21 of age are not permitted. For the rest, limitations are 1 ounce of useable Cannabis, 16 ounces of cannabis-infused product (solid), 72 ounces of cannabis-infused product (liquid form), and 7 g of cannabis concentrate.

4.46 West Virginia

There is no specific age limitation in the Mountain State (West Virginia) for medicinal use, but no more than a 30-day supply. This state does not currently allow the usage of Cannabis as a recreational drug.

4.47 Wisconsin

There is no particular age restriction in the Badger State, America's Dairyland (Wisconsin) for therapeutic use. Cannabis products without a psychoactive effect can be used for medicinal use. This state does not currently allow the usage of Cannabis as a recreational drug.

4.48 Wyoming

There are no specific age restrictions in the Equality State (Wyoming) for medicinal purposes for cannabis products that contain less than 0.3 percent THC. Wyoming state does not currently allow the usage of Cannabis as a recreational drug.

5 Conclusion

In the USA, cannabis use and possession laws vary among the states/regions and are continually evolving. The doses and forms of cannabis and cannabis products vary among the age groups. Therefore, more than knowing which states have legalized the products, it is crucial to know the amount authorized to possess, whether it may be shipped, and who is permitted to use it. Thus, the legality of Cannabis for therapeutic and recreational usage in the US remains controversial and continually evolving. However, increasing scientific research and evidence-based knowledge on Cannabis will significantly impact policies concerning the use of Cannabis, and cannabis-infused products.

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Cannabis in Healthcare: Ethnobotanical and Pharmaceutical Perspectives and Legal Status in Turkey and the Middle East

Nadire Özenver

Abstract Cannabis refers to the plants in the genus *Cannabis* (Cannabaceae) and has been used traditionally for assorted purposes by human beings since ancient times. In addition to the ethnobotanical aspects, cannabis- associated products were evidenced to possess numerous beneficial effects on health, suggesting its therapeutic potential. On the other hand, these products exert adverse effects, which may constitute incontrovertibly detrimental outcomes and limit its use by communities. Therefore, cannabis cultivation, use, and traffic are mostly illegal globally although people have attributed a great value to cannabis throughout history. In the present chapter, cannabis will be mentioned in terms of ethnobotanical and pharmaceutical perspectives. Besides, the cannabis situation in Turkey and the Middle East will be explained. The importance of cannabis, in particular for medical purposes, will be emphasized in the light of current scientific data. Thus, a notion concerning the positive and negative impacts of cannabis-based substance use on health together with a future perspective providing the potential of cannabis-based therapeutics for public health will be discussed.

Keywords Cannabis · Tetrahydrocannabinol · Cannabinoid · Ethnobotany · Effects of cannabis · Cannabis situation in Turkey

Abbreviations

CB1	Cannabinoid receptor type 1
CB2	Cannabinoid receptor type 2
CBD	Cannabidiol
CDC	Centers for Disease Control and Prevention
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration

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MHRA	Medicines and Healthcare products Regulatory Agency
PD	Parkinson's disease
SAMHSA	Substance Abuse and Mental Health Services Administration
THC	Delta-9 tetrahydrocannabinol
WHO	World Health Organization

1 Introduction

Cannabis is one of the most valuable plants representing an undeniable part of human culture for millennia globally. Despite the general overview as a "drug plant", cannabis is used for assorted purposes such as medicine, food, fiber, paper, etc. (Clarke and Merlin 2013). Cannabis is the most extensively cultivated, trafficked, and abused illicit drug as nearly 147 million people covering 2.5% of the world's inhabitants use up cannabis annually, while the ratio of individuals consuming either cocaine or opiates is 0.2% (World and Health Organization 2021). According to the World Health Organization (WHO), several descriptions exist in the terminology germane to cannabis. To clarify, cannabis is a generic term specifying various psychoactive preparations of the plant *Cannabis sativa*, while the Mexican term "Marijuana" is mostly denoting cannabis leaves or other crude plant material. Furthermore, unpollinated female plants are termed hashish, whereas cannabis oil is referring to a concentrate of cannabinoids gained via solvent extraction of the resin or the raw plant material. Delta (Δ)-9 tetrahydrocannabinol (THC) is the substantial psychoactive compound in cannabis and the compounds structurally similar to THC are assigned as cannabinoids (World and Health Organization 2021). Despite the terms cannabis and marijuana slightly differ in reference to WHO, both usually hold the same denotation and are used interchangeably, indeed. The results from the 2015 National Survey on Drug Use and Health indicated that cannabis is by far the most widely used illicit drug in the United States, with nearly 22.2 million users (Substance Abuse and Mental Health Services Administration (SAMHSA) 2016; Centers for Disease Control and Prevention (CDC) 2021).

According to the comprehensive book on cannabis edited by Clarke and Merlin (2013), many names are available in order to express the plant of interest such as "weed", "hemp", "marijuana" and "cannabis". If people call the plant a weed, they may refer to a plant growing where it is undesirable. Others describe a weed as a plant that has got away from cultivation. Because cannabis was known to escape from fields as a savage plant. The term "hemp" still formally points to *Cannabis sativa* that is substantially cultured for its bark fiber. Although hemp has been employed as a corporate name of many fiber-containing plants, "true hemp" mentions cannabis, or more specifically European *C. sativa*. Another expression "marijuana" refers to either the plant or the dried flowers and leaves that are smoked for the alteration of mentality. The word "sinsemilla" mentions seedless marijuana. Numerous conversational or cultural names with a special focus on their mind-

altering property are further of existence such as grass, pot, hashish, *ganja*, *kif*, etc. However, scientists count all marijuana or true hemp plants in the genus *Cannabis* and currently the word "cannabis" refers to all these plants globally (Clarke and Merlin 2013).

Based on the taxonomical classification, three species were characterized as *Cannabis sativa* Linnaeus, *Cannabis indica* Lamarck, and *Cannabis ruderalis* Janisch (Cannabaceae) (Anderson 1980; Schultes et al. 1974, 2011). These three species are distinct from each other in point of psychoactive content and plant height. Besides, the existence of allozymes resulted in geographical discrimination of *Cannabis* species as *C. sativa* (European), *C. indica* (South Asiatic-African), and *C. ruderalis* (Central Asiatic) (Gilmore et al. 2003; Hillig 2005).

The plant cannabis is an annual dioecious plant, cultivated substantially in Central Asia for millennia (Farag and Kayser 2017; Russo et al. 2008). Although people have attributed a great value to cannabis throughout history, it is mostly illegal to cultivate, use and sell globally. In the present chapter, we are going to make mention of cannabis with a special focus on ethnobotanical and pharmaceutical perspectives. Besides, we are going to refer to the cannabis situation in Turkey and the Middle East. Within the context of the chapter, we aim to provide a notion about the magnitude of cannabis on health and a future perspective concerning its use, particularly for medical purposes.

2 Cannabis: Ethnobotanical Perspective

Cannabis has been used for various purposes globally throughout history. The plant is of great value representing assorted purposes for human use as a foodstuff, fiber, and pharmaceutical product (Russo 2007). Despite the controversial character of the plant, it possesses botanical, ecological, and archeological importance. Cannabis has been ordinarily used as a recreational plant drug and is a source of notorious mind-altering compounds THC and other psychoactive compounds. The stalks of cannabis may be utilized as a fuel. In addition, the persistent tissue in their outer barks may supply fiber for various purposes including furnishing, clothing, sails, rope, paper, and so on. Cannabis seeds are rich in nutrients providing food for humans and animals, and the seed oil is beneficial for cookery and heating as lamp fuel (Clarke and Merlin 2013).

Cannabis has been known for its countless traditional applications worldwide for a long time (Fig. 1). The oldest documentation associated with medicinal utilization of cannabis goes back to around 4700 before the present in China in addition to the other ancient records in India, Egypt, Persia, Greece, and Rome (Abel 1980). Starting with the Chinese around 2900 B.C., different utilizations of cannabis in both medically relevant and -irrelevant conditions have been transcribed by many cultures. For instance, in Ancient Egypt, cannabis was employed in rope making, the treatment of fungal infections, the contraction as an obstetric agent (Farlow 1889;

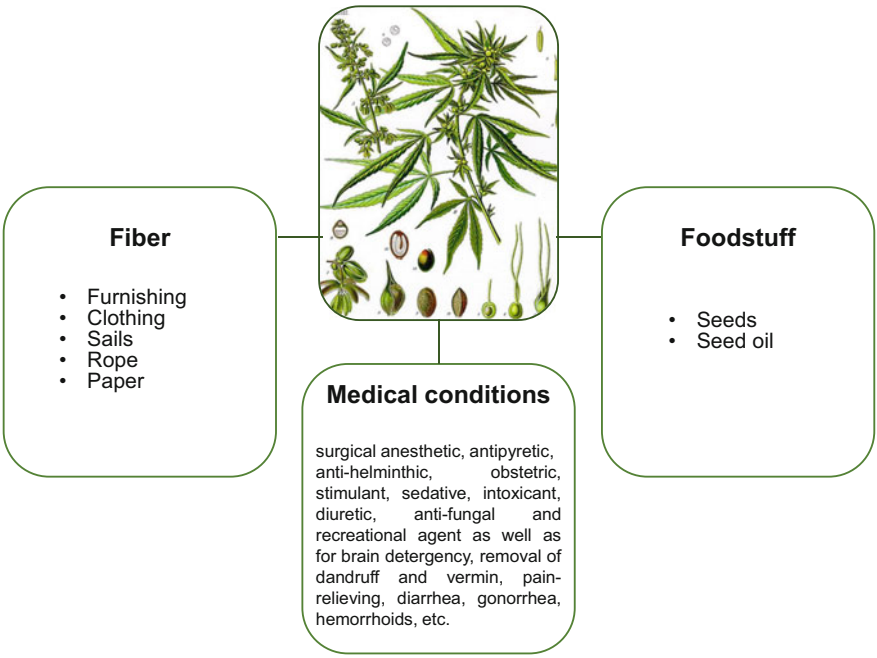

Fig. 1 Substantial traditional applications of cannabis worldwide

Faulkner 1969; Ghalioungui 1987; Manniche 1989; Russo 2007; Shafik and Elseesy 2003).

The Chester Beatty VI Papyrus dating back to 1300 B.C. indicated a set of paragraphs associated with cannabis (Bardinet 1995), which may provide a basis for its antipyretic effects, or, even quite likely, a beneficial effect on urinary incontinence (Russo 2005) or diarrhea, confirming its application in cholera intervention in nineteenth century India (O'Shaughnessy 1843; Russo 2005).

Cannabis, mixed with wine, was indicated as a surgical anesthetic in the second century in China. Crushed cannabis seeds were applied as an anti-helminthic similar to the use of which in Middle Eastern and Indian civilization (Russo 2007).

Persian medical text *Makhzan-al-Adwiya* written by M. Husain Khan in the eighteenth century, a representation of Arabic traditional medicine defined cannabis preparations as a stimulant, sedative, intoxicant, insecticide, diuretic as well as for brain detergency, removal of dandruff and vermin, pain-relieving, diarrhea, gonorrhea and so on (O'Shaughnessy 1843).

Cannabis has been existing in sub-Saharan Africa for at least 2000 years with various medical applications as a pain killer in headache and obstetrical agent (Du Toit 1980; Merwe 2011).

Cannabis has been used in Brazil for the treatment of rheumatism and toothache since the early fifteenth century (Hutchinson 1975).

Indian hemp was introduced to the West in the nineteenth century (Russo 2005). *Ganjah* and *Bhang* were used as intoxicants as well as for the treatment of diarrhea and hemorrhoids (Ainslie 1813).

In western medicine, corn plasters consisting of cannabis resin were conventional in the nineteenth and early twentieth century for sore nails (Russo 2007). Most Renaissance herbalists applied *Cannabis sativa* strains rich in cannabidiol with little or no THC content, whereas Asian *Cannabis indica* strains containing THC were employed after 1840. The *Berlin Papyrus* holding two prescriptions dated to 1300 B. C. germane to cannabis (Bardinet 1995), among which one was burned ceremonially and this remedy, in a subsequent study, was attributed to the anti-parasitic effects of cannabis (Bryan 1988). Likewise, it was included to incense burners in shamanic and religious rites before 570 C.E. (Reardon-Anderson 1986).

Cannabis has occupied a substantial place traditionally for both medically relevant or -irrelevant conditions since ancient times. Many investigations have evidenced medicinal applications of cannabis till now, providing a basis to move their traditional applications into the scientific ground for future studies.

3 Cannabis: Pharmaceutical Perspective

Recently, cannabis-based medicines have come into prominence for pharmaceutical purposes in many countries. However, there is still insufficient scientific evidence on the medical use of cannabis-associated substances as well as their affected targets in the human body. Aroma, taste, or cannabinoid content [(THC) or cannabidiol (CBD)] of cannabis type determine the property of medical intervention. The ratio of these two phytocannabinoids describes *Cannabis sativa* strains, called as either "high in CBD"/*indica*-originated (De Meijer 2014) or "high in THC"/*sativa*-originated (Hanuš et al. 2016).

The phytochemical composition of cannabis includes hundreds of different cannabinoids, terpenoids, and other cannabimimetic phytochemicals (Aizpurua-Olaizola et al. 2016; Bonini et al. 2018; Pavlovic et al. 2019; Potter et al. 2008). Recent studies have disclosed that the favorable effects of cannabis do not only linked to a single pure compound in their composition but also other secondary metabolites such as terpenoids, flavonoids, and sterols (Blasco-Benito et al. 2018; Koltai et al. 2019; Russo 2011), indicating synergistic interactions. Such synergism, termed as "entourage", may arise between cannabinoids as well as cannabinoids and terpenes (Ferber et al. 2020; Mazuz et al. 2020). Therefore, characterization and standardization of cannabis products administered in medical circumstances is an undeniable necessity in order to obtain the optimized, reproducible effect and expected outcomes.

Cannabis sativa is the substantial source to obtain cannabis and cannabis-relevant products, in the composition of which over 120 cannabinoids were generated (Turner et al. 2017). Cannabinoids broadly refer to a set of compounds that can bind to cannabinoid receptors, among which cannabinoid receptor type 1 (CB1) is

prevalent in assorted brain regions, specifically in excitatory and inhibitory neurons, while cannabinoid receptor type 2 (CB2) is broadly expressed in spleen and leukocytes (Cristino et al. 2020; Katona and Freund 2008; Kendall and Yudowski 2017; Liu et al. 2009). CB1 and CB2 are included in the G protein-coupled receptor family and are efficiently activated by the lipids anandamide and 2-arachidonoylglycerol (endocannabinoids) in the human body (Cristino et al. 2020; Mechoulam et al. 1995).

THC, the major psychoactive constituent of cannabis, exhibits physical and psychological effects that are equivalent to those of smoking cannabis (Wachtel et al. 2002). THC, in particular, interacts with the CB1 receptor in the brain, disinhibiting dopaminergic signals and thus trigerring psychoactive effects (Ketcherside et al. 2017; Lupica et al. 2004). Cannabis and THC both act through the same receptor in the brain (Iversen 2009). Cannabidiol (CBD), another major phytocannabinoid in cannabis, is not psychoactive and has been demonstrated modulating behavioral influences of THC (Englund et al. 2013; Peres et al. 2018), and possessing therapeutic effects on assorted conditions (Zuardi 2008). THC and CBD, the most important and thoroughly studied phytocannabinoids, principally function via endogenous cannabinoid receptors CB1 and CB2 (Munro et al. 1993).

The consequences of cannabis use are two-sided representing either beneficial or toxic influences. Cannabis-relevant impacts may differ based on the way of administration, the dose received, individual's previous exposure as well as the circumstances or the environment in which cannabis was used (Hall and Pacula 2003).

3.1 Acute and Chronic Effects of Cannabis on Health

Cannabis use mediates the emergence of many acute and chronic effects, affecting human health (Table 1).

Acute effects of cannabis provide positive as well as negative mood states, among which acute effects usually comprise the sense of happiness, calmness, relaxation, pensiveness, jocoseness, sociability, and creative thinking (Andrew 2017; Green et al. 2003; Warnick et al. 2021; White et al. 2015). Many of the investigations pointed out the influence of cannabis in the enhancement of appetite (Ko et al. 2016), the attenuation of pain, relieving temporary symptoms of post-traumatic distress disorder (LaFrance et al. 2020), the improvement of symptoms of attention-deficit/hyperactivity disorder (Strohbeck-Kuehner et al. 2008). Cannabis was announced to improve sports performance, particularly in extreme sports (Gillman et al. 2015), while inducing decreased physical activity in case of its chronic use (Greydanus et al. 2013). In addition to positive mood effects, cannabis may result in negative mood states including the sensation of anxiety, excitement, tenseness along with paranoia, cognitive dysfunction, suspicion, forgetfulness, and arrhythmia (Buckner et al. 2012; Coutinho et al. 2019; Ford et al. 2017; Kariyanna et al. 2019; Shrivastava et al. 2011).

Table 1 Acute or chronic influences of cannabis on health

Cannabis or -related product	Acute or chronic effect	Outcomes of cannabis or -related product	Reference
Cannabis	Acute	Positive mood states such as sense of happiness, calmness, relaxation, pensiveness, jocoseness, sociability, and creative thinking	Andrew (2017), Green et al. (2003), Warnick et al. (2021), White et al. (2015)
Cannabis	Acute	Negative mood states such as the sensation of anxiety, excitement, tenseness along with paranoia, cognitive dysfunction, suspicion, forgetfulness, arrhythmia	Buckner et al. (2012), Coutinho et al. (2019), Ford et al. (2017), Kariyanna et al. (2019), Shrivastava et al. (2011)
Cannabis	Acute and chronic	Enhancement of appetite	Ko et al. (2016)
Cannabis	Acute and chronic	The attenuation of pain	LaFrance et al. (2020)
Cannabis	Acute and chronic	The improvement of symptoms of attention-deficit/hyperactivity disorder	Strohbeck-Kuehner et al. (2008)
Cannabis	Acute and chronic	Improvement of sports performance	Gillman et al. (2015)
Cannabis	Chronic	Decreased physical activity	Greydanus et al. (2013)
Cannabis	Acute and chronic	Psychiatric effects such as anxiety, depression, stress, and psychosis	Gobbi et al. (2019), Hanna et al. (2017), Hser et al. (2017)
THC	Chronic	Alterations in the brain, leading to impaired cognitive functions and the occurrence of cannabis-associated psychiatric disorders	Lorenzetti et al. (2020), Manza et al. (2020), Weinstein and Sznitman (2020), Yanes et al. (2018), Yu et al. (2020)
THC	Acute	Psychiatric symptoms, as well as negative and psychotic effects	Hindley et al. (2020)
Cannabis	Chronic	Cannabis dependence characterized by social, physical, psychological outcomes such as inadequate life satisfaction, low self-respect, a sense of culpability, family and relationship troubles	Gruber et al. (2003), Stephens et al. (2002)
Cannabis	Chronic	Withdrawal symptoms following a surcease of cannabis use in a period of time such as insomnia, depression, anxiety, irritability, anger, appetite disturbance, somatic symptoms	Bahji et al. (2020)
Cannabis	Acute or chronic	Immunosuppressive effects providing a therapeutical approach for the treatment of autoimmune diseases and graft rejection	Eisenstein and Meissler (2015), Gonçalves and Dutra (2019), Katchan et al. (2016), Namdar and Koltai (2018)

Acute and chronic uses of cannabis were demonstrated to be associated with psychiatric outcomes such as anxiety, depression, stress, and psychosis (Gobbi et al. 2019; Hanna et al. 2017; Hser et al. 2017). Outcomes of epidemiological and experimental investigations in rodents or humans unraveled that psychiatric effects depend on (1) cannabinoids type (*e.g.* THC is attributable to the emergence of cognitive and psychiatric effects while CBD is less prone to these effects or even it may antagonize these effects), (2) the continuance and level of exposure, (3) individual susceptibility, (4) the age of exposure (Curran et al. 2019; Krebs et al. 2019; Mandolini et al. 2018). The chronic aspect of THC may encompass changes in the brain (Manza et al. 2020; Yanes et al. 2018), leading to impaired cognitive functions and the occurrence of cannabis-associated psychiatric disorders (Lorenzetti et al. 2020; Weinstein and Sznitman 2020; Yu et al. 2020). Confirmingly, a recently published systematic review and meta-analysis highlighted the potential risks of THC-containing cannabis and other cannabinoids for recreational use. Psychiatric symptoms, as well as negative and psychotic effects of a single THC application, were interpreted (Hindley et al. 2020).

Chronic use of cannabis was characterized as nearly daily use of cannabis for a period of time (Budney 2006; Budney et al. 2007). Cannabis dependence is represented by losing control of cannabis use and getting trouble in the termination of their use despite its harmful effects. Individuals with cannabis dependence suffer from social, physical, psychological outcomes such as inadequate life satisfaction, low self-respect, a sense of culpability, family and relationship troubles (Gruber et al. 2003; Stephens et al. 2002). They face withdrawal symptoms following a surcease of cannabis use in insomnia, depression, anxiety, irritability, anger, appetite disturbance, somatic symptoms (Bahji et al. 2020).

In contrast to the potentially harmful effects of cannabis and cannabis-containing products as immunosuppressive agents on individuals with cancer, immunosuppressive property of which may still render a therapeutic capacity for the treatment of inflammatory and autoimmune diseases. Emerging evidence was immunosuppressive effects of cannabinoids through the CB2 receptor which is predominantly expressed by the cells of the immune system. Cannabis-based products may target this receptor in immune system under over-activated circumstances and may selectively interact with CB2, paving the path for the discovery of selective CB2 agonists that may possess therapeutic value for the treatment of autoimmune diseases and graft rejection where the immune system is over-active (Eisenstein and Meissler 2015; Gonçalves and Dutra 2019; Katchan et al. 2016; Namdar and Koltai 2018).

3.2 Potential Adverse Effects of Cannabis on Health

The legalization of cannabis for medical and recreational purposes remains a controversial issue due to its potential adverse and therapeutic effects on health. Several adverse effects regarding the use of cannabis or cannabis-relevant products have been reported until now (Fig. 2). The scientific community is still under debate

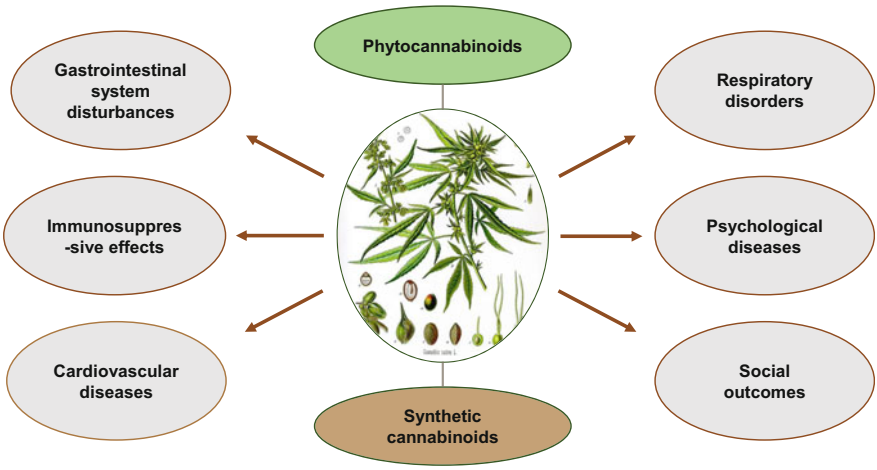

Fig. 2 Major adverse effects of cannabis and cannabis-related products

regarding its safety despite its increased utilization by the public. The regular intake of cannabis, specifically during adolescence, holds a substantial prominence in that this age group may be pertinent to an enhanced possibility of deleterious outcomes. Adverse effects of cannabis use differ based on the duration of exposure. Short-term uses may lead to impaired short-term memory, impaired motor coordination, altered mind, and even, paranoia and psychosis at high doses. In case of long-term or heavy use, and addiction, cognitive deterioration, impaired respiratory function, unsatisfactory educational performance, lessened life satisfaction, and accelerating risk of chronic psychosis disorders have been reported (Cohen et al. 2019; Hall and Solowij 1998; Lynskey and Hall 2000; Tartaglia et al. 2017; Underner et al. 2013; Volkow et al. 2014).

The substantial reason behind cannabis intake especially among the young population is the sense of reaching a so-called high, characterized by relaxation, perceptual changes, mild euphoria (Green et al. 2003), and increased laughing, talkativeness, sociableness in a social manner (Iversen 2009).

Reproductive effects of cannabis use were also have been resporte in several animal and human studies. Despite malformations and growth retardation that occurred in animals, no increased risk of birth defects was monitored among women consuming cannabis but only eased birthweight (Fergusson et al. 2002). On the other hand, the possibility of the emergence of mild developmental abnormalities, some behavioral problems, poor performances on verbal skills, and memory were indicated in children born to cannabis consumers (Corsi et al. 2020; Fried and Smith 2001; Goldschmidt et al. 2000).

Cannabis dependence and withdrawal syndrome constitute another noteworthy issue in that they cause negative consequences on physical, social, psychological conditions among adolescents and adults (summarized above in Sect. 3.1) (Budney et al. 2007). An association was reported between cannabis use and violence when

the persistence of cannabis exposure was more than once in individuals (Dugré et al. 2017). Many epidemiological studies pointed out higher rates of motor vehicle accidents if users drive while intoxicated (Li et al. 2012; Mura et al. 2003; Ramaekers et al. 2004).

Cannabis use has been reported to be linked with the development of several respiratory and immune-related adverse effects until now. These were revealed to comprise symptoms of chronic bronchitis and to lead to lower respiratory infection, functional changes in lung alveolar macrophages as well as the substantial immune-effector cells in the distal lung, and even to cause malignancy (Gates et al. 2014; Hancox et al. 2010; Tashkin et al. 2002). A dose-dependent association between cannabis smoking and airflow obstruction was shown, suggesting an impaired pulmonary function (Aldington et al. 2007; Owen et al. 2014).

Many case reports have documented the associations between cannabis use and an increased risk of cardiovascular diseases so far. For instance, the risk of the occurrence of acute myocardial infarction, heart failure, and ischemic stroke increased in users in comparison to those of nonusers (Kalla et al. 2018; Melaragno et al. 2021).

Cannabinoids exert immunosuppressive effects, holding a biphasic role as either providing a therapeutic function against inflammatory and autoimmune diseases or worsening the conditions of people with cancer (Bar-Sela et al. 2020; Blázquez et al. 2006).

A systematic study comprising 23 randomized controlled trials and 8 observational studies indicated adverse effects of medical cannabinoid use on the gastrointestinal system, which are vomiting, nausea, diarrhea, gastroenteritis, duodenal ulcer, abdominal pain, and constipation (Wang et al. 2008).

3.3 Cannabis as a Therapeutic Agent: Clinical Studies

Cannabis is particularly rich in various cannabinoids, among which tetrahydrocannabinol (THC) is the most prominent one and concerns its psychoactive properties. Cannabinoids are described as endogenous cannabinoids, phytocannabinoids, and synthetic cannabinoids. Endogenous cannabinoids exist in animals and humans, phytocannabinoids are generated in the cannabis plant, and synthetic cannabinoids are produced in a laboratory (Sarfaraz et al. 2008). Specific cannabinoids possess unique pharmacological characters leading to the development of assorted drugs which can be used either for their cognitive functions or other purposes. The US Food and Drug Administration (FDA) has approved the use of few cannabinoids until now (Table 2). To exemplify, nabilone and dronabinol, synthetic cannabis-related drug products, were approved for chemotherapy-induced nausea and vomiting in 1985 in addition to the further indication of dronabinol in appetite stimulation (*e.g.* circumstances that cause weight loss such as AIDS) in 1992. Another example, cannabis-derived drug product CBD was approved by the FDA for the treatment of Dravet syndrome and Lennox-Gastaut syndrome in patients two

Table 2 Cannabis-based products approved by regulatory authorities for medical purposes

Cannabis-based product	Containing substance	Relevant application	Approving regulatory authority	Reference
Nabilone	Synthetic cannabinoid	Chemotherapy-induced nausea and vomiting	FDA	Hill (2019), Food and Drug Administration (FDA) (2021)
Dronabinol	Synthetic cannabinoid	Chemotherapy-induced nausea and vomiting as well as in the conditions that cause weight loss such as AIDS to stimulate appetite	FDA	Hill (2019), Food and Drug Administration (FDA) (2021)
Cannabidiol	Phytocannabinoid	Management of Dravet syndrome and Lennox-Gastaut syndrome in patients 2 years of age and older	FDA	Devinsky et al. (2017), Thiele et al. (2018), Hill (2019), Food and Drug Administration (FDA) (2021)
Nabiximols	A complex botanical formulation that contains the principal cannabinoids THC and CBD in addition to specific minor cannabinoids and other non-cannabinoid component	Multiple sclerosis	MHRA	GW Pharmaceuticals (2020), Sastre-Garriga et al. (2011)

years of age and older (Devinsky et al. 2017; Food and Drug Administration (FDA) 2021; Hill 2019; Thiele et al. 2018).

Cannabis-related drugs have come into prominence providing a broad-spectrum action so far. Sativex® (GW Pharmaceuticals Ltd., Cambridgeshire, UK), a cannabinoid-based medicine combining botanical extracts enriched with THC and CBD, was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) for the intervention of pain and spasticity in patients with multiple sclerosis (GW Pharmaceuticals 2020; Sastre-Garriga et al. 2011) (Table 2), operating through cannabinoid receptors-irrelevant antioxidant mechanisms (Moreno-Martet et al. 2014).

Many clinical studies demonstrate the potential use of cannabis and cannabis-associated substances in medical conditions. For instance, cannabinoids are usually referred to as efficient agents in the management of pain. A number of meta-analyses exist indicating the role of cannabinoids in acute or chronic pain. According to the systematic review and meta-analysis published by Gazendam et al. (2020), 678 patients with acute pain receiving oral (5 trials) and intramuscular (1 trial)

cannabinoids experienced reduced pain, with intramuscular administration inducing a greater decrease in comparison to oral-based on low-quality evidence. However, evaluated in higher quality, the requirement of long-term randomized-controlled trials was emphasized (Gazendam et al. 2020). Many investigations have unraveled the capacity of cannabis preparations as efficacious agents in the intervention of chronic pain despite the presence of legal and ethical issues and the probability of potential harms tied to cannabis (Aviram and Samuelly-Leichtag 2017; Guillouard et al. 2020; Iskedjian et al. 2007; Martín-Sánchez et al. 2009; Whiting et al. 2015).

Recent clinical studies have been examining the anti-convulsant property of CBD along with its safety profile. Many clinical investigations are of existence underlining CBD in reducing severity and frequency of seizures as well as associated adverse effects in various treatment-resistant pediatric epilepsies (Devinsky et al. 2018; Gofshteyn et al. 2017; Szaflarski et al. 2018).

Likewise, the effects of cannabis-based medicines relative to those for placebo for chronic pain, cannabinoids have been evidenced to alleviate subjective chronic pain of patients arising from various medical conditions based on meta-analytic outcomes. Meta-regression results further indicated that drug administration condition and sample size are important factors in patients' responses affecting pain reduction properties (Yanes et al. 2019). Another study conducted by Johal et al. (2020) assessed the outcomes of 4006 patients participating in thirty-six trials, in which individuals examined smoked cannabis (4 trials), oromucosal cannabis spray (14 trials), and oral cannabinoids (18 trials). Relative to placebo, cannabinoids demonstrated a critical decrease in pain which was greatest in the case of the therapy duration of 2–8 weeks, suggesting moderate evidence tied to the use of cannabinoids in the treatment of chronic, non-cancer pain at 2 weeks (Johal et al. 2020).

A phase 2 placebo-controlled clinical study of a proprietary THC: CBD combination possessed an 83% one-year survival rate in comparison to 53% for patients with glioma in the placebo group. Median survival for the placebo cohort was 369 days, which is extremely shorter than the THC: CBD group with above 550 days of survival (GW Pharmaceuticals 2017).

Numerous clinical studies have examined the role of CBD in Parkinson's disease (PD) to discover a multimodal approach integrating both the dopaminergic and non-dopaminergic systems. Affecting multiple targets in the central nervous system, CBD was demonstrated to represent a potential lead for PD, providing therapy options not only for motor symptoms but also for non-motor symptoms, among which only motor features of PD may be repaired by conventionally used dopaminergic drugs (Rieder 2020). An endocannabinoidome mediator palmitoylethanolamide exhibited supportive effect as adjuvant therapy in patients with PD and provided efficient therapy when co-micronized together with antioxidants for assorted pathological conditions represented by pain, neurodegeneration, and neuroinflammation (Brotini et al. 2017; Petrosino and Di Marzo 2017). In another clinical study, emerging evidence proved the role of the endocannabinoid palmitoylethanolamide in the enhancement of lung function in people suffering from amyotrophic lateral sclerosis (Palma et al. 2016).

Cannabis and cannabis-relevant products have been widely used by individuals and examined in many studies to date. Scientists conclude that further evidence via larger, well-designed trials is warranted to disclose the actual balance of profits or damages of cannabis-based drugs in conventional medicine.

4 Cannabis Situation and Its Legal Status in Turkey and the Middle East

Legitimation of non-medical use of cannabis, and sale holds vital importance in substance use policy for many years. The influence of legalization is a miscellaneous procedure rather than a single occasion based on the regulation of legal markets. Growing jurisdictions have legalized the non-medical use of cannabis in many countries. For instance, Canada in 2018 and the numerous US states starting in 2012 regulated markets concerning product standards, labeling, and caution, level of public education, retail policies, marketing, and taxation (Anonymous 2019; Government of Canada 2018; Hammond et al. 2020).

In Anatolian, psychoactive compounds- bearing cannabis have been cultivated and used for various purposes in different fields such as health, food, and textile (Akgür and Aydoğdu 2018). Turkey is a critical transit point between Europe and the Middle East. It also holds a profound significance in that it is a key point on the Balkan drug trafficking route. According to the data regarding illegal substances and prevalence studies of Turkey published by the Turkey Drugs and Drug Addiction Monitoring Center, cannabis is the most commonly used illicit substance in Turkey, despite being on the list of prohibited drugs to be trained, used, or sold under the Turkish Penal Code (Aldemir et al. 2020; Ates and Banazili 2020; Türkiye Uyuşturucu ve Uyuşturucu Bağımlılığı İzleme Merkezi 2017).

In contrast to the increased legalization status of cannabis throughout the world, cannabis cultivation areas in Turkey have decreased (Aldemir et al. 2020; Temel et al. 2018). Under the "Regulation on Cannabis Breeding and Control" published by Official Gazette in 2016, cannabis cultivation can be carried out in 19 provinces and in all districts of these provinces in various regions that differ in terms of climate, depending on special permission in our country (Kenevir Yetiştiriciliği ve Kontrolü Hakkinda Yönetmelik 2016). Turkey evaluates cannabis to possess a very high addictive potential and is among the substances that do not have medical uses or are used with restrictions in very limited areas. Based on the TEK Convention on narcotic drugs to which Turkey put signature in 1966, cannabis was assessed to possess a very high addictive potential and be among the substances that do not have medical uses or be used with restrictions in very limited areas (Anonymous 1961). According to Article 191 of the Turkish Penal Code, the person who purchases the drugs (cannabis, heroin, cocaine, etc.) for personal use, accepts the drug in any way and keeps it for use, commits the crime of using or possessing drugs. In addition, it has been reported that the cultivation of cannabis exclusively for making cannabis

and the issuance, import, export, and sale of cannabis in any way are prohibited under the legal regulations (Anonymous 2009; Türk Ceza Kanunu 2004).

When it comes to the Middle East, the use of cannabis is mostly forbidden although the legal landscape of cannabis has strikingly altered over the last few years globally. For instance, over 20 countries have legitimized the medical use of cannabis in the world. In the USA, more than 30 states have legalized the medical use of cannabis, in addition to 10 states allowing its recreational use (Levinsohn and Hill 2020). Among the Middle East countries, only Lebanon legitimated cannabis for both medical and industrial purposes in 2020, thus, representing the first Arab country legalizing cannabis in the Middle East (Shirah and Ahmed 2020). Cannabis and cannabis-derived products are still entirely prohibited in other Middle Eastern and Arab countries (Jaffal et al. 2020).

The utilization of illicit drugs is banned due to becoming detrimental in Islamic culture. Likewise, cannabis or any drug with psychoactive property is religiously banned if used for recreational purposes in Islam. However, it permits the use of cannabis as well as narcotic drugs in the case of medical conditions such as anesthesia and pain control. Thus, Islam legalizes cannabis for medical uses allowing the prescription of cannabis and cannabis-relevant products by health professionals (Robinson et al. 2020). The middle East and Arabic countries lack relevant data about the medical use of cannabis due to limited scientific research and financial support. Therefore, further studies are needed to represent evidence about the medical use of cannabis and cannabis-derived products in Islam countries to legalize their use.

Despite strict restrictions and legal regulations regarding cannabis cultivation for medical purposes in Turkey and the Middle East, industrial hemp cultivation has attracted attention to obtain both fiber and seed for the last ten years. The growing interest in industrial hemp arises from preferences for natural products and environmentally friendly products, especially in North America and Western Europe (Wang and Shi 1999).

Cannabis cultivation and the use of products obtained from cannabis in Turkey date back to the Ottoman Empire period. Assorted materials needed for the navy (e.g. ropes) were produced from cannabis. In the Ottoman Empire, numerous provinces came to the fore in cannabis generation. However, there was a decrease in cannabis production after World War I. Although cannabis production decreased in the first years of the Republic compared to the previous years, efforts were made to revive the production by bringing experts from Europe. In the first years of the Republic, Turkey ranked tenth in the world with 10,000 tons of cannabis production (Aydoğan et al. 2020). According to 2017 data of the Food and Agriculture Organization of the United Nations (FAO), industrial hemp was grown in 16 countries to produce fiber and in 12 countries to produce seed worldwide. Evaluated hemp growing countries and planting areas by FAO, cannabis cultivation has been quite limited for obtaining fiber and seed in Turkey thus far, which is similar to the situation in the Middle East (Aydoğan et al. 2020; FAO 2017). Cannabis cultivation for fiber and seed purposes only takes place in a few provinces and districts and cannabis cultivation for any purpose is prohibited outside of these provinces and

districts. According to the regulation on cannabis planting and control, analyzes showing the presence of cannabinoids in the seed extract (hemp oil) should be done and the total amount of cannabinoids in the seed extract should be at most 5 mg/kg if the plant is cultivated for their seed (Kenevir ekimi ve kontrolü hakkinda yönetmelik Bakanlığı 1990; Republic of Turkey Ministry of Agriculture and Forestry 2021). Cannabis cultivation in Turkey came back to the agenda in 2018 and special interest was shown by the public. In this regard, emphasis has been placed on breeding studies, new varieties registration studies, and infrastructure studies for the development of the industry.

5 Conclusion

Cannabis has maintained its importance throughout history and has become one of the most prominent products globally. The prevalence of cannabis-related drugs has gained progressive popularity in recent decades despite assorted contradictions on human health (therapeutic or toxic) regarding their use (Cohen et al. 2019). Apart from a few countries, cannabinoids usually remain illicit, holding negative repute due to their adverse effects rather than their therapeutic advantages and medical utilization (Isaac et al. 2016). Emerging evidence has emphasized acute adverse effects of cannabinoid-related drugs despite their therapeutic capacity (De Luca and Fattore 2018; Murray et al. 2016; Sachs et al. 2015). Recreational and medical cannabis uses are linked to the emergence of cardiovascular, psychological, respiratory, cognitive, and public health effects (Sachs et al. 2015). Despite these unwanted effects, the therapeutic potential of cannabis-related products has drawn attention for several purposes in recent clinical studies (Haleem and Wright 2020; Koppel et al. 2014; Whiting et al. 2015). Cannabis-associated adverse effects differ concerning genetic predisposition of individuals, cannabis dose, and other factors (Karcher et al. 2019). Therefore, these factors should be taken into consideration to prevent probable side effects before the prescription of medical cannabis.

Another point to bring medical cannabis into the market is the necessity of recruitment of adequate medical standards for cannabis application. In this context, the molecular profile of cannabis-dependent products comprising either individual cannabis compounds or mixtures in which substances can jointly act and possess synergistic behavior as well as their related effects should be comprehensively described. Furthermore, biological and signaling pathways targeted by these products should be delineated accurately. Characterization of pharmacokinetic and toxicity profiles of lead products/compounds is another significant entity for drug development. Following the determination of therapeutic doses and the assurance of the quality, herbal or synthetic cannabis products may establish reasonable grounds for the pharmaceutical industry.

Taken all, although many studies pointed out the therapeutic value of medical cannabis, it remains a dilemma due to potential adverse effects regarding their medicinal use. Double-blind, large-scale, placebo-controlled clinical trials are

warranted for the comprehensive evaluation and detailed clarification of their therapeutic role and adverse effect profile for public health.

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Understanding the Pharmacokinetics, Safety Profile, and Scope of the Concerned Issue to Evade the Consumption of Cannabis/Marijuana

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Abstract Cannabis use has attracted much attention as a potential therapeutic target for cancer, cancer-related disorders, and neurological diseases. Cannabinoids play a role in various physiological processes, including appetite stimulation, energy homeostasis, pain modulation, and chemotherapy-induced nausea and vomiting control. However, because pharmacokinetic and pharmacodynamic interactions can be experienced in drug combinations, we endeavored to describe the various pharmacokinetic and pharmacodynamic interactions, as well as potential therapeutic cannabis drug interactions and the cannabis safety profile. Evidence on cannabinoids' adverse drug responses and drug-drug interactions with other prescription drugs has been delivered. Although cannabis is usually well-tolerated, bidirectional actions by metabolizing enzymes with concurrently administered drugs cannot be ruled out. To ensure their wellness, caution should be exercised in thoroughly scrutinizing the responses of cannabis users to various medications. This is remarkably true for aging individuals who have multiple medical conditions. Once a balanced approach is developed, the legal use of Cannabis might be productive and valuable for therapeutic applications.

Keywords Cannabis · CBD · Drug-interactions · Pharmacokinetics · Safety · THC

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Abbreviations

AUC	Area under the curve
CBD	Cannabidiol
CNS	Central nervous system
ECS	Endocannabinoid system
FDA	Food and drug administration
NIDA	National Institute on drug abuse
PNS	Peripheral nervous system
THC	Tetrahydrocannabinol
USA	United States of America

1 Introduction

Studies show that Cannabis has been present for about 11,700 years in Central Asia (Pisanti and Bifulco 2019) and Himalayan regions (Russo 2005). Cannabis was then subsequently introduced to Europe, Africa, and then America. Cannabis has provided many resources like fibers for ropes and nets, food, and seeds for oil. Many alternative names have been developed for cannabis or marijuana; ganja is one of the oldest nicknames. Some examples of street nicknames are weed, pot, and dope. In the USA, the use of Cannabis medically began during the nineteenth and early twentieth centuries (Holland 2010). There began a federal restriction for cannabis use and cannabis sale dating back to 1937; the Marihuana Tax Act was issued (Musto 1972). This tax act gave an excise tax on specific dealers in marijuana. The tax act placed such a hefty tax on marijuana that it prevented individuals from buying it, and then eventually, pharmacopeia prohibited cannabis. After this act was published in 1942, the action was dropped, and there began to be legal penalties for the possession of Cannabis. After that, many changes occurred, and there was control beyond criminalization, including a limitation on research. The legal status of cannabis has been changed many times in the USA. At times, it was legal, but now, in the twentieth century, a higher percentage of Americans want legalization of the drug than in the previous centuries. Classical ancient records show the use of Cannabis for medical purposes. China has some of the earliest forms of the use of Cannabis for anesthesia purposes. Other uses for Cannabis in other countries during this time were topical, for inflammation, and in clay tablets, called azallû in Akkadian, and was used for depression (Scurlock and Andersen 2005). When medical Cannabis became present in western medicine in the nineteenth and twentieth centuries, legal restrictions still hindered its applications in various therapies.

In Israel, the main structure of the psychoactive compound tetrahydrocannabinol (THC), a phytocannabinoid, was determined by Mechoulam and Gaoni (1965). They identified the psychoactive effect of cannabis by testing it on monkeys and then later on people. They experimented on volunteers by feeding them with cannabis-containing cake and noting their psychological reactions. Mechoulam's research

and discovery opened an exploration into the endocannabinoid system (ECS). This system plays a role in different cognitive functions and is part of the brain signaling system. The National Academy of Medicine report stated that Cannabis is limited to three general therapeutic uses, including (1) relief through treatment for chronic pain in adults, (2) antiemetics for chemotherapy-induced nausea and vomiting, and (3) the healing in patient-reported multiple sclerosis spasticity symptoms. As a result, a new phase of using cannabis derivatives as medicine begins, which is more reliable than in the past. The structures of cannabis-derived chemical compounds are currently recognized. The discovery of an endogenous cannabinoid system elucidates the mechanisms of their activity in the body, and treatment effectiveness and safety are being scientifically examined.

2 Scope of Cannabis issue

According to the National Survey on Drug Use and Health conducted in 2015, more than 22 million Americans older than 12 years old consumed cannabis (Center for Behavioral Health Statistics and Quality 2016). Adolescent users were 1.8 million, while young adults were 6.0 million, and adults were 13.6 million (Center for Behavioral Health Statistics and Quality 2016). In recent years, there has been a significant rise in marijuana use among college students. The daily use of marijuana among college students has increased from 3.5% in 2007 to 4.6% in 2015 (Johnston et al. 2016). The dependence and addiction to marijuana increase in adults when using before 18 (NIDA 2019).

Marijuana has both short and long-term effects on the central nervous system (CNS). Tetrahydrocannabinol (THC) is a mind-altering chemical, and when smoked, THC passes from the lungs to the bloodstream. When THC is in the bloodstream, it enters the CNS and peripheral nervous system (PNS). The effects include mood alteration, body movement, and thinking ability. The use of marijuana during the adolescent years and long-term use has effects on physical and mental health. Physically, marijuana affects breathing, heart rate and alters development during and after pregnancy. Heart rate increases with use, and breathing problems are induced. Also, marijuana-induced mental effects of long-term use include temporary hallucinations, temporary paranoia, and worsening symptoms in patients with schizophrenia (NIDA 2019). Cannabis use also alters alertness, concentration, and coordination. When under the influence of marijuana while driving, skills for driving safely are impaired and affected. Marijuana's effects have a negative correlation linked to educational outcomes. The intake of this drug affects learning by decreasing attention span and memory. The National Institutes of Health; US Department of Health and Human Services have shown that marijuana users are more likely to get lower grades and drop out of high school than individuals who do not use cannabis products. Also, higher levels of THC in marijuana increase the risk of a harmful reaction. Moreover, incorporating marijuana in food products can cause dangerous

effects because the marijuana ingested takes much longer to digest and produce a high. An individual may consume more, which can cause hazardous effects like dizziness, nausea, and facial flushing. The increased levels are also shown to have a greater risk for addiction. It has been suggested that marijuana is potentially a gateway drug into other substances of abuse. Research suggests that the use of marijuana may induce the use of other drugs, and users are linked to the addiction to alcohol and nicotine (NIDA 2019).

3 Common Modes of Administration and Formulations

3.1 Absorption

3.1.1 Smoking and Inhalation

The rate of the drug absorption depends on the route it is administered. Smoking has one of the most rapid absorption rates because the drug is directly delivered from the lungs' blood supply to the brain. Smoking causes almost immediate exposure to the central nervous system resulting in intense pleasurable and reinforcing effects (Ohlsson et al. 1980). Average bioavailability by the smoked route is reported to be 31% (Ohlsson et al. 1980). The duration of smoking affects the degree of drug exposure. The number, duration, spacing of puffs, and hold time influence the degree of drug exposure (Ramesh et al. 2013). Many prefer this method due to its rapid delivery and immediate effects.

3.1.2 Oral

When cannabis products are administered orally, the effects begin around 30–90 min after ingestion, reaching their peak after 2–3 h, and last approximately 4–12 h (Grotenhermen 2003). The use of oral intake is recommended for therapeutic applications. (*Marinol*®) is commonly taken orally but is also available rectally (Law et al. 1984; Ohlsson et al. 1980). The absorption rates are slower when cannabinoids are ingested orally and result in lower plasma peak concentrations. The bioavailability and absorption change with the different oral administration routes (Law et al. 1984; Ohlsson et al. 1980). Maximum measured plasma concentration over the time specified (Cmax) and the area under the plasma concentration vs. time curve (AUC) following oral administration also appear to be dose-dependent (Millar et al. 2018). Bioavailability is low through oral administration; hence other routes are often used.

3.1.3 Oromucosal Drops/Spray

Oromucosal administration involves the mucous of the oral cavity. Sprays, aerosol, and nebulizers are a few examples of oromucosal administrations. This method has been developed through the use of cannabis for medicinal purposes. Cannabis used for medicinal purposes has been present for many years now. In *Sativex*®, THC and CBD have almost equal concentrations with the remaining containing other chemicals (Russo and Guy 2006). *Sativex*® is administered under the tongue to avoid the first-pass metabolism by the liver associated with oral administration (Russo and Guy 2006). The absorption rates are much slower than smoking but have faster rates than oral intake.

3.1.4 Rectal

The use of suppositories accomplishes rectal administration. Formulations were developed to evaluate various matrices to maximize cannabinoid delivery by the suppository route in monkeys (Munjal et al. 2006). Rectal administration of 2.5–5 mg of THC produced maximum plasma concentrations of 1.1–4.1 ng/ml within 2–8 h. When cannabis is introduced into the body by the suppository method, drug absorption is nearly twofold slower than the oral route due to higher absorption metabolism (Munjal et al. 2006).

3.1.5 Transcutaneous

Transcutaneous drug absorption following topical administration improves bioavailability. This route of absorption avoids the first-pass metabolism and improves THC bioavailability (Stinchcomb et al. 2004). However, the delivery of the drug by this route is slow. The transport across the aqueous layer of the skin is a rate-limiting step in diffusion due to the hydrophobicity of cannabis. Delivery of cannabinoids by the transdermal route is a method designed to reduce the adverse effects of smoking. The transdermal patch bypasses the first-pass metabolism, and these properties are beneficial in medication. Treating related nausea and vomiting with a transdermal patch applied several hours before chemotherapy and worn for many days may be a great option. Also, instead of taking dronabinol twice a day orally, wearing a patch for a week to promote appetite could be an ideal option. THC abuse is also expected to be significantly reduced due to the delivery of THC concentrations to the brain via transdermal patches.

3.1.6 Intravenous

THC does not appear to be abused by the intravenous route of administration. This method has been used primarily on a research basis. The intravenous route indicated the THC association between cannabinoids and psychosis. D'Souza and team performed a study where 0, 2.5 and 5 mg of THC were administered to healthy individuals and have had cannabis exposure but were not diagnosed with cannabis abuse (D'Souza et al. 2004). The THC concentrations in the plasma after 10 min were 82 ± 87.4 and 119.2 ± 166.5 for intravenous doses of 2.5 and 5.0 mg, ng/ml, respectively (D'Souza et al. 2004). THC produced positive and negative symptoms associated with schizophrenia (euphoria and altered aspects of cognitive function). THC caused a wide range of acute or temporary symptoms, behaviors, and cognitive deficits similar to endogenous psychoses in healthy adults. The researchers hypothesized that the function of brain-cannabinoid-receptors and drug concentrations could be a key element in the pathophysiology of psychotic illnesses.

3.2 Distribution

Plasma THC, after absorption, is readily distributed throughout the body into the tissues and liver. THC is highly lipophilic, which means it partitions fats and lipids. Due to THC being lipophilic, it is taken up by the tissues of the heart, liver, and lungs. THC has such an extensive distribution volume that it takes a very long time to be eliminated. Smoking allows for a high lung intake of THC accumulation. THC distribution to the brain is used to analyze the effects of behavior related to the amount/concentration of THC intake. In vivo studies showed that after intravenous administration of labeled THC, higher levels of radioactivity were present in the lung than in other tissues (Lemberger et al. 1970). The distribution of THC into peripheral organs and the brain was found to be similar in THC-tolerant vs. non-tolerant dogs (Dewey et al. 1973). Furthermore, these researchers discovered that tolerance to THC's behavioral effects in pigeons was not attributable to decreased cannabinoid uptake into the brain. Hunt and Jones (1980) discovered that tolerance develops in people after chronic oral administration of THC (30 mg of THC every 4 h for 10–12 days). There were few pharmacokinetic alterations during chronic treatment; however, total metabolic clearance and initial apparent volume of distribution increased from 605 to 977 ml/min and 2.6 to 6.4 l/kg, respectively. The observed behavioral and physiologic tolerance could not be explained by pharmacokinetic changes following continuous oral THC administration, implying that tolerance was related to pharmacodynamic adaptation. THC rapidly crosses the placenta. However, concentrations were lower in canine and ovine fetal blood and tissues than in maternal plasma and tissues (Lee and Chiang 1985). The levels of blood concentration vary on the frequency of cannabis administration.

3.3 Metabolism

The metabolism of cannabis depends on the route of administration. Oral consumption leads to the drug's absorption and distribution to the liver resulting in its metabolism (Figs. 1 and 2). THC in the liver is metabolized in rabbits and rhesus monkeys to the primary THC metabolites, 11-OH-THC and THC-COOH (Burstein et al. 1972; Huestis 2007). Additionally, allylic and aliphatic hydroxylation, oxidation of alcohols to ketones and acids, oxidation, and degradation of the pentyl side chain are all seen in the phase-I oxidation processes of THC.

A frequent Phase-II reaction is the conjugation of glucuronic acid. 11-OH-THC was the most abundant metabolite in all three species, followed by 8-OH-THC in mice and rats and 8-OH-THC in guinea pigs. All three species had a high rate of side-chain hydroxylation. The mouse and rat had higher THC-COOH levels, while the guinea pig had higher THC-COOH glucuronide levels. The liver, lungs, heart, and spleen all store THC. CYP2C and CYP3A are the metabolizing enzymes of THC (Abouchedid et al. 2016). CYP2C is responsible for forming 11-OH-THC, while CYP3A catalyzes the formation of 8-OH-THC, epoxy-hexahydro cannabinol, and other minor metabolites. The inactive metabolite THC-COOH is formed when the psychoactive 11-OH-THC is oxidized. (Lemberger et al. 1970; Mechoulam et al. 1973).

In most species, including humans, THC-COOH and its glucuronide conjugate are the primary end products of the biotransformation (Huestis 2007). THC-COOH concentrations steadily rise and become more significant than THC concentrations 30–45 min after using the drug by smoking/inhalation (Huestis 2007). As early as 1 h after taking a single oral dose of Marinol® (10 mg THC), plasma THC-COOH concentrations were greater than THC and 11-OH-THC (Huestis 2007). THC and 11-OH-THC concentrations are equal following oral THC treatment, unlike after

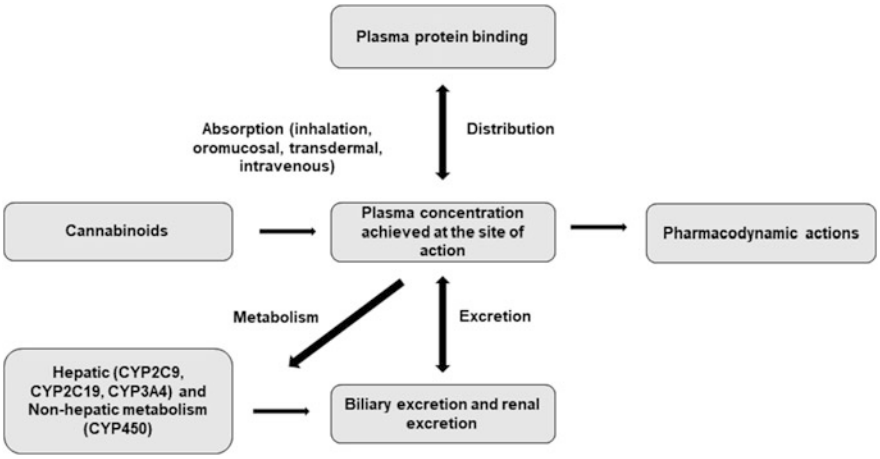

Fig. 1 Pharmacokinetic actions of cannabinoids

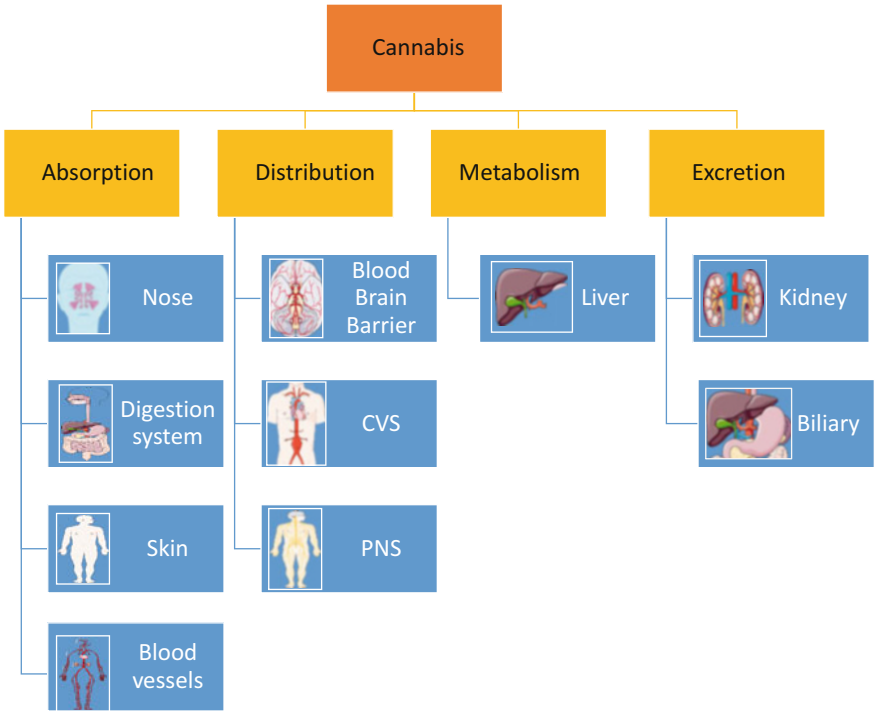

Fig. 2 Pharmacokinetics of Cannabinoids

smoking (Fig. 3). Besides hepatic metabolism, the brain, intestine, and lung may also contribute to the metabolism of THC. Watanabe et al. discovered that brain microsomes oxidized THC to monohydroxylated metabolites in a study on THC metabolism in mice, rats, guinea pigs, and rabbits' brains. In the brains of these animals, hydroxylation of C(4) on the pentyl side chain produced the most prevalent THC metabolite, which was analogous to THC metabolites produced in the lungs. (Watanabe et al. 1988). These metabolites are pharmacologically active, but their relative activity is unknown. Metabolism can affect THC bioavailability and half-life. The bioavailability for THC through inhalation is between 10% and 35% (Grotenhermen 2003; Ohlsson et al. 1980). The plasma half-life of THC is 1–3 days in light users and 5–13 days in heavy users (Huestis et al. 1992).

3.4 Elimination

Hydroxylated and carboxylated metabolites of THC are predominantly excreted in urine and feces (Huestis 2007; Wall et al. 1983. The primary metabolite excreted in the urine is the acid-linked THC-COOH glucuronide conjugate, while 11-OH-THC

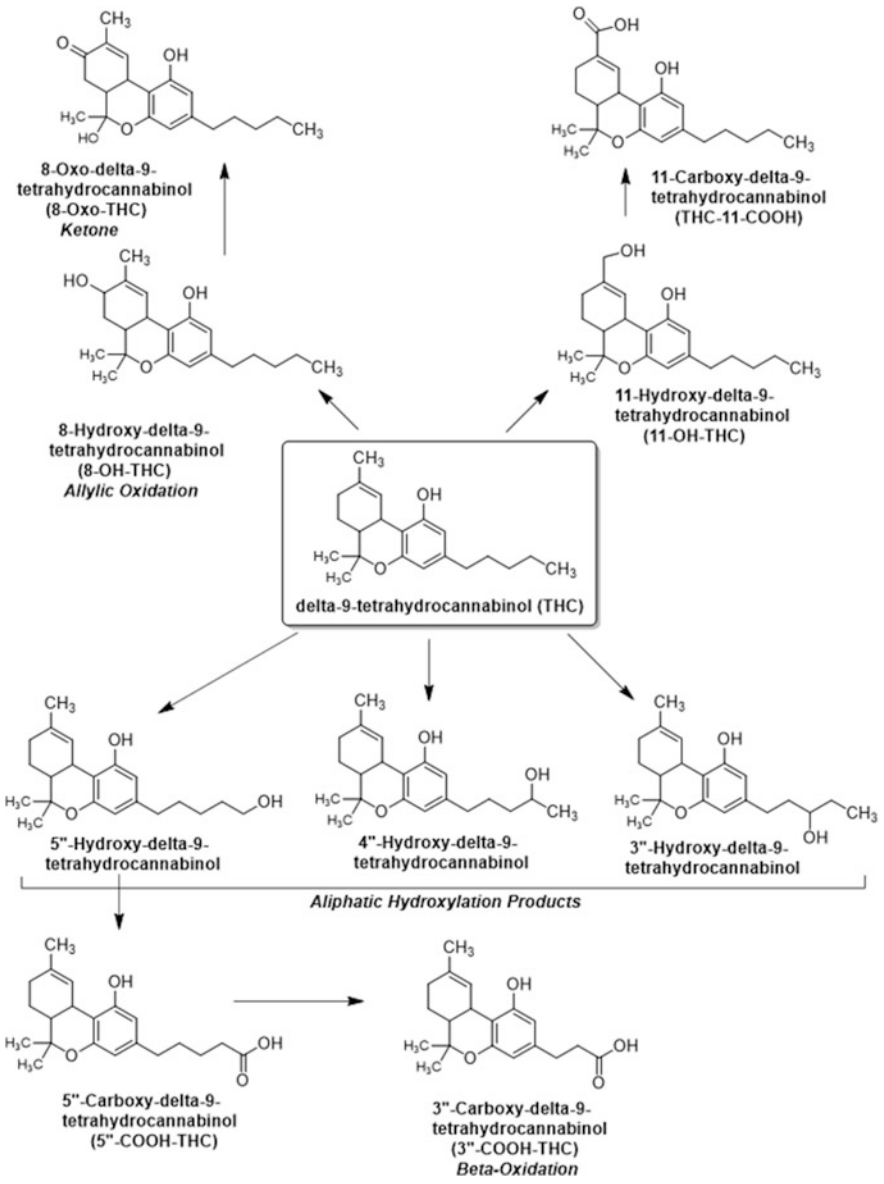

Fig. 3 Metabolism of THC

is the primary metabolite predominant in the feces (Williams and Moffat 1980; Gonçalves et al. 2019). The slow release of THC from lipid-storage compartments and significant enterohepatic circulation contribute to a long terminal half-life of THC in plasma. There are no significant pharmacokinetic differences between chronic and intermittent users (Chiang and Rapaka 1987).

4 Cannabis Safety Profile

Cannabis safety has been a topic of varied and conflicting views. The analysis of the safety of cannabis includes assessments of long and short-term effects from the usage of the drug. The effects on physical health are distributed all over the body involving the cardio vasculature, lungs, and CNS function. Cardiovascular effects include short-term and long-term effects. The short-term effects include tachycardia, increased cardiac labor, systemic vasodilation, and increased blood pressure (Schatman 2015). Some effects are more severe and detrimental to the cardiovascular system. Some of the more severe effects are angina which causes pain in the chest because of the reduced blood flow to the heart, heart attacks, and cardiac death (Sachs et al. 2015). The long-term effects of cannabis use include bradycardia and hypotension (Sachs et al. 2015; Parakh 2010; Tormey 2010). The respiratory system is greatly affected by smoking, one of the primary routes of cannabis intake. Short and long terms effects on the respiratory system are caused primarily due to smoking cannabis. The effects include the increased inflammation of the large airways and the destruction of lung tissue (Schatman 2015; Repp and Raich 2014).

Meanwhile, there is also a correlation between the quality of sleep and cannabis usage. Cannabis decreases slow-wave sleep, showing a correlation between increased sleep time and reduced sleep quality (Schatman 2015; Tobe et al. 1989). Cannabis use has evident effects on cognition. The short-term effects on cognition have been reported to impair free recall, acquisition, working memory, and procedural memory (Schatman 2015; Crane et al. 2013; Repp and Raich 2014; Crane et al. 2013). Short-term effects are much more transparent and more evident than long-term effects, but the long-term effects are still apparent among cannabis users. The frequency and duration of use are two factors that lead to the long-term effects (Schatman 2015). Long-term effects show to increase with earlier age of usage (Grotenhermen 2007). The studies have reported that early-onset users had cognitive defects that resulted in a more significant loss of IQ (Meier et al. 2012b). Public health safety has clear concerns and effects in addition to the physical and cognitive effects. Drugged driving and motor vehicle accidents are some of the many severe effects of cannabis intake (Sachs et al. 2015; Grotenhermen 2007).

Driving under the influence of cannabis increases the risk of a motor vehicle accident by two- to sevenfold (Repp and Raich 2014). Cannabis use also is related to addiction and dependence. It is estimated that 9–10% of individuals who intake cannabis become addicted (Benbadis et al. 2014; Repp and Raich 2014; Volkow et al. 2014). This percentage increases among individuals who start consuming cannabis as adolescents and use it daily (Repp and Raich 2014). There may be a correlation between heavy cannabis use and negative consequences of a higher need for socio-economic assistance, unemployment, and lower life satisfaction (Volkow et al. 2014). Despite the varied and conflicting views on the safety of cannabis, there are many apparent adverse effects on physical, cognitive, and public health safety.

5 Common Adverse Effects

Cannabis has a wide range of uses, from recreational to medical purposes. The variety of various intake options comes with a variety of adverse effects with the usage of cannabis. The use of cannabis products elevates the risks of addiction, poor school performance, poor mental health, and cancer. The long-term use of cannabis has been associated with addiction. There are correlations between the early onset age of cannabis use and a higher rate of addiction. While the use at an adolescent age can bring a higher tendency of addiction, so can the amount of use. The use of cannabis daily has a 25–50% increase in the risk of addiction (Hall and Degenhardt 2009). Cannabis dependence is a common effect of cannabis from an early age. Daily use also increases the risk of using other illicit drugs. The impact on the brain is the cause of cannabis addiction. The brain undergoes changes starting from the prenatal period throughout childhood and adolescence (Gogtay et al. 2004). The development of the brain during this time is very vulnerable and is going through continuous changes and developments. Because of this vulnerable state, the use of cannabis can cause effects that can even be long-term. The primary ingredient in marijuana, tetrahydrocannabinol (THC), has been shown to cause sensitivity of the reward system to other drugs during early exposure (Dinieri and Hurd 2012). The risk of developing a mental illness and having an increased risk of anxiety and depression are associated with prolonged marijuana use (Patton et al. 2002).

Psychosis has also been associated with marijuana use, and if there is preexisting genetic vulnerability, this increases the risk for psychosis (Caspi et al. 2005). While altering effects in the body occur, this then affects school performance and lifetime achievement. The frequent use of marijuana has shown higher dropout rates and inadequate performance in school (Bray et al. 2000). While under the influence of marijuana and days after, many students function at a lower cognitive level than their natural state (Meier et al. 2012a). The acute and long-term use of marijuana has been shown to impair attention and memory, and these may increasingly worsen as time proceeds (Solowij et al. 2002). The association of risks to school performance and life needs is shown through the effects of acute and long-term use of marijuana. Even the recreational use of marijuana has various adverse effects related to health and performance (Fig. 4).

6 Drug Interactions

Drug interactions can occur by pharmacodynamic mechanisms, when two or more drugs have similar or different mechanisms of action, or by pharmacokinetic mechanisms involving drug absorption, distribution, metabolism, and excretion. For example, one drug may inhibit or induce the metabolism of a second drug. Cannabis is metabolized by enzymes that may be subject to inhibition or induction by other drugs present concurrently (Fig. 5). The two active cannabinoids in marijuana are

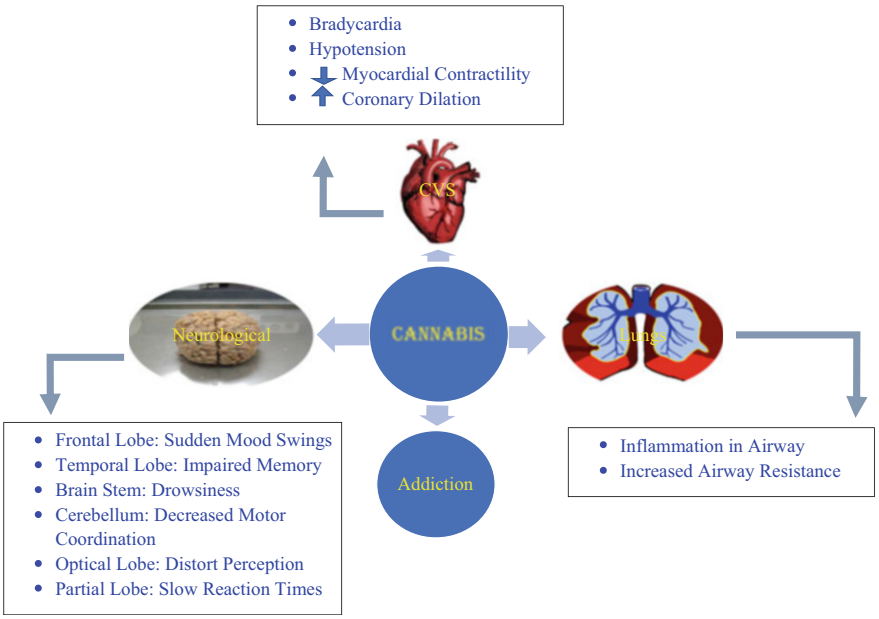

Fig. 4 Common adverse effects of cannabis

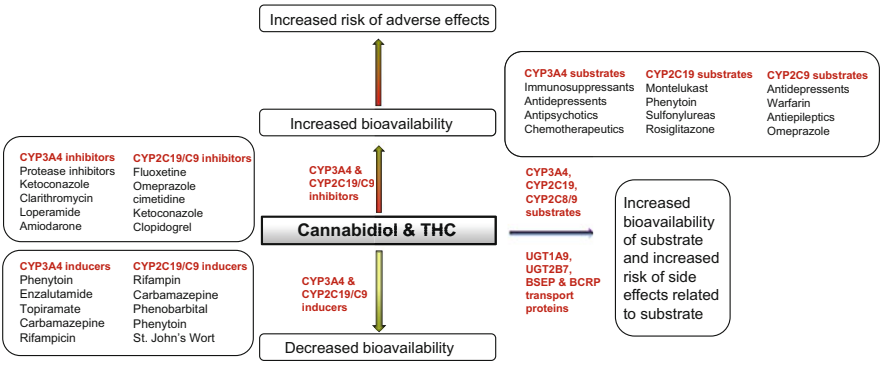

Fig. 5 Potential drug interactions of cannabinoids

Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), and these are metabolized by cytochrome P450 (CYP)3A4 and CYP2C9. CYP3A4 inhibitors can inhibit the metabolism of THC and increase levels and pharmacological effects (Cox et al. 2019).

An interaction between warfarin, an anticoagulant, and marijuana has been reported to have increased bleeding incidence (Cox et al. 2019). The intake of marijuana administered through smoking can increase the clearance of multiple different drugs. Smoking marijuana has seen an increase in theophylline clearance

(Cox et al. 2019). The interaction of cannabis with other drugs can also have synergistic or additive pharmacodynamic effects. Additive effects occur when a drug is combined with different drugs, and an effect occurs that is increased than the natural state. Additive effects can occur when marijuana is mixed with sympathomimetics, depressants, opioids, alcohol, and many other substances (Lucas et al. 2018). The results of these may include ataxia, drowsiness, hypertension, and numerous different effects (Lucas et al. 2018).

Cannabis has various forms and different THC and cannabinoid ratios. Because of these different forms and proportions, not all interactions with the same drug are the same. Therefore, the drug interactions with cannabis and other drugs are caused by the chemical components, ratios, and profile, not just the specific drug itself. There's a scarcity of data on how medicinal cannabis interacts with other drugs. As a result, there are still gaps in the evidence-based clinical guidelines for medication interactions with medicinal cannabis. However, extreme caution should be exercised in constantly monitoring the reactions of cannabis users to certain pharmaceuticals to ensure their safety, particularly for the elderly and persons with chronic liver and kidney illnesses.

7 Contraindications/Toxicity

Contraindication is defined as a symptom or condition that makes a particular treatment or procedure inadvisable (Medicinenet 2021). When an individual uses cannabis with certain preexisting conditions, it can induce a harmful or more extreme effect. Contraindications with Cannabis are apparent with individuals with cardiovascular disease, arrhythmias, poorly controlled hypertension, severe heart failure, history of psychotic disorder, patients under eight years old, pregnant women, or nursing women (Cavazos-Rehg et al. 2019; Kahan and Srivastava 2014). Contraindications can be divided into two categories, absolute and relative. Absolute contraindications include short time psychosis and other psychiatric conditions (Pertwee 2014). Relative contraindications include cardiovascular, immunological, liver, or kidney disease (Pertwee 2014). The psychotropic effect of Cannabis is a contraindication, particularly to individuals with mood and personality disorders. Preexisting genetic variations have also indicated a link between the use of marijuana and psychiatric disorder (Radhakrishnan et al. 2014). Di Forti and coworkers recently found that the gene AKT1 in humans can have variations. The variant of AKT1 is a gene that codes for an enzyme that affects dopamine signaling in the striatum (Di Forti et al. 2012). Studies have indicated that individuals with this variant gene and who use marijuana are seven times more likely to risk psychosis than individuals who do not use or infrequently use marijuana (Di Forti et al. 2012). Dopamine signaling is shown to be altered in individuals with schizophrenia; AKT1 has been connected to susceptibility to schizophrenia (Di Forti et al. 2012). Because of this connection, individuals who use marijuana daily are more susceptible to developing psychosis when they have a variant of this gene.

Synthetic forms of tetrahydrocannabinol (THC) are used as treatments for several medical conditions. Dronabinol is a synthetic form of THC approved by the US Food and Drug Administration (FDA) in 1985 to treat anorexia, chemotherapy-induced nausea, and vomiting. (Carley et al. 2018). Individuals do not respond well to this treatment, and the drug's use is limited by side effects such as dysphoria, anxiety, and panic (Grotenhermen and HäuBermann 2017). Hypersensitivity to dronabinol has occurred to individuals after administering the substance (Cavazos-Rehg et al. 2019). The adverse effects include lip swelling, hive rash, oral lesions, skin burning, and throat tightness (Badowski and Yanful 2018).

Toxicity is a term that indicates the degree to which a substance can harm humans or animals (Jameson et al. 2018). There are two categories of toxicity; acute and chronic (Jameson et al. 2018). Acute toxicity is the short-term effects caused by a toxic substance, and chronic toxicity is the long-term effects that can even extend over a lifetime (Jameson et al. 2018). The toxicity of Cannabis is correlated with the dose and the amount ingested. The mode of consumption also influences the toxicity of Cannabis because the route of administration affects how much and where the body absorbs Cannabis first. The serum concentrations vary with the amount administered and the route of administration (Kelly and Nappe 2021). The inhalation peak of serum concentration occurs in less than 30 min (Kelly and Nappe 2021). The ingestion peak of serum concentration is much longer than inhalation, around 2–4 h after consumption (Kelly and Nappe 2021). The duration of toxicity is also different for each mode of administration. The duration of inhalation is approximately 2–6 h, and for ingestion, it is about 8–12 h (Kelly and Nappe 2021).

The component of Cannabis, which seems to be the most toxic through animal studies, is THC. The cause of death in the tested animals was apnea or cardiac arrest because of the high doses of THC levels. With preexisting medical history and other comorbidities, there are more dangerous effects. The lethal dose of Cannabis is much lower than other recreational drugs (Rosenkrantz et al. 1974). In humans, it has been calculated that the lethal dose is 70 kg, and this dose is not achievable in humans from the consumption through smoking the substance (Gable 1993; Lachenmeier and Rehm 2015). Tolerance develops with THC, which indicates that higher doses can be ingested with regular cannabis users because of the higher tolerance they have formed (Bowman and Pihl 1973). Smoking has a higher potency than some of the other modes of administration (McCain et al. 2018; Alipour et al. 2019; Costiniuk et al. 2019).

The treatment of cannabinoid toxicity differs from adult patients to pediatric patients (Kelly and Nappe 2021). Adult patients improve on their own most of the time with little observation and intervention (Kellyn and Nappe 2021). The observation is more extended for pediatric patients, and more intervention is required to guarantee their safety at home (Kelly and Nappe 2021). Cannabis toxicity is becoming common in emergency rooms all over the nation. Due to limited quality control over the manufacturing of marijuana, there may be varying contaminants and levels of THC. Many individuals intake marijuana with other illicit substances. Marijuana toxicity affects several organ systems; thus, an interprofessional healthcare team that includes internists, psychiatrists, and cardiologists should manage the patient.

8 Conclusion

For ages, medicinal, cultural, and recreational uses of cannabis have been evident. Throughout the years, the use of cannabis has changed through laws. Pharmaceutical and illicit forms of cannabis are available to individuals, although toxicity and abuse are evident. Therefore, healthcare providers need the knowledge to identify symptoms and the ability to respond to these effects. Although abuse and toxicity are effects, medical conditions that use cannabis for treatment and medical professions should understand these conditions and give the proper dosage of cannabinoids when administering them. Many individuals' views and concerns about cannabis differ. There have been many findings of the effects of cannabinoids and the care for individuals who have adverse interactions with the drug. Cannabinoids affect individuals differently and are used for different reasons. Even though Cannabis has been around for a long time, there is still a significant gap and questions about many components and interactions. Due to the renewed worldwide interest of people in Cannabis products, there is a need for intensified research efforts regarding its efficacy, safety, and long-term effects on health.

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Traditional Uses of Cannabis in the Middle East and the Pathway to Cannabis-Based Healthcare in Israel

Hinanit Koltai, Boaz Albo, and Zohara Yaniv

Abstract *Cannabis sativa* is one of the oldest cultivated plants, being used by humanity for thousands of years for medicinal and food purposes, ritual, and social activities. Ancient and Traditional uses of cannabis-based on archeological and written evidences are several, as it was used in the Middle East and ancient Israel for ritual and therapeutic purposes. These days, cannabis holds significant medical potential. However, cannabis is considered to be a dangerous substance, of which possession or use must be as per Israeli law and international conventions. Hence, to facilitate proper medical use of cannabis, the State of Israel in 2011 took several primary actions to regulate medical cannabis. These efforts resulted, among others, with the "Israeli Cannacopeia", the collection of formal documentation which was created for ensuring high quality of medical-grade cannabis products. Research-based knowledge is a pillar of cannabis medicalization. This research led to the identification of cannabis-produced molecules and their synergistic interactions while promoting a better understanding of the 'entourage' or 'parasitage' effects. Lab experiments along with clinical trials conducted in Israel are expected to improve cannabis-based medical treatments. Future developments might be based on the development of cannabis chemovars with improved designation and cannabis products with standardized and indication-specific medical activity.

Keywords *Cannabis sativa* · Ancient use · Chemovars · Medicalization · Phytocannabinoids · Terpenes · Synergy

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Abbreviations

API	Active plant ingredients
ASD	Autism spectrum disorder
CB1	Cannabinoid receptor type 1
CB_2	Cannabinoid receptor type 2
CBCA	Cannabichromenic acid
CBD	Cannabidiol
CBDA	Cannabidiolic acid
CBGA	Cannabigerolic acid
CBN	Cannabinol
GCP	Good clinical practice
IMC	Israeli medical Cannabis
PTSD	Post-traumatic stress disorder
THC	Δ9-Teterahydrocannabinol
THCA	Δ9-Tetrahydrocannabinolic acid

1 Introduction

Cannabis sativa has been in use by humanity for thousands of years, for medicinal purposes, ritual and social activities, as raw fiber material for ropes, fabrics, and textiles, or as a food source (e.g., the use of seeds for oil). Cannabis is one of the oldest cultivated plants and appears in ethnological myths and cultural activities of different traditional communities around the world (Long et al. 2017). Israel has been scientifically investigating this plant for more than 50 years. The earliest scientific studies were conducted by Prof. Raphael Mechoulam and his co-workers, identifying the main phytocannabinoids present in the plant (Mechoulam and Ben-Shabat 1999). Following, research of various groups identified multiple compounds in cannabis, and their medicinal activity began to be elucidated. Over the last decade, cannabis has been promoted in Israel to become a well standardized and controlled medical drug in a process of `medicalization`. This process is led by the Israeli authorities in close collaboration with scientists in Israel and abroad and is based on the scientific knowledge, which is still accumulating.

2 Ancient and Traditional Uses of Cannabis-Based on Archeological and Written Evidence

2.1 The Uses of Cannabis in the Ancient Middle East

2.1.1 Mesopotamia

Cannabis was known by several names in ancient Mesopotamia (3000–600 B.C), i.e., Azallu (in Assyria), Azalla (in Sumaria), Qunnabu (in all Mesopotamia). The name Ganz-gun-nu, which is similar to ganja in India, was used in Assyria too. Cannabis was known in Assyria as the drug that "takes away the mind" (Mechoulam 2005) and based on written information on stone tablets, dating from the 1800 BC, was used by ancient Sumerian and Akkadian for treating a number of ailments such as nocturnal convulsions (Friedman and Sirven 2017). Cannabis preparations were used on the skin to treat swelling and injuries. For weakness of the lower limbs, roasted azallu was added to a water bath in which the patient would sit. Cannabis fumes were used for arthritis. Azallu was given as food or a drink in cases of "depression of the spirits", impotence and kidney stones. Seeds, immersed in juniper oil, were given as a remedy against the evil eye (Mechoulam 2005). In addition, cannabis was used as an incense in the temples of Assyria and Babylon (Fig. 1) "because its aroma was pleasing to the Gods" (Benet 1975).

Fig. 1 Illustration of cannabis use as an incense in the temples of Assyria, underneath cartography of the Goddess Ishtar (illustrated by Omer Koltai)

2.1.2 Ancient Egypt

The word *"shemshemet"* also known as *"sm-sm-t"* mentioned in the Ebers papyri may stand for *C. sativa*. The Ebers papyri, discovered in the nineteenth century in Luxor, Egypt, contain medical information including the use of medicinal plants, and is dated to the sixteenth century BC. Cannabis medical use included oral consumption for the prevention of hemorrhage development during childbirth and as an incense for treating eye problems. An ancient papyrus dated to 1800 BC describes its use for infections, pain, and vaginal contractions (Friedman and Sirven 2017). Cannabis was also used in Ancient Egypt in bandages for skin injuries (Mechoulam, 2005). The historian Diodorus Siculus (about 60 B.C.) reported that the ancient Egyptian women used *C. sativa* to reduce pain and improve their mood. Yet, it is surprising that there is no indication for its use in Ancient Egypt as a psychoactive plant, unlike other ancient cultures of the region. It could be that such ceremonies in Ancient Egypt were secretive and therefore not recorded in manuscripts (Bonini et al. 2018).

2.1.3 Ancient Greece and Rome

C. sativa was also well known among the ancient Greeks and Romans. The Roman historian Pliny the Elder described the use of *C. sativa* roots for easing pain. At the same period of the first century, Pedacius Dioscorides, a Greek physician, described *C. sativa* and its useful benefits in his book "De Materia Medica". One of these uses is the treatment of ear pain (Lev 2002). A Roman physician, Galen, wrote some notes about *C. sativa*. In particular, he described a practice, popular habit among Roman aristocrats to conclude their lunch with a cannabis-based dessert (Bonini et al. 2018).

2.2 The Uses of Cannabis in Ancient Israel

According to some authors, the word Cannabis was present in Semitic languages, including Hebrew. Both in the original Hebrew text of the Old Testament and the Aramaic translation, the word 'kaneh' or 'keneh' is used either alone or linked to the adjective 'bosem' in Hebrew and 'busma' in Aramaic, meaning aromatic. These findings lead to the belief that cannabis was both known and used since biblical times (Bonini et al. 2018). According to Sula Benet (1936), the origin of the name 'cannabis' is in the times of the Bible, and the Scythians borrowed both its name and forms of use from the people of the Near East (Benet 1975).

Evidently, in some passages of Exodus, Isaiah, Jeremiah, and others, the use of *C. sativa* as incense and sacred oil is mentioned (Bonini et al. 2018). For example, Jeremiah 6:20 "To what purpose cometh there to me incense from Sheba, and the

Fig. 2 Illustration of a monolith in the shape of a sacrificial altar with a ceremonial platter and cannabis offering on top, similar to the one found in Judahite shrines. Jars of olive oil and a high minister are shown (Illustrated by Omer Koltai)

sweet cane from a far country? your burnt offerings are not acceptable, nor your sacrifices sweet unto me"; and Ezekiel 27:19: "Vedan and Javan paid for your merchandise from Uzal; wrought iron, cassia, and *spice reed* were among your merchandise" Also, Isaiah 43:24: "Thou hast bought Me no *sweet cane* with money, neither hast thou satisfied Me with the fat of thy sacrifices; but thou hast burdened Me with thy sins, thou hast wearied Me with thine iniquities".

Traditionally, cannabis was used in ancient Israel during the middle Ages (from the seventh to the fifteenth century according to Lev (2002), for several treatments of medical problems. Medical treatments of epilepsy and madness, for alleviation of earaches, to induce sleep, to stop hemorrhage, and to ease pains including joint pains were mentioned. Moreover, special attention was given to the danger of intoxication (Lev 2002).

A remarkable discovery was recently reported, indicating an ancient use of cannabis in the eighth century B.C., during the Iron Age (Arie et al. 2020). Two limestone monoliths, deduced to be altars, were found in the Judahite shrine at Tel Arad, Israel (Fig. 2). Residues of cannabinoids were detected on the smaller altar, including Δ9- tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN), along with a variety of terpenes and terpenoids. Hence, it was suggested that cannabis inflorescences had been burnt on the altar. Organic residues were also found, attributed to animal dung that might have been used to mix with the cannabis

Fig. 3 Illustration of the skeleton of a girl of about 14 years old in a tomb with bronze coins (Illustrated by Omer Koltai)

resin to enable mild heating. The larger altar of the two limestone monoliths contained triterpenes that probably derived from frankincense. The authors suggest that cannabis was used as an incense offering in Judea during the Iron Age (Arie et al. 2020).

Another important and unusual evidence for cannabis uses in the late Roman period (dating to the fourth century AD) was found in central Israel, in the town of Beit Shemesh, near Jerusalem (Murphy et al. 2011). There, archaeologists uncovered the skeleton of a girl of about 14 years old in a tomb who died in childbirth, possibly from excessive bleeding. Three bronze coins dating to 315–392 AD were found in the tomb, indicating that the tomb was in use during that time (Fig. 3; Zlas et al. 1993). In the abdominal area of the skeleton, a small amount of dark burnt material was discovered, preserved in the skeleton because it had been carbonized through the burning of the plant material. The chemical analysis identified the ancient material as a mixture of cannabis resin (hashish), and dried seeds and fruit of common reed grass (Phragmites). It was suggested that the drug material was used as an aid in childbirth, since it may have increased the strength and rate of recurring contractions during giving birth. However, it might have been used for rituals during childbirth as well (Merlin 2003; Zlas et al. 1993).

2.3 The Use of Cannabis at Recent Times

Along with the long history of medical use of cannabis, between the years 1850 to 1937, cannabis was a part of the US Pharmacopeia. The plant appeared in the first edition of Merck's manual as a treatment for various medical conditions. Nevertheless, in 1937, cannabis was outlawed by the federal American authorities. Other countries followed this act, and by 1960 cannabis was banned in most western countries. In 1961, The United Nations Conference for the Adoption of a Single Convention on Narcotic Drugs was assembled and endorsed a regime of control and regulation regarding the use of cannabis. For example, in *Article 22* it was stated that cannabis cultivation, like the opium poppy or the coca bush, is prohibited for protecting the public health and welfare and preventing the diversion of drugs into the illicit traffic (UN 1961) In 1973, The Israeli Dangerous Drug Ordinance (New Version) (Anonymous 1973) was published, defining cannabis and its products as a "Dangerous Drug" and stating that any holding or usage of cannabis requires a license. A year later, in 1974, Israel signs the "The international Single Convention on Narcotic Drugs" protocol.

In the early 1990s, a request for approval of the use of cannabis for medical purposes was petitioned to the Israeli Ministry of Health; the first patient permitted to use cannabis for medical reasons suffered from asthma. As the trend expanded and the number of patients increased, it was found necessary to regulate licensing in a more comprehensive and controlled manner. The controversy in the regulation of cannabis medical use in Israel was originated from two opposite perspectives. On the one hand, cannabis use seems to hold significant medical potential. On the other, cannabis is considered to be a dangerous substance, and its possession or use must be in accordance with Israeli law and international conventions. Moreover, much is yet unknown regarding its safety of use and efficacy.

3 Cannabis Medicalization in Israel

As of 2011, the State of Israel initiated a number of primary actions to regulate medical cannabis. These actions included the establishment of an inter-ministerial steering committee and the establishment of a government agency. The government agency aimed to build regulation, maintain its supervision, and set criteria for the determination of medical conditions that justify cannabis treatment. While these measures supported the accessibility of cannabis treatment to patients, there were still many gaps in regulation. For example, only a limited number of growers supplied the cannabis, and the supply was directly from farmers to patients. Cannabis received by patients suffered from high variability and lack of standardization. There were no clear standards for the growth process, the final product, and the method of patient treatment.

The guiding principles of cannabis medicalization were to promote cannabis treatments to that of a registered medicine or medicinal product (as possible), to facilitate cannabis treatment based on prescription by a physician authorized to do so and to facilitate the development of products that meet the required medical level.

Three main pillars may be defined in the medicalization reform. One, the quality chain that aims to provide patients with medical cannabis products. These products should be as standardized as possible and available as reproducible products with constant and controlled concentrations. Two, the clinical care that aims to enable proper treatment using these products. Three, research aiming for supporting the development of cannabis-based products and technologies while deepening the evidence-based medical knowledge.

The "Israeli Cannacopeia" is the collection of formal documentation that was created for ensuring the high quality of medical grade cannabis products and applying proper treatment with these products. This collection includes a set of licensing procedures as per the Israeli law for the licensing of treatment, practice, research, import, and export of cannabis. It also includes a set of quality-assuring procedures (Israeli Medical Cannabis - good practices or IMC-GxP), specifying the standards and conditions for agriculture and cultivation ($x = A$), Manufacturing of cannabis products ($x = M$), distribution of cannabis products including their dispensing ($x = D$), and waste disposal of cannabis plants and cannabis-products ($x = \mathrm{WD}$). In addition, a procedure was developed to promote the protection and security of locations associated with cannabis-related activities ($x = S$).

In 2016 the Israeli government published a comprehensive outline on the subject of "cannabis for medical use and research" (Landschaft et al. 2019), which formed the basis for the reform of medicalization of cannabis in Israel. This reform intended to provide patients with a proper source of cannabis for medicinal purposes while maintaining public safety and preventing misuse of the drug. On top of all, clinical methodology for applying treatment with medical cannabis, i.e., IMC-Good Clinical Practice (IMC-GCP) or "the green book", was generated. IMC-GCP aims to outline a clear methodology for treatment with medical cannabis. The outlines, being continuously updated, serve as a textbook for medical doctors in Israel to provide treatment using cannabis products. Up until today, around 300 physicians have been trained and certified to apply medical cannabis treatment in Israel.

Production and distribution of medical cannabis products are carried out through a Regulated Quality Chain, separated into specific steps of activity allocated to specific sites to achieve a high level of quality and to avoid cross-contaminations. Reproduction, growth, post-harvesting, production, storage, and waste disposal are each done at separate sites specializing in this operation. This is in contrast to pre-reform activities where all these stages were carried in the same complex without defined physical separation between them. If in the past a certain agricultural batch carried contamination, this may have led to cross-contamination endangering all batches and products produced in the same complex. Today, a batch that does not meet the analytical threshold requirements or is not free of hazardous contaminants will not be processed in the next stage of the production chain, reducing cross-contamination of batches and products. Each step of activity must withstand its

relevant quality standards (as detailed above). For example, IMC-GAP in agricultural sites, IMC-GMP in manufacturing sites, and IMC-GDP in distribution sites. Finalized Medical Cannabis Products that meet all quality conditions are marked with the Israeli Quality Trademark CANNAAN.

More than 100,000 patients in Israel are licensed for medical cannabis treatment. Most of them suffer from medical conditions approved for treatment with cannabis, including symptoms resulting from cancer and cancer therapy, side effects of intestinal bowel inflammation (i.e., Crohn's disease and ulcerative colitis), neuropathic pain, cachexia resulting from the human immunodeficiency virus infection, multiple sclerosis, Parkinson's disease, Tourette's syndrome, epilepsy, terminal conditions, and post-traumatic stress disorder (PTSD). The most recent indication approved in 2021, based on results of clinical studies conducted in Israel is on childhood autism. These studies have supported the beneficial role of CBD-rich cannabis in children with severe behavior related to autism (Aran et al. 2019, 2021).

Despite the knowledge that was already accumulated in recent years regarding the medical use of cannabis, there is still not enough scientific evidence nor evidence-based medicine regarding the clinical use of cannabis. In 2017, a large-scale metanalysis by the National Academies of Science, Medicine, and Engineering (NASEM) of the US showed the current state of evidence in cannabis. This publication emphasizes that currently there is still only little conclusive evidence regarding the efficacy of cannabis in human beings for medical conditions (NASEM 2017).

To summarize, cannabis medicalization reform in Israel is a complex and pioneering process. It includes industrial activity for producing cannabis products at the medical-grade level, professional assimilation of the clinical method, training of medical personnel, and promoting customized treatment. The cannabis medicalization reform supports extensive research to expand knowledge and to support future developments of cannabis-based medical technologies and products.

4 Directions for Israeli Research on Cannabis for Medical Use

Promoting research-based knowledge is one of the pillars of cannabis medicalization. Israel has created a clear regulation that allows cannabis-related research. To date, more than 500 research proposals have been approved in Israel by The Ministry of Health, which are classified into agricultural studies (e.g., plant cultivation and agro-technology), technological studies (e.g., for development of medical and industrial cannabis-based devices), and medical studies (e.g., pre-clinical and clinical research).

4.1 Cannabis Taxonomy

Treatment of patients is commonly done with a specific cannabis 'strain'. On the one hand, these 'strains' are not well defined in terms of biological activity or chemical composition, neither morphological features, and there is no clear definition of a cannabis 'strain' (Mudge et al. 2018). This lack of a clear definition of a cannabis 'strain' is also due to the uncontrolled interbreeding, spontaneous or manmade, between different cannabis chemovars (Mudge et al. 2018). Indeed, chemically identical or very similar cannabis 'strains' are sold by various producers under several different names (McPartland and Guy 2017). On the other hand, cannabis produces hundreds of phytomolecules, including phytocannabinoids, terpenes, and flavonoids (Aizpurua-Olaizola et al. 2016; Hanuš et al. 2016; Berman et al. 2018). Therefore, it is important to characterize the chemical composition produced by each 'strain' and thereby to define a 'chemovar' (Koltai and Namdar 2020).

Moreover, the general taxonomy for chemovars up to date is based only on the relative concentrations of THC and CBD, the two predominant forms of cannabis-produced phytocannabinoids following the process of decarboxylation (Small and Beckstead 1973). Chemovars producing high levels of THC (>85% of total phytocannabinoids, with CBD < 0.5%) were categorized as chemotype I. Chemovars high in CBD (CBD > 85% of total phytocannabinoids) were classified as chemotype III and those containing both CBD and THC at high levels were classified as chemotype II (Small and Beckstead 1973). Yet, this dichotomic (THC/CBD-based) chemotaxonomy disregards the plethora of other phytomolecules produced by cannabis chemovars (Elzinga et al. 2015).

4.2 Cannabis Chemical Constitutes

Cannabis chemovars produce around 150 phytocannabinoids, a structurally homogenous class of monoterpenoids. The two main phytocannabinoids, THC and CBD, were identified in Israel by Prof. Rafael Mechoulam during 1963–1964 (Mechoulam and Ben-Shabat 1999). Phytocannabinoids produce exclusively in *C. sativa* and may be divided into 11 main subfamilies (Hanuš et al. 2016). The plants synthesize phytocannabinoids in their acid form (e.g., Δ9-tetrahydrocannabinolic acid [THCA], cannabidiolic acid [CBDA], cannabichromenic acid [CBCA]); three possible biosynthesis pathways were recognized for phytocannabinoid from the precursor cannabigerolic acid (CBGA) (Hanuš et al. 2016). For decarboxylation, i.e., to release the acidic residue from the molecules, extensive heating is needed. Decarboxylation of THCA results with THC, the mind-altering phytocannabinoid. However, once a therapeutic activity is considered, the acid forms of the phytocannabinoids may also be active (Palomares et al. 2020).

Several phytocannabinoids were suggested to bind to specific, endocannabinoid receptors present in different cells and tissues in the human body (Izzo et al. 2009).

These cannabinoid receptors, type 1 (CB_1) and type 2 (CB_2) bind with even higher affinity endocannabinoids, which are the endogenous ligands of the endocannabinoids system (Izzo et al. 2009).

Hundreds of other compounds are produced by cannabis including terpenes and flavonoids. Terpenes are a family of compounds, including mono-, sesqui-, and diterpenes, terpenoids, and terpene alcohols. Terpenes are volatile and semi-volatile hydrocarbons and account for the typical aroma of cannabis (Breitmaier 2006; Aizpurua-Olaizola et al. 2016), yet, they are not unique to cannabis (Chen et al. 2011).

Other molecules produced by cannabis are flavonoids, mostly polyphenols, and flavones. These include cannflavins A and B, which are unique to cannabis (Rea et al. 2019), and others such as chyrisins and apigenins that are commonly found in other plant species (ElSohly and Gul 2014).

4.3 Entourage

Several studies suggested that the beneficial activity of cannabis could not be attributed to a single compound. Rather, improved biological activity was found to a mixture of cannabis compounds in comparison to that of a single compound (Russo 2019; Blasco-Benito et al. 2018; Nallathambi et al. 2018).

Indeed, also for other medicinal plants and plant extracts the biological effect of the whole plant extract (e.g., galenic preparation, solvent extraction, or crude oil) has the enhancement of activity over that of a single purified molecule. This preferred activity detected in phytomedicines was denoted as the 'entourage' effect (Ribeiro 2018; Williamson 2001). The 'entourage effect' as the enhanced activity of combinations of phytocannabinoids was first recognized by Mechoulam in Israel (Mechoulam and Ben-Shabat 1999).

More recent Israeli studies identified synergistic interactions between cannabis molecules for different biological activities associated with medical conditions (Mazuz et al. 2020; Namdar et al. 2019; Nallathambi et al. 2018; Anis et al. 2021). These synergistic interactions might lay the basis for the 'entourage effect' reported for cannabis preparations.

Several research groups in Israel demonstrated synergy in cannabis between phytocannabinoids (Berman et al. 2018; Mazuz et al. 2020) and synergy between phytocannabinoids and terpenes (Namdar et al. 2019).

Although the mechanism of the synergistic interactions between cannabis compounds is not known yet, at least partially they may be a result of the activation of new biological pathways not activated by each of the components alone (Mazuz et al. 2020; Nallathambi et al. 2018).

4.4 Entourage and Cannabis Domestication

Extensive ancient cannabis usage was recorded in the Middle East (detailed above) and other parts of the world, e.g., for ritual or medical purposes. This, we suggest, enhanced the 'entourage effect' developed during the domestication of cannabis (Koltai and Namdar 2020). Ancient people may have selected and bred different cannabis chemovars for properties that support the needs of medical treatments and ritual performance, based on experiential knowledge. As a result, the modern cannabis chemovars used today consist of a mixture of phytocannabinoids and terpenes that interact to confer an 'entourage effect', manifested these days as increased medical effectivity (Koltai and Namdar 2020).

4.5 Parasitage

We previously found that the richness of compounds in cannabis chemovars could depress or enhance biological activity (Namdar et al. 2020). Whole extracts (e.g., solvent extraction, crude oil, or galenic preparation) contain in many cases compounds that do not contribute to the desired biological or clinical effect and even negate it. Indeed, it was demonstrated in our studies that the removal of either antagonistic or non-active compounds resulted in higher specific activity, i.e., lowered the required concentrations of the remaining compounds for specific biological activity (Mazuz et al. 2020; Anis et al. 2021). We called this phenomenon the 'parasitage effect', a contra-'entourage effect', in which co-produced compounds interfere with each other to result in reduced chemo-biological activity (Namdar et al. 2020).

The mechanism that underlay the 'parasitage effect' is unknown, but we previously suggested it might result from e.g., the blockage of activated pathways by active cannabis compounds and/or blocking of receptors binding by these compounds (Namdar et al. 2020).

4.6 Identification of Synergism Between Molecules-API

Israeli studies suggested that using 'strains' only for designation of medical care may be problematic, due to the plethora of compounds produced by each of the 'strain' and the combinations thereof that confer different biological activities (Baram et al. 2019; Koltai et al. 2019; Koltai and Namdar 2020; Namdar et al. 2020). Therefore, we suggest that cannabis preparations should be optimized by selecting combinations of highly active plant ingredients (API) that show the greatest synergistic activity for the optimal efficacy of cannabis (Koltai and Namdar 2020). For manufacturing of improved cannabis-based drugs, extract fractions that contain

API and/or mixtures of purified API may be prepared and should be examined in clinical trials. These steps would lead to cannabis-based pharmaceutical drugs for a certain medical condition (Koltai et al. 2019; Koltai and Namdar 2020; Namdar et al. 2020).

4.7 Chemovar-Based Taxonomy and Breeding

Each cannabis chemovar produces tens of phytomolecules in particular combinations. We have found a statistical correlation between the major phytocannabinoids and certain terpenes co-produced in various cannabis chemovars (Namdar et al. 2019). For obtaining chemovars that produce the desired API in a combination beneficial to a certain medical condition, one, a generation of a comprehensive and functionally relevant taxonomy should be sought; chemovars may be divided into sub-groups based on statistical correlations between the main phytocannabinoids and their co-produced terpenes or based on biological and medical activities (Koltai and Namdar 2020). Two, rational, conventional selective breeding of cannabis may be considered for obtaining effective chemovars with proper composition and activity (Russo 2019).

4.8 Clinical Trials

Data on anecdotal evidence of successful cannabis treatment was received from licensed patients. This data included mainly information regarding cannabis 'strain (s)' (see Sect. 4.1 for Cannabis taxonomy) used for the best treatments, based on patients' opinions. However, anecdotal evidence may not fully support evidence-based medicine, and controlled clinical trials are needed. Many of the clinical studies done up to date with cannabis were carried in Israel. Many of them were focused on testing new routes of administration and examining cannabis as a possible add-on treatment for medical conditions that do not have a satisfactory pharmacological result following common treatments. These clinical studies are in a variety of medical fields, including rheumatology, dermatology, hematology, and neurology. Of note are the studies by Aran et al. (2019). In a retrospective clinical study, the tolerability and efficacy of CBD-rich cannabis treatment was examined in 60 children with autism spectrum disorder (ASD) and severe behavioral problems. It was found that behavioral outbreaks were improved in 61% of patients following the cannabis treatment (Aran et al. 2019). Moreover, a proof-of-concept, randomized, double-blind, placebo-controlled trial on 150 ASD participants was conducted in a single Medical center in Israel. In this clinical trial, it was proved that disruptive behavior was either much or very much improved in 49% of participants treated by high CBD

whole-plant extract versus 21% of participants treated by placebo, with no treatment-related serious adverse events (Aran et al. 2021). As indicated above, this study supported adding ASD to the list of approved indications for cannabis treatment by the Israeli Ministry of Health.

5 Conclusions

The ancient roots of cannabis use in Ancient Israel and the vicinity facilitate the importance of this plant for medical use on the one hand and its high potential on the other. In the cannabis-medicalization reform in Israel different medical conditions were defined as eligible for cannabis-based treatments. Both anecdotal shreds of evidence and clinical trials proved cannabis efficacy. Still, the active compounds and combinations of active molecules from cannabis that act to alleviate different symptoms associated with a medical condition are unknown. Research in Israel is focusing on the identification of active compounds and their combinations as an essential step towards improving *C. sativa* medical use. Results obtained in scientific labs should be further tested in clinical trials. The accumulated scientific knowledge is expected to facilitate cannabis medicalization in Israel. Future improvements might include the development of cannabis products with medical indication-specific activity. They might also support breeding for cannabis chemovars designated to support specific medical treatments.

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Traditional and Modern Health Uses of *Cannabis sativa* L. in Africa and Its Phytochemical and Pharmacological Profile

Esezah Kakudidi, Patience Tugume, Savina Asiimwe, and Godwin Anywar

Abstract Cannabis has been used for recreation and in traditional medicine in Africa for centuries since its introduction by Arab traders from India. Though Cannabis contains a variety of phytochemicals, its psychotropic activity is attributed mainly to the psychoactive compound Δ-9-tetrahydrocannabinol (Δ-9-THC). Additionally, cannabidiol (CBD) and cannabinol (CBN) are two main non-psychoactive cannabinoids present in cannabis/marijuana. Cannabis leaves are predominantly used in herbal preparations to manage both human and animal ailments in Africa and elsewhere. Among humans, cannabis leaves are used to treat over 20 ailments, mainly including asthma, measles, diabetes, dysentery, tuberculosis, cancer, cough, malaria, and also as an abortifacient. In animals, Cannabis is used to manage over 15 ailments, with the common ones being: East Cost fever, heartwater, pneumonia, dysentery, and trypanosomiasis. Pharmacological research has highlighted the benefit of Cannabis in managing chronic diseases like cancer, Alzheimer's disease, multiple sclerosis, and diabetes mellitus. Despite its medicinal uses, prolonged use of unprescribed Cannabis in humans results in social, psychological, physiological, and medical risks. This calls for regulated use and further pharmacological studies to establish efficacious but safe dosages. This chapter focuses on traditional ethnomedicinal uses in humans, ethnoveterinary uses, medical marijuana, and risks associated with cannabis use in Africa.

Keywords Medical cannabis/marijuana · Psychoactive · Cannabinoids · Ethnomedicine · Africa

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Abbreviations

ACDM	Advisory Council on the Misuse of Drugs
CBC	Cannabichromene
CBCA	Cannabichromenic acid
CBD	Cannabidiol
CBDA	Cannabidiolic acid
CBN	Cannabinol
EVM	Ethnoveterinary medicine
HIV	Human immunodeficiency virus
MMJ	Medical marijuana
NIDA	National Institute on Drug Abuse
OR	Odds ratio
p-CT	p-Coumaroyltyramine
PRO	Patient-reported outcomes
PTSS	Post-traumatic stress syndrome
RCTs	Randomized controlled trials
THC	(−)-Trans-Δ^9-tetrahydrocannabinol

1 Introduction

Marijuana (*Cannabis sativa* L.) is an ancient psychotropic plant that has reached Africa from China through India during the fifteenth century (Henschke 2019). Ethnographic and anthropologic evidence reveal longstanding consumption and cultural acceptance of Cannabis in most sub-Saharan Africa (Du Toit 1991). In Southern Africa, cannabis use was integrated into traditional culture (Maule 2015). Arab communities along the east African coast domesticated Cannabis for its fiber but used the wild variety as medicine and a mind-altering substance (Ahmad and Khalifa 1975). Though it was introduced in Egypt around the same time as its introduction to the East African coast, its acceptance in the form of dried leaves met some resistance but was eaten as hashish and much later used in pipes. The unacceptability of Cannabis in Egypt was because it was not integrated with an established cultural pattern (Du Toit 1991). Arab conquerors who spread the Islamic faith in North Africa introduced Cannabis to Morocco at the end of the seventh century (Merzoukia and Mesa 2002). Its cultivation was not common until the golden era of the Islamic civilization between the eleventh and fifteenth centuries and resulted in the distribution in other parts of North Africa. By the 1800s, Moroccans used Cannabis widely. However, by the end of the nineteenth century, strict laws to combat its trade were issued (Merzoukia and Mesa 2002). However, Morocco legalized its use for medicine, cosmetics, and industrial purposes (Oduor 2021).

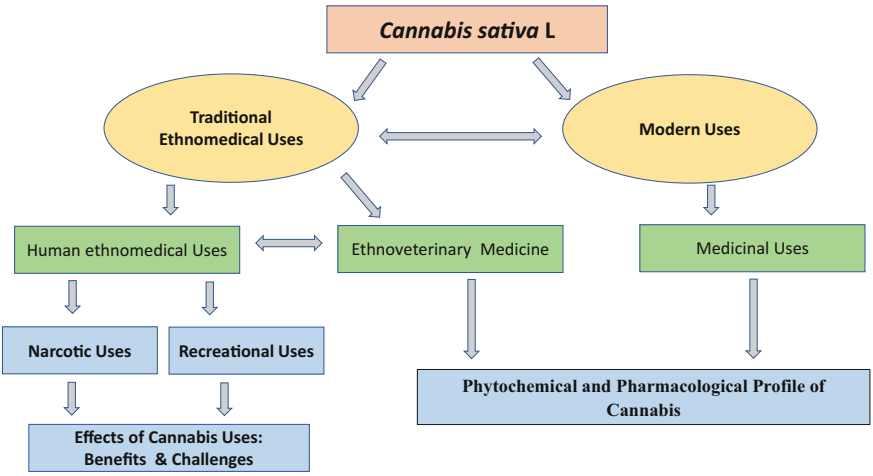

Fig. 1 Traditional and modern uses of cannabis

As a psychotropic substance, its medicinal properties have been recognized in modern times. Its activity is attributed to over 540 phytochemicals, but the primary psychoactive constituent is Δ-9-tetrahydrocannabinol. The current debate over its medical use is hinged on its bioactivity regardless of the risks associated with its continued use (Maule 2015). The debate has raised the curiosity of different researchers about the health benefits and risks of cannabis use. Consequently, pharmacological studies and a few clinical trials have validated the traditional use of medical Cannabis (Campbell et al. 2001). Large-scale clinical trials have not been given due attention despite over 20,000 publications on Cannabis, of which 50% were from 2010–2016 (Lawal et al. 2014; Paruk and Burns 2016; Radwan et al. 2015; Thomas and Elsohly 2015; Ware et al. 2010). In some instances, there have been disagreements between patient-reported outcomes (PROs) and the respective strength of the evidence from randomized controlled trials (RCTs), which therefore necessitate further research (Schlag et al. 2021).

In this chapter, we have reviewed the literature on the traditional uses of Cannabis in Africa. Our search focused on traditional ethnomedicinal uses in humans, ethnoveterinary uses, and its use as medical marijuana in Africa. We searched Web of Science, Google Scholar, PubMed, Scopus for research papers, reports, and books. We also searched other sources, such as government and other institutional reports, court rulings, local newspapers, and rulings for relevant cannabis content. The traditional and modern uses of Cannabis coupled with various effects, challenges, and benefits are depicted in Fig. 1.

Table 1 Traditional medicinal uses of Cannabis in Africa

Traditional/ ethnomedicinal uses	Part used	How it is used	Where it is used	References
Asthma	Not given	Not given	South Africa	Sorsdahl et al. (2009)
Cough/tuberculosis, cancer, pain reliever, blood cleanser/ asthma, diarrhea	Leaves	Decoction	Uganda	Anywar et al. (2020a)
Cough, tuberculosis	Leaves	Boiled with cow ghee and 1 teaspoon drunk 3 times a day	Uganda	Asiimwe et al. (2013)
Tuberculosis	Not given	Not given	South Africa	Lawal et al. (2014)
Boosting immunity in people living with HIV	Leaves	Decoction	Uganda	Anywar et al. (2020b)
HIV infections	Not given	Not given	South Africa	Peltzer and Mngqundaniso (2008)
Measles	Leaves	Decoction or cooked with silver cyprinid (small fish)	Uganda	Nalumansi et al. (2017)
Malaria	Leaves	Decoction	Uganda	Nalumansi et al. (2014)
		Infusion: two teaspoons are taken thrice a day	Uganda	Lee et al. (2019)
Diabetes mellitus	Not given	Not given	South Africa	van de Venter et al. (2008); Afolayan and Sunmonu (2010)
Cancer	Not given	Not given	South Africa	Koduru et al. (2007)
Abortifacient, induce labor, menstrual cramps, asthma	Roots Seeds	Hot water extract is taken orally	South Africa	Simon and Lamia (1991); Hillestad et al. (1977)
Induce labor, pain reliever, fever, catarrh, anorexia	Leaves	Aqueous extract drunk	Africa	Ahmed et al. (2018)

2 Traditional Ethnomedical Uses of *Cannabis Sativa* L in Humans

For centuries, plant resources have been and continue to be used by different human societies and cultural groups for their wellbeing. Many cultural groups rely on different plants as their primary means of healing, both in the form of traditional preparations and pure active principles (Asati et al. 2017). Cannabis is one of the world's oldest crops, and its use had started in the early Holocene (Mercuri et al.

2002). It was first used as medicine in India before the common era and before its introduction to western medicine (Li and Lin 1974). In Africa, cannabis herbal preparations for managing various diseases are similar to those in India, from where it was introduced by Arab traders (Du Toit 1980). Cannabis has a wide range of applications in traditional medicine in Africa (Table 1).

3 Ethnoveterinary Use of Cannabis

Ethnoveterinary medicine (EVM) is the scientific term for traditional animal health care (Ibironke and Olutayo 2010). EVM involves skills, knowledge, methods, practices, and beliefs among pastoral farmers. The use of EVM provides low-cost alternatives compared to modern veterinary services and drugs that are expensive and inaccessible to especially many rural pastoralists. The pastoralists know the symptoms and vectors of diseases, seasonal effects, and animal species affected by a particular malady (Ole-Miaron 2003). This is usually because elders mainly possess EVM knowledge, and like all other indigenous traditional knowledge, it is also transmitted orally from generation to generation (Tabuti et al. 2003). Accordingly, Ole-Miaron (1997, 2003) noted that the ability to diagnose livestock diseases was comparable with that of modern veterinary practitioners. The reliance on EVM is strengthened by the strong dependence on livestock for livelihood and the cultural history and biodiversity richness explored (Gradé et al. 2009). Apart from Africa, *Cannabis sativa* is one of the species that has been explored in EVM in various countries (Duvall 2019). Although *C. sativa* is used to manage various livestock diseases in different African countries, there are some cultural, ethnic, and/or regional differences in methods of preparation and administration (Table 2).

4 Medical Use of Cannabis

Cannabis is a generic term that refers to all aspects of the plant, exclusive of its products and how they are used (Small 2016). Cannabis has been used and cultivated by humankind for some 6000 years (Li and Lin 1974), and according to UNODC (2006), Africa was the highest cannabis producer globally. Medical Cannabis or medical marijuana (MMJ) refers to the therapeutic use of herbal Cannabis and its constituents (Murnion 2015). It is administered under medical supervision after establishing the target symptom-disease(s) (Van Rensburg et al. 2020).

Cannabis contains more than 540 phytochemicals, of which 100 are cannabinoids, the major ones being (−)-trans-Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Parry and Myers 2014). Historically, Cannabis has been used medically and is currently recognized under the UN drug control system (WHO 2020; Zuk-Golaszewska and Golaszewski 2018; Small 2016). Cannabinoids can be ingested orally, inhaled through vaporizers, used trans-dermally, and via

Table 2 Ethnoveterinary use of *Cannabis sativa* in Africa

Disease	Plant part used	Preparation	Dosage	References
Anorexia and debility: stimulate appetite	Leaves	Leaves eaten fresh	Not given	Nok et al. (1994)
Bloody diarrhea	Leaves	Pound fresh, or boiled and cooled, mixed with water, or soured milk	Drenching[a] with 1/2 to 1 L of decoction	Katunguka-Rwakishaya et al. (2004)
Cough	Leaves	Decoction drunk	Not given	Ssegawa and Kasenene (2007)
Colibacillosis	Leaves	Decoction, mixture of *Ficus* sp., *Parvonia* sp., *Paullinia pinnata*, *Pseudanlria hookeri*, *Thunbergia alata, Vernonia amygdalina* pounded, added to soured milk or water	Calf drenched for 2–3 days (dose not given)	Katunguka-Rwakishaya et al. (2004)
Diarrhea/ dysentery	Not given	Cold infusion	Not given	Gakuubi and Wanzala (2012)
East Coast fever	Leaves	Decoction; infusion After adding *Securidaca longipedunculata* roots	125 ml a day	Tabuti et al. (2003)
Heartwater	Leaves	Decoction	Drenching with 1 L	Katunguka-Rwakishaya et al. (2004)
Headache	Leaves	Leaves squeezed into the left nose and right ear	Not given	Katunguka-Rwakishaya et al. (2004)
Helminthiasis	Leaves/ shoots	A handful (300 g) plus seeds pounded, add 1 L of water, sieve or boil 0.5 kg leaves/seeds in 2 L of water	Drenching adult animals with 300 ml and 50–70 ml to calves	Matovu et al. (2020)
	Leaves	Boil 100 g of leaves with *Justicia betonica* (100 g) and *Tetradenia riparia* (150 g) in 2 L of water	Drenching with ¼ of extract to calves, small ruminants, and 1/2 L to adult cattle	Nalule et al. (2011)
Microbial infection	Leaves	Infusion drunk	Not given	

(continued)

Table 2 (continued)

Disease	Plant part used	Preparation	Dosage	References
Newcastle disease	Leaves	Soaked in drinking water	Not given	Abdu et al. (2000), Gakuubi and Wanzala (2012), Onwubiko et al. (2020), Saganuwan (2017), Uwagie-Ero et al. (2017)
	Leaves	A teaspoon of ash and water	1 teaspoonful +1 L of water + leaves	Lagu and Kayanja (2010)
Pneumonia	Not given	Cold infusion	Not given	Gakuubi and Wanzala (2012)
Prolapsed uterus in goats	Leaves	Liquid from squeezed leaves topically applied	Not given	Abdu et al. (2000)
Raises appetite in goats	Leaves	Liquid from squeezed leaves or animals fed on leaves	Not given	Abdu et al. (2000)
Trypanosomiasis	Leaves	Boiled with *Albizia coriaria* decoction drink	Not given	Katunguka-Rwakishaya et al. (2004)

[a] Drenching is the forced pouring of liquid preparations down the throat of an animal

suppositories. However, synthetic Cannabis is often delivered in pill form under medical supervision (Parry and Myers 2014).

Many scientists remained unaware of the therapeutic potential of Cannabis until the discovery of its main active ingredient, THC, in the 1960s (Atakan 2012; Taylor 2008). Medical cannabis-derived, purified, and standardized drugs are prescribed. However, the herbal form used in medicine remains controversial in many countries (Small 2016) since Cannabis is grouped in Class C or Schedule I based on harmfulness (ACDM 2008).

However, the use of medical Cannabis is on the rise due to the perception that it produces fewer side effects, controls symptoms better, and increases relief compared to mainstream medications (Coomber et al. 2003). The therapeutic potential of Cannabis has been established in the management of post-traumatic stress disorder (Greer et al. 2014; Roitman et al. 2014), chronic pain (Martin and Martin-Sanchez 2012), controlling nausea, stimulating appetite, and decreasing ocular pressure (Glauser 2012). Other therapeutic benefits include relaxed and heightened senses, muscular relaxation, analgesic, and anticonvulsant effects, relief from fibromyalgia, sleep apnea, and alleviation of cancer symptoms (Mujuru and Sekhejane 2014). Cannabinoids are effective in treating chemotherapy-induced nausea and vomiting in cancer patients (Sharkey et al. 2014). The benefits of Cannabis in healthcare have been confirmed by anecdotal reports and randomized clinical trials

(Zuk-Golaszewska and Golaszewski 2018). Preclinical and some clinical studies revealed positive effects of medicinal Cannabis on Alzheimer's disease, amyotrophic lateral sclerosis, chronic pain, multiple sclerosis, diabetes mellitus, dystonia, fibromyalgia, incontinence, gastrointestinal disorders, various cancers, atopic dermatitis, brain injuries, eating disorders, epilepsy, glaucoma, Huntington's disease, neuromuscular disorders, rheumatoid arthritis, sleep disorders, and Tourette's syndrome, though in many cases the supportive evidence is equivocal (du Plessis et al. 2014; Ebbert et al. 2018). While medical Cannabis is beneficial to the aforementioned health conditions, its safe use would require that healthcare practitioners be adequately equipped with knowledge of the evidence, indications, and legislation to support the use (Van Rensburg et al. 2020).

5 Adverse Effects of Cannabis

5.1 Effects on Health

Cannabis is important in managing different health conditions, though its consumption in doses other than those prescribed can result in serious medical consequences due to drug abuse and addiction (NIDA 2018). Drug addiction is a chronic relapsing disorder in which compulsive drug-seeking or drug-taking behavior persists despite serious negative consequences (Iyalomhe 2009). In Africa, Cannabis is the main substance for which patients seek treatment. Cannabis effects begin immediately when the drug enters the brain lasting 1–3 h. However, its consumption in food or drink results in short term effects within 1 h and may last for as long as 4 h (NIDA 2018).

A consistent association between lung cancer and cannabis smoking was observed in case studies conducted in North Africa (Mehra et al. 2006). A Tunisian case-control study of 110 cases of hospital-diagnosed lung cancer and 110 community controls found an association with cannabis use (odds ratio (OR) = 8.2) that persisted after adjustment for cigarette smoking. A pooled analysis of three Moroccan case-control studies also found an elevated risk of lung cancer among cannabis smokers who smoked tobacco (Berthiller et al. 2008). Smoking cannabis resulted in malignant changes in the respiratory tract, oropharyngeal cancers, and myocardial infarction (Ashton 2001). Cannabis smoking increased the risk of nasopharyngeal carcinoma in North Africa (Feng et al. 2009).

Adverse effects of medical Cannabis include; cannabis hyperemesis syndrome (Dezieck et al. 2017), impaired driving (Asbridge et al. 2012), and sleep disturbances (Wong et al. 2019). Cannabis is a central nervous depressant that produces drowsiness, slower reactions, decreased memory and attention, poor psychomotor task and driving performance that increases the risk of motor accidents (Asbridge et al. 2012; Li et al. 2012).

5.2 Effects on Social and School Life

Cannabis use weakens social interactions, problems at school, work, and with family and friends, legal and financial implications, and attracts negative judgment from society. In South Africa, cannabis users faced public stigma (Sorsdahl et al. 2012). Problematic cannabis use was associated with severe post-traumatic stress syndrome (PTSS), especially hyperarousal symptoms (Short et al. 2015). Paruk and Burns (2016) stipulated that Cannabis affects the brain resulting in memory loss, compromised academic performance, and increased dropout rates from school or universities. In West Africa, cannabis use resulted in laziness and other psychosocial problems, absenteeism, and lack of interest in school activities (Olurishe 2019). In Ghana University, students who used Cannabis reported health complications such as chest pains, itchy eyes, dehydration, and chronic cough (Adu-Gyamfi and Brenya 2015). In addition, the students reported dullness, oversleeping, and dizziness. Despite the adverse effects of cannabis use by students, a section of them reported that Cannabis increased their productivity, prolonged study hours, improved memory, and concentration (Adu-Gyamfi and Brenya 2015).

5.3 Crime

A study by Plüddemann and Parry (2003) revealed a high crime rate in cannabis-positive arrestees in South Africa. The main crimes were related to property offenses, violence, supply, possession, production, importation, exportation, and cultivation of Cannabis. Despite its role in fueling crime, cannabis use was reported to ease labor and fuel creativity (Leggett 2001).

5.4 Effects on Mental Health

As reported in many studies, mental health illness has been associated with cannabis use (Bostwick 2012; Rey and Tennant 2002). THC, the main psychoactive component of Cannabis, produces cognitive disturbances affecting long-term memory (Mechoulam and Parker 2013). However, some scholars believe that both risks and benefits of cannabis use have not been evaluated (Radhakrishnan et al. 2014; Zammit et al. 2008). Students in Cape Town who had used Cannabis showed symptoms of high-risk aggressive behavior and mental health disorder (Plüddemann et al. 2010).

Cannabis intoxication leads to acute transient psychosis (Arseneault et al. 2004; Regier et al. 1990; Sewell et al. 2009). Asuni and Pela (1986) reported a high percentage of cannabis-associated psychosis in patients in African hospitals. In South Africa, cannabis smokers were reported to be prone to psychosis with

hypomanic features (Rottanburg et al. 1982). Parents and healthcare professionals cited a cannabis-induced motivational syndrome (Arseneault et al. 2004). It was also reported to lead to dependence that manifests in restlessness, irritability, mild agitation, insomnia, nausea, and cramping (Brunton et al. 2008; Lüscher 2015), especially in daily users that stop cannabis use abruptly. Other problems associated with longtime cannabis abuse include lack of concentration, memory problems, and impaired judgment. In South Africa, adolescents exhibited psychotic symptoms after lifetime cannabis use (Paruk et al. 2009; Lachman et al. 2012). Additionally, large doses of potent cannabis products resulted in toxic psychotic disorder that manifested as amnesia and confusion (Solomons et al. 1990).

Cannabis use damages memory, distorts perceptions, impairs judgment and motor skills, alters heart functions, exhibits paranoia and lethargy (Abiodun and Afolayan 2007; Affinnih 1999). It is also associated with bipolar disorder (Leweke and Koethe 2008), increased risk of schizophrenia, depersonalization, fear of dying, irrational panic, and paranoid ideas (Thomas 1993). In Nigeria, cannabis abusers were admitted for schizophrenia (Odejide 2006).

Various studies reported emotional, social, and psychiatric problems associated with cannabis use in Nigeria. Psychiatric problems manifested as depression, anxiety, low-stress tolerance, low self-esteem, isolation, and delusions (Abiodun and Afolayan 2007; Adelekan et al. 2001; Eneh and Stanley 2004). Abuse of Cannabis manifested emotionally as anger, hate, and resentment among adolescent patients in Port Harcourt and Enugu state in Nigeria (Stanley et al. 2005; Okwaraji 2003). Three psychiatric hospitals in Ghana recorded mental and behavioral disorders resulting from cannabis abuse in 22.8% of in-patients (Ofori-Atta et al. 2010). Several patients reported at Sunyani Regional Hospital's psychiatric unit in 2012 had psychiatric illnesses related to cannabis abuse (Appiah 2014).

A Study in Kampala, Uganda, found that 22% of students used and abused drugs, the commonest being alcohol and Cannabis (UHRN 2013). Records indicate that 8% of mental illnesses registered in Butabika Hospital, Uganda are related to cannabis use (Hassan 2015).

5.5 Cannabis Use in Pregnancy

The use of Cannabis during pregnancy can cause abortion (Du Toit 1980; Henschke 2019), and it also affects unborn babies by altering responses to visual stimuli, increasing tremulousness, and high-pitched cries that are all indicators of neurological development problems (NIDA 2018). Prenatal cannabis exposure affected neural activity in the bilateral frontal cortex and right premotor cortex during response inhibition (Smith et al. 2004). It also resulted in low birth weight that required special medical observation under intensive care. However, there is inadequate data regarding the utilization of medicinal Cannabis during pregnancy and its effects on infants. Cannabis use during pregnancy resulted in anemia which was not observed in non-cannabis users during pregnancy (Gunn et al. 2016). Available data

indicate the presence of higher amounts of THC in maternal breast milk in contrast to the serum. However, there is no conclusive evidence of its effect on the neurodevelopment of infants when Cannabis is used by breastfeeding mothers (Henschke 2019).

5.6 Physiological Effects

Minor physiological effects of cannabis use include coughing and overeating, leading to weight gain (Bigand et al. 2019), while severe effects include seizures, anaphylaxis, burning red eyes, dry mouth, nausea, and heart palpitations. High levels of Cannabis were detected in urine in adult trauma patients in Johannesburg (Peltzer et al. 2008) and those below 20 years in Cape Town and Durban (Parry et al. 2004).

Abrupt stopping cannabis use results in a withdrawal syndrome that manifests as anger, anxiety, depression, loss of appetite, restlessness, sleep difficulties, chills, fever, headache, stomach pains, sweating, and tremors (Budney and Hughes 2006). Chronic cannabis use was associated with chronic bronchitis, emphysema, and other lung diseases (Perkel 2005).

6 Phytochemical and Pharmacological Profile of Cannabis

The identification of the chemical structure of Cannabis and its components was a result of the increase in scientific interest in the plant. This led to the identification and isolation of cannabinoids, which later led to their use as medication after scientific approval. This chapter highlights the phytochemistry, pharmacological actions, and/or therapeutic uses of Cannabis and its derivatives. *C. sativa* is characterized by complex chemical composition, including terpenes, carbohydrates, fatty acids, esters, amides, amines, phytosterols, phenolic compounds, and e cannabinoids (Andre et al. 2016).

Cannabis contains about 540 natural compounds, of which more than 100 have been identified as phytocannabinoids due to their shared chemical structure. The plant produces unique phytochemical compounds that consist of alkyl resorcinol and monoterpene groups (Asati et al. 2017). The primary psychoactive compound is Δ-9-tetrahydrocannabinol (Δ-9-THC) in addition to non-psychoactive cannabidiol (CBD) and cannabinol (CBN) which are responsible for the different pharmacological effects of Cannabis. For instance, Δ-9-THC, as an isolated form, induces acute psychotic reactions in normal individuals (Asati et al. 2017). CBD and CBN have shown to be partial agonists or antagonists at the prototypical cannabinoid receptors, CB1 and CB2. They have been reported to act as analgesics, anti-emetics, anti-inflammatory agents, anti-seizure compounds, and protective agents in neurodegeneration. Cannabis has for long been used as a medicinal agent to relieve pain and seizures. The presence of cannabinoids makes the plant good for treating

nausea, epilepsy, or vomiting associated with cancer chemotherapy, loss of appetite, and weight in HIV/AIDS patients.

Other minor cannabinoids include cannabichromenic acid (CBCA), cannabichromene (CBC), cannabinolic acid (CBNA), and cannabinol (CBN) (Hartsel et al. 2016; Appendino et al. 2011; Thomas and Elsohly 2015; Brighenti et al. 2017; Pellati et al. 2018a, b; De Backer et al. 2009). Cannabis contains over 200 terpenes and terpenoids (Shapira et al. 2019) that give Cannabis its scent. Terpenes are volatile compounds, while terpenoids are organic chemicals similar to terpenes but additionally contain oxygen in their composition (Chandra et al. 2017). Terpenes are divided into five classes, namely, monoterpenes, sesquiterpenes, diterpenes, triterpenes, and other compounds of terpenoid origins (Turner et al. 1976, 1980). The growing interest in the chemical compounds from *C. sativa* has led to the isolation of 8 tetrahydrocannabinol - type compounds whose structures were established using NMR and GC-MS analytical methods (Ahmed et al. 2018). The phytochemicals and pharmacological effects of Cannabis are included in Table 3.

Despite the pharmacological effects of cannabinoids, some studies have reported their toxic effects. For instance, high doses of THC produced hypothermia, hypolocomotion, catalepsy, and antinociception in animal models (Beaulieu 2005). Oral administration of Δ9-THC to rats was lethal at 800–1900 mg/kg, but non-lethal in dogs at 3000 mg/kg and monkeys at 9000 mg/kg (Thompson et al. 1973). Intracerebroventricular injection of feruloyltyramine (FT) and p-coumaroyltyramine (p-CT) isolated from cannabis seeds, roots, leaves, and resin caused hypothermia and motor incoordination in mice 160–240 min after the injection while p-CT also exhibited cataleptogenic effect in mice (Yamamoto et al. 1991).

7 Conclusion

This review highlights *Cannabis sativa's* contribution to the traditional ethnomedicine in Africa. The cannabis herbal preparations for managing various diseases in Africa are similar to those of India from where it was introduced. It is used to treat human ailments such as asthma, cough and tuberculosis, blood cleanser, measles, malaria, diabetes, cancer, catarrh, anorexia, dysentery/diarrhea, and boosting immunity/relieving stress in HIV patients. Despite being an abortifacient, it is used to induce labor and manage menstrual cramps. *C. sativa* has also been used in ethnoveterinary in managing anorexia and debility, anthrax, bloody diarrhea/dysentery, cough, colibacillosis, east coast fever, heartwater, and helminthiasis, Newcastle disease, pneumonia; prolapsed uterus in goats, trypanosomiasis and to stimulate appetite.

Medical Cannabis remains outlawed in many countries since its consumption is associated with social, psychological, physiological, and medical risks. Medical Cannabis controls disease symptoms better than several conventional medications. This has led the United Nations to recognize it under the drug control system.

Table 3 Phytochemistry and pharmacological effects of cannabis

Phytochemical compounds	Dosage	Pharmacological activity	References
1. 8β-hydroxy-Δ9-tetrahydrocannabinol	Not given	Dose-dependent hypolocomotive effect	Radwan et al. (2015)
2. Ajulemic acid (AJA), also known as CT-3 and IP-751	Not given	Non-steroidal anti-inflammatory properties	Burstein et al. (2004)
3. Arachidonyl ethanolamide (AEA)	Not given	Anti-tumor activity	Contassot et al. (2004)
4. Benzopyranepiridine	4 mg	Analgesic in animal models	Duran et al. (2004)
5. Cannabichromene (CBC) and Cannabidiol (CBD)	20 and 200 mg/kg	Significant anti-depressant effect in mice at $p < 0.01$)	El-Alfy et al. (2010)
6. Cannabigerol	5–20 mg/kg	Anti-epileptic and active in Huntington's disease models	Stone et al. (2020)
7. Cannabichromene (CBC)	10–75 mg/kg	Anti-seizure, active and in Huntington's and Parkinson's disease	Stone et al. (2020)
	Not given	Dose-dependent anti-inflammatory effects in polysaccharide induced paw edema in a close dependent manner	Delong et al. (2010)
8. Cannabidiol (CBD)	Not given	Anxiolytic and/or anti-psychotic actions	Zuardi et al. (2006)
	Not given	Anticancer effects in animal models	Pellati et al. (2018a, b)
	Not given	Inhibited cell proliferation and increased apoptosis	McPartland and Russo (2001)
	Not given	Reduced colon injury, inducible iNOS expression, and interleukin-1β, interleukin-10, and endocannabinoid changes associated with 2,4,6-dinitrobenzene sulfonic acid administration in mice (colitis). Antioxidant activity	Cascio and Pertwee (2014), Pertwee and Cascio (2014), Friedman and Devinsky (2015), Devinsky and Friedman (2015), Blair et al. (2015), Borrelli et al. (2009)
9. Cannabidiol, cannabinol, δ 9- and δ 8-tetrahydrocannabinol	Not given	Anti-seizure effects	Izquierdo et al. (1973)
10. Cannabidiolic acid, (CBDA)	Not given	Anticancer activity	Pellati et al. (2018a, b)
11. Cannabidivarin	0.2–400 mg/kg		Stone et al. (2020)

(continued)

Table 3 (continued)

Phytochemical compounds	Dosage	Pharmacological activity	References
		Anti-epileptic, active in Huntington's disease epilepsy models	
12. Dronabinol	2.5–20 mg/day	Anti-emetic activity in clinical trials	Asati et al. (2017)
13. Δ9-tetrahydrocannabinolic acid	20 mg/kg	Anti-seizure, active and in Huntington's and Parkinson's disease	Stone et al. (2020)
	Not given	Anticonvulsant, euphoric, psychoactive, analgesic	Cascio and Pertwee (2014), Pertwee and Cascio (2014), Friedman and Devinsky (2015), Blair et al. (2015)
14. Δ9-tetrahydrocannabinol (THC)	0.025–2.5 mg/kg	Anti-seizure, active and in Huntington's and Parkinson's disease	Stone et al. (2020)
	100 mg/kg	Dose-dependent anti-inflammatory effects in the lipopolysaccharide (LPS)-induced paw edema model	Stone et al. (2020)
	Not given	Locomotor suppressant, catalepsy, hypothermia suppressant, mild antinociceptive	DeLong et al. (2010)
	2.5 mg/kg ($p < 0.05$)	Antidepressant-like effects in mouse forced swim (FST) models	El-Alfy et al. (2010)
15. Levonantradol	2.5 3 mg	Analgesic efficacy	Blake et al. (2006)
16. Nabinolene	2–6 mg/day	Anti-emetic activity in clinical trials	Asati et al. (2017)
17. Tetrahydrocannabivarin	20 mg/kg	Anti-seizure, active and in Huntington's and Parkinson's disease	Stone et al. (2020)

Anecdotal reports and randomized preclinical and some clinical trials revealed positive effects of medicinal Cannabis on many ailments, though the supportive evidence is equivocal in many cases.

Unprescribed long-term use of cannabis results in addiction disorders. Various studies in some African countries have attributed cannabis smoking to cancer and cognitive disturbances. It affects social and school life, and it is associated with a high crime rate and aggressive behavior. Cannabis use can cause abortion but also affects unborn babies and infants through breastfeeding. However, there is no conclusive evidence of its effect on the neurodevelopment of infants. Narcotic and

recreational uses of Cannabis have been part of the history of African cultures. Such uses have resulted in potential addictiveness, especially among the youths. It impacts behavior, health, and society negatively by causing a heavy financial burden for rehabilitation.

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Traditional Claims on Cannabis: An Indian and Global Scenario

Swagata Dilip Tavhare and Rabinarayan Acharya

Abstract *Bhanga* (Cannabis) has been reported with numerous therapeutic, traditional, commercial, and sacred uses in India and across the globe. Its uses are deeply rooted in the cultural, social, and economic lives of the people. The inclusion of Cannabis under 'Scheduled E1' drugs in India restricts its use. However, being a crop of economic and medicinal importance, the pharmaceutical and various other sectors are showing much interest in the plant. The present review article delineates traditional, culinary, cosmetic, ritual, social, spiritual, recreational, economic, and therapeutic uses of Cannabis. The review illustrates various uses of Cannabis across the globe; noted from articles, publications, and books providing description of various parts, viz. leaves and seeds (*Bhanga*), flowering and fruiting tops (*Ganja*), resin (Charas), extract, tincture, and whole plant, stalks (Fibers). The review may be helpful to researchers, clinicians, and pharmaceutical companies to carry out further research for developing cost-effective healthcare options.

Keywords *Bhanga* · Cannabis · Folklore · Traditional · *Vijaya*

Abbreviations

AD	Anno Domini
BCE	Before the Christian era
CE	Common era
CNS	Central nervous system

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E External application of Cannabis
GI Gastrointestinal
I Internal route of administration for Cannabis

List of English Equivalents of Sanskrit/Ayurveda Terms Used in the Chapter

Non-English term	English equivalent
Ananda	Pleasure
Bahuvadini	Talkative
Bhanga	Leaves of cannabis, destroys diseases of *Kapha*
Chidalhada	Internal pleasure
Divya, *Kalaghni*	Supernatural, overcomes death, liberates creatures from earthly bonds
Ganja	Delirium
Harshini	Creating excitement
Jaya	Cures diarrhea
Madini	Causes intoxication
Manonmana	Accomplishes objects of mind
Matulani	Male and female flowers are separate
Mohini	Causes hypnotism
Ranjika	Create entertainment
Samvidamanjiri	Flower blooms in bunches, i.e., have inflorescences
Shakrashana	Worthy food of Lord Indra
Shivamuli	Favorite to Lord Shiva
Shunthi	Dry ginger
Siddhapatri	Leaves are used for achieving victory over diseases
Siddhi, *Siddhida*, *Bhanga*, *Trailokyavijaya*, *Vijaya*	Gives special blessings and is victorious in all three worlds
Tandrakruta	Create drowsiness
Unmattini	It creates intoxication

Note: Terminologies for disease names before Christ, medieval period may not resemble modern terms

1 Introduction

Bhanga(Cannabis) is an indigenous herb to central and western Asia, long cultivated in China, Nepal, India, Asia, Europe, and other tropical and temperate regions. Since dawn, all plant parts are being used commercially, agriculturally, medically, and

socially (Ayenigbara 2012). Therapeutic importance, various formulations, multivariant actions, and indications of Canabis have been well documented. (Acharya et al. 2015; Tavhare and Acharya 2016, 2017). Due to psychoactive action, it is banned as a therapeutic agent in many countries, and in India included in 'Schedule E-1'of Drugs & Cosmetics Rules 1945 of India (Malik 2005). However, in recent times, based upon its multi-therapeutic effects, many researchers are making sincere efforts to retrieve this drug in clinical medicine for the betterment of humankind. Notwithstanding the legal difficulties, it must be done to preserve the folk medicine associated with Cannabis. It is need of the hour that, Cannabis folklore needs further research and attention as folklore use bespeaks man's achievements in his climbing an evolutionary scale.

Various methods for using Cannabis have been deeply rooted in the cultural, social, and economic lives of societies. A serious, scientific, and purposeful outlook towards the folklore lifestyle is required, which could penetrate the mystery of Cannabis ethnicity. Beyond criminalization, legislative actions created limitations on research by restricting the procurement of Cannabis for academic and research purposes. This review is a step towards collecting all available traditional and ethnomedicinal claims at a single glance for understanding the therapeutic importance of Cannabis to readers. Various literature sources like journals of ethnobotany, books, manuscripts, and e-sources like 'Google Scholar', 'PubMed', 'Science Direct' and 'J-Gate', etc. were assessed by using mesh terms like '*Bhanga'*, 'Cannabis*'*, 'Marijuana', 'Hemp', 'Traditional', 'Folklore', 'Ethno-medicinal', 'Ethnobotanical', etc. The inclusion criteria were nomenclature, legal perspective, habitat, collection practices, etc., along with claims related to traditional and folklore practices of Cannabissuch as historical, culinary, cosmetic, economic, industrial, ritual, social, therapeutic, uses in pregnancy and post-partum, adverse effect, etc. Recreational claims of Cannabis were excluded from the review, and data were collected from January 2016 to Aug 2021. Selected data are presented sequentially as per the table of content.

2 Nomenclature for Cannabis

2.1 Nomenclature across Globe

Cannabis is known by various names in different countries across the globe (Alakbarov 2001; Lookyweed.com 2021; Pinho 1975; Ross 2005) as described in Table 1.

2.2 Nomenclature in Ayurveda Classics

Classical texts of Ayurveda describe Cannabis by various synonyms based on its mythological origin, pharmacognostical characters, and pharmacological actions on

Table 1 Worldwide names for Cannabis

SN	Language	Regional names	SN	Language	Regional names
1	Afrikaans	Dagga	23	Kashgar	Kandir
2	Arabi	Hinab, Kanab, Kinab, Nebatulqunb	24	Madagascar	Jea, Soroma
3	Arabic	Kinnab or Quinnab	25	Malaya	Forhmah
4	Brazil	Maconha, diamba, liamba	26	Mauritius	Gandia
5	Burma	Ben, Bhenbin, bin, Sechaub, Sejaubin	27	Mexican	Merihuana
6	Canton	Fu-ma	28	Mizab	Kif
7	Celtic	Kanas	29	Morocco	Hatchis
8	Chinese	Fuma, ma, Tama, Tangma	30	Norwegian	Hampefro
9	Dutch	Hennip, Indische, Hennepkruid, Kennip	31	Persian	Darakhtebang, Darakhtekinab, Nebatulqumab
10	English	Hemp, Indian hemp	32	Polish	Konop
11	French	Beuh,Canabier, Canabon, Canadi, Caneba, Cannab, Chambrie, Chamure, Chanvre, Churbe, Chanvreindien,Chauvenon, Cheneves, Haschisch, Herbe aux fakirs	33	Portugese	Canamo, Canhamo, Ordinario, Linhocanhamo
12	German	Hanf, Indischerhanf	34	Proberical	Canebe, Carbe
13	Greece	Cannabis	35	Roumanian	Canipa
14	Greek	Kánnabis	36	Russian	Konaplya
15	Hova	Rongonilahy, Rongony	37	Sadaxi	Ganja
16	Hungarian	Indian Kender	38	Sinhalese	Ganjagaha, Kansagaha, Matkansa
17	Italian	Canapa, canape Indian	39	Spanish	Canamo
18	Italian	Canapa	40	Sparish	Bangue de la India, Canano, CanamoIndiano
19	Indian	Bhanga, Vijaya	41	Swedish	Hampa
20	Ja Reunion	Amale, Gandia	42	Turkish	Hintkeneviri, Esrar
21	Janguedor	Caribe, carve	43	Vietnamese	Cansa
22	Japanese	Taima	44	Zulu	Intsanga

the central nervous system (CNS), gastrointestinal (GI) system, magical actions, psychological action, and adverse effect, etc. (Kaiyadeva 2006; Singh 1971; Tripathi 2009) (Table 2).

Table 2 Synonyms for cannabis mentioned in ayurveda

Basis of synonyms	Synonyms
Mythological origin	*Shivamuli*, *Shakrashana*
Pharmacognostical characters	*Matulani*, *Samvidamanjiri*
Action on CNS	*Bahuvadini*, *Ganaja*, *Ananda*, *Chidalhada*, *Harshini*, *Madini*, *Mohini*, *Ranjika*, *Tandrakruta*
Action on the GI system	*Jaya*, *Bhanga*
Magical drug, blessings	*Siddhi*, *Siddhida*, *Trailokya-vijaya*, *Vijaya*, *Siddhapatri*
Psychological effects	*Manonmana*
Adverse reactions	*Tandrakruta*, *Unmattini*

2.3 Nomenclature According to Parts of Cannabis Plant

Marijuana is the name for Cannabis obtained from *Cannabis sativa*. It is mainly used in forms like Charas, Hashish, *Ganja*, and *Bhanga*. *Charas is a separated resin; crude or purified*, obtained from the *Cannabis* plant and includes concentrated preparation and resin known as *hasish oil* or *liquid hashish*. *Ganja* is the flowering or fruiting tops (excluding the seeds and leaves when not accompanied by the tops). *Bhanga* is prepared from the leaves (and seeds), and it does not fall within the definition of Cannabis(hemp) (Anonymous 2017). Hemp seed was called *shahdanah*, which means royal seed (Alakbarov 2001).

3 Habitat

Cannabis *sativa* was among the plants grown in the early human sedentary communities. Taxonomically, *Cannabis sativa* Linnaeus, *Canabis indica* Lamarck, and *Cannabis ruderalis* Janisch are three different species described in terms of height and content of psychoactive molecules (Schultes et al. 1974). *Cannabis sativa* is a dioecious, rarely monoecious, annual plant of *Cannabaceae*, having erected stems. Depending on the environmental conditions and the genetic variety, it can reach up to 5 m (Farag and Kayser 2017). *C. sativa* preferably grows in wet places and near water bodies (Small 2015) and flowers in the month of July–August (Rana and Datt 1997).

4 Uses of Cannabis

4.1 Historical Perspective

Since historical times, Cannabis has been extensively used in various countries across the globe.

4.1.1 Collection of Cannabis

Cannabis collected on the full moon yields more amount of high-quality resin. Thus, collecting it on full moon occasions during spring and early summer when the plant produces copious amounts of resins becomes practical (Sharma 1977).

4.1.2 Cultivation of Cannabis

Cannabis is one of the oldest cultivated crops having a history of cultivation about 12,000 years ago. Archeological and written records facts regarding the cultivation of Cannabis for various purposes are found in Southeast Asia, India, The Middle East, Africa, South Africa, and South America for millennia, Central Asia, specifically Mongolia and southern Siberia, the Huang He River valley, the Hindu Kush mountains, South Asia, or Afghanistan (Warf 2014).

4.1.3 Culinary Uses of Cannabis

Food recipes prepared from Cannabis were into practice in some traditions of India, China, Nepal, Persia, etc. are described in Table 3.

4.1.4 Traditional Uses of Cannabis before and at the Beginning of the Christian Era

Cannabis has been extensively used for industrial, culinary, medicinal, religious, ritualistic, etc., as described in Table 4.

4.1.5 Traditional Uses of Cannabis at the Beginning of the Christian Era to the Eighteenth Century

At the beginning of the Christian era, up to the eighteenth Century, mostly it has been explored for various therapeutic uses like a diuretic, digestive, anti-flatulent, analgesic, antiepileptic, etc. are given in Table 5.

4.1.6 Traditional Therapeutic Application of Cannabis in the Medieval Period

During the medieval period, Cannabis was used extensively in various dosage forms for various indications (Table 6).

Table 3 Various recipes prepared by using parts of cannabis

N	Name of recipe	Part used	Recipe	Reference
1	*Bhanga* Pakoras	Leaves	Fresh or dried cannabis leaves are mixed with chick-pea flour	Sharma (1977)
2	*Bhanga* parathas	Seeds	Large, round wheat bread dough is stuffed with crushed or powdered roasted seeds and then baked in an earthen oven or shallow-fried in a skillet	
3	*Bhanga* balls	Fresh, tender leaves	Fresh, tender leaves of cannabis are crushed or finely powdered and mixed with a small amount of water. Seeds are added at times. These balls are taken as snacks with tea or coffee	
4	Pillai legiyam	*Ganja*	Ganja fried in ghee, strained, and mixed with sugar	Chopra and Chopra (1957)
5	Purnadhilegiyam	*Ganja*	Ganja washed several times in hot water, dried, powdered, then mixed with ghee, sugar, dry ginger, pepper, and spices	
6	Majiyam	*Ganja*	A kind of fire-dried and powdered majun prepared from ganja and with Palmyra jaggery, spices, and even added plantains	
7	Purnadhi	*Ganja*	*Ganja*, dried ginger, sittarattai (lesser galingale), black pepper, nutmeg, cloves, cinnamon, aniseed, licorice, cumin, rose-buds, gallnut, ghee, and sugar, pounded together and heated over a fire till they take the consistency of a thick jelly. One-eighth proportion is of *ganja* (excluding ghee and sugar)	
8	*Lutki*	*Bhanga*	A beverage that was prepared by soaking bhanga in wine	Alakbarov (2001)
9	*Mudra*	*Bhanga*, *opium*, *herbane*	A beverage that was prepared by soaking *Bhanga*, opium, and herbane in wine	

4.2 *Traditional Claims of Cannabis in Modern Era Reported from India*

During the nineteenth and twentieth centuries, cannabis was researched upon through animal and human experimentation.

4.2.1 Traditional Claims on Oral Administration of Cannabis Leaves

In India, in folklore practice, it has been internally used for the management of diarrhea, dysentery, eye troubles, stomach/digestive complaints, uterine gas, gonorrhea, piles, convulsions, asthma, hemorrhages, tetanus, hydrophobia, depression, hypertension, bladder inflammation, nervous disorders (Table 7).

Table 4 Traditional uses of Cannabis before and at the beginning of the Christian era to the eighteenth century

Timeline	Uses	Country	References
Since 4000 B. C.	Earliest plants cultivated by man for fibers	China	Li and Lin (1974)
104–87 B.C.	Manufacturing of strings, ropes, textiles, paper, etc. from cannabis stem	China	Dai (1989)
206 B.C. - 220 A.D.	Fruits as food	China	Touw (1981)
2700 B.C.	As a medication for management of rheumatic pain, intestinal constipation, disorders of the female reproductive system, malaria	China	Aldrich (1997)
110–207 A. D.	Wine prepared from cannabis was used for anesthesia during surgical procedures, seeds as medicine, and laxative. Cannabis was mentioned as a psychoactive &hallucinogenic drug	China	Li and Lin (1974)
B.C. era	Seeds for making kitchen oil	Nepal	Touw (1981)
1000 years B. C.	As a recreational drug, one among five sacred plants used for religious purposes, known for psychoactive effects, also used as medicine	India	Touw (1981)
B.C. era	Sacred; little description about its religious or medicinal use	Tibet	Touw (1981)
Ninth century BC	Described as a psychoactive	Assyria	Li (1978)
B.C. era	Biphasic effect	Persia	Touw (1981)
450 B.C.	Ritualistic and euphoric purposes	Europe	Aldrich (1997)

4.2.2 Traditional Claims for External Application of Cannabis Leaves

In India, Cannabis is reported for its external uses to manage photophobia, ophthalmia, piles, orchitis, hydrocele, cuts and wounds, inflammations, erysipelas, neuralgia, dandruff, ear problems, worm infestation, skin diseases, and initial stages of uterine prolapse (Table 8).

4.3 Traditional Applications for Cannabis in the Modern Era Reported in Countries outside India

4.3.1 Traditional Claims for Cannabis Seed

Internally, the administration of seed is indicated for the management of gonorrhea, leucorrhoea, galactorrhoea, and post-partum hemorrhage, etc. Externally, seeds are used to treat rheumatism (Trivedi 2012), suppurated or delayed wound healing

Table 5 Traditional uses of Cannabis at the beginning of the Christian era to the eighteenth century

Timeline	Uses	Country	References
18th A. D.	Highly used for medicinal purpose	India, the Middle East, and Africa	Fankhauser (2002)
1000 A. D.	Quoted in a medical compendiums, as Avicena	Arabica	Fankhauser (2002)
1464	Used as a diuretic, digestive, anti-flatulent, 'to clean the brain,' and to soothe the pain of the ears Resin treatment cured epilepsy, but the addiction was reported	Arab	Aldrich (1997)
15 A.D.	Used for management of snakebite, to facilitate childbirth, malaria, fever, anthrax, asthma, and dysentery	Africa	Pinho (1975)
16 A.D.	The use of seeds is quoted for the treatment of diseases	Brazil	Pinho (1975)
16 A.D.	Cannabis used for toothache and menstrual cramps	Africa	Pinho (1975)
16 A.D.	Cultivation exclusively for food	Europe	Aldrich (1997)
1150	Manufacturing of paper	Spain, Italy	Aldrich (1997)

(Sharma 1977), hardening, contraction of the uterus, uterine tumors (Russo et al. 2003), burns (Nautiyal et al. 2000) (Table 9).

4.3.2 Traditional Claims for Various Parts of Cannabis

Various parts like flowers, flowering tops, resins derived from leaves and flowers, latex, bark, whole plants, etc., have been reported to treat diseases like menstrual disorders (Nautiyal et al. 2000), asthma, cataracts, headaches, etc. leucorrhoea, epistaxis, palpitation (Rajan et al. 2009), diarrhea (Manandhar 1993), strangulated hernias (Manandhar 1993), hydrocele, prolapsed of the uterus (Touw 1981), mania, hysteria, asthma, tetanus (Mikuriya 1969), colds (Shah 1982), and sleeplessness. In which opium is contraindicated, prevention and curing of sick headaches, malarial and periodical headaches, acute mania, whooping cough, asthma, dysuria, and dysmenorrhea (Siddique et al. 2006), healing wounds, cuts, and burns, gonorrhea, menorrhagia, diarrhea, cholera, hydrophobia, tetanus, and rheumatism (Rawat et al. 1997), hemorrhoids, inflammations, hydrocele (Nadkarni 2010; Rana and Datt 1997), and cutaneous eruptions (Rajwar 1983).

Cannabis mixed with *Dhatura* (*Dhatura metel* L.) is reported as an anti-aphrodisiac (Touw 1981). The action of Cannabis and strychnine were counteracting (Kabelilk et al. 1960).

Cannabis extract in a dose of 1 grain in combination with 1/fourth grain of ipecacuanha, 0.25–2 grains, and 20 mg was used to treat chronic pain, asthma, tetanus, and gonorrhea. Tincture in a dose of one drachm internally is indicated for

Table 6 Therapeutic applications of different parts use of Cannabis in the medieval period

Part use of cannabis	Dosage form	Method of application of Canabis leaves	I/E[a]	Indication	
Leaves	Fresh leaves	Oral administration juice after food	I	Loss of appetite	Mu'min (1669)
		Juice as nasal drops	E	Cold	Mu'min (1669)
		Apply the juice to the ear	E	Earache	Mu'min (1669)
		In poultice form on eyes	E	Photophobia	Tibbnama (1712)
		Paste on head	E	Vermin	Mu'min (1669)
		Application of paste on hairs	E	Dandruff	Mu'min (1669)
		In poultice form on the rectum	E	Hemorrhoids	Tibbnama (1712)
		In poultice form on the skin	E	Inflammation of skin	Irawani and Bin (1700)
	Dried leaves	Chew the leaves	I	Bowel complaints	Shah (1982)
		Oral administration of dry leaves powder by mixing with sugar, fry well in ghee, add some black pepper	I	Chronic diarrhea	Manandhar (1993)
		Oral administration 1. Mix with poppy seeds and take 2. Mix about 1.5 g leaves with a bit of sugar and black pepper powder and eat	I	Dysentery	Dymock (1884), Russo et al. (2003)
		Oral administration by mixing with asafoetida	I	Hysteria	Russo et al. (2003)
	Decoction	Oral administration	I	Nervousness	Alakbarov (2001)
		Gargles, several times a day	E	Quinsy	Alakbarov (2001)
Seed	Decoction	Oral administration	I	Vomiting, flatulence, anuria	Alakbarov (2001)
	Seed-oil	Application on damaged skin	E	Burns	Alakbarov (2001)
		Apply liniment prepared from seed-oil	E	Inflammation of mucus membranes	Alakbarov (2001)
		Apply on the affected part	E	Neuralgias	Alakbarov (2001)

(continued)

Table 6 (continued)

Part use of cannabis	Dosage form	Method of application of Canabis leaves	I/E[a]	Indication	
		Pour drops in the ear	E	Earache and worms infestation	Aldrich (1997)
		Apply seed oil on joints	E	Rheumatism	Pellegrini et al. (2020)
		Apply on the external surface of the tumor	E	Uterine tumors	Jain and Puri (1984)
Roots	Decoction	Application of bandage	E	Abscesses	Mu'min (1669)
		Gargle/rinse the mouth	E	Toothache	Tibbnama (1712)
		Apply bandage of decoction	E	Ulcers	Mu'min (1669)

[a]*I* internal route of administration, *E* external application

dilatation of half-crown Os uteri and rapid labor and delivery within an hour-and-a-half (Dymock 1884).

One tablespoon of decoction prepared from seeds and flowers added with one glass of water is suggested to treat the mild and moderate types of diabetes (Alakbarov 2001).

Cannabis possesses various properties like an astringent, tonic, aphrodisiac, intoxicant, stomachic, analgesic (Dymock 1884), abortifacient (Prajapati 2010), digestive, astringent, narcotic (Shrivastav et al. 1980), anti-flatulence (Dymock 1884), stimulant (Dhiman 2004), anti-diarrheal (Shrivastav et al. 1980), diuretic (Rawat et al. 1997) as illustrated in Fig. 1.

4.3.3 Disease Indication for Cannabis

Traditional use of Cannabis has been reported from countries like Afghanistan, China, Guatemala, Iran, Jamaica, Mexico, Morocco, Nepal, Pakistan, Saudi Arabia, Senegal, South Africa, United States, West Indies, Vietnam, Yugoslavia, Zimbabwe, etc. Various parts of Cannabis were used for more than 27 indications like wasting diseases, relief in fluxes, rheumatism, gout, migraine, muscular pains, gastric cramp, abdominal pain associated with indigestion, cancer, cancer pain, neuralgia, hallucinogen, coughing, hysteric conditions, epilepsy, cholera, breast engorgement, urinary incontinence, diabetes, diarrhea, dysentery, headache, asthma, malaria and cramps, constipation, vomiting due to lead poisoning, etc. conditions (Table 10).

Table 7 Traditional claims on oral administration of Cannabis leaves in India

Method of application/dose	Uses/indications	Reference
Two-three pieces of fresh leaves are chewed	Diarrhea, eye trouble, stomach diseases, digestive disorders like dyspepsia and other bowel complaints	Shah (1982), Khongsai et al. (2011), Trivedi (2012)
Half a drachm[a] of dried tender leaves mixed with little sugar and black pepper powder	Acute or chronic diarrhea	Dymock (1884)
With seed	Uterine gases, fibroid, hemorrhage	Russo et al. (2003)
With seed and sugar	Stomach trouble, indigestion	Sahu (1984)
With stem	Relieve irritant and painful sting of the wasp and also reduce swelling	Negi et al. (1999)
Fresh juice	Discharge in diarrhea and gonorrhea	Aziz et al. (2018)
Fresh juice	Piles	Shrivastav et al. (1980)
Mixed with sugar and well fried in ghee with the addition of black pepper	Chronic diarrhea	Manandhar (1993)
With poppy seed	Dysentery	Russo et al. (2003)
Powder	Convulsions, otalgia, abdominal disorders, diarrhea, somatalgia, and haematorrhoea	Prajapati (2010)
Powder	Eye trouble, dysentery	Shah (1982)
Mixed with maize flour for animals	Diarrhea and dysentery (in humans and animals)	Dhiman (2004), Rawat et al. (1997)
Mixed with asafoetida	Hysteria	Tibbnama (1712)
Fried powder administered with honey	Diarrhea and dysentery	Trivedi (2012)
Leaves, flowering tops of female inflorescence mixed with tobacco	Asthma, hemorrhages, tetanus, hydrophobia, depression, hypertension, bladder inflammation, gonorrhea, and nervous disorders.	Shah (1982), Small (2015), Retnam and Martin (2006)
Roasted leaves of the female plant and the unripe fruits with honey	Sedative	Shrivastav et al. (1980)
Five grams per day	Pain and swelling in orchitis	Harborne (1994)
Nasal route	Deterging of brain	Sultana and Rahman (2017)
Leaves boiled in milk	Digestive, astringent, and narcotic	Nadkarni (2010)
Boiled in water to prepare an aqueous extract and cool it in a dose of about 15 g	Hydrophobia	Trivedi (2012)

[a] 1 Drachm = 1/8 of a fluid ounce is equal to 3.69 ml or 60 grains

4.3.4 Pharmacological Actions of Cannabis

Literature available across the world depicts the use of Cannabis for various actions like abortifacient, parturifacient, emmenagogue, hypnotic, tranquilizer, diuretic,

Table 8 Traditional claims for external applications of cannabis leaves in India

Method of application/dose	Indication	Reference
Over bruised area	Affections of the eye with photophobia; ophthalmia, swelling in orchitis, hydrocele, wounds, and cuts healing, local inflammations, erysipelas, neuralgia	Dastur (1962)
	Piles	Chopra (1940)
	Hemorrhoids	Sultana and Rahman (2017)
Applied to the head	Dandruff	Harborne (1994)
	Vermin	Dastur (1962)
Applied on hairs and hair roots	Dandruff and head lice killer	Qureshi et al. (2011)
Applied on tumor growth	Dissolve tumor	Khongsai et al. (2011)
Applied on skin	Skin diseases, burns, and piles	Shah and Jain (1988)
Turmeric, onions, and warm gingelly oil	Painful piles	Touw (1981)
Paste with water, then mixed with milk and sugar	Intoxicating liquor producing euphoria	Trivedi (2012)
Put the leaves in a soft muslin cloth and kept inside the vagina at bedtime	Initial stages of uterus prolapsed	Trivedi (2012)

antispasmodic, anodyne, hallucinogen, narcotic, ant-helminthic, antiseptic, hemostatic, psychotropic, analgesic, aphrodisiac, anti-galactagogue, etc. to achieve a desired therapeutic result (Table 11).

4.4 Traditional Aspect on Industrial Uses of Cannabis

Hemp fibers were used to make garments and the seeds to medicate in vapor baths (Dymock 1884). The seeds contain a fixed oil used as a varnish. It is used as a fish poison in Bengal and as a spread on beds to drive away bugs (Sharma et al. 2008). Cannabis has been cultivated for fiber, nutritious seeds, and medicinal value (Conrad 1997). The Chinese used hemp widely to prepare rope, garments, paintings, sails, bowstrings (Li 1974).

Table 9 Traditional claims for Cannabis seed on internal and external administration

Method of application/dose	Use	Reference
Internal		
Infusion	Gonorrheal disease	Trivedi (2012)
Mixed in a portion with lentils and vinegar	Reduced female genital lubrication	Dymock (1884)
Dry seeds	Inhibit maternal milk production	Dymock (1884)
	Post-partum hemorrhage	Stuart (2014)
External		
Seeds oil	Rheumatism	Pellegrini et al. (2020)
	Suppurated or delayed wound healing, hardening, contraction of the uterus	Touw (1981)
	Hard tumors	Zuardi (2006)
	Uterine tumors	Manandhar (1993)
	Burns	Jain and Puri (1984)
Seed juice dropped in the ear	Earache and worms infestation	Aldrich (1997)

5 Traditional Claims for the Use of Cannabis in Pregnant and Breastfeeding Mother

The use of Cannabis in human pregnancy remains a great concern. Available traditional, historical and epidemiological data support low toxicity to mother or child even in pregnancy. Traditionally, Cannabis has been used for treating nausea, vomiting during pregnancy (Russo et al. 2003), in fatal cases of hyperemesis gravidarum (Dreher et al. 1994), management of pain during pregnancy and labor (Westfall et al. 2006). The use of Cannabis by pregnant women has no association with prematurity or congenital anomalies in the baby (Witter and Niebyl 1990).

6 Adverse Effects of Cannabis

In Greek & Rome, the drug has been mentioned as psychoactive since the beginning of the Christian era (Fankhauser 2002). Traditional manuscripts and books have also pointed out the adverse effects of excessive use of various parts of Cannabis (Mu'min 1669), as given in Table 12.

Crude resin (7 mg/ml) and phenolic compound (7 mg/l) from leaves are highly toxic to small fish (*Lebistes reticularis*) with mortality of 85 and 97%, respectively. (Sharma et al. 2008).

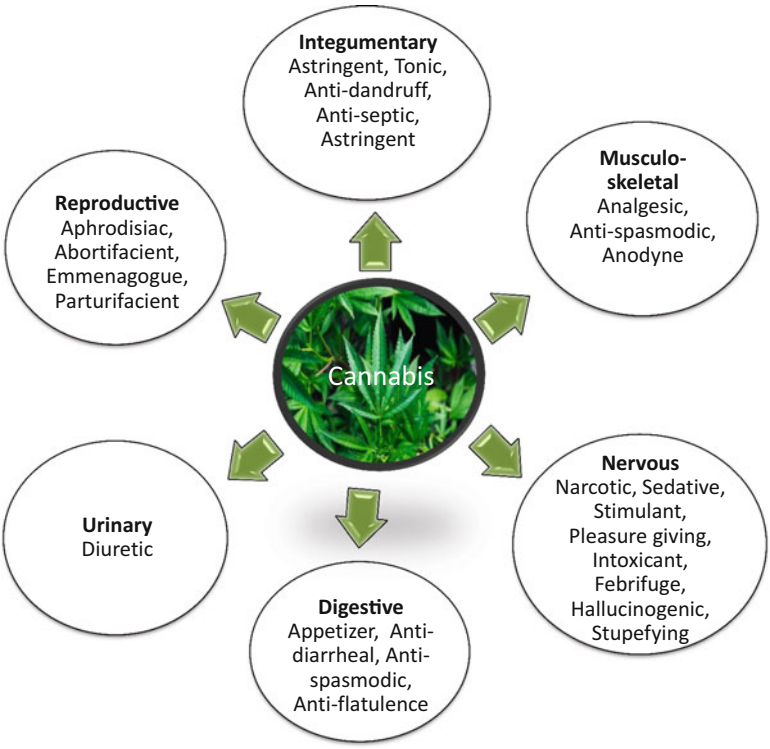

Fig. 1 System-wise pharmacological actions of cannabis

7 Processing of Cannabis

7.1 Traditional Aspect of the Cannabis Processing

Extensive diverging opinions were seen on the substances counteracting the effects of Cannabis or serve as an antidote. Persian people were using cow's milk to decrease Cannabis ill effects (Sharma et al. 2012). Bhanga prepared with milk is considered purified in India (Johnstad 2020; Nadkarni 2010). It is used as an aphrodisiac and taken for recreational purposes.

7.2 Ayurvedic Aspect of the Cannabis Processing

Ayurveda classics have mentioned processing of Cannabis leaves by washing with water till greenish color of water fades away (Acharya 2003; Anonymous 2010), by overnight dipping it underwater (Sharma 2001), by boiling it in cow's milk for three

Table 10 Traditional applications, indications of cannabis reported outside India

Country	Part used	Method of application/dose	I/E[a]	Indication	Reference
China	Inflorescence	Hot water extract	I	Wasting diseases, relief in fluxes, rheumatism	Li and Lin (1974)
	Seed	Decoction	I/E	Migraine, cancer, and hallucinogen. Externally for rheumatism	Li (1977)
Guatemala	Leaves	n.a.[b]	E	Muscular pains	Manandhar (1993)
Iran	Dried flowering top or the dried fruit	Fluid extract	I	Abdominal pain associated with indigestion, cancer-associated pain, rheumatoid arthritis, gastric cramps or neuralgia, coughing	Zagari (1992)
	Seed	Infusion	I	Rheumatoid arthritis, gout, hysteria, epilepsy, cholera	Li (1977)
	Seed	Oil	E p. r.[c]	Cramps, constipation, vomiting due to lead poisoning	Li (1977)
	Seed	Oil	E	Breast engorgement	Li (1977)
	Seed	2 g of seed oil several times a day	I	Urinary incontinency	Li (1977)
Jamaica	Resin	Hot water extract	I	Diabetes	Morrison and West (1982)
	Powdered leaf	Mixed with cattle feed	I	Diarrhea	Morrison and West (1982)
	Leaves	Dried leaves are ground with *Datura Stramonium* leaves, *Picrorhizaschrophulariflora* stem, and water	E	Headache	Morrison and West (1982)
	Seed	Crushed seeds mixed with curd	I	Dysentery	Morrison and West (1982)
Nepal	Leaves	n.a.	I	Stomach pain and flatulence	Siwakoti and Siwakoti (2000)

Pakistan	Leaves	Paste	E	Lice killer	Leporatti and Lattanzi (1994)
South Africa	Whole plant	Hot water extract	I	Asthma	Simon and Lamla (1991)
Yugoslavia	Seeds	Hot water extract	I	Diabetes	Tucakov (1978)
Zimbabwe	Aerial parts	Hot water extract	I	Malaria	Asprey and Thornton (1955)
Iran	Seed	Infusion	I	Rheumatoid arthritis, gout, hysteric conditions, epilepsy, cholera	Morrison and West (1982)
	Seed	Oil	E	Reduces breast engorgement or reduces milk secretion	Bose et al. (1964)
	Dried fruit	Fluid extract	I	Whooping cough	Li (1977)

[a] *I* internal route of administration, *E* external application
[b] *n.a.* details not available
[c] *p.r.* per rectal

Table 11 Traditional applications and pharmacological actions of Cannabis reported outside India

Country	Part used	Method of application/ dose	I/ E[a]	Action	Reference
Afghanistan	Resin	Hot water extract	I	Abortifacient	Ross (2005)
South Africa	Root and seed	Hot water extracts	I	Abortifacient	Woo et al. (1981), Lee et al. (1977)
Pakistan	Whole plant	Hot water extract	I	Parturifacient	Ahmad (1957)
Iran	Dried fruit, dried flowering top or the dried fruit	Fluid extract	I	Hypnotic and tranquilizer	Zagari (1992)
	Seed	Fluid extract	I	Diuretic	Bose et al. (1964)
Jamaica	Flower, leaf, and twig	Hot water extract	I	Antispasmodic, anodyne	Asprey and Thornton (1955)
Mexico	Aerial parts	Smoke	I	Hallucinogen	Diaz (1977)
Morocco	Aerial parts	n.a.[b]	I	Narcotic	Bellakhdar et al. (1991)
Nepal	Leaves, seed	Decoction	I	Anthelmintic (in adults)	Bhattarai (1992)
Nepal	Leaves	Juice	E	Antiseptic, haemostatic	Bhattarai (1993)
Nepal	Seed	Two teaspoonfuls of powdered seeds are made into a paste with sesame (*Sesamum indicum*L.) oil applied intra-vaginally during labor	E	Parturifacient	Bhattarai (1994)
Saudi Arabia	Aerial parts	Mixed with honey, sugar, and nutmeg	I	Psychotropic	Anonymous (1946a,b)
United States	Inflorescence	Fluid extract	I	Narcotic, analgesic, antispasmodic, aphrodisiac	Ross (2005)
	Aerial parts	Dried and smoke	I	Aphrodisiac (for both sexes)	Smith et al. (1977)
	Flowering top	Hot water extract (one teaspoon of plant material is steeped in 2 cups of boiling water) taken two to four times a day	I	Potent antispasmodic, anodyne, narcotic	Meyer (1934)
West Indies	Whole plant	Hot water extract	I	Antispasmodic	Ross (2005)
China	Inflorescence	Hot water extract	I	Stupefying, hallucination	Kabelilk et al. (1960)

(continued)

Table 11 (continued)

Country	Part used	Method of application/ dose	I/ E[a]	Action	Reference
China	Seed	Decoction	I/ E	Anodyne, emmenagogue, febrifuge	Kabelilk et al. (1960), Li (1977)
Iran	Seed	Infusion	I	Analgesic, sedative, diaphoretic	Bose et al. (1964)
Iran	Seed	Oil	E	Lactation suppressant	Bose et al. (1964)
Iran	Dried fruit	Fluid extract	I	Hypnotic and tranquilizer	Bose et al. (1964)
South Africa	Root and seed	Hot water extracts	I	Abortifacient, Parturifacient, Emmenagogue	Woo et al. (1981), Lee et al. (1977)
South Africa	Root and seed	Hot water extracts	I	Abortifacient	Woo et al. (1981), Lee et al. (1977)

Claims indicated the use of Cannabis against the venom of poisonous fish bites, scorpion stings, and post-partum anal fissures (Tavhare and Acharya 2016)
[a] *I* internal route of administration, *E* external application
[b] *n.a.* details not available

Table 12 Adverse effects of excessive cannabis use

Part of the cannabis	Adverse reactions to excessive use
Cannabis resin and leaves	Mental exaltation, intoxication, a sense of double consciousness, finally loss of memory, gloominess
Leaves	Injurious to organs of sense, liver, stomach, deteriorates color of the face, leads to dropsy, mental disorders, dries the brain, decreases sexual desire, and dries the sperm
Seeds	Injurious to human health, dries sperm, decreases sexual ability, causes ulcers in the bowels

hours (Acharya 2003) and by boiling in a decoction of *Acacia arabica* L. bark for 12.5 minutes (Dwivedi 1997).

7.3 Research Aspect of the Cannabis Processing

Experimental studies demonstrated that Cannabis leaves processed by washing with water eliminated sedative effect in animals (Tavhare et al. 2021) as well as humans (Tavhare et al. 2019).

8 Antidotes for the Adverse Effects of Cannabis

Milk, pepper with honey, curd prepared from cow's milk with *Shunthi* (dry ginger) or *Nimbuka* (*Citrus limon* L.) juice are reported as an antidote for Cannabis. Cow's milk and dry ginger or crushed wet root of *Sandesada* (*Delonix elata* L.) with water can neutralize the adverse effects caused by *Bhanga* (Nadkarni 2010). To mitigate the side effects of hemp seeds, hempseeds were suggested to be combined with poppy seeds and *iskanjabin*(a boiled mixture of honey and vinegar) (Mu'min 1669). As per Ayurveda, cow's milk is helpful for the absorption of toxic principles. As Cannabis increases the secretion of Pitta (Acidic components in the stomach and intestine), if used in excess, it creates hyperacidity and ulceration in the GI tract. Milk neutralizes acidic components and helps heal ulcers; hence, it serves as an antidote for adverse effects due to hypersecretion of acids. Dry ginger also effectively neutralizes the acid.

It would be interesting to carry out scientific research to find out the effects of these traditional antidotes of adverse psychotropic influences of Cannabisat the molecular level. Finding the mechanism of interaction of traditional antidotes with natural cannabinoids and endocannabinoid receptors like CB1 and CB2 would help develop scientifically proven antidotes in case a person needs after Cannabis use (inhalation or ingestion).

9 Spiritual Analogous of Cannabis

Cannabis has a long history of use in spiritual contexts. Archaeological evidence points to ritual uses in China 2500 years ago and in Judahite worship in Israel dating back to the eighth-century BCE claiming connection of Gods and great men with *Bhanga*(Johnstad 2020). Various names like *Shivamuli* (Favorite to Lord Shiva, known as Adiyogi, i.e., the first Yogi who propounded Yoga), *Shakrashana* (Worthy food of Lord Indra), *Siddhi*/*Siddhida* (gives special blessings and is victorious in all three worlds), *Trailokya-vijaya*/*Vijaya* (helps to conquer). These names and attributes to *Bhanga* suggest mythological and spiritual uses of the drug (Tavhare and Acharya 2016).

10 Conclusion

Cannabis is a treasure trove of phytochemicals and has vast therapeutic importance and traditional, culinary, cosmetic, ritual, social, spiritual, economic uses. Though some of its traditional uses for treating various ailments have been established through preclinical and clinical researches, many are still yet to be established scientifically. In this respect, the role of Cannabis in providing medicinal benefits

may need to be reconceptualized, not as a recreational vehicle of escapism but as a serious attempt to deal with difficult physical, psychological, social, economic circumstances. The present review enumerated the traditional applications of Cannabis for researchers and pharmaceutical companies to carry out further research for developing cost-effective healthcare medicinal remedies from Cannabis.

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Cannabis (*Bhanga*) in Classical Text of Ayurveda: An Evidence-Based Rationale

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Abstract Ayurveda has delineated a unique classification entitled 'Upavisha varga' comprising of certain semi-poisonous medicinal plants. *Bhanga* (Cannabis) is one amongst them in this category depicting its narcotic nature from Sanskrit synonyms. *Bhanga* has been in use since the Vedic age under the controversial plant of Soma that had special importance due to its mystical effects on the brain. All the texts of Ayurveda have described *Bhanga* in detail of its pharmacological properties, indications, various dosage forms, doses, pharmacovigilance aspects, and its extensive use in Indian Alchemy. The following review throws light on the occurrence and usage of *Bhanga* in excerpts from classical texts of Ayurveda from a pharmacological and pharmaceutical point of view thus, providing a rationale for its safe medical usage.

Keywords Ayurveda · *Bhanga* · Cannabis · Classical · Evidence · Review · Upavisha · Vijaya

Abbreviations

CNS	Central nervous system
ECS	Endocannabinoid system
GI	Gastro-intestinal

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IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
NDPS	Narcotic drugs and psychotropic substances
THC	Tetrahydrocannabinol

1 Introduction

Ayurveda has a unique branch named 'Agadtantra', dealing with toxicology wherein drugs of poisonous plants, minerals, and animal origin have been classified. Among the group of poisonous plants, namely, Upavisha Varga (group of semi-poisonous plants), *Bhanga* (*Cannabis)* is an important plant falling under the natural source of narcotics. *Bhanga* is mentioned under schedule E1 of the Drugs and Cosmetics Act (Anonymous 2016). Tetrahydrocannabinol and many other cannabinoids are the important phytoconstituents from *Bhanga*. In India, *Bhanga* is commonly referred to as Cannabis leaves. There are three psychotropic products of Cannabis, namely Charas/Hashish (resin), Ganja (flowering tops), and Bhang (leaves). There are restrictions on the use of Cannabis owing to its narcotic effects under the Narcotic Drugs and Psychotropic Substances (NDPS) Act, 1985 (Anonymous 1985). Since leaves (commonly known as Bhang) and seeds are not included in the definition of Cannabis, these are technically not banned under Federal Law (NDPS). However, growing the plant is banned as it produces banned Charas and Ganja. The law in several states restricts people from the cultivation of Cannabis and consuming Cannabis or any of its byproducts.

As per Ayurveda, *Bhanga* can be used therapeutically after some useful traditional processing techniques. It has been included in numerous formulations in various lexicons, treatises, and compendiums of Ayurvedic literature. The following review is an effort to highlight the therapeutic usage of *Bhanga* as denoted in the classics of Ayurveda.

2 Brief History of *Bhanga* in Classical Texts

Soma is a highlighted but mysterious plant in Vedic literature, especially in Rigveda and Atharvaveda (Shah 2015). It has been attributed to many botanical sources. *Cannabis* is considered to be one of the sources of *Soma*. The word *Soma* is related to the moon, ambrosia, nectar, etc. The plant's habitat has been quoted as Kailash mountains, Munjawat mountain, which lies northwest of the Himalayas. Geographically Cannabis has the same distribution up to Punjab, which again coincides with the dispersal of *Soma* seeds to the Kurukshetra region. The way of a traditional preparation of *Soma* drink quoted in Vedas match the preparation of *Bhang*. Also,

the effects produced by *Soma* are equivalent to that of *Bhanga (Cannabis)* (Ray 1939). Chris Bennet has expressed some similar views in his book (Bennet 2010).

Cannabis is also present in archaeological artifacts depicting *Soma* as a composite psychoactive substance comprising *Ephedra* and *Cannabis* (Merlin 2003). The word '*Bhanga'* has been described in Atharvaveda among five sacred plants along with *Soma* (Bapat 2015). There is no direct reference to *Bhanga* in Samhitas (Basic canonical Hindu scriptures comprising hymns, prayers, and liturgical formulas), including the Rig Veda, the Yajur Veda, and the Sama Veda, and the Atharva Veda (https://www.merriam-webster.com). At the same time, Rasa Granthas (books of Indian Alchemy) have a thorough description of *Bhanga*.

3 *Botanical Source a*nd Ayurvedic Nomenclature

The botanical source of *Bhanga* is a dioecious erect herb named *Cannabis* belonging to the family Cannabinaceae. Almost 2 meters in height, spread widely among Uttarakhand, Punjab, West Bengal, extending southwards (Anonymous 1986). The Ayurvedic description of the plant includes specification of *Sanskrit* synonyms which depict its morphology viz. *Matulani*, *Samvida Manjiri* referring to the presence of flowers as separate male and female appearing in bunches/inflorescence (Sivaram et al. 2018). Some synonyms refer to the action of *Bhanga* on the central nervous system like *Bahuvadini*—one that produces delirium, *Harshani*, *Madini* and *Mohini* refer to producing hallucinations/stage of euphoria; *Tandrakruta* refers to drowsiness, *Vijaya/Jaya/Bhanga* refers to usage in gastrointestinal disorders, etc. (Tavhare and Acharya 2017). After a thorough review of *Nighantus* (lexicons), it has been observed that almost forty synonyms are attributed to *Bhanga*, indicating its wide therapeutic usage. It has been classified under various *Varga* (classes) of drug groups by seers, namely *Abhayadi*, *Guduchyadi*, *Karveeradi*, *Shatapushpadi*, etc. (Acharya et al. 2015).

4 Pharmacological Properties and Actions

Ayurveda, based on its fundamental principles, describes the pharmacological properties of a plant on five attributes known as *Rasapanchak* comprising of *rasa* (taste), *vipaka* (post-digestion effect), *Veerya* (potency), *Guna* (quality), and *Prabhava* (special effect) (Ranade et al. 2021).

Bhanga possesses *Tikta Rasa (*bitter taste), *Ushna Veerya (*hot in potency), and *Katu vipaka* (post-digestive pungency that influences specific *dosha*). Most lexicons have quoted *Bhanga* to possess *Grahi* (~intestinal fluid absorbents), *Dipana* (appetizer), and *Pachana* (improves digestion) helps further in absorbing the excessive moisture of the intestinal mucosa, thereby helpful in conditions like diarrhea where stool consistency is liquified (Tavhare and Acharya 2017).

5 Formulations in *Chikitsa Grantha* (Compendia) and *Rasagrantha* (Indian Alchemy Text)

The review has been made from almost twenty-six *chikitsa granthas* (classical texts of Ayurveda dealing with treatment) and forty-one *Rasashastra granthas* (Alchemy texts). On keen reading, it has been observed that the indications comprise of one primary indication followed by its usage in other disease conditions. Besides, we also get information regarding *Prayojyanaga* (partly used), *Karma* (action), K*alpana* (dosage forms), *Anupana* (vehicle), *Aushadha Sevana Kala* (time and period of administration), *Pathya- Apathya* (do's and dont's/contra-indications), specific uses and instructions of the formulations. Further, these indications can be classified for internal administration and external/topical administration. The list of various formulations for internal administration wherein *Bhanga* forms an integral part has been cited alphabetically along with their indications, doses, and references in Table 1, 2 and 3.

5.1 Indications

In classical texts of Ayurveda in India, a total of 193 formulations are recommended for internal administration, among which 102 formulations have *Bhanga* as a major constituent. The majority being indicated in *Vajeekarana-33* (Aphrodisiacs) (Table 2), *Grahani/Sangrahani-28* (malabsorption/sprue) (Table 1), followed by *Rasayana* (rejuvenation), *Atisara* (Diarrhoea), *Jwara* (Fever), etc (Table 3).

Jatiphaladi Churna for *Sangrahani* (malabsorption), *Atisara* (Diarrhea), *Grahani* (sprue/malabsorption), *Kaphachintamani Rasa* for *Kapha Roga* (ailments due to dysfunction of *Kapha*), *Lakshmivilasa Rasa* for *Vatavyadhi* (Musculoskeletal disorders), *Rasayana* (rejuvenators), *Vajeekarana* (Aphrodisiac) and *Kameshwara Modaka* for *Vajeekarana* (Aphrodisiac) *Rasayana* (rejuvenators) have been continually advocated by classics.

Recent studies have reported that cannabis could possess peripheral antagonizing effects on erectile function by stimulating specific receptors in the cavernous tissue. Also, some inherent differences between primate and non-primate species concerning cannabis effects on erectile functions have been documented (Gratzke et al. 2010). The endocannabinoid system (ECS) plays a role in gut homeostasis, modulates gastrointestinal motility, developing visceral sensation and inflammation, and being recently referred to in pathogenesis of Inflammatory Bowel Disease (IBD). The therapeutic potential for the endocannabinoid system has been identified through numerous subsequent studies investigating the effects of cannabinoid agonists and endocannabinoid degradation inhibitors in rodent models of IBD (Kulkarni and Brown 2000).

Ninety-one formulations have been observed with *Bhanga* as a minor ingredient. In contrast, seventeen formulations of *Bhanga* have been denoted for its external use

Table 1 Formulations for the internal administration of *Bhanga* mentioned in *Grahani* (Sprue/malabsorption)

S. No.	*Yoga* (formulation)	*Adhikara* (indications)	Matra[a] (dose)	Reference
1	*Agnikumara rasa*	*Grahani* (sprue/malabsorption)	1 Shana (=4 g)	Bhatt (2011), Shah (2005b)
2	*Anya Kalpa*	*Sangrahani* (malabsorption)	1 Gunja (=125 mg)	Vallabhacharya (1996)
3	*Anyat Lai Churna I*	*Sangrahani* (malabsorption)	1–4 Masha (=1–4 g)	Mishra (1999)
4	*Anyat Lai Churna II*	*Sangrahani* (malabsorption)	1.5 Masha (1.5 g)	Mishra (1999)
5	*Lai Churna (Bruhat)*	*Grahani* (sprue)	1 Masha (=1 g)	Shah (2005c)
6	*Bruhat Lai Churna (i)*	*Sangrahani* (malabsorption)	1 Masha (=1 g)	Mishra (1999)
7	*Gangadhara Churna (Bruhat)*	*Grahani* (sprue/malabsorption)	1–3 Masha (=1–3 g)	Pandit (1990)
8	*Grahanigajakesari rasa*	*Sangrahani*, *Grahani* (sprue/malabsorption)	2 Ratti/1 Maricha (=250 mg)	Shah (2005a), Pandit (2004a)
9	*Grahanikapata rasa (II)*	*Grahani*, *Kaphapitta Sangrahani* (sprue/malabsorption)	1 Masha (=1 g)	Pandit (2004a), Shastri (2010), Vaishya (1993)
10	*Grahanikapata rasa*	*Grahani* (sprue/malabsorption)	2 Masha (=2 g)	Pandit (2004a)
11	*Grahanishardula Churna*	*Grahani* (sprue/malabsorption)	2 Masha (=2 g)	Pandit (2004a)
12	*Grahanyari rasa*	*Grahani* (sprue/malabsorption)	1 Chanaka/andika (=250 mg)	Pandit (2004a), Das (2011)
13	*Jatiphaladi Churna*	*Sangrahani*, *Grahani* (sprue/malabsorption) *Atisara* (Diarrhoea)	1 Karsha, 1 Tola (=10 g)	Shah (2005a), Bhatt (2008), Bhishagvara (2000), Shastri (2010), Vaishya (1993)
14	*Kameshwara Modaka*	*Grahani*(sprue/malabsorption)	n.a.	Bhishagvara (2000)
15	*Lai Churna (Laghu)*	*Sangrahani*, (sprue/malabsorption) *Atisara* (Diarrhoea) *Grahan I* (sprue/malabsorption)	1 Tanka (=4 g)	Chaubhe (2000), Mishra (2002), Vaishya (1993)
16	*Lai Churna*	*Sangrahani* (sprue/malabsorption)	n.a.	Vaishya (2005)
17	*Lai Churna (Madhyama)*	*Grahani* (sprue/malabsorption)	1 Masha (=1 g	Shah (2005c)
18	*Lai Churna*	*Grahani* (sprue/malabsorption)	1 Masha (=1 g)	Shah (2005c)

(continued)

Table 1 (continued)

S. No.	*Yoga* (formulation)	*Adhikara* (indications)	Matra[a] (dose)	Reference
19	*Lai Churna/ Madhya Lai Churna*	*Sangrahani* (sprue/ malabsorption)	4 Masha (=4 g) 2 Masha (=2 g)	Shah (2005c), Chaubhe (2000)
20	*Lai Churna (4) (Laghu)/Lai Rasa*	*Grahani*, *Atisara* (sprue/malabsorption, Diarrhoea)	1–4 Masha (1–4 g)	Shah (2005c), Mishra (1999)
21	*Lavika Churna I (Madhyama)*	*Grahani* (sprue/ malabsorption)	1 Tola (=10 g)	Shah (2005c), Chaubhe (2000)
22	*Lavika Churna II (Mahat)*	*Grahani* (sprue/ malabsorption)	n.a.	Shah (2005c), Chaubhe (2000)
23	*Madana Modaka*	*Grahani* (sprue/ malabsorption)	n.a.	Vagbhata (2010), Shah (2005c)
24	*Mundyadi Gutika I*	*Sannipata Sangrahani* (sprue/ malabsorption)	3 Nishka (=9 g)	Vaishya (1993), Shah (2005c)
25	*Talisadi Churna*	*Grahani*, *Atisara* (sprue/malabsorption, Diarrhoea)	1.5 Masha (=1.5 g)	Shah (2005a), Shastri (2010), Bhatt (2008)
26	*Vijaya Gutika*	*Sangrahani* (sprue/ malabsorption)	2 Tola (=20 g)	Mishra (1999)
27	*Vyoshadi Churna*	*Sangrahani* (sprue/ malabsorption)	3 Masha (=3 g)	Vaishya (1993)
28	*Madanodaya Modaka*	*Rajayakshma*, *Sangrahani*	3–6 Masha (=3–6 g)	Mishra (2009)

[a] *n.a.* doses information not available

in various diseases like scalp disorders, musculoskeletal disorders, headache, skin diseases, and fever.

5.2 Cannabis Plant Parts Used

Seeds and leaves separately or leaves and seeds together of *Bhanga* have been exclusively mentioned as ingredients in almost all the formulations followed by whole plant usage (Fig. 1).

5.3 Dosage Forms

On review, it has been observed that there are almost twenty-two types of dosage forms of *Bhanga* in classics.

Table 2 Formulations for the internal administration of *Bhanga* mentioned in *Vajeekarana* (aphrodisiac)

S. N.	*Yoga* (formulation)	*Adhikara* (indications)	Matra[a] (dose)	Reference
1	*Bruhat Kameshwara Modaka*	*Vajeekarana* (aphrodisiac)	6 Masha (=6 g)	Shah (2005c)
2	*Churna (ii)*	*Vajeekarana* (aphrodisiac)	n.a.	Bhatt (2008)
3	*Daradadi Vati*	*Vajeekarana* (aphrodisiac)	1 Makushtha[c]	Pandit (2004b)
4	*Gokshura Paka (ii)*	*Vajeekarana* (aphrodisiac)	3 Masha to 1 Tola (3 g to 10 g)	Pandit (2004a)
5	*Kamagnisandiapana Modaka*	*Rasayana* (rejuvenation) *Vajeekarana* (aphrodisiac)	1 Karsha (=10 g)	Mishra (2003), Das (2011)
6	*Kamadeva rasa*	*Vajeekarana* (aphrodisiac)	2 Masha (=2 g)	Pandit (2004a)
7	*Kamadeva Vati*	*Vajeekarana* (aphrodisiac)	4 Tola (=40)	Bhatt (2008)
8	*Kamadeva Vati*	*Rasayana*, *Vajeekarana (*rejuvenation, aphrodisiac)	2 Tola (=20 g)	Shah (2005b)
9	*Kamadeva Modaka Rasayana*	*Vajeekarana* (aphrodisiac)	n.a.	Das (2019)
10	*Kamadeva Modaka Rasayana II*	*Vajeekarana* (aphrodisiac)	n.a.	Das (2019)
11	*Kameshwara Modaka*	*Vajeekarana* (aphrodisiac)	1 Modaka[b]	Pandit (2004b)
12	*Kameshwara Modaka*	*Vajeekarana* (aphrodisiac), *Rasayana* (rejuvenation)	1/2 Karsha (=5 g) 1 Tola (=10 g)	Vagbhata (2010), Shah (2005b), Soori (1990), Das (2011)
13	*Kameshwara Modaka*	*Vajeekarana* (aphrodisiac)	1/2 to 1 Tola (5–10 g)	Pandit (2004a)
14	*Kameshwara Modaka*	*Vajeekarana* (aphrodisiac)	4 Masha (=4 g)	Pandit (2004a)
15	*Kameshwara Modaka*	*Vajeekarana* (aphrodisiac)	1 Tola (=10 g)	Pandit (2004a)
16	*Kameshwara Modaka*	*Rasayana* (rejuvenation), *Vajeekarana* (aphrodisiac)	6 Masha (=6 g)	Pandit (2004a)
17	*Kameshwara Modaka*	*Vajeekarana* (aphrodisiac)	n.a.	Bhatt (2008)
18	*Kameshwara Modaka*	*Vajeekarana* (aphrodisiac)	1–3 Masha (=1–3 g)	Pandit (2004a), Das (2011)

(continued)

Table 2 (continued)

S. N.	*Yoga* (formulation)	*Adhikara* (indications)	Matra[a] (dose)	Reference
19	*Kamasundara Modaka*	*Vajeekarana* (aphrodisiac)	1–4 Masha (=1–4 g)	Shah (2005b), Pandit (2004a)
20	*Laxmivilasa A valeha*	*Vajeekarana* (aphrodisiac)	n.a.	Bhishagvara (2000)
21	*Madana Modaka*	*Vajeekarana* (aphrodisiac), *Rasayana*	2 Tola (=20 g)	Das (2019)
22	*Madananda Modaka*	*Vajeekarana* (aphrodisiac)	2 Masha to 0.5 Tola (2–5 g)	Shah (2005c)
23	*Mahakameshwara I*	*Vajeekarana* (aphrodisiac)	n.a.	Shah (2005c)
24	*Maha Kameshwara Modaka*	*Vajeekarana* (aphrodisiac)	n.a.	Shah (2005c)
25	*Pushti Dava*	*Vajeekarana* (aphrodisiac)	7 Masha (=7 g)	Das (2019)
26	*Rasayana yoga*	*Vajeekarana* (aphrodisiac)	n.a.	Bhishagvara (2000)
27	*Rativallabha Modaka*	*Vajeekarana* (aphrodisiac)	1 Tola (=10 g)	Shah (2005c)
28	*Rativallabha Modaka*	*Vajeekarana* (aphrodisiac)	1 Tola (=10 g)	Shah (2005c), Pandit (2004b), Das (2011)
29	*Stambhana Avaleha*	*Vajeekarana* (aphrodisiac)	n.a.	Shah (2005b)
30	*Vati (Bhanga)*	*Vajeekarana* (aphrodisiac)	4 Tola (=40 g)	Bhatt (2008)
31	*Vati (Bhanga)*	*Vajeekarana* (aphrodisiac)	n.a.	Bhatt (2008)
32	*Veeryastambhakari Vatika*	*Vajeekarana* (aphrodisiac)	1 Masha (=1 g)	Shah (2005c), Bhishagvara (2000)
33	*Vijaya Ghruta*	*Vajeekarana* (aphrodisiac)	n.a.	Shah (2005c)

[a] *n.a.* doses information not available
[b] No direct reference for metric equivalents of modak is available
[c] No direct reference for metric equivalents of makushtha (size of a mat bean) and badarasthi (size of Ziziphus seed) is available

It is evident from Fig. 2 that *Bhanga* has been mainly advocated in *Churna* (powder) form followed by its wide usage in herbo-mineral preparations of Indian alchemy, *Modaka* (larger than a tablet usually greater than 10 g), *Vati* (tablets), and *Avaleha* (confectionaries).

Among the above-mentioned 22 dosages forms; powder, herbo-minerals, tablets, *Dhoopa* (powder for fumigation), *Loha* (preparation containing iron ash), *Pottali* (here it is a mercurial preparation) fall under solid dosage forms. In comparison,

Table 3 Formulations for the internal administration of *Bhanga* mentioned in other disorders

S. No.	*Yoga* (formulation)	*Adhikara* (indications)	Matra[a] (dose)	Reference
1	*Agnikumara rasa III*	*Agnimandya* (lowered digestion status)	3 Masha (=3 g)	Pandit (2004a)
2	*Bhanga Churna (ii)*	*Kushtha* (skin disorders)	n.a.	Bhatt (2008)
3	*Bhanga Churna (Bharjita)* (iii)	*Jwara* (fever)	n.a.	Bhatt (2008)
4	*Bhanga Churna*	*Jwara* (fever)	n.a.	Mishra (2002)
5	*Bhanga Churna*	*Amatisara* (amoebic dysentry)	n.a.	Shastri (2010)
6	*Bhanga Putapaka*	*Nasaroga* (nasal disorders)	n.a.	Mishra (2002)
7	*Bruhat Lai rasa (ii)*	*Atisara* (diarrhea)	1 Masha (=1 g)	Mishra (1999)
8	*Churna (i)*	*Putanaroga* (pediatric disorder)	n.a.	Das (2019)
9	*Dhananjaya*	*Agnimandya* (lowered digestion status)	n.a.	Bhatt (2008)
10	*Dnyanodaya rasa*	*Jwara* (fever)	n.a.	Bhishagvara (2000), Shah (2005b)
11	*Dyanodaya rasa*	*Rasayana* (rejuvenation)	1–2 Masha (1–2 g)	Pandit (2004b)
12	*Gokshura Paka*	*Kshaya* (~tuberculosis)	–	Bhatt (2008)
13	*Gokshuradi Paka*	*Prameha* (~diabetes mellitus)	1 Aksha (=10 g)	Bhishagvara (2000)
14	*Jaya patra Churna*	*Nasaroga* (nasal disorders)	n.a.	Das (2011), Shah (2005a)
15	*Jayadi Vati*	*Shoola*, *Vandhyatwa* (pain, infertility)	1 Chanaka (=250 mg)	Shah (2005a)
16	*Jayakhanda Churna*	*Atisara* (diarrhea)	n.a.	Shah (2005a)
17	*Jwalanala rasa*	*Ajeerna* (indigestion)	4 Masha (=4 g)	Vaishya (1993)
18	*Kameshwara Modaka III*	*Rasayana* (rejuvenation)	1 Karsha (=10 g)	Pandit (2004b)
19	*Karpuradya rasa*	*Prameha* (diabetes mellitus)	As per Agni[b]	Chaubhe (2000), Bhatt (2011), Pandit (2004a)
20	*Katukadi Kwatha*	*Jwara* (fever)	n.a.	Shah (2005b)
21	*Kumaryasava III*	*Gulma* (lump in the abdomen)	As per Agni[b]	Shah (2005b)
22	*Majuma Usaba Magarabi*	*Sarvaroga*	n.a.	Das (2019)
23		*Sannipata Jwara*		Das (2019)

(continued)

Table 3 (continued)

S. No.	*Yoga* (formulation)	*Adhikara* (indications)	Matra[a] (dose)	Reference
	Mrutsanjeevana rasa(ii)		2–3 Ratti (250–375 mg)	
24	*Shweta Aparajita Nasya*	*Apasmara* (epilepsy)	n.a.	Vagbhata (2010)
25	*Sparshavataghna rasa*	*Sparshavata* (tenderness)	n.a.	Vagbhata (2010), Shah (2005b)
26	*Stambhana Vati*	*Rasayana* (rejuvenation)	1 Ratti (=125 mg)	Pandit (2004b)
27	*Takra* (prepared with *Bhanga*)	*Shotha* (inflammation)	1 Badarasthi[c]	Das (2011)
28	*Talakeshwara rasa*	*Vatavyadhi* (musculoskeletal disorders)	1–4 Ratti (=125–500 mg)	Mishra (2003), Das (2011), Chaubhe (2000)
29	*Talavatika*	*Rasayana* (rejuvenation)	3 Ratti (=375 mg)	Shah (2005a)
30	*Trailokyavijaya Vati*	*Atisara* (Diarrhoea)	1 Ratti (=125 mg)	Mishra (2009)
31	*Trivruttadi Modaka*	*Parinamashoola* (duodenal ulcer)	4 Masha (=4 g)	Shah (2005a)
32	*Udayaditya rasa*	*Sparshavata* (Tendernesss)	8 Ratti (=1 g)	Pandit (2004a)
33	*Vangeshwaradi Vati*	*Jwara* (fever)	1 Tola (=10 g)	Shah (2005c)
34	*Vijaya Avaleha*	*Atisara* (Diarrhoea)	2 Masha (=2 g)	Shah (2005c), Mishra (2002)
35	*Vijaya yoga (i)*	*Vataja Jwara* (fever)	n.a.[a]	Shah (2005c), Vaishya (1993)
36	*Vijaya yoga(ii)*	*Rasayana* (rejuvenation)	n.a.	Shah (2005c)
37	*Vijaya yoga(iii)*	*Nasaroga* (nasal disorders)	1 Masha (=1 g)	Shah (2005c)
38	*Vijayadi Gutika*	*Kasa*, *Shwasa* (cough, Asthama)	n.a.	Lolimbaraja (2001)
39	*Vijayeshwara rasa*	*Twakavikara* (skin disorders)	4 Masha (=4 g)	Vaishya (1993)

[a] n.a. doses information not available

[b] As per *Agni:* meaning after assessing the digestive power of the individual using the classical diagnostic methodology used in Ayurveda

[c] No direct reference for metric equivalents of makushtha (size of a mat bean) and badarasthi (size of Ziziphus seed) is available

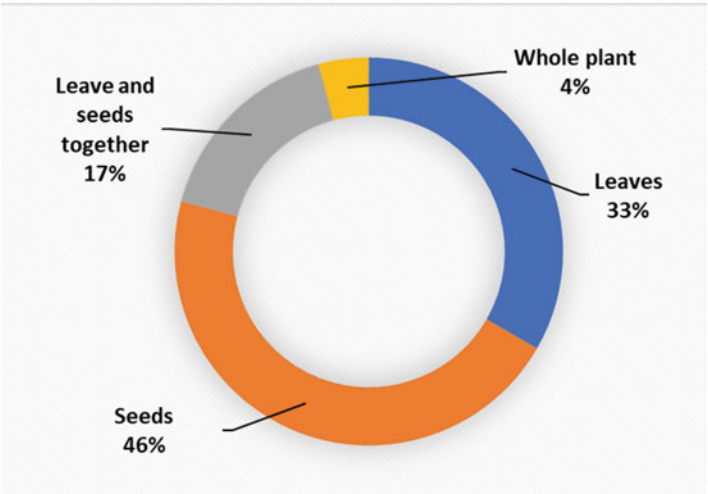

Fig. 1 Parts of *Bhanga* used in formulations mentioned in classical literature

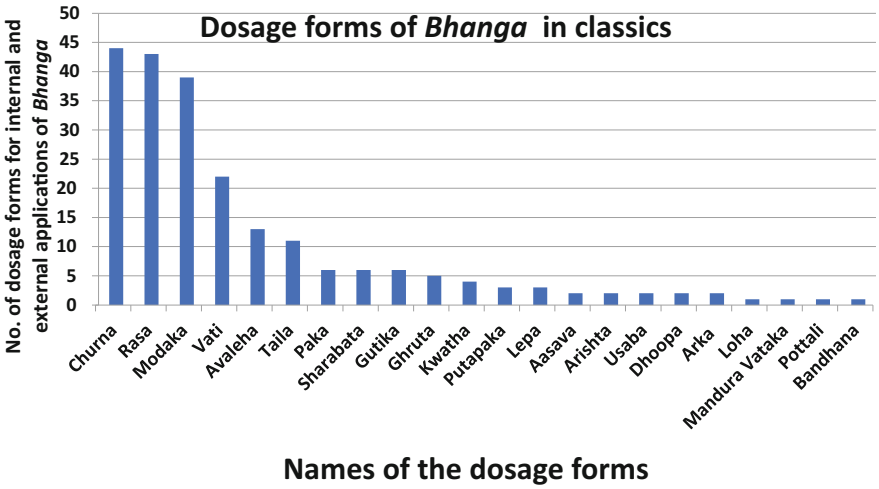

Fig. 2 Dosage forms of *Bhanga* as per classical literature in Ayurveda

Avaleha (confectionaries) *Paka* (contain semi-solid sugar, honey or jaggery), *Lepa* (creamlike applications), and *Bandhana* [Bandage filled with *Kalka-Dravya* (semi-solid preparation of herbal powders)] lie under semi-solid variety whereas *Taila* (oil), *Ghrita* (medicated ghee), *Asava*, *Arishta* (self fermented alcohol), *Arka* (distillate), *Kwatha* (decoction), *Usaba* (Unani preparation) lie under liquid dosage forms. Thus, *Bhanga* could be possibly soluble in aqueous as well as alcohol as well as lipid-based media.

5.4 Doses

Bhanga has been advocated to be used in the above-said doses by different seers. The range is broad, depending upon the indications and the dosage forms for which it has been referred to in the classical literature. Highest recommended dose of *Bhanga* formulation is specified in its *Avaleha* dosage in a quantity of one *pala*, which corresponds to 48 g, followed by *Modaka* in a quantity of two *tola* corresponding to 24 g. The least dose is found for alchemy-based preparation in an amount of 125 mg.

5.5 Time and Mode of Administration

Formulations for their therapeutic usage as *Rasayana* (rejuvenation) should be administered early morning on an empty stomach. In contrast, those indicated for aphrodisiac properties have been mentioned to be taken at night. The period of administration ranges from 7 days in case of decoctions containing *Bhanga* up to 365 days in case of *Modaka* dosage forms.

6 Use of *Bhanga* in Pharmaceutics Mentioned in *Rasa Shastra* (Indian Alchemy)

Rasashastra division of Ayurveda deals with information on traditional pharmaceutical processing of drugs to manufacture herbo-mineral or metal-based formulations. The traditional processing involves *Shodhana* (purification), *Bhavana* (impregnation), *Swedana* (boiling), *Marana* (calcination), *Mardana* (grinding), *Manthana* (churning), wherein certain medicinal plants from semi-poisonous groups are used to convert metal into *Bhasma* (calcinated ash). *Bhanga* has also been used as a *Bhavana* (impregnation) drug to increase the potency of formulations. *Bhavana* can be carried out by adopting methods like levigation and soaking. The media used in these methods change the qualities of the principal ingredients, the major being metal-based compounds. A thorough review has documented that *Bhanga* has been used for trituration media, i.e., *Bhavana* (impregnation) in 154 formulations and for *Swedana Dravya* (boiling media) in three formulations (Tavhare and Acharya 2016).

Rasayogasagara has quoted the highest formulations containing *Bhanga* as *Bhavana* (impregnation) media, followed by *Bruhatrasarajasundara* and *Rasajalanidhi*. In the majority of formulations, the part used are leaves in expressed juice form. Compared to the resinous material and buds of *Bhanga*, *the* leaf consists of less tetrahydrocannabinol (THC) (psychoactive content) and more cannabidiol

(non-psychoactive) content (Atakan 2012). Thus, the use of leaves in an optimum amount in pharmaceutical procedures without harmful effects is justifiable.

Bhanga has been used in *Bhavana* (impregnation) form in formulations for forty disease conditions. Maximum formulations have been advocated in the management of *Jwara* (~ pyrexia) followed by *Grahani* (malabsorption) and *Atisara* (Diarrhea) (Tavhare and Acharya 2016). Thus, a purified form of *Bhanga* is therapeutically valuable for gastrointestinal (GI) diseases. Research reports that the endocannabinoid system manifests protective activities in the GI tract, thereby proving to be an essential therapeutic target against various GI conditions such as inflammatory bowel disease (especially Crohn's disease), irritable bowel syndrome (IBS), and intestinal motility-related disorders (Goyal et al. 2017).

7 Pharmacovigilance Aspects of *Bhanga* as per Classical Literature

As stated earlier, *Bhanga* was a well-known narcotic in classics, clearly manifested from its Sanskrit synonyms. Thus, various texts have also provided crucial information, stating that *Bhanga* must be used therapeutically only after its *shodhana* (traditional purificatory measures to minimize its adverse effects on the central nervous system) (Acharya et al. 2021).

7.1 Dietary Restrictions for Formulations Containing Bhanga

Seers have recommended peculiar dietary advice for individuals consuming formulations comprising *Bhanga*, which must be followed with prudence (Table 4).

7.2 Contra-Indications of Formulations Containing Bhanga

Certain characteristic contra-indications pertain to conduct during intercourse, conduct while consuming meals, and sleep cycles in Table 5.

Table 4 Dietary restrictions for formulations containing *Bhanga*

Name of Formulation	Dietary advice/restriction	Reference
Mahakameshwara Kalpa	The predominance of milk in the diet	Mishra (2018)
Udayaditya rasa	Predominance of rice and ghee in diet	Pandit (2004a)
Grahanikapata rasa	It can be administered along with curd by adding *Dugdhika (Euphorbia hirta* Linn.*) Churna* (powder), *Jeeraka* (Cuminum cyminum *Linn.*), *Saindhava* (rock salt), *Maricha* (*Piper nigrum* Linn.)	Vagbhata (2010)
Rajayoga	An individual is advised to keep *Javitri* (mace of nutmeg) in the mouth during consumption of this formulation	Shah (2005c)
Sauvarchaladi churna	Must be consumed with buttermilk prepared from cow's milk	Vagbhata (2010)
Upadanshghna Modaka	Must be consumed with milk and meat soup	Pandit (2004a)
Vajeekarana yoga	Must be consumed with *payasam* (porridge made from milk, jaggery, wheat, and ghee	Anonymous (2000)

Table 5 Contra-indications of formulations containing *Bhanga*

Name of Formulation	Contra-indications	Reference
Kesara paka	Avoid meals at night	Pandit (2004a)
Bruhatpaka	Sexual intercourse must be avoided during the administration span, i.e., 40 days	Das (2019)
Praneshwara rasa	Vegetables, pulses, oil massage, have been contra-indicated while consuming this preparation	Shah (2005d)
Rajayoga	Salt, curd, and sour foodstuffs are contra-indicated	Shah (2005c)
Lai Churna	Buttermilk advised to be avoided	Chaubhe (2000)
Buttermilk made from *Bhanga*	Salt intake is prohibited	Das (2011)
Udayaditya rasa	Night awakening is prohibited	Pandit (2004a)

7.3 *Special Attributes for Certain Formulations Containing* Bhanga

Certain formulations viz. *Kameshwar Modaka* (Pandit 2004a), *Kamagnisandipana Modaka* (Mishra 2003), *Dnyanodaya* Rasa (Bhishagvara 2000) have been strongly recommended for their aphrodisiac properties and also warned to be consumed with caution in the prescribed dose. Secondly, *Mahakameshwar modaka* and *Lai churna* have been exclusively advocated as *Dipana*, i.e., they significantly increase an

individual's appetite (Pandit 2004a). The third peculiar attribute is *Karpursundar vati* which has been recommended in the de-addiction of opium (Shah 2005d).

7.4 Management of Possible Adverse Effects of Bhanga

The classical literature of Ayurveda also describes measures to overcome untoward effects caused by *Bhanga* due to faulty purificatory procedures or faulty manufacturing of drugs or improper adherence to the conduct rules prescribed during its consumption. To manage the adverse effects, it has been opined to administer curd prepared from cow's milk with *Shunthi* (*Zingiber officinale* Roxb.) or lemon juice (Dwivedi 1997). Further, cow's milk and *Shunthi* or crushed wet root of *Sandesada* (*Delonix elata* L.) with water have been proposed for neutralizing the adverse effects caused by the *Bhanga* administration (Acharya 1972).

8 Conclusion

Thus, it can be stated that classical literature of Ayurveda portrays a meticulous record of the known psychoactive drug Cannabis particularly known as *Bhanga*. The documentation, from its mythological value, botanical source abiding its Sanskrit synonyms, parts used, indications in various diseases, dose range, dosage forms, numerous formulations, and effects on various systems, is exceptional. In addition to this, it is evident that seers had a comprehensive understanding of its narcotic effects, which could be curbed using traditional purificatory measures. The delineation of pharmacovigilance aspect and management of untoward effects discussed in the scriptures outlines the depth of facet of toxicology in Ayurveda. This can be a rationale for future scientific analysis on this plant and exploring its therapeutic potential, especially in GIT disorders.

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Cannabis-Based Cosmetic Products and Their Uses

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Abstract The development of medications or cosmetics from botanicals such as the cannabis plant is the current major topic of interest in the pharmaceutical and cosmetic industry. Currently, several countries have legalized the use and dispensing of cannabis products. Cannabis is one of the most commonly abused or used addictive natural products after alcohol and tobacco. Concerning the cosmetic world, cannabis-based products are used extensively in various formulations. The most common personal care products are the skin, hair, eye, nails, or face formulations which are generally used to improve the appearance and prevent aging or risk of other diseases. This chapter deals with various cannabis-based cosmetic products and their uses.

Keywords Cannabis · Cosmetics · Cosmeceuticals · Dermal care products · Ophthalmic care products · Facial care products · Haircare products · Mouth care products

Abbreviations

BB	Beauty balm
BCC	Basal cell carcinoma
CBD	Cannabidiol
CBG	Cannabigerol

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CDC	Centers for Disease Control and Prevention
DNA	Deoxyribonucleic acid
FDA	Food & Drug Administration
HIV	Human Immunodeficiency Virus
NRS	National Rosacea Society
OCT	Over-The-Counter
SPF	Sun protection factor
THC	(−)-*trans*-Δ^9-tetrahydrocannabinol
US	United States of America
UV	Ultraviolet
WHO	World Health Organization

1 Introduction

Cosmetics are products considered for use for care, maintenance, prevention, and treatment with the expected intention to restore or enhance the appearance of an animal/human. Cosmetics can refer to merchandise mainly applied to the external body part (s), particularly the skin, hair, eye, nails, or face, to improve their appearance. Recently, the global corporate world and individuals worldwide frequently refer to cosmetics as personal care products for animals and humans. Unique care products broadly describe a comprehensive selection of products that incorporate chains' health and beauty divisions or individually owned medical (drug) department stores and are readily available on online websites. According to the United States Food & Drug Administration (FDA), many cosmetic products and personal care products are currently defined by the law and well regulated. Cosmetic or a personal care product is not considered as a "Drug" because a drug is a synthetic/natural medicinal product or other substances which affect the anatomy (structure) and/or function (physiology) when ingested or otherwise introduced into the body of an animal or human (Pandey et al. 2021). Globally, medicine (drugs) should get approval from FDA or other international drug approval agencies before use. A medication is mainly approved for diagnosing, preventive, or treating a specific disease state/pathological condition. Also, medication is usually considered therapeutically safe and pharmacodynamically effective, with minimal adverse effects in animals/humans. However, cosmetic products are not subjected to FDA premarket approval authority, except color additives. Hence, cosmetic companies are accountable for corroborating the safety of their content/products before marketing and the use for animals and humans.

The major cosmetic-based personal care products predominantly consist of dermal (skin) care products, fragrances (perfumes/deodorants), fingernail products (polishes, removers), ophthalmic (eye) products, facial makeup preparations, hair care products, and mouth care products. Furthermore, few personal care products belong to other regulatory categories, including medical devices (hair removal

products and microdermabrasion- skin renewal, skin tone, and texture devices), dietary supplements (vitamin or mineral capsules/tablets), and other personal care products (Gabriella and Kenneth 2015). Some personal care products that contain drugs are referred to as cosmeceuticals. Cosmeceutical products have two intended indications (uses), one primarily for cosmetic purposes and the other for the prevention and/or treatment of medical ailments, pathological conditions, or disease states (Pandey et al. 2021). Some classical cosmeceutical products are shampoo with antidandruff drugs, toothpaste with fluoride, deodorants with antiperspirant drugs, and moisturizers with sunscreen/sun-protectant. These products must comply with the requirements for both cosmetics and pharmaceuticals.

Humans worldwide have been exposed to cannabis for thousands of years (Bridgeman and Abazia 2017). Remarkably, this natural product (botanical) has survived various calamities, has been widely cultivated and found its way into innumerable cultures and customs for multiple purposes in daily life (Abrams and Guzman 2015). Cannabis-based products have been used mainly for recreational, medicinal, cosmetic, commercial, and spiritual purposes (Morean and Lederman 2019; Walsh et al. 2013; Hamilton et al. 2017). Moreover, cannabis-based products have recently flooded the current therapeutic and cosmetic/personal care products market and have been used extensively for medicinal and cosmetic purposes (Bonini et al. 2018). Clinically approved, off-label and recreational use of cannabis has tremendously increased worldwide (Minerbi et al. 2019). There is numerous literature on the medicinal and recreational use of cannabis (Page et al. 2020; Turna et al. 2020). However, relatively little research on cosmetic aspects of cannabis has shown to be relatively safe (Bergamaschi et al. 2011). Hence, more research is required to validate the chronic safety of cosmeceutical products. Several research reports exhibited mixed results on cannabidiol (CBD) (toxic effect) (Huestis et al. 2019). However, more words have had overwhelmingly favorable positive results for the use of animals/humans (Hamilton et al. 2017). Thus, it appears that CBD is safe and effective. Therefore, there is a significant surge in cannabis-based cosmetic/cosmeceutical products in the market (Baswan et al. 2020). However, there are very few reports on the cosmetic effects of cannabis (Tóth et al. 2019; Mounessa et al. 2017). Since there are very few publications and addresses that explicitly address the cosmetic-based products and use of cannabis, this chapter reveals the cosmetic benefits of cannabis. The current chapter deals with various dermal (skin), ophthalmic (eye), facial, hair, and mouth care cannabis-based (mainly CBD) cosmetic/cosmeceutical products (Fig. 1).

2 Cannabis-Based Cosmetic Products

2.1 Cannabis-Based Dermal (Skin) Care Products

The therapeutic applications of cannabis are an increasingly evident issue since the decriminalization and legalization of these products, which has resulted in its

Fig. 1 Benefits of cannabis-based cosmetic products for various organs

development and broadening of its uses (Hill and Palastro 2017). For a specific set of situations, a small number of cannabis compounds have been approved. The current significance of cannabis in the therapy of dermatological disorders, however, is unknown. The most common dermal (skin) care cosmetic products with cannabis are skin moisturizers, lotions, creams, cleansers, exfoliators, gels, lotions, oils, solutions, ointments, sunscreen, chemical peel, toner, and serums (Bíró et al. 2009). The cannabis-based skincare products are used in the prevention/treatment of acne, dark spots, hyperpigmentation, excessive perspiration (hyperhidrosis), fine lines and inflammation, and rash (skin, diaper) (Eagleston et al. 2018). The most common skincare products are vitamins (thiamine, ascorbic acid, and tocopherol), retinol, retinoic acid, niacinamide, salicylic acid, glycolic acid, lactic acid, azelaic acid, hyaluronic acid, ceramides, and omega-3 fatty acids (Draelos 2010). Since cannabidiol possesses sebostatic, antioxidant, and anti-inflammatory action (Oláh et al. 2014), several cannabis-based dermal (skin) care products have been developed (Eagleston et al. 2018). The sebostatic activity of CBD is attributed to inhibition of lipogenic actions of compounds such as arachidonic acid and a combination of linoleic acid and testosterone and suppressed sebocyte proliferation via the activation of transient receptor potential vanilloid-4 (TRPV4) ion channels (Oláh et al. 2014). The CBD-laced lotion or cream is used on sore joints or muscles for quick relief (Miller and Miller 2017). Several dermal formulations with cannabis are effective for dry skin, wrinkly skin, eczema, soothing topical pain, and acne (Oláh et al. 2014).

Recently, oral care giant Colgate-Palmolive Company (US) has filed a patent on personal care compositions containing antiperspirant active ingredients and a cannabinoid source present in an amount to achieve an anti-irritant effect on the skin (Hernandez et al. 2021).

Furthermore, moisturizers and serum with cannabis and hemp seed oil can rebuild healthy skin cells (keratinocytes, melanocytes, and Langerhans cells) and have an anti-aging effect (Sheriff et al. 2020). Also, these products deliver calming, hydrating, antioxidant effects, decrease inflammation, and have a soothing effect on the

Table 1 List of cannabis-based dermal (skin) formulations

Dermal (skin) formulation	Dermal (skin) cannabis products
Skin moisturizers	High beauty high five cannabis facial moisturizer
Skin lotion	Vertly hemp-CBD relief lotion
Skin cream (skin, hand)	Myaderm CBD blemish cream
Skin serum (soothing/tissue repair)	CBD daily soothing or tissue repair serum
Skin soap/body bar	Nooks and crannies
Skin salve/balm	CBD skin salve
Skin oil	Hemp CBD oil
Skin exfoliator	CBD exfoliating cleanser

Table 2 Dermal cannabis cosmeceuticals

Dermal (skin) ailment	Cannabis cosmeceuticals
Acne	CBD oil, gummies
Atopic dermatitis (Eczema)	Weed cream, THC lotion, CBD salve
Shingles (Herpes Zoster)	Cannabis cream, edibles
Hives (Urticaria)	Topical CBD gels, lotions, oils
Sunburn	CBD, THC sunscreen
Contact dermatitis	Weed cream, THC lotion, CBD salve
Diaper rash	CBD oils, salve, and CBD baby zinc ointment
Rosaceae	CBD balm and Endoca hemp salve
Athlete's foot (tinea pedis)	CBD/hemp oil
Basal cell carcinoma	Transdermal patch, oral, vaporize, smoke

skin (Tóth et al. 2019; Iffland and Grotenhermen 2017; Andre et al. 2016; Atalay et al. 2019). Skin CBD balms relieve sore muscles, stiffness and provide intense hydration to the skin (Palmieri et al. 2019). CBD/hemp exfoliating cleanser cleanses and soothes the skin (Zagórska-Dziok et al. 2021). Some cannabis-based formulations for skincare are listed in Table 1.

The foremost common dermal (skin) associated problems around the world are acne, atopic dermatitis (Eczema), Shingles (Herpes Zoster), hives (urticaria), sunburn, contact dermatitis, diaper rash, Rosacea, athlete's foot (Tinea Pedis), and Basal Cell carcinoma (Yew et al. 2020). Cannabis-based products are the leading drug target investigated for prophylactic and therapeutic dermotrophic effects (Eagleston et al. 2018). Several skin aliments and available cannabis-based cosmeceuticals have been listed in Table 2, and illustrated in Fig. 2.

Acne vulgaris (acne) is the most prevalent inflammatory dermal (skin) pathological condition where young girls (between 14 and 19 years of age) normally develop acne earlier than boys, and it is becoming more persistent and prevalent in adult women. Acne is a disorder that arises due to excess oil, dirt, and dead skin cells clog pores (Dréno 2017). The bacteria *Propionibacterium acnes* can build up in the pores, causing irritating and red blemishes (McLaughlin et al. 2019). The current therapy for acne is retinoids and retinoid-like drugs (tretinoin, adapalene, tazarotene), antibiotics (clindamycin, erythromycin), benzoyl peroxide, oral contraceptives

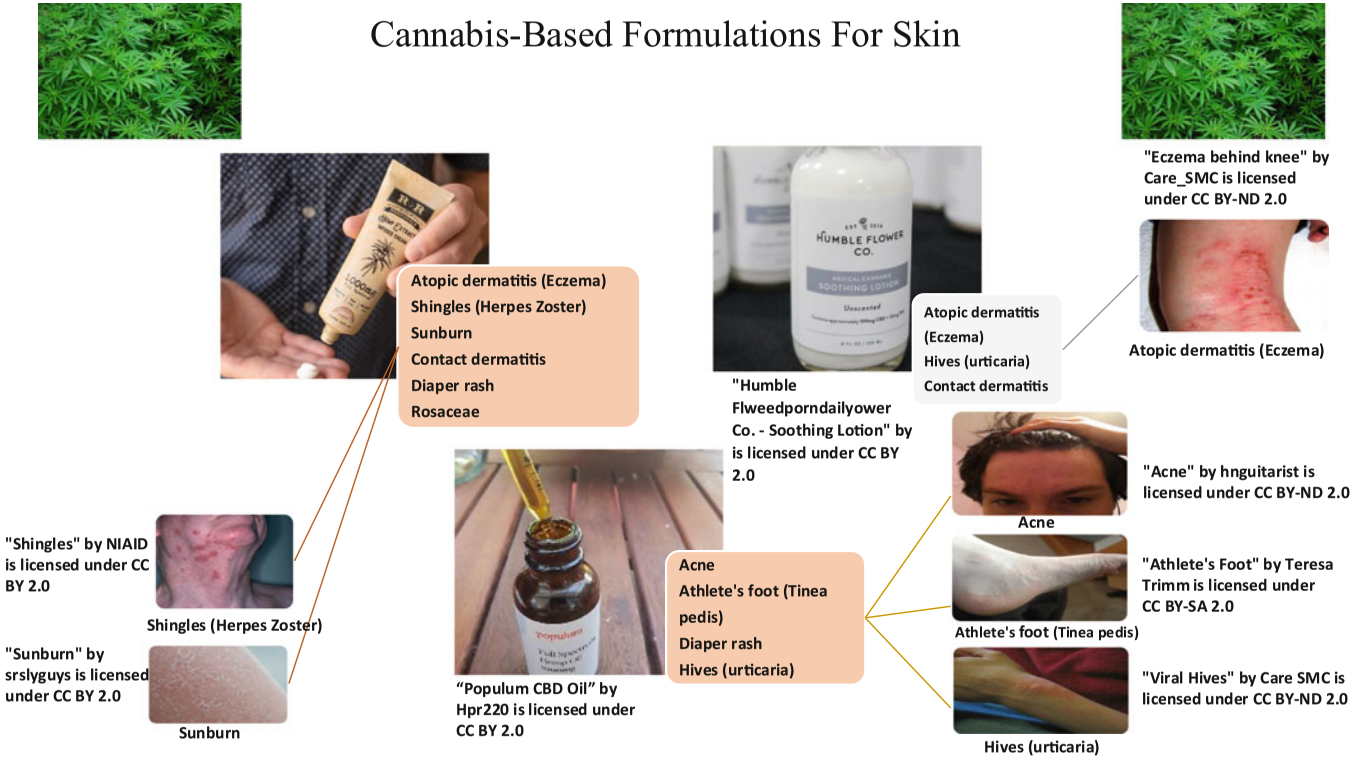

Fig. 2 Cannabis-based formulations for skin (dermal) disease conditions

(progestin and estrogen), keratolytic soaps, alpha hydroxy acids, azelaic acid, salicylic acid, anti-androgen (spironolactone) and anti-seborrheic (Tan et al. 2017). Cosmetics (Nonprescription) and cosmeceuticals can balance the efficacy and tolerability of prescription acne treatment (Dréno et al. 2020; Nasri et al. 2015). Currently, there are cannabis-based cosmeceuticals for the treatment of acne (Cohen 2021). CBD oil and gummies have a sebum-regulating effect, and CBD oil products used twice per day have an anti-acne skincare effect (Oláh et al. 2014).

Atopic dermatitis (eczema) is an inherited ailment associated with red and itchy skin (Langan et al. 2020). This chronic dermal pathological condition occurs in children commonly (Lyons et al. 2015). However, it also can occur at any age and tends to flare periodically. Mostly atopic dermatitis arises due to a combination of genetic and environmental factors (David et al. 2017). Usually, atopic dermatitis (eczema) is escorted by asthma or hay fever (Wang et al. 2021). However, contact dermatitis is a skin condition characterized by skin inflammation (dermatitis) due to contact with an allergen that initiates and triggers an allergic manifestation (Brar 2021). There are non-pharmacological and pharmacological approaches to treat dermatitis. The lifestyle options include averting known triggers, providing routine bathing, a moisturizing schedule, good quality sleep, a healthy diet, and avoiding stress (Simpson 2010). However, the various therapeutic strategies include corticosteroids (topical formulations), non-steroidal topicals, and biologics (monoclonal antibody, dupilumab) (Lee et al. 2016; Deleanu and Nedelea 2019). Intriguingly, endocannabinoid formulations inhibited mast cell activation leading to decreased histamine release when activated, which decreased itching and loss of sleep (Theroux and Cropley 2016; Bíró et al. 2009; Nam et al. 2016; Kupczyk et al. 2009; Baswan et al. 2020).

The varicella-zoster virus causes shingles (Herpes Zoster), and a common complication is chronic nerve pain (postherpetic neuralgia), and the rare complications are blindness, pneumonia, hearing problems, encephalitis, or death (Gershon et al. 2015). Acyclovir, valacyclovir, and famciclovir are the common antiviral drugs used in the treatment. The non-pharmacological approaches are wet compresses, calamine lotion, and colloidal oatmeal baths (Ayoade and Kumar 2021). Currently, cannabis-based products are available for controlling shingles-associated complications (Russo 2008; Rahn and Hohmann 2009). Medical cannabis (inhaled, pipes, cigarettes, and ingestion) reduces inflammation and decreases pain caused by shingles and thus protects the nerves/neurons (Xiong et al. 2012). Hives (urticaria) are a dermal condition typified by the outbreak of swollen, red welts and itching ranging from mild to severe that appear suddenly due to the body's response to allergens or an unknown cause (Schaefer 2017). There are various triggers which range from food, drugs, bug (stings/bites), external stimuli (pressure, cold, heat, exercise, or sun exposure), blood transfusions, microbial infections, including urinary tract infections, and strep throat and pet dander and pollen (Hennino et al. 2006). The current therapy includes avoiding triggers and treating with antihistamines and corticosteroids (Grattan 2012). According to Innocan Pharma, there are Topical CBD Gels, oils, and lotions that are very effective in reducing hives (urticaria).

Sunburn is the word or phrase that refers to erythema (red), swollen, and painful dermal reaction caused by overexposure to sun ultraviolet (UV) rays (Guerra et al. 2021). The non-dermal-based symptoms are fever, chills, nausea/vomiting, fatigue, shock, hypotension, fainting, and extreme weakness (Guerra et al. 2021). This dermal condition can vary from mild to severe sunburn and significantly increase the risk for skin cancer (Wu et al. 2016). The methods to prevent or treat sunburn are to reduce exposure to the sun, consume fluid (drink water), apply moisturizer, sunscreen, and hydrocortisone cream (Guerra et al. 2021). Several sunscreen products with a sun protection factor (SPF) and cannabinoids (specifically, (−)-*trans*-Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD) soothe and protect the skin (Rough 2017).

Diaper rash is a frequent form of dermatitis due to wet or occasionally changed diapers, skin sensitivity, chafing that occurs to the baby, and seen as a patchwork of bright red skin that scares the parents and annoys babies. Diaper rash also can be seen in the bottom, thighs, and genitals of the baby. The usual approach to prevent diaper rash is changing diapers regularly, cleaning the baby appropriately, and using petroleum jelly and zinc oxide ointment (Benitez and Mendez 2021). Additionally, according to Apollyon, CBD oils, salve, and CBD baby zinc ointment are currently available to prevent or treat diaper rash (Apollyon 2021).

As per the National Rosacea Society (NRS), Rosacea is a frequent dermal disorder/illness in the face and can affect everybody (https://www.rosacea.org/). Nevertheless, it is widespread in light skin middle-aged women (Reinholz et al. 2016). The common symptoms are redness, visible facial blood vessels with small, red, pus-filled bumps that flare up for few days to several months. Usually, this dermal condition can wrongfully diagnose acne or other dermatological issues due to similar dermatological reactions (redness, swollen bumps, and enlarged nose (Reinholz et al. 2016). There is no specific cure for Rosacea, but treatment can control and reduce the signs and symptoms (Rainer et al. 2017). The current therapy is drugs acting on alpha-adrenergic receptors (oxymetazoline, reduce redness by vasoconstriction), azelaic acid, metronidazole, and ivermectin (Rainer et al. 2017). According to Innocan Pharma (Innocan Pharma Corporation 2020a), using cannabis-based products (CBD) for Rosacea is very common since no effective remedies for this chronic dermal ailment are available. Cannabis-based products (CBD balm and Endoca Hemp salve) bind with cannabinoid and glycine receptors and interact with leukocytes (macrophages, other white blood cells) and microglia to lessen inflammation and pain (Stocker 2019; Liz 2021).

The athlete's foot (Tinea pedis) occurs due to a fungal infection. The symptoms include toe-web maceration, scaly rash, itching, stinging, and burning that generally starts between the toes and spreads to the hand, tail, and groin (Crawford 2009). The therapy includes keeping the feet clean and using antifungal preparations (prescription or non-prescription) Tolnaftate, Haloprogin, Ciclopirox, Clotrimazole, Miconazole, Ketoconazole, Sulconazole, Oxiconazole, Econazole, Butenafine, Naftifine, and Terbinafine (Gupta et al. 2018). According to Innocan Pharma Corporation Ltd., CBD oils exhibit significant antifungal activities and induce the entourage effect (Innocan Pharma Corporation 2020b). The prevalent form of skin cancer is Basal

cell carcinoma (BCC), characterized by abnormal and uncontrolled growth of basal cells (McDaniel et al. 2021). Basal cells are one of the three types of cells present in the outermost layer of skin (epidermis). The etiology of BCC is due to the chronic exposure to ultraviolet radiation (due to sun exposure or tanning) that triggers DNA damage in basal cells and causing in uncontrolled growth (Sehgal et al. 2014). BCCs typically exhibit red patches, open sores, shiny bumps, pink changes, and scars (Göppner and Leverkus 2011). The clinical treatment includes surgery (Surgical excision, Mohs surgery), Curettage and electrodesiccation, radiation, freezing, oral/topical targeted drug therapy, immunotherapy, and chemotherapy (5-fluorouracil, Imiquimod, Vismodegib, Sonidegib, Cemiplimab-rwlc) (Smith and Walton 2011; Göppner and Leverkus 2011). Cannabis has been shown to enhance patient's prognosis of basal cell cancer and reestablish their quality of life (Casanova et al. 2003; Mamo et al. 2021). A Japanese study (Tokyo Metropolitan Institute of Public Health) validated cannabinoids to decrease skin cancer effectively by 90% (Nakajima et al. 2013). Transdermal patch, oral, vaporize, and smoke products with cannabis formulations (Northern Lights-Indica), ACDC (A hybrid between Ruderalis and Cannatonic with very high CBD), Chocolope (Sativa), Charlotte's Web (Sativa), and Granddaddy Purple (Indica) have shown to be effective against BCC (Rosado 2020). The cannabis-based formulations can uplift and energize the patients by reducing fatigue, increasing appetite, relieve pain in addition to the anticancer effects (Barrington 2021).

2.2 Cannabis-Based Ophthalmic (Eye) Care Products

CBD's widespread legal status and anti-inflammatory qualities have made it a potential component in the beauty business, including eye care, cropping up everything from mascara to eye serums, and towards greater marijuana legalization (Pacula and Smart 2017). CBD has become a full-fledged phenomenon due to its potential to help in treating eye conditions (Mack 2000). The major ophthalmic cosmetics (eye makeups) are mascara, eye makeup remover, eye color, eyeliner, eyebrow pencil, eyelash primer, eyeshadow primer, curlers, eyebeam gel highlighter, lengthening mascara, volumizing mascara, as per cosmetics info (Cosmeticsinfo 2021). In addition, there are several ophthalmic formulations (topical or systemic), solution, suspension, ointment, emulsion, eye drops, ointments, in situ gels, inserts, multicompartment drug delivery systems (Lu 2010; Dubald et al. 2018). Several therapeutic molecules are biological targets potentially used for various clinical applications (Souto et al. 2019). Due to the prophylactic and therapeutic potential and cosmetic value, several cannabis-based ophthalmic products, e.g., eye cream, eye serum, CBD eye oil, have been developed (Punyamurthula et al. 2017; Taskar 2019). These cannabis-based formulations reduce dark circles, puffiness, and wrinkles, as mentioned in the recently published article (Tyrrell 2019).

2.3 Cannabis-Based Facial Care Products

According to Cosmetic Product Category Codes US FDA, the facial cosmetic products include face primer, foundation, BB (beauty balm) Cream, concealer, blush, highlighter, bronzer, face setting Spray/Powder, facial sleeping mask, lip gloss, lipstick, applications, shaving cream, shaving soap, pre-shave lotions, and aftershave lotions (FDA 2020). In addition to the aesthetic look and great smell, these cannabis-based products help minimize the appearance of scar tissue and have a significant potent anti-aging effect, according to the Innocan Pharma (Innocan Pharma Corporation 2020c; Gnam 2021).

2.4 Cannabis-Based Hair Care Products

The common hair products are wet shampoos, dry shampoos, conditioners (deep and leave-in), hair masks, hair sprays, anti-frizz serums, volumizing sprays, hair mousses, anti-stress hair oil, anti-breakage detangling spray, hair oil, scalp oil, hair foams, hair coloring agents, air rebuilder, hair repairer, hair gloss, detangling hair milk, hairstyle spray, hair thickeners, firm hair hold spray, anti-frizz hair sheets and anti-dandruff, as mentioned in Headcurve website (Headcurve 2021). Currently, several hair products contain CBD/hemp, e.g., CBD Scalp Calming Shampoo, Ultra-hydrating herbal conditioner with hemp, CBD hair and scalp oil, Cannabis leave-In conditioner, CBD oil as hair builder/repairer, hemp hydrating and deep-conditioning hair mask, hair CBD anti-stress oil, CBD regeneration cream, and CBD anti-dandruff shampoo (Telek et al. 2007; Cooper 2020).

2.5 Cannabis-Based Oral (Mouth) Care Products

The prevalent oral (mouth) care cosmetics include mouthwashes, breath fresheners, breath spray, toothpaste, toothpowder, teeth whitener, pastes, powders, liquids, or other preparations for cleaning the teeth. According to the Centers for Disease Control and Prevention (CDC) (CDC 2020) and World Health Organization (WHO 2020), the general maladies that impact oral health comprise cavities (tooth decay), gum (periodontal) disease, oral cancer, oral manifestations of HIV infection, oro-dental trauma, noma and cleft lip, and palate (Koutlas 2013). An oral care product aimed to act as a prophylactic to prevent the formation of cavities (carries) is regulated by the Food and Drug Administration as an Over-The-Counter (OTC) drug (FDA 2017). These products reduce the problems associated with oral cavity pathologies and other non-communicable diseases, according to the federal register (FDA 2003). The vital components to prevent oral cavity disorders are consuming a balanced diet (low carbohydrates/sugar, high fruit, and vegetables), drinking plenty

of water, avoiding different forms of tobacco products, evading chewing of areca nuts, reducing alcohol intake, and suitable exposure to fluoride (Vodanović 2013). Historically, peppermint, clove, sage, and cinnamon have been used globally as breath fresheners and to alleviate oral cavity inflammation. In the past two decades, many botanicals (*Azadirachta indica, Calendula officinalis, Cinnamomum zeylanicum, Citrus paradisi, Commiphora myrrha, Echinacea Angustifolia, Eugenia caryophyllus, Syzygium aromaticum, Mentha piperita, Myrica cerifera, Olea europaea, and Zanthoxylum americanum*) have been investigated for their protective effects to enhance oral health care (Halberstein 2008). Natural herbs and essential oils exhibit antioxidant, anti-inflammatory, antimicrobial, antibacterial, antifungal, and antiviral effects (Parham et al. 2020). Thus, natural herbs can improve oral health and well-being when used daily in personal care. Based on the above concept, as mentioned in the Cannadorra webpage, there are toothpastes and tooth powders with cannabis and hemp oil (CBD toothpaste, hemp toothpaste). Also, there are CBD/CBG (cannabigerol) infused mouthwashes, CBD breath spray (Vasudevan and Stahl 2020). These CBD-based formulations can further restore pH balance, increase remineralization, and reduce bone loss associated with gum disease (Napimoga et al. 2009).

Recently, oral care giant Colgate-Palmolive Company (US) has filed three patents on CBD oral care blends for antibacterial efficacy and anti-inflammatory action. Researchers claim to have developed oral care compositions comprising a CBD source and several other ingredients (Arora et al. 2021a, b, c).

3 Possible Future Cannabis-Based Novel Cosmetic Products

Future innovative cannabis-based cosmetic and cosmeceutical formulations must be designed to achieve pertinent pharmacokinetics and pharmacodynamic effects with minimal adverse effects and relatively common hypersensitivity reactions. The novel cannabis-containing formulations in the future can be conjunctival inserts, nanoparticles, mucoadhesive polymers, nano-enhanced inserts, dendrimers, intraocular implants, in situ gelling nanosystems, liposomes, nano micelles, oral implants, and hair implants (Spindle et al. 2019).

4 Conclusion

The recreational and therapeutic use of cannabis has tremendously increased in recent years. Consumers and patients spend billions of dollars and thousands of hours globally on cosmetics, prophylactic and therapeutic supplements (natural products), and drugs. Due to its multiple-targeted pharmacodynamic effect, there

is a definite possibility to use cannabis-based products in the cosmetic and personal care market. Hence, there is an imminent need for cannabis-based novel cosmetic formulations (facial, oral, ophthalmic, hair, and dermal) in addition to their aesthetic cosmetic effects and also exert multipotent beneficial effects to prevent and treat harmful conditions. Several cannabis-based (facial, oral, ophthalmic, hair, and dermal) cosmetic/cosmeceutical products are used globally. These formulations must be rigorously tested using appropriate in vitro and in vivo models to validate their beneficial and harmful effects for cosmetic, cosmeceuticals, diagnostic, prophylactic, and therapeutic use.

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Cannabis as a Unique and Valuable Nutraceutical Formulation for the Current and Future Global Wellbeing

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Abstract Nutraceuticals are a type of nutritional supplement used for healthcare in addition to nourishment. They can be used to maintain the body's structure and function to promote health, slow down the aging process, prevent chronic diseases, and extend life. Echinacea, ginseng, green tea, glucosamine, omega-3, lutein, folic acid, and cod liver oil have been popular global nutraceuticals in the past few decades. The majority of nutraceutical products are regulated like pharmaceuticals, food additives, and dietary supplements. Nutraceuticals can be classified based on the source, methods of action, chemical structure, composition, etc.

In addition to the recreational and medicinal value, Cannabis has been widely established globally as a primordial source of fiber, protein, and fat with great nutritional value. Cannabis has been legally utilized as human food in the United States for the past 10 years. The hemp seed oil is an excellent prophylactic and therapeutic potential to prevent and treat various human-related health ailments. Cannabis contains active bioactive ingredients and oils with polyunsaturated fatty acids, which can be a potent nutraceutical for the current and future generations. Cannabis alone or in combination with the other existing nutraceutical (s) can provide additive or synergistic protective effects to improve human healthcare. It is estimated that by 2028, the worldwide cannabis nutraceuticals market is projected to be worth 19.25 billion USD. The present chapter dwells on the concept of nutraceuticals, the classification of nutraceuticals, their health benefits, and the potential of cannabis as a nutraceutical source.

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Abbreviations

ALA	α-Linolenic acid
CBD	Cannabidiol
CNS	Central nervous system
CVDs	Cardiovascular diseases
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
FAO	Food and Agriculture Organization
IBD	Inflammatory bowel disease
ISO	International Standards Organization
NSP	Non-starch polysaccharides
PUFA	Polyunsaturated fatty acids
THC	Delta-9-tetrahydrocannabinol
USA	United States of America
US-FDA	United States of America Food and Drug Administration
WHO	World Health Organization

1 Introduction

The word "nutraceuticals" was initially coined in 1989 by Dr. Stephen DeFelice, a physician, and founder and chairman of the Foundation for Innovation in Medicine. The term "nutraceutical" originates from the word "nutrition" and "pharmaceutics." Nutraceuticals are commonly used to describe natural and/or synthetic substances or products made from herbal extracts, dietary supplements (nutrients, particular diets), and processed foods, including cereals, soups, and beverages utilized for not only nourishment but also for the wellness of animals and humans (Nasri et al. 2014). Ginseng, Echinacea, green tea, glucosamine, omega-3, lutein, folic acid, and cod liver oil are the popular nutraceuticals (Zeisel 1999) currently in use throughout the globe. Nutraceuticals are currently deemed as a reliable alternative to modern-day science-validated drugs or allopathic medicine. They can be viewed as a dietary supplement that aims to boost the health of animals and humans by supplementing the diet with one or more of the following dietary ingredients: a vitamin, mineral, amino acid, herb, or other botanical. Furthermore, it is a dietary substance intended for ingestion (oral route of administration) in the form of a capsule, granules, soft gel, or gel-cap, to supplement the diet by increasing total dietary intake and is not represented as a conventional food or as a sole item of a meal or the diet. For example, withal nutraceuticals are extensively used for wound healing effects as a

dermal preparation and part of antiaging cosmetics in different dosage forms (ointments, drops).

Nutritional/dietary supplements, nutraceuticals, and functional foods (foods that have a potentially positive effect, promote optimal health, reduce the risk of disease) provide an essential supplementary complement to the human diet by increasing the intake of bioactive chemicals to improve health and fitness. Individuals have always been interested in the healing effects of foods, regardless of their social or economic status. Herbs and spices have a long history of use in this context, both for their flavor-enhancing and prophylactic properties (Kaefer and Milner 2008). Nutraceutical products are not strictly regulated like pharmaceuticals but are handled similarly to food additives and dietary supplements in the United States of America (USA). Perspectively, the term "nutraceutical" isn't always defined or viewed the same way globally. However, it is frequently characterized as a food-derived product with beneficial or curative effects and possesses healing properties. Currently, a substance with health benefits or protection against acute and chronic diseases in animals and humans can be considered a nutraceutical product. Nutraceuticals at present are in heavy demand throughout the world because they maintain the body's structure and function, promote health and wellbeing, slow down the aging process, prevent acute & and chronic diseases, and extend life (Kalra 2003). Although pharmaceuticals and nutraceuticals may be used to prevent or treat illness, each country's government or regulating agency approves only pharmaceutical compounds (Baby et al. 2013) for therapeutic applications. Contrary to pharmaceutical drugs, nutraceuticals are not generally protected by patents.

Most nutraceuticals have a variety of medicinal uses. Recent research has demonstrated that nutraceuticals have promising health outcomes in reducing the risk or treating various pathological consequences. Nutraceuticals can reduce the risk of diseases associated with the central nervous system (CNS), eye, gastrointestinal tract, cardiovascular system, lungs, hormones (endocrine), integumentary system (skin), kidney, skeletal (bone), and muscles. Therefore, nutraceuticals are considered a safe drug alternative with prophylactic and/or therapeutic effects (Crescente et al. 2018).

Cannabis is being consumed or used in numerous cultures and different religions for the past thousands of years. One of the reasons for its continuous use throughout the centuries may not be attributed only to its healing, beneficial or commercial properties, but mainly due to the lack of significant toxic effects. Like the nutraceuticals, Cannabis (synonym = dope, grass marijuana, pot, weed,) a natural botanical, is currently used as a prophylactic/therapeutic medication and a recreational substance throughout the world. Like the nutraceuticals, Cannabis (because of its potent bioactivity) can also exert multi-pharmacodynamic effects. The healthcare and food industries are currently looking for novel, safe, and affordable natural/synthetic products to prevent health defects and improve animal/human acute and chronic health conditions. Thus, Cannabis may be a promising nutraceutical product for the present and future generations.

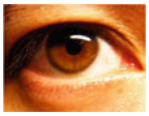
2 Beneficial Effects of Nutraceuticals

Nutraceuticals have been shown to exert central and peripheral neuroprotection by decreasing the rate of neuronal death, increasing the level of cellular energy, decreasing hyperarousal (stress and anxiety), and counteracting depression (Williams et al. 2015; Dhanasekaran et al. 2007, 2008; Tharakan et al. 2006; Pondugula et al. 2021). In the eye, nutraceuticals have been shown to prevent glaucoma (increased intraocular pressure), macular degeneration, retinopathy, xerophthalmia, and inflammation (Morrone et al. 2018; Stice and Kolanos 2021). Nutraceuticals can significantly affect gastrointestinal motility and acid secretion in the gastrointestinal tract. They have been shown to exhibit hepatoprotective and gastrointestinal protective effects and decrease and/or prevent the risk of several gastrointestinal-related diseases and disorders (Romano et al. 2012; Gao et al. 2020). Similarly, in the respiratory tract, nutraceuticals have been associated with a decreased risk for cancer, pulmonary fibrosis, asthma, and chronic obstructive pulmonary disorder (Gulati et al. 2021; Hwang and Ho 2018; Allam et al. 2021; Ciprandi et al. 2019). In the cardiovascular system, nutraceuticals significantly reduce the risk of heart disease and prevent hypertension (Sosnowska et al. 2017). Nutraceuticals possess nephron-protective and diuretic effects in the renal system and reduce renal dysfunction (Gwaltney-Brant 2016; Cosola et al. 2018). Endocannabinoids are present in both the male and female gonads, and they help signal fertility in the cycle of reproduction, regulate gonadic hormones, and aid in the function of spermatozoa. Thus, they can significantly increase the reproductive functions in males and females and reduce reproductive dysfunction (Zhao et al. 2021). In the skeletal system, nutraceuticals and thus prevents sarcopenia and skeletal muscle wasting (Rao et al. 2021; Gras et al. 2021; Pandey et al. 2018). Skin being the largest organ of the human body needs more care and protection. Several nutraceuticals can prevent skin-related diseases and have been used as cosmeceuticals (Lu et al. 2021; Geng et al. 2021; Michalak et al. 2021). Nutraceuticals possess significant immunomodulatory and endocrinological effects. Thus, the nutraceuticals can reduce the risk of several immunological and endocrinological disorders (Hepler and Bass 2021; Miao et al. 2021; Goyal et al. 2021; Upton 2021; Berberich and Hegele 2018) (Table 1).

3 Classification of Nutraceuticals and Their Healthcare Benefits: Inclusion of Cannabis

Nutraceuticals can be classified in various ways to make them easier to understand and apply, such as academic, clinical trial design, functional food production, or dietary advice. Nutraceuticals can be classified by food sources, methods of action, chemical composition, and so on. All of the food sources used as nutraceuticals are natural and fall into the following categories (Kalia 2005; Kokate et al. 2002):

Table 1 Beneficial effects of nutraceuticals

Organ system	List of nutraceuticals	Beneficial effect
Nervous (Central and Peripheral)  "Brain" by Rev314159 is licensed under CC BY-ND 2.0	• Antioxidants (vitamin-E, vitamin-C) • Polyphenols • Vitamin-B (folate, pyridoxine, cobalamin) • Plant sterols • Caffeic acid • Allicin • Melatonin • Coenzyme-Q10 • Traditional/tribal medicines (Trichopus, Bacopa, Centella, Oroxylum, Mucuna, turmeric)	• Retard the rate of neurodegenerative diseases (Alzheimer's disease, Parkinson's disease) • Anti-fatigue action • Anti-stress effects • Reduce anxiety • Mood elevators (decrease depression) • Increase mitochondrial function • Decrease oxidative stress • Combat apoptosis • Reduce inflammation
Ophthalmic "Sleepy eye" by emrank is licensed under CC BY 2.0 	• Alpha-lipoic acid • Citicoline • Coenzyme-Q10 • Curcumin • Flavonoids (kaempferol 3-O-rutinoside, quercetin, rutin) • Forskolin • Lutein • Lycopene • Polyunsaturated fatty acids (PUFA) • Resveratrol • Taurine • Traditional/tribal botanicals (*Ginkgo biloba*) • Vitamins (A, C, D, E, folic acid, thiamine, pyridoxine, cobalamin) • Zeaxanthin • Zinc	• Prevents macular degeneration • Anti-glaucoma effect • Prevents cataract • Decrease retinopathy • Prevents retinitis pigmentosa • Reduce the risk of diabetic retinopathy • Decrease age-related ophthalmic degeneration • Decrease xerophthalmia (dry eye) • Decrease glutamate induce excitotoxicity • Provides antioxidant effect • Promote cell survival signaling pathways • Anti-inflammatory effect
Gastrointestinal (GIT)  "Stomach pic for food poisoning thingy" by danxoneil is licensed under CC BY 2.0	• Allicin • Anthraquinone • Curcuminoids • Fiber (soluble and insoluble) • Flavonoids/isoflavones • Pentacyclic triterpene • Polyphenols • Prebiotics and probiotics • Psyllium • Resveratrol • Traditional/tribal medicines (*Aloe vera, Curcuma longa, Aegle marmelos,* garlic, croton species, natural honey, *Nigella sativa*, apple, Cordyceps *Sinensis*, Senna, cascara,	• Reduce constipation • Treat diarrhea • Decrease the risk of chronic gastritis-*H. pylori* • Decrease the risk of proctitis • Decrease the risk of Crohn's disease • Decrease the risk of adenomatous polyps • Hepato-protective effect • Decrease the risk of various types of GIT cancer/polyps/neoplasia (colorectal, colon) • Reduce the risk of

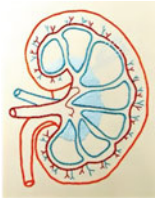
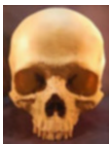
(continued)

Table 1 (continued)

Organ system	List of nutraceuticals	Beneficial effect
	Saccharomyces *cerevisiae, Andrographis paniculate*, *Curcuma longa*, ginger, purple potato, green tea)	inflammatory bowel disease (irritable bowel syndrome) • Possess antibacterial effects • Possess wound healing properties • Reduce ulcer • Ability to stimulate • Increase collagen synthesis and fibroblast activity • Decrease diverticular disease • Reduce the risk of increased gastric acid associated or reflux diseases (dyspepsia, gastroesophageal reflux disease, ulcerative colitis)
Respiratory  "[H] Ma Han—Breathing Systems—Lungs (2008)" by Cea. is licensed under CC BY 2.0	• Calcium • Flavonoids • Natural products from animals (fish oil- omega-3 fatty acids, docosahexaenoic acid-DHA/eicosatetraenoic acid-EPA, heparin) • Traditional/tribal medicines (green tea- epigallocatechin gallate)	• Reduce the risk for cancer • Decrease pulmonary fibrosis • Decrease the risk of chronic obstructive pulmonary disease • Decrease bronchoconstriction • Induce bronchodilation • Decrease the risk for asthma • Decreases the production of pro-inflammatory cytokines (IL-8, TNF-α) • Decrease necrosis
Cardiovascular  "Human heart W/color" by brick red is licensed under CC BY-ND 2.0	• Antioxidant (vitamin-E, vitamin-C) • Polyphenols • Potassium • Omega-3 fatty acids (DHA, EPA) • Coenzyme-Q10 • Spirulina (*Cyanobacterium*) • Sterols/stanols • Traditional/tribal medicines (green tea- epigallocatechin gallate)	• Reduce the risk of heart disease • Decrease hypertension • Reduce endothelial dysfunction • Decrease hypercholesteremia • Reduce obesity • Reduce coronary heart disease • Fight against cardiometabolic risk factors
	• Catechins • Curcumin • Curcumin • Dietary protein	• Possess diuretic effect • Reduce renal dysfunction • Decreases chronic kidney disease

(continued)

Table 1 (continued)

Organ system	List of nutraceuticals	Beneficial effect
Renal  "Framed embroidery kidney anatomy art. Hand embroidered." by hey Paul studios is licensed under CC BY 2.0	• Fatty acids • Fiber • Resveratrol • Traditional/tribal medicines (*Stevia rebaudiana,* green tea, coffee)	• Exhibit antioxidant action • Exhibit anti-inflammatory effect • Possess antifibrotic activities • Protects against infectious • Reduce inflammatory conditions • Protects against hypoxia or ischemia • Blocks nephrotoxicity • Protects against metabolic derangements, • Prevents neoplastic conditions • Decrease the production of uremic toxin • Decrease ammonia production • Protects against glomerulonephritis • Protects against hypertension-related nephrosclerosis
Reproductive	• Acetyl L-carnitine • Coenzyme Q10 • Fertility vitamins • Ferulic acid • Onion • Quercetin • Quercetin glucoside • Red-fleshed apple anthocyanin extracts • Traditional/tribal medicines: (fennel, berberine, dietary soluble flaxseed oil, palm dates, *Trigonella foenum-graecum* L., *Coleus Amboinicus)*	• Menopausal symptoms (hot flushes) • Increases sperm count • Reproductive protective • Increase breast milk production • Attenuate male reproductive system dysfunction • Fertility booster • Increase the possibility to conceive (give birth) • Erectogenic properties
Skeletal (bones)  "Object 3" by bansidhe is licensed under CC BY 2.0	• Calcium • Chondroitin • Cocoa flavanols • Collagen • Copper • Creatinine • Ferulic acid • Glucosamine • Green tea catechins • Raspberry ketone • Vitamin-D • Whey protein	• Decrease osteoporosis • Reduces osteoarthritis • Decrease sarcopenia • Blocks bone degradation • Prevents sarcopenia and skeletal muscle wasting

(continued)

Table 1 (continued)

Organ system	List of nutraceuticals	Beneficial effect
Integumentary (dermal)	• Allicin • Carotenoids • Curcumin • Fatty acids • Green tea catechins • Minerals • Polyphenols • Probiotics • Sesame oil • Vitamins	• Skin softener • Decrease the risk of melanoma • Treat fungal infection • Possess antibacterial effect • Prevents psoriasis • Prevents erythema • Possess wound healing effect • Prevents skin photoaging induced by ultraviolet (UV) irradiation
Immune	• Omega-3 fatty acids (DHA, EPA) • Zinc • Coenzyme-Q10	• Possess immunomodulatory action
Endocrine	• Calcium • Vitamin D • Plant sterols • Fiber (soluble and insoluble) • Garlic • Probiotics • Synbiotics • Phytoestrogens	• Reduces the risk of diabetes mellitus • Decrease the cholesterol (hypercholesterolemia) • Prevents insulin resistance • Prevents polycystic ovary syndrome • Decrease thyroid dysfunction • Neuroprotective role in Parkinson's disease • Decrease obesity • Decreases the risk of metabolic syndrome

(1) Dietary Fiber (2) Probiotics, Prebiotics, and Synbiotics (3) Polyunsaturated fatty acids (4) Vitamins; (5) Polyphenols (6) Spices.

3.1 Dietary Fiber

Dietary fiber refers to botanical-based carbohydrates, significantly distinct from other carbohydrates such as monosaccharides, disaccharides, and starch. Dietary fibers are not digested in the small intestine and reach the large intestine or colon to exert pharmacological effects. The primary fiber-rich foods are wholegrain/wheat (cereals, pasta, bread, oats, barley, rye), fruit (berries, pears, melon, oranges), vegetables (beans, broccoli, carrots, peas, pulses, sweetcorn), nuts and seeds, potatoes with skin. The dietary fibers are classified as water-insoluble/less fermented, water-soluble/well fermented or soluble fiber, and insoluble fiber. Soluble fiber

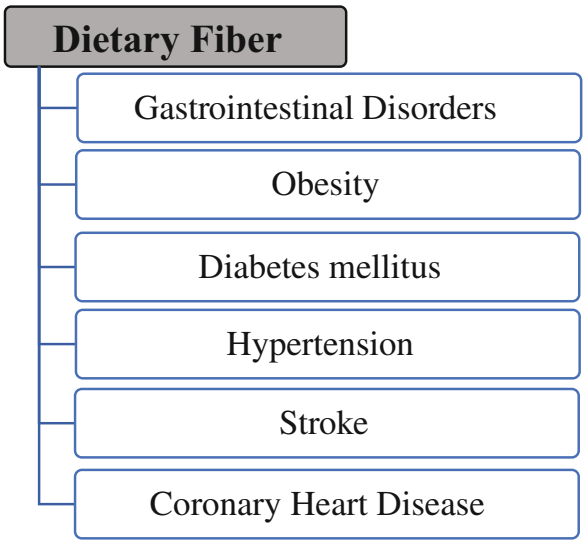


Fig. 1 Potential protective effects of dietary fiber in healthcare

dissolves in water and lowers glucose and cholesterol content in humans and animals. Nutrients and diets with soluble fiber include oatmeal, nuts, beans, lentils, apples, and blueberries. Insoluble fiber typically does not dissolve in water but accelerates the bowel movement of food in the digestive system, fosters bowel movement consistency, and avoids constipation. Foods with insoluble fibers include wheat, whole wheat bread, whole grain couscous, brown rice, legumes, carrots, cucumbers, and tomatoes.

Based on the above observation, there are several dietary fiber products containing cannabis/hemp. Cannabis/hemp seed (*Cannabis sativa*), like other botanicals such as faba bean (*Vicia faba*), lupin (*Lupinus angustifolius*), rapeseed press cake (*Brassica rapa/napus*), flaxseed (*Linum usitatissimum*), buckwheat (*Fagopyrum esculentum*), and quinoa (*Chenopodium quinoa*), is an excellent resource of dietary fiber, essential amino acids, and minerals (Dhingra et al. 2012; Mattila et al. 2018; Farinon et al. 2020). Cannabis/hemp oil is used as dressing in salads, sprinkled on yogurt, cereals, oatmeal, baked in muffins, cookies, bread, granola, and meal bars.

Dietary fiber is a type of food, specifically a type of plant material, that is not hydrolyzed by digestive enzymes and is instead digested by gut bacteria. Non-starch polysaccharides (NSP) such as celluloses, hemicelluloses, gums and pectin, lignin, resistant dextrin, and resistant starches make up the majority of dietary fibers (Das et al. 2012). The potential protective effects of dietary fiber in healthcare are depicted in Fig. 1.

3.2 Probiotics, Prebiotics and Synbiotics

Probiotics and prebiotics assist the beneficial bacteria and yeasts in the body to thrive, resulting in healthy living. The terminology of probiotics has undergone many modifications (Fuller 1989). Currently, the probiotics must be viable microorganisms that positively impact their host to emphasize their microbial origin, and one or more microbial strains may be present in probiotic supplements. Lactobacillus, Bifidobacterium, Lactococcus, Streptococcus, and Enterococcus are the most commonly found bacteria in human probiotics. Additionally, gram-positive bacteria strains from the genus *Bacillus* and certain yeast strains from the family Saccharomyces are often utilized in probiotic products (Fuller 1989).

Prebiotics are specified by the Food and Agriculture Organization (FAO) and World Health Preorganization (WHO) as a non-viable dietary component that provides health benefits to the host by modulating the body's microbiota. Prebiotics are a varied collection of carbohydrate components whose origins, fermentation characteristics, and doses needed for health benefits are not well understood. Breast milk, soybeans, inulin sources (Jerusalem artichoke, chicory roots, and others), raw oats, unprocessed wheat, unrefined barley, yacon, and non-digestible carbohydrates, particularly non-digestible oligosaccharides, are all excellent sources of prebiotics.

Since the term "synbiotics" implies synergism, it should only be used for the products in which the prebiotic compound(s) benefit the probiotic organism preferentially (s) (Pandey et al. 2015). By selectively boosting the development and/or activating the metabolism of one or a restricted number of health-promoting bacteria, a synbiotic product aids the host in enhancing the survival and implantation of live microbial dietary supplements in the gastrointestinal system. Synbiotics have been reported to combat inflammatory bowel disease (IBD), reduce diarrhea, decrease lactose intolerance, and the combination of prebiotics and probiotics that may boost the host immune system, decrease obesity and hyperglycemia (Benisek 2021).

Cannabis oil is a potentially beneficial probiotic for human use. Recent research has shown CBD probiotics to have the ability to protect joints, support the immune system, strengthen bones, relax emotions, enhance prostate, and vaginal health, protect neurons and increase neuronal function, increase sleep quality, as well as help with pain relief. Additionally, researchers have found that CBD oil can treat skin problems (acne, dark spots, and xeroderma). Currently, Cannabis-based nutraceuticals are available as topical creams and ointments and can be ingested orally as gummies, soft gels, and pills (WebMD 2020).

3.3 Polyunsaturated Fatty Acids (PUFA)

Polyunsaturated fatty acids (PUFAs) are also referred to as "essential fatty acids" because they are required for the body's normal physiological function and are obtained through the diet (Mahan and Escott-Stump 2004). PUFA's provide

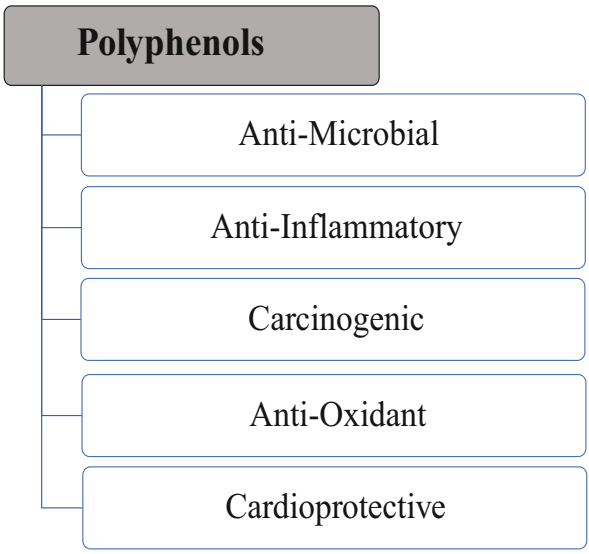


Fig. 2 Major health benefits of polyphenols

essential structural and functional components of the plasma membrane. PUFA's are designated by the number of unsaturated bonds in their structure by the letter "n" (Fig. 2). PUFA's with either n-3 or n-6 (ω-3 or ω-6) are beneficial in the ideal ratio of n-3 to n-6 is 1:5. The amount of n-3 or n-6 PUFAs in food has a direct impact on their bioavailability. PUFA's accumulate into the neuronal phospholipids mostly during brain development. PUFA's also influence synaptic function by changing the neuronal membranes' dynamic and enhancing the functionality of membrane-associated proteins. Additionally, PUFA's can aid in neurogenesis and neuroprotection. Interestingly, PUFA's are also precursors are endocannabinoids (Al-Khalifa et al. 2007; Layé 2016).

Endocannabinoid neurotransmission is a newly studied and researched transmitter system compared to the cholinergic, serotonergic, GABAergic, and glutamatergic neurotransmitter systems. This transmitter system significantly regulates the central and peripheral signaling mechanisms associated with food intake, lipids synthesis and turnover in the liver and adipose tissue, and glucose metabolism in muscle cells. This system significantly influences the central nervous system, peripheral nervous system, immune systems, and hormones. The endocannabinoids regulate the secretion of hormones related to reproductive functions and stress response. Furthermore, endocannabinoids control energy homeostasis and significantly affect food intake centers/regions of the brain/central nervous system and gastrointestinal tract activity.

Cannabis-based nutraceuticals have been reported to improve gonadotrophin pulsatility, fertilization ability and decrease the risk of various neurodegenerative (Alzheimer's, Parkinson's, and Huntington's diseases) and neurological disorders (epilepsy, anxiety, and stroke). Thus, a new or an existing cannabis-based nutraceutical selectively act on central and peripheral cannabinoid-1 receptor (CB1) receptor and reduce body weight, improve metabolic syndrome (decrease hyperglycemia and

hypercholesteremia), decrease cardiovascular diseases in obese patients by increasing blood HDL-cholesterol, adiponectin, and lowering LDL-cholesterol, leptin, and C-reactive protein (a pro-inflammatory protein). Furthermore, linoleic acid, alpha-linolenic acid, and gamma-linolenic acid are three polyunsaturated fatty acids in hemp seed oil. The fatty acid ratio of hempseed omega-6 (linoleic acid) to omega-3 (alpha-linolenic acid) is 3:1. According to the current literature, the 3:1 fatty acid ratio is beneficial for human health.

3.4 Vitamins

Vitamins are synthetic or natural substances essential for physiologic function, can help prevent or delay certain types of cell damage, and prevent the initiation and progression of a disease. Casimir Funk, the Polish-born biochemist, coined the term "*vitamine"* in 1912. Vitamins are organic molecules with a wide variety of functions within the body. They act as coenzymes/cofactors for enzymatic reactions. Generally, vitamins cannot be synthesized by mammalian cells and therefore must be supplied in the diet. Vitamins are classified mainly based on their solubility (water-soluble and fat-soluble vitamins) (Table 2). Important features of fat-soluble vitamins (A, D, E, K) are given in Table 3.

In general, deficiency of Vitamin-B leads to various types of anemia, such as pernicious anemia (B_{12} deficient), folic acid deficient anemia, riboflavin deficient anemia, pyridoxine deficient anemia, and sideroblastic anemia.

3.4.1 Thiamine (Vitamin B_1)

The dietary requirement for thiamine is 1–1.5 mg/day. It is mainly present in lentils and whole grains. The primary functions are that it acts as a cofactor for pyruvate and alpha-α-ketoglutarate dehydrogenase and helps in forming acetyl-CoA. The major symptoms of thiamine deficiency are constipation, appetite suppression, nausea, mental depression, peripheral neuropathy, fatigue, ataxia, loss of eye coordination,

Table 2 Water-soluble and fat-soluble vitamins

The water-soluble vitamins	The fat-soluble vitamins
• Thiamin (B_1) • Riboflavin (B_2) • Niacin (B_3) • Pantothenic acid (B_5) • Pyridoxamine (B_6) • Biotin (B_7) • Cobalamin (B_{12}) • Folic acid • Ascorbic acid (vitamin C)	• Retinol, retinal, retinoic acid (vitamin A) • Calcitriol (vitamin D) • α Tocopherol (vitamin E) • Phylloquinone (vitamin K)

Table 3 Important features of fat-soluble vitamins (A, D, E, and K)

Vitamin	Structure/chemical name	Precursor	Function	Storage	Deficiency symptoms	Toxicity
A	Reinol, retinal, retinoic acid	Beta-carotene	• Photoreception: Opsin bound to vitamin A • Retinol helps in mucous production & normal growth regulation	Liver	• Night blindness • Xerophthalmia • Cancer • Infection	• Liver toxicity • Bone pain • Nausea • Diarrhea • Hepto-splenomegaly • Headache • Acne, skin disorder
C	Ascorbic acid	Glucose L-gulonolactone oxidase absent in primates	• Reduce cytochrome a, c, and oxygen of the respiratory chain • Cofactor for hydroxylation of proline in collagen • Catabolism of tyrosine • Synthesis of bile acids, steroid • Enhances the absorption of iron	Adrenal cortex	• Wound healing (proline-collagen) • Scurvy	• Indigestion • Diarrhea
D	Steroid hormone, biologically active = Calcitrol-1,25-(OH)2-D3	Ergosterol, 7-dehydro-Cholesterol	• With parathyroid hormone regulates calcium and phosphorus level • Promotes bone formation • Stimulates immunogenic and antitumor activity • Decreases risk of autoimmune disorders	Adipose tissue	• Children: Rickets • Adults: Osteomalacia	• Hypercalcemia

(continued)

Table 3 (continued)

Vitamin	Structure/chemical name	Precursor	Function	Storage	Deficiency symptoms	Toxicity
E	α-Tocopherol, β,γ, δ-tocopherols, 4-tocotrienols		• Free radical scavenger • Prevents peroxidation of polyunsaturated membrane fatty acids	Absorbed in the intestine and packed in chylomicrons and transported to the liver Stored in adipose tissue, cellular membrane, circulating lipoproteins	• Increase in red cell fragility • Neurological disorders	• Increased risk for cancer
K	Phylloquinone (K1 green vegetables) Menaquinone (K2 intestine) Menadione (K3 synthetic)		• Blood clotting • Conversion of inactive enzymes to the active form (carboxylation)	Absorbed in the intestine in the presence of lipids and bile salt	• Hemorrhage syndrome	• Increases the risk for coagulation

cardiovascular problems, and musculature defects. The deficiency diseases are Beriberi, Wernicke-korsakoff syndrome, and dementia. It is prophylactically used to reduce the risk of cataracts, Alzheimer's disease, congestive heart failure, and various cancers. The significant adverse effect or toxicity associated with the use of thiamine is anaphylactic shock.

Thiamine has several drug and herbal interactions, and they are listed below:
Interaction with therapeutic drugs:

- Phenytoin (anticonvulsants) reduces thiamine levels in the blood and cerebrospinal fluid
- Antacids may lower thiamine levels in the body by decreasing absorption and increasing excretion or metabolism.
- Barbiturates may lower thiamine levels in the body by decreasing absorption and increasing excretion or metabolism.
- Loop diuretics (furosemide, Lasix®) have decreased thiamine levels by increasing urinary excretion (and also possibly by reducing absorption)
- Tobacco use decreases thiamine absorption and may lead to decreased levels
- Oral contraceptives (birth control pills)
- Chemotherapy Patient receiving fluorouracil-containing drug therapy
- Antibiotics destroy gastrointestinal flora (normal bacteria in the gut). It may decrease thiamine (slight depletion because thiamine is obtained through the diet and not via bacterial production).

Interactions with Herbs and Dietary Supplements:

- Consumption of betel nuts (*Areca catechu* L.) may reduce thiamine due to chemical inactivation
- Horsetail (*Equisetum arvense* L.) is used as a diuretic for the treatment of edema. It contains a thiaminase-like compound that can destroy thiamine in the GI tract. The Canadian government requires that horsetail products should be certified free of thiaminase activity.

3.4.2 Riboflavin (Vitamin B_2)

Important features of vitamin B_2 like functions, use, deficiency symptoms, deficiency disorders, adverse effects, and drug interactions are given in Table 4.

3.4.3 Niacin (Vitamin B_3, Pyridine-3-Carboxylic Acid, Nicotinic Acid)

The dietary requirement of niacin is 13–19 niacin equivalents. This water-soluble vitamin is required to synthesize NAD^+ and $NADP^{+,}$ which functions as a cofactor for various dehydrogenase enzymes (lactate, malate dehydrogenase). Niacin deficiency can result in reduced capacity to generate energy (ATP). The symptoms of niacin deficiency are glossitis, dermatitis, diarrhea, depression, dementia, and weight

Table 4 Important features of riboflavin

Functions	Deficiency symptoms	Deficiency disorder	Uses	Adverse effects	Drug-interaction
Precursor for FMN & FAD	Glossitis, seborrhea, angular stomatitis, cheilosis, photophobia	Skin problems	Cosmetic use: Maintains the health of hair, nails, and skin	Urine coloration	The dose must be increased while consuming alcohol, antibiotics, and birth control pills or during a restricted diet

loss. The primary disease that occurs due to niacin deficiency is Pellagra. Prophylactically niacin is used in the treatment of hypercholesterolemia. The other clinical benefits of niacin are to control atherosclerosis and osteoarthritis. The primary adverse effects associated with elevated niacin levels include increased uric acid and glucose production. Hence, niacin should be used carefully in diabetes mellitus patients and patients suffering from gout. Niacin has a significant dug-interaction when used with the antitubercular drug isoniazid.

3.4.4 Pantothenic Acid (B_5)

Williams and his coworkers in 1933 isolated the crystalline product from yeast and named it pantothenic acid (Williams et al. 1933). Chemically, pantothenic acid (vitamin B_5) is 3-[(2,4-dihydroxy-3,3-dimethyl-butanoyl)amino] propanoic acid. It is synthesized from beta-alanine and pantoic acid. Vitamin B_5 is necessary for synthesizing acetyl-CoA (acetyl coenzyme A) and is required for the metabolism of carbohydrates via the tricarboxylic acid cycle (TCA). Furthermore, acetyl-CoA is also involved in other biochemical reactions associated with protein and lipid metabolism. Acetyl-CoA is also required for the biosynthesis of the neurotransmitter acetylcholine, a reaction catalyzed by the enzyme acetyltransferase. The primary source of pantothenic acid is whole grain cereals, legumes, meat, and the dietary requirement is 5 mg/day adult. Deficiency of this vitamin can lead to fatigue (reduced capacity to generate energy), glossitis, dermatitis, diarrhea, depression, dementia, weight loss. The diseases due to the deficiency include adrenal insufficiency, hepatic encephalopathy, Hartnup disease, and malignant carcinoid syndrome. Vitamin B5 is prophylactically used for hair care and to reduce acne and diabetic peripheral polyneuropathy. The major adverse effects are an upsurge in alanine transaminase (ALT) and creatine phosphokinase (CPK) content, pain (abdominal, joint, and muscle), constipation, dizziness, flu-like symptoms, headache, infection (urinary tract), nausea, pancreatitis, and sore throat. Furthermore, several Type-I hypersensitivity reactions such as hives, itching, rash, and swelling have been reported with Vitamin B_5 ingestion. Vitamin B_5 has very minimal pharmacodynamic drug interactions with other drugs. However, moderate drug interactions have been reported with some antibiotics (azithromycin, clarithromycin, erythromycin, and roxithromycin).

3.4.5 Pyridoxine (Vitamin B_6)

Vitamin B_6 possesses a pyridine ring with hydroxyl, methyl, and hydroxymethyl substituents. It is mainly found in adults, whole grain cereals, legumes, meat, and the dietary requirements are 1.4–2.0 mg/day. The three major forms of vitamin B-6 are pyridoxine, pyridoxal, and pyridoxamine. Three forms of vitamin B-6 are precursors of an activated compound known as pyridoxal 5′-phosphate (PLP), which plays a vital role as the cofactor of many essential enzymes, including neurotransmitter decarboxylases used in the biosynthesis of dopamine, norepinephrine, and serotonin. Vitamin B_6 is generally indicated for pathological conditions that occur due to Vitamin B_6 deficiency. These include alcoholism, malabsorption, congestive heart failure, severe diarrhea, congenital metabolic dysfunction, hyperthyroidism, renal and hepatic disease, drug-induced conditions, and during pregnancy and lactation. It is also used to treat pyridoxine-dependent syndromes (pyridoxine-dependent seizures in infants, homocystinuria, pyridoxine-responsive anemia, and hyperoxaluria). Pyridoxine is also an antidote for isoniazid, hydrazine, and ethylene glycol-induced toxicities. Vitamin B_6 deficiency symptoms are anxiety, depression, loss of libido, insomnia, fluid retention, inability to process glucose (weight loss/gain). Adverse effects of Vitamin B6 overuse include a feeling of disembodiment common with the loss of proprioception and increased dream vividness. The primary drug interactions are with isoniazid and oral contraceptives.

3.4.6 Biotin (Vitamin B_7)

The chemical structure of biotin consists of an ureido (tetrahydroimidizalone) ring fused with a tetrahydrothiophene ring. It includes a valeric acid substituent is attached to one of the carbon atoms of the tetrahydrothiophene ring. Intestinal bacteria mainly synthesize it. Physiologically, it is essential in the catalysis of essential metabolic reactions to synthesize fatty acids, gluconeogenesis, and metabolize leucine. It is also a cofactor required for enzymes involved in carboxylation reactions (acetyl-CoA carboxylase). Since biotin is found in numerous foods, deficiency syndromes and symptoms are very rare and mild. It is prophylactically used to prevent Cradle cap (seborrheic dermatitis), diabetes mellitus, hair, and skin problems. It is reported to have significant drug interactions with antibiotics, antiepileptics (carbamazepine, phenobarbital, phenytoin), and various herbal products.

3.4.7 Cobalamin (Vitamin B_{12})

The vitamin cobalamin contains a corrin ring with cobalt in the center, like the porphyrin ring found in heme, chlorophyll, and cytochrome. It is mainly found in foods of animal origin. Cobalamin is required for the physiological functioning of the TCA cycle (methylmalonyl mutase requires vitamin B12), in converting

homocysteine to methionine, and folate generation. It can be stored in the liver for 6 years; hence deficiency is rare (however, vegetarians can develop deficiency). The deficiency symptoms are neurological syndromes (cognitive impairment, movement impairment), anemia, and impaired DNA synthesis. Pernicious anemia occurs due to cobalamin deficiency. An intrinsic factor in the stomach is required for its physiological action, which helps in its absorption. It is prophylactically used to treat anemia, cyanide poisoning, and various types of dementia. The adverse effects associated with cobalamin overuse include allergy, diarrhea, and thrombosis. The major drug interactions are with alcohol, antibiotics, birth control pills, histamine (H_2) antagonist, metformin, and nicotine.

3.4.8 Folic Acid

Folic acid is found in leafy plants, yeast, and the liver. Normally body stores 10–20 mg; hence it takes 3–4 months for the deficiency to occur when the diet is deficient in this vitamin. Folic acid is required for DNA, RNA, and protein synthesis as well as normal cell division. Impaired cell division (mainly in the rapidly proliferating cells) occurs due to increased folic acid requirement (pregnancy), decreased folic acid intake, impaired folic acid absorption, Crohn's disease, chronic use of anticonvulsants, and the use of dihydrofolate reductase inhibitors (methotrexate, trimethoprim). Poor absorption of folic acid can result in disorders of the small intestinal and alcoholism. Folic acid deficiency leads to megaloblastic anemia. The major symptoms are fatigue, dizziness, increased cardiac output leading to heart failure, gastrointestinal symptoms (diarrhea), glossitis (tongue beefy and red), and muscle wasting. Neurological symptoms are rare, with folic acid deficiency and usually not present.

3.4.9 Ascorbic Acid (Vitamin C)

Important features of vitamin C such as precursor, functions, storage in the organ, deficiency symptoms, and toxicity are given in Table 5.

3.5 Polyphenols

Polyphenols are naturally occurring compounds present in certain beverages (tea, coffee, and red wine), cereals, fruits, and vegetables (legumes). In food, polyphenols may contribute to bitterness, color, flavor, and odor. Polyphenols are plant metabolites and are generally involved in defense against ultraviolet radiation or harmful pathogens. Polyphenols are grouped into two major classes, flavonoids and phenolic acids. Flavonoids are further subclassified into flavones, flavanones, flavonols, flavonols, isoflavones, and phenolic acids are subclassified into hydroxybenzoic

Table 5 Important features of ascorbic acid (Vitamin C)

Chemical name	Precursor	Functions	Storage	Deficiency symptoms	Toxicity
Ascorbic acid	Glucose L-gulonolactone oxidase absent in primates	• Reduce cytochrome a, c, and oxygen of the respiratory chain • Cofactor for hydroxylation of proline in collagen • Catabolism of tyrosine • Synthesis of bile acids, steroid • Enhances the absorption of iron	Adrenal cortex	• Wound healing (proline-collagen) • Scurvy	• Indigestion • Diarrhea

and hydroxycinnamic acids. The most common explanation for the beneficial effects of polyphenols is the "biochemical scavenger theory." This theory proposes that polyphenolic substances neutralize free radicals by creating stable chemical complexes, limiting further reactions that can lead to pathology at the cellular and tissue levels. Another method by which polyphenols protect against oxidative stress is via the production of hydrogen peroxide, which may subsequently assist in controlling immune response activities such as cellular development (Cory et al. 2018).

Polyphenols' beneficial effects are either as protective/prophylactic chemicals or as therapeutic molecules, may be obtained by consuming a naturally polyphenol-rich diet, ingesting dietary supplements, or using pharmaceutical drugs/nutraceuticals formulations (Silva and Pogačnik 2020). Polyphenols offer the benefit of providing a sufficiently active dosage, but they also have a range of adverse effects. Polyphenols invariably interact with other nutrients; in meals may slow down the rate of carbohydrate digestion, reducing postprandial glucose rises. A supplement would have no impact on this parameter if taken without food; therefore, the optimum scenario would be to ingest the polyphenol with foods. Similarly, polyphenol supplements may alter bioavailability, discouraging people from eating a 'healthy diet' instead of augmenting poor food (Williamson 2017).

Industrial hemp (*Cannabis sativa* L.) belongs to the family Cannabaceae. The plant contains many bioactive compounds, mostly polyphenols, including flavonoids, phenolic acids, phenol amides, and lignanamides, which are well known for their therapeutic properties. The phytochemical characterization of Cannabis highlights various non-cannabinoid components, including various phenolic compounds, steroids, and alkaloids. Many polyphenols-related products consisting of herbal extracts are marketed and benefit health (Smeriglio et al. 2016; Pandey and Rizvi 2009; Pollastro et al. 2018). Based on the above scientific fact, the phenolic compounds within industrial hemp inflorescence showcase an innovational source of bioactive compounds to be used in nutraceutical formulations and can commonly be observed in products such as cold-pressed seed oil (containing the Finola cultivar of industrial hemp). Significant in vitro evidence suggests that dietary polyphenols

may influence various cellular processes, including gene expression, apoptosis, platelet aggregation, and intercellular communication, which may have anti-carcinogenic and anti-atherogenic effects (Duthie et al. 2003). Major health benefits of polyphenols are depicted in Fig. 2.

3.6 Spices

Spices are abstruse food additives that have been used to improve the overall aesthetic quality of foods for thousands of years. They are natural substances that primarily consist of substances obtained from the bark, fruit, root seed, and other botanicals. According to the United States of America Food and Drug Administration (US-FDA), spices are "aromatic vegetable compounds, in whole, broken, or crushed form, whose main role in food is flavoring rather than nutrition." According to the above FDA's description, onions, garlic, celery, and seeds like poppy and sesame are generally considered food and not spices. Various spices are used predominantly internationally for flavoring or coloring food, where a minimal quantity can considerably enhance the aesthetic property, quality, and taste (deliver a unique flavor). Many foods without spice (s) are usually flavorless, bland, and odorless. Some spices like paprika, turmeric, and saffron are used in cuisine to improve color and taste. Thus, these spices are categorized as "flavoring and coloring" agents when used or added to a cuisine. The majority of spices come from bark (cinnamon), fruit (red and black pepper), and seed (cumin and nutmeg). Interestingly, spices are generally distinguished from herbs, leaves, flowers, or stalks/stems of plants used as a garnish. Herbs used in cooking are usually made up of leaves and stems.

Similar to FDA, The Geneva-based International Standards Organization (ISO) defines spices and condiments as "Vegetable products or mixtures thereof, free from extraneous matter, used for flavoring, seasoning and imparting aroma in foods." Furthermore, any aromatic botanical/vegetable (cinnamon, cloves, mace, nutmeg, pepper, ginger) used to season and flavor sauces, pickles, or other food/drink, usually in the form of a powder; collectively are also considered spices. A standard and traditional classification of spices are based on the degree of taste and flavor. The spices are classified as mild (paprika, coriander), aromatic (pimento, cardamom, cassia, cinnamon, clove, cumin), and hot (Capsicum/chilies, Cayenne pepper, black and white peppers) spices.

According to recent research studies, dietary spices may considerably benefit human health due to diverse pharmacological profiles. The multiple actions reported for spices include antioxidant, chemopreventive, antimutagenic, anti-inflammatory, and immunomodulatory effects. Due to the above multi-potent pharmacological actions, spices exhibit many positive, beneficial effects on human health. Spices can significantly affect the human body's neurological, ophthalmic, gastrointestinal, cardiovascular, respiratory, metabolic, reproductive, renal, skeletal, and other physiological functions.

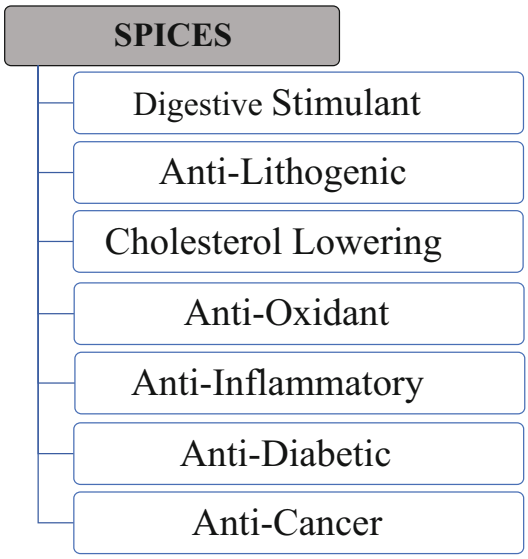


Fig. 3 Major health benefits of spices

Several flavorful cannabis-infused seasonings are currently available (https://www.keithlorren.com/shop/keith-lorren-canna-spice, https://emilykylenutrition.com/cannabis-taco-seasoning/, https://www.evolvecannabiscompany.com/product/cured-cbd-infused-spices/, https://nevadawellnesscenters.com/?product=edible-soul-dlicious-vegetable-infused-seasoning-thc-100-69mg).

Hemp/Cannabis extracts (organic cold-pressed) are commonly added to omega 3,6,9 essential fatty acids, garlic, trace minerals, and other substances. These Cannabis-based spice combinations are usually added at the end of the cooking process to conserve the beneficial effects of Cannabis. The Cannabis-infused spices can be added to burgers, burritos, baked potatoes, pasta, roasted vegetables, sliced fruit, and steak. Moreover, Cannabis-infused spice combinations can also be added to any drink (Elliott 1999; Lampe 2003). The major health benefits of spices are depicted in Fig. 3.

Moreover, in general, nutraceuticals can be divided into two categories:

1. Nutraceuticals with potential
2. Nutraceuticals that are well-established

Only after reliable clinical data on a potential nutraceutical's health and medical advantages is collected can it become a well-established product. It's worth noting that many nutraceutical products are still classified as "potential" (Pandey et al. 2010).

4 Cannabis as a Nutraceutical

Cannabis has been widely established as a primordial source of fiber, protein, and fat with great nutritional value, whether raw, boiled, or squeezed into the oil. In addition, Cannabis has been employed in traditional oriental medicine for thousands of years to treat and prevent diseases. Cannabis has been utilized as a food or medicine source in China for at least 3000 years, whether raw, baked, or roasted. Traditional Asiatic diets and treatments continue to use the seed, both crushed and whole. Cannabis has been legally utilized as human food in the United States for the past 10 years. Cannabis is primarily used for animal feed, but their products (oil, meal, flour, protein powder) are gaining popularity in human nutrition as a source of nutrients (Andre et al. 2016).

4.1 Chemical Constituents

Cannabis products comprise all essential amino acids and fatty acids in significant quantities and proportions to meet human dietary requirements. They include 25%–35% lipids, 20%–25% proteins, 20%–30% carbs, 10%–15% insoluble fibers, and a wide range of minerals, including phosphorus, potassium, salt, magnesium, sulfur, calcium, iron, and zinc. Protein (25%) and vitamin E (90 mg/100 g). Concerning the chemistry of *Cannabis sativa*, more than 750 natural compounds of different chemical classes have been reported (Upton 2021). Major chemical classes reported in C Sativa are depicted in Fig. 4.

Additionally, Cannabis comprises more than 30% oil, with polyunsaturated fatty acids accounting for more than 80% of the total, mainly linoleic ω-6 and -linolenic

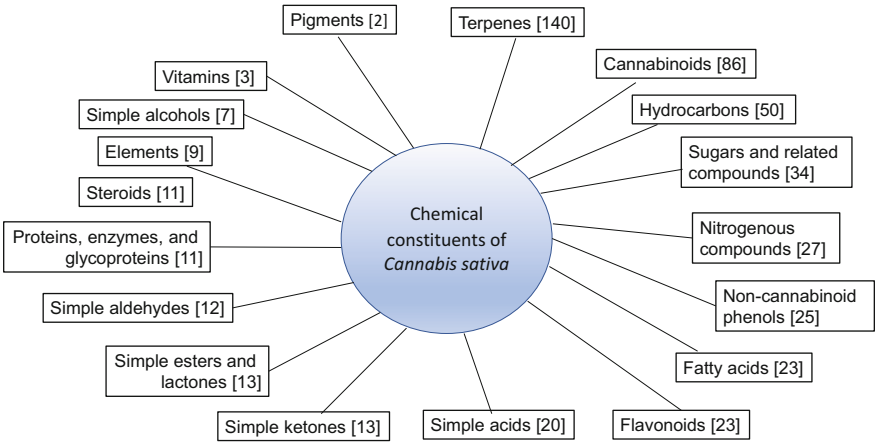


Fig. 4 Major chemical classes of compounds reported in *Cannabis sativa.* The numbers in parentheses are the number of compounds identified under each class

ω-3 acids. Anti-cancer, anti-inflammatory, and anti-thrombotic effects and an increase of general metabolism and fat burning have all been linked to ω-3 (Callaway 2004). The hemp seed oil has a ω-6/ω-3 ratio of roughly 3:1, which is excellent for human health. Recent research has found that these fatty acids and dietary hemp seeds have favorable impacts on platelet aggregation, ischemic heart disease, and other aspects of cardiovascular health. Furthermore, hemp seeds and derivatives have been discovered as a valuable antioxidant diet for the favorable effects of hemp bioactive molecules; further research and clinical studies for any potential adverse effects of hemp products in the diet have been advised. Several researchers have found that dietary hempseed has modestly positive effects on contractile dysfunction associated with atherosclerotic arteries in the cholesterol-fed rabbit (Frassinetti et al. 2018; Gavel et al. 2011).

Hemp seeds also contain minerals and nutrients such as Vitamin C, Calcium, Iron, Omega-3 fatty acids, Magnesium, and B vitamins, many of which are antioxidants. Many of these nutrients provide the body with necessary minerals and also contribute to overall health. Hemp seeds additionally contain a significant amount of iron, which can help prevent iron deficiency or anemia. Furthermore, Hemp seed oil is used as a remedy for a range of conditions (Atalay et al. 2019; Koekkoek and van Zanten 2016).

Based on the previous information, hemp seed oil and other hemp-based products contain minerals and antioxidant vitamins that can work individually and in combination to prevent oxidative processes that contribute to cancer, cardiovascular disease, cataracts, protect the body by scavenging free radicals and other degenerative disorders, and reduced bodily inflammation (Elliott 1999). While there are several research publications on the health advantages of hemp seeds, oils, and meals, there are few references on hemp sprouts' biological activities and possible health benefits. One study indicated that hemp sprouts might be used as a new anti-inflammatory hemp food product. Thus, Cannabis, due to its bioactive contents and its action, can be a valuable nutraceutical in the future.

4.2 Products and Their Uses

Cannabis is now used by nearly 147 million people globally, mainly due to its recreational and medicinal properties. The vast majority of individuals who only know Cannabis as a recreational substance are unaware of its immense social, industrial, and economic benefits (Cerino et al. 2020). According to the FDA (https://www.fda.gov/media/131878/download), THC and CBD products are exempt from the dietary supplement classification under section 201(ff)(3)(B) of the FD&C Act [21 U.S.C. § 321(ff)(3)(B)]. Based on the FDA's current requirements, if a substance (such as THC or CBD) is an active ingredient in a drug product approved under section 505 of the FD&C Act [21 U.S.C. § 355], or has been authorized for investigation as a new drug for which substantial clinical investigations and the existence of such investigations has been made public, then products

containing that substance are prohibited. The demand for cannabidiol-based products has increased tremendously (by 500% since 2017). Several nutraceutical companies market cannabis nutraceutical products like CBD capsules, CBD tinctures, water soluble cannabinoids and dietary supplements to reduce stress boost immunity, maintain muscle and bone structure pain relief, insomnia, muscle spasms, nervous system degradation, and anxiety.

Cannabinoid extracts have been added to a wide range of foods, including beverages (both dairy and non-dairy), breakfast cereals, cookies, brownies, ice cream, snacks, bread, pizza, vegan burgers and sausages, and, more recently, beer, wine, hemp-infused milk, barley-based sodas, health beneficial honey, and fortified sports products. In the USDA's Food Data Central database, 680 branded food items containing hemp seed derivatives in the form of oil, extract, flour, or powder have been registered till now. To be legal in the United States, any of these items must have less than 0.3% THC (King 2019; Martínez et al. 2020). Additionally, hemp seeds, which are often used to enhance the flavor of healthful salads, can also be ground into a multipurpose flour that can be used to create a variety of meals. Hemp flour has 21% fewer calories than "00-flour" produced from conventional cereals and has a bitter, rustic taste similar to the whole meal. It is also gluten-free, making it a perfect option for celiac disease patients. An additional advantage of Cannabis is that it is vegan-friendly and contains plant-based protein. Hemp may be utilized instead of pea protein or rice protein, which are the most common plant-based proteins currently in the market. Hemp oil is a good source of fatty acids (EFAs) and is generally allergy-friendly and gluten-free. Aside from celiac disease, other diseases benefit from gluten-free diets, such as Hashimoto's thyroiditis, and hemp may be included in protein powders. It's a good option for individuals who are allergic to dairy or soy in other foods. Hemp is a plant source of Vitamin D. It has been observed that an increased requirement for Vitamin D is required to prevent or protect against COVID-19 induced pathological effects (Grant et al. 2020). Hemp flour is a byproduct of the hemp oil manufacturing process and is contains high fiber, microelements, and phytosterols. The above bioactives help to maintain normal cholesterol and decrease the risk of hypercholesteremia and cholesterol-mediated adverse effects in the body (Sorrentino 2021). CBD has been demonstrated in various pre-clinical models to have anticonvulsant, anxiolytic, anti-inflammatory, immune-modulating, and antineoplastic action (Cerino et al. 2020).

4.3 Health Benefits

Similarly, hemp seed also has been linked to a variety of health benefits and possible treatments. As hemp seed has a healthy omega-6 to omega-3 PUFA ratio, which might have the following nutraceutical values to exhibit the following pharmacological and therapeutic benefits: antitumor, anti-inflammatory, analgesic, antidepressant, antispasmodic and anticonvulsant, diuretic, antiemetic, appetite enhancer, anticancer, antibacterial, virucidal, sleep aid, cardiovascular aid, neuroprotective

and Neurorestorative to combat various neurological disorders (Alzheimer's disease, Parkinson's disease, brain trauma, and stroke) (Rupasinghe et al. 2020). Moreover, CBD contains immunomodulatory properties, such as reducing inflammatory responses, suppressing cellular and humoral immunity, and inducing the death of specific lymphocytes. Therefore, these properties are helpful in the treatment of inflammatory disorders (Booz 2011). Diabetes mellitus is primarily an endocrine disorder. However, inflammation may also play an essential aspect in the pathology of this devastating chronic illness. This hyperglycemic disorder may significantly benefit from preventive CBD therapy. Furthermore, non-obese hyperglycemic mammals administered with CBD exhibited a delayed onset of diabetes mellitus and substantially reduced leukocyte activation (Lehmann et al. 2016).

4.4 Future Prospects

Due to the rising obesity and related endocrine and neurological diseases, rising health consciousness, and increased scientific knowledge about the advantages of cannabidiol nutraceuticals, demand for CBD nutraceuticals is projected to rise substantially in the future. Interestingly, CBD has been reported to exert several physiological, biochemical, and psychological effects that can benefit adults of all ages, individuals with anxiety disorders and have the potential to benefit performance athletes. Early pre-clinical and clinical data suggest that CBD has anti-inflammatory, neuroprotective, analgesic, and anxiolytic properties and the potential to protect against GI damage caused by inflammation and aid the repair of severe skeletal injuries (McCartney et al. 2020). The legalization of hemp-derived goods in late 2018, along with rising consumer disposable income and a growing trend toward health and wellness products, has resulted in a substantial rise in demand for cannabidiol nutraceuticals. The market is divided into various CBD products and formulations (capsules, tinctures, candies, bubble gum, chocolates) and other products based on the kind of product. Cannabidiol tinctures are rapidly being utilized for various ailments, including pain alleviation, sleeplessness, muscular spasms, nervous system degeneration, and anxiety. Governments all around the world are progressively enacting legislation to encourage the development of cannabidiol nutraceuticals. Therefore, by 2028, the worldwide CBD nutraceuticals market is projected to be worth 19.25 billion USD.

5 Conclusion

Due to various health benefits, Cannabis-based products are attracting much worldwide attention in addition to the existing sources of nutraceuticals. Though all parts of a Cannabis plant have significant values, seed and oil are mainly used in food preparations. Every year market size is increasing, and governments worldwide are

progressively enacting legislation to encourage the development of cannabidiol nutraceuticals. It is estimated that by 2028, the worldwide CBD nutraceuticals market is projected to be worth 19.25 billion USD. Therefore, it is important to carry out intensive, evidence-based research in this promising area.

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Traditional, Cultural, and Nutraceutical Aspects of Cannabis in India

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Abstract Historically, India has continued to produce and use Cannabis for medicinal, nutritional, spiritual-religious, and socio-cultural purposes, as documented in ancient Indian literature. Furthermore, various indigenous medicinal practices unique to India, such as the Ayurveda, Siddha, and Unani, indicate wide use of Cannabis in treating various disorders. Cannabis has had a very long unbroken tradition of cultivation and application in India for ages till the present. Various parts of the plant (*Cannabis sativa* Linn.), such as the flowers, leaves (and the resinous matter derived from there), fruit, young twigs, and stalk/stem, are commonly used in India and other parts of the world for different purposes. This book chapter gives an overview of the broad applicability of Cannabis in India, including cultural, medicinal, agricultural, commercial, and recreational uses.

Keywords Cannabis · Cultural use · Medicinal use · Nutraceuticals · Recreational use

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Abbreviations

BCE	Before Common Era
CBD	Cannabidiol
NDPS	Narcotic drugs and psychotropic substances
THC	Tetrahydrocannabinol

1 An Introduction to the Traditional Uses of Botanicals in India

Natural products are generally referred to as substances (any molecules and other primary and secondary metabolites) produced inherently and endogenously by any living organisms (animals, plants, and microbes). Natural products can refer to small molecules (coenzyme-Q10 and urea) and larger and complex molecules (phytocannabinoids, alkaloids, terpenoids, taxol, etc.). These natural products with specific chemical structures are usually produced in small isolatable quantities that yield a biological activity. This has resulted in using them as an agricultural product, dietary supplement, recreational substance, and prophylactic and therapeutic substance for medicinal purposes. Thus, natural products have been utilized in religious ceremonies, recreational purposes, food, and supplements for their nutritional value and pharmacological effects. Accordingly, natural products have played an important part in the development of global and local communities.

Usually, the usage and consumption of numerous natural products have progressed from the practice, usage, and knowledge gained over several centuries (a prolonged period). The word "traditional use" refers to the wisdom of concepts and knowledge associated with natural products that have been passed on from the forefathers to the next several generations where the information regarding the agricultural wealth of medicinal value was usually kept as a family secret or was shared to the public as a philanthropic act.

Interestingly, the ancient and traditional Indian medicinal Systems have constantly promoted global wellness and healthcare in the past and present and intend to play a critical role in the future. The Indian medicinal system has its roots/origin from India; however, few have come from foreign origins and have been embraced and integrated into the Indian culture as the "Indian Systems of Medicine." India has the distinct honor and excellence of having different well-accepted and established medicinal systems. Ayurveda, Homoeopathy Naturopathy, Siddha, Unani, and Yoga are considered the "Indian Systems of Medicine" (Lad 2002; Pandey et al. 2013a).

Cannabis-based herbal products' commercial, recreational, and health benefits rely on conventional and customary use/claims, supported by encouraging results obtained from *in vitro*, animal, preclinical studies, and early phase clinical trials. However, the results, except in a few cases, are not entirely validated by chronic safety and efficacy studies approved by regulatory agencies. Although the popularity

of Cannabis-based herbal goods/products is growing rapidly, current healthcare professionals should be careful in recommending their use because of the inadequate and scarce database regarding their safety and potency. Therefore, this book chapter examines the various uses of Cannabis in India and the role of integrating these with globally used botanicals into the mainstream contemporary commercial businesses and therapeutics in India and cues that provide the impetus for their use in the future.

2 Uses of Botanicals in India

2.1 Medicinal Aspect of Botanical Use in India

The Indian population comprises chiefly rural/village communities where 70% of the people use herbals/botanicals and other natural products as prophylactics and therapeutics to improve their health and wellness (Vaidya and Devasagayam 2007). India has a powerful history of traditional healing using botanicals and natural products. Indian medicinal plants provide rich sources of caloric value and beneficial effects (antioxidants, anti-inflammatory, anti-apoptotic, immune-active, and mitochondrial energy enhancer), which has been shown to prevent/delay different diseases states. India is well-known regarding the traditional medicinal systems, such as Ayurveda, Siddha, and Unani. Ayurveda, dating back to over 3000 BCE, means "science of life" and "science of longevity" because the Indian health system focuses on perspectives of human and illness, as well as promoting a healthy and longer life (Lad 2002; Pandey et al. 2013a). The alternative traditional medicines used in India are derived from herbs, minerals, animals, microbes, and organic matter.

The use of botanicals as medicine in the Indian health care system is an ancient practice and is vital to the traditional healthcare system. About 70% of the Indian rural population relies on the traditional Ayurvedic system of medicine (Pandey et al. 2013a). India is the largest producer of medicinal plants, where 20,000 medicinal plants have been reported, and traditional practitioners use ~7000 plant species for different disease states. Greater than 1500 herbals are marketed as dietary supplements or traditional medicines. According to the Botanical Survey of India in 2020, India houses 8000 species of medicinal plants (Perinchery 2020). By 2050, it is expected that the overall international trade in medicinal plants and their products will value US$5 trillion. The botanicals also contain other beneficial nutrients and compounds. Functional foods promote health and prevent chronic illness. The active components present in the botanicals are dietary fibers, vitamins, minerals, antioxidants, oligosaccharides, essential fatty acids, lactic acid, phytoestrogens, and lignins (Vaidya and Devasagayam 2007). Other common prophylactic and therapeutic indications displayed by various botanicals include effectiveness against aging, neurological disorders (dementia, parkinsonism, depression), hypertension, cancer, irritable bowel syndrome, infection, inflammation, nausea, sexual dysfunction, and an ulcer (Table 1) (Vaidya and Devasagayam 2007).

Table 1 Uses of botanicals in India

Medicinal use	• Antioxidants • Anti-inflammatory • Anti-apoptotic • Immune-active • Mitochondrial energy enhancer • Anti-aging • Phytoestrogens • Dementia • Anti-cancer • Parkinsonism • Irritable bowel syndrome • Cognition • Antimicrobial • Anti-inflammatory • Anti-malarial • Antinausea • Antiulcer activity • AIDS wasting • Epilepsy • Neuropathic pain • Multiple sclerosis

Agricultural use	• Pesticides
	  • Insecticides—Insects
	  • Herbicides—Plants
	  • Rodenticides—Rodents (rats and mice)
	  • Bactericides—Bacteria
	  • Fungicides—Fungi
	  • Larvicides—Larvae

Commercial use	• Holistic rituals • Obituaries • Birth announcement • Marriage and marriage announcement • Birthdays • Religious function
Recreational use	• Reduce stress • Party drug • Hiking and camping • Hunting and fishing • Air sports • Skiing and snowboarding
Other use	• Nutraceutical • Tea • Coffee • Flavoring • Fragrance • Coloring • Thickening • Preservative

2.2 Agricultural Aspect of Botanical Use in India

Nearly billions of people on the planet Earth directly or indirectly depend on agricultural products for their nutrition (food), health & wellness (medications), apparel/attire (clothing), housing (shelter), recreation, etc. In the modern world, botanicals are an essential requirement globally, and this current situation is very similar to the period of our forefathers centuries ago. Contemporary agriculture is the foundation of the global survival of human beings. The field of agriculture has revealed exceptional vital responsibilities in finances (economics), power dynamics, land use, and cultural influence internationally. Understanding the history of agriculture and emphasizing its practices and the procedures upon which human lives have been sustained are critical aspects of teaching future generations regarding the usefulness and sustainability of botanicals to the happiness and safety of humanity and civilization.

Apart from nutritional, medicinal, and commercial values, botanicals are also often utilized for pest management in the agricultural field (Table 1). Herbal pesticides are derived naturally from phytochemicals and are as effective as synthetic pesticides. Botanical biocides (insecticides, pesticides, and weedicides) are a viable alternative to synthetic or chemical pesticides for crop protection to avoid adverse effects caused by synthetic formulations (Kumbhar 2020). Neem-based pesticides are vital to India for agricultural pest management, followed by pyrethrum and Eucalyptus oil-based pesticides. Botanical pesticides are preferred because they are safe for the environment and public health. They contain a unique mode of action and are a rich source of biologically active compounds. Botanicals are also cost-effective, eco-friendly, and efficacious for managing pests (Kumbhar 2020). Pyrethrins, azadiractin, nicotine, rotenone, sabadilla, and ryania are newer botanical pesticides formulated to be safer for handling by humans (Kumbhar 2020). Overall, botanical pesticides are beneficial as they are environmentally friendly, biodegradable, contain less residue, are target-specific, and safe to agricultural-needed organisms, such as pollinators, predators, and parasites. Natural botanical pesticides create a complex environment for insects to confer resistance. More than 2500 plant species from 235 families contain characteristic properties for ideal botanical insecticide (Raghavendra et al. 2016).

2.3 Commercial Aspect of Botanical Use in India

Vrikshayurveda is an ancient Indian plant life science that composes organic farming principles (Botanical Healthcare 2021). Botanic Healthcare, located in India, commercially markets this principle and is an Indian herbal extract manufacturing company. Products range from health and nutrition, food and beverage, essential oils, personal care, and spice products. A study from 2005–2006 commissioned by the National Medicinal Plants Board in India reported that international trade of

medicinal plants from India is approximately 56,500 metric tons, holding a value of Indian rupees 354.80 crores (equal to US$73.92 million) (Ved and Goraya 2008). Three species making up the bulk of exports in volume and value include psyllium seed and husk, a bulk laxative ingredient, senna, a stimulant laxative, and henna, a natural hair coloring agent (Table 1). In 2019, the total world herbal trade was assessed to be at US$120 billion (Press Information Bureau (2019). The export of herbs is increasing as India exported US$330.18 million worth during 2017–2018 with a growth rate of 14.22% from the previous year (Das 2021). The export of value-added extracts of medicinal herbs is also increasing, as demonstrated by India exporting $456.12 million (USA dollars) worth with a growth rate of 12.23% from the previous year. According to the World's Top Exports in 2019, Cannabis oils exported totaled US$ 2.9 billion. This trade value reflects a 23.3% increase as compared to 2015 for all cannabis oil exporters. Interestingly, India was the second-largest exporter with US$ 20.8 million (11.1% stake) in revenue, after China which exported US$ 964 million (33.4% share). Although the export growth in India is adequate, other small countries in Asia, Africa, and Europe are all doing extremely well (Vietnam, Madagascar, Morocco, and the Netherlands). According to a report by the market research firm *Research and Data,* the Cannabidiol market is projected to grow at a rate of 21.8% in terms of value, from US$ 5.49 billion in 2019 to reach US$ 26.25 billion by 2027. The market is primarily driven by the increase in Cannabidiol (CBD) usage in medical applications, supplements, beverages, and skincare (Suhayl 2021).

2.4 Recreational Use of Botanicals in India

Recreational substances/drugs are chemicals taken by humans globally for pleasure, enjoyment, or leisure purposes rather than for medicinal purposes. Recreational substances/drugs are commonly consumed to provide pleasure, reduce stress (Table 1). Cannabis has a long history of recreational use and also is used to treat diseases. However, these substances can lead to addiction, which leads to health and social problems and crime. Most recreational substances/drugs are illegal; thus, their use/abuse happens with all the consequences of a criminal offense (lawbreaking).

3 Commonly Used Botanicals in India

Well-known botanicals utilized in Ayurvedic medicine include the following: ginger, tulsi (*Ocimum tenuiflorum*), turmeric (*Curcuma longa*), ashwagandha (*Withania somnifera*), Indian frankincense (*Boswellia serrata*), and amla (*Phyllanthus emblica*) (Anonymous 2018). Ginger (*Zingiber officinale*) is an essential natural resource used in food, spices, medicines, dyes, and perfumes (Kumar et al. 2013). Ginger has a history of being used for colds, nausea, arthritis, migraines, and

hypertension (Bode and Dong 2011). Tulsi herb (*Ocimum tenuiflorum*) has been used for thousands of years to support a healthy response to stress, natural detoxification, increased stamina, endurance, energy, and restores balance and harmony (Shagoury 2017). Tulsi can also be used for fevers, skin problems, insect bites, heart disease, and respiratory problems (Anonymous 2021a). Turmeric is commonly used as a coloring agent in Indian cooking and exhibits anti-inflammatory and antioxidative properties. Ashwagandha (*Withania somnifera*) has been used to relieve stress, increase energy levels, and improve concentration with a history of use over 3000 years. Ashwagandha is considered one of the more important herbs in Ayurveda. Indian frankincense (*Boswellia serrate)* is an herbal extract from the Boswellia tree containing anti-inflammatory effects that may improve inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and asthma. Amla (*Phyllanthus emblica*) is a berry representing anti-aging effects in traditional Indian medicine. Regular intake of amla results in healthy, glowing skin, improved eyesight, boosts the immune system, and regulates metabolic functions such as blood sugar and lipids (Narain 2015). *Allium sativum, Eugenia jambolana, Momordica charantia, Ocimum sanctum, Phyllanthus amarus, Pterocarpus marsupium, Tinospora cordifolia, Trigonella foenum graecum,* and *Withania somnifera* are herbal medicines used for diabetes mellitus treatment in India because the formulations provide fewer side effects and lower costs than other traditional diabetes pharmacological approaches (Modak et al. 2007).

4 High Demand of Medicinal Botanicals in India

The medicinal plants in high demand in India include the following: Indian barberry (*Berberis aristata*), liquorice (*Glycyrrhiza glabra*), bael (*Aegle marmelos)*, isabgol or psyllium husk (*Plantago ovate*), atis (*Aconitum heterophyllum*), guggal (*Commiphora wightii*), chandan or sandalwood (*Santalum album*), senna (*Cassia acutifolia or Cassia angustifolia*), baiberang (*Embelia ribes*), long pepper (*Piper longum*), brahmi (*Bacopa monnieri*), jatamansi or tapaswani (*Nardostachys jatamansi)*, madhunashini or gurmar (*Gymnema sylvestre*), kalmegh or green chiretta (*Andrographis paniculata*), shatavari (*Asparagus racemosus*), ashwagandha (*Withania somnifera*), chirata (*Swertia chirata)*, kutki (*Picrorhiza kurroa*), shankhpushpi (*Convolvulus prostrates*), Ashoka (*Saraca indica*), giloy (*Tinospora cordifolia*), kokum (*Garcinia indica*), and safed musli (*Chlorophytum borivilianum*) (IBEF 2020). The values and various properties of these botanicals are described below. Indian barberry (*Berberis aristata*) has been used for over 2500 years. It has a role in treating diarrhea, reducing fever, improving appetite, relieving stomach upset, and promoting health and well-being (Anonymous 2021b). Liquorice (*Glycyrrhiza glabra*) is an herb used for the treatment of cough and cold as well as a flavoring in drinks or herbal infusions. The bael (*Aegle marmelos)* leaf has a religious role in worshiping Lord Shiva as it symbolizes Shiva's trident. Isabgol (*Plantago ovate*), also known as psyllium husk, is commonly used to treat constipation, diarrhea, and

symptoms related to anal fissures. Another popular botanical used for constipation in modern times is senna (*Cassia acutifolia or Cassia angustifolia*). Atis, or ativisha (*Aconitum heterophyllum*), is an herbal solution used for resolving digestive issues, such as diarrhea, by absorbing excess water from the body. Guggal has a long history of use because of its anti-inflammatory and antioxidative properties. Currently, guggul is being investigated as a potential anti-cancer agent (Stuart 2020). Also referred to as sandalwood, Chandan is used as an antiseptic and astringent for relief from headaches or stomachaches and urinary or genital disorders. The essential oil, emulsion, or sandalwood paste can treat inflammatory skin diseases. Baiberang (*Embelia ribes)* has many therapeutic uses such as skin diseases, anti-fertility, antipyretic, antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*, and treatment of cough or diarrhea. Indian long pepper (*Piper longum*) can be used to improve appetite, digestion, heartburn, indigestion, intestinal gas, diarrhea, and lung issues such as asthma, bronchitis, and cough. Brahmi (*Bacopa monnieri*) is an herb used as a memory enhancer by improving brain functions and strengthening cognition. Jatamansi (*Nardostachys jatamansi*) is mainly used for epilepsy, hysteria, syncope, convulsions, and muscle weakness (Pandey et al. 2013b). Madhunashini (*Gymnema sylvestre*) is a proprietary ayurvedic medication for treating and managing diabetes mellitus by regulating blood sugar levels. Kalmegh or green chiretta (*Andrographis paniculata*) is used for stomachache and contains antipyretic, anti-fertility, anti-inflammatory, antibacterial, antiviral, immunostimulatory, and antioxidant properties. Shatavari (*Asparagus racemosus*) is popularly used as a cough remedy in India. Chirata (*Swertia chirata)* can be used for fever, constipation, stomach upset, decreased appetite, intestinal worms, skin diseases, and even cancer. India has used chirata (*Swertia chirata)* with the seeds of divi-divi (*Libidibia coriaria*, synonym *Caesalpinia coriaria)* for malaria. Kutki (*Picrorhiza kurroa*) benefits include healing liver ailments, weight loss, promoting heart functions, respiratory issues, preventing ulcers, shielding against infections, promoting digestion, and even regulating glucose metabolism. Shankhpushpi (*Convolvulus prostrates*) uses include improvement of memory, coughs, colds, headaches, anti-aging, and improved longevity. This remedy uses all plant parts, including leaves, flowers, and roots (Anonymous 2020). Ashoka's (Saraca indica) usage is different as it relieves grief and decreases sorrow. In some parts of India, the Ashoka tree is worshipped and holds a great religious significance. Giloy (*Tinospora cordifolia*), like other herbs/botanicals, is used to treat fever, infections, diarrhea, and diabetes. Kokum (*Garcinia indica*) is primarily used in Indian cuisine and contains many nutrients such as vitamin A, vitamin B3, vitamin C, calcium, iron, manganese, potassium, and zinc. Safed musli (*Chlorophytum borivilianum*) is considered a rare herb originating in India. It is traditionally used in medicine to treat arthritis, cancer, diabetes, improving sexual performance and vitality.

5 Cannabis in India

Vijaya is one of the most commonly used Ayurvedic names of the dried leaves of the dioecious herb *Cannabis* belonging to the family Cannabinaceae. The plant can be found in the wastelands, along roadsides, and in irrigation channels of the gardens of India, from sub-Himalayan tracts to across the country (Aldrich 1977). Indian Hemp is the common name for Cannabis, which can grow up to 2 m in height in 3–-4 months. This plant can be cultivated in rotation with flax and grasses (Balhara et al. 2020). The plant's stem is rich in cellulose and fiber for making mechanically strong paper from bleached pulp. The plant is known for its psychotropic activity of cannabinoid constituents through cannabinoid receptors, mainly located in the brain and also distributed in the body.

Cannabis has three main species, namely *C. Ruderalis, C. Indica*, and *C. Sativa,* having different plant/leaf shapes and sizes. Tetrahydrocannabinol (THC) and Cannabidiol (CBD) contents also vary in these species (Chaturvedi and Agrawal 2021). However, due to cross-fertilization/hybridization, mixed variants of these species are found in nature. *Cannabis indica* is one of the most sacred plants consumed for deliverance and happiness. It is considered to alleviate anxiety and the fear of life. Marijuana is the other name of this plant, which is believed to provide compassion when consumed by the devotees of Lord Shiva, who is also called *'Lord of Bhang.'* During the *Holi* (festival of colors in India) and *Maha Shivratri* (another popular festival for Lord Shiva in India), *Bhang* is distributed as 'Prashad' (holy offering) during the festival and spiritual rites of the celebrations every year. Lord Shiva is connected to consuming bhang and smoking weeds (Ganja).

The drug Marijuana has anti-anxiety components used by the soldiers who entered the war front. The Ayurveda has called Cannabis in the name of *Vijaya*, the substance which provides victory or achievement. There are three different names according to the part of the plant and the therapeutic purpose for which it is consumed. *Ganja* is the dried flowering tops of the female plant, smoked in a *Chillum* (a cigarette pipe made with baked earthen pot). The second name is *Bhang*, a drink made from the leaves of male and female plants and/or flowers ground with milk or any other liquid. The third name is *Charas*. The resin of the plant leaves exudate in the midrib of the lower epidermis and is collected. It has potent narcotic properties when compared with the earlier two preparations. In India, Bhang (leaves and seeds), when not accompanied with flowering tops, are not included in the definition of Cannabis, and hence leaves and seeds are not federally banned by Narcotic Drugs and Psychotropic Substances (NDPS). However, states can ban or legalize the use of cannabis leaves and seeds. However, cultivation storage and trafficking is illegal, like that of alcohol without a license (Chaturvedi and Agrawal 2021).

The history of using Cannabis is long and cannot be directly approached as a new drug. The plant yielding the drug seems to have been discovered and cultivated for its medicinal purpose in Ayurvedic medicine long ago. It was used for specific medical and non-medical purposes by the traditional systems of Medicine of India. It

is also embedded in the cultural and devotional heritage of the subcontinent. As a hemp plant, Cannabis was used as a fiber source in manufacturing rope and textiles. The resin of the plant brought out the biological activities of the plant. The pharmacological use of the plant was first identified in the Himalayan region and then to India, followed by other Asian countries and the rest of the world. In religious festivals of India, the use of 'bhang' was primarily to induce relaxation of the mind, enhance appetite, and promote calmness to the soul to concentrate on the rites of the festivals. 'Bhang' is a weaker preparation of Cannabis and is allowed for consumption by people during festival times. 'Ganja' is a slightly stronger preparation indicated for smoking with a chillum and improved concentration during meditation to remove distractions. The use of 'charas' has a habit-forming property that could result in detrimental effects. However, the traditional Indian medicine systems, on the other hand, used Cannabis (mainly leaves) for analgesic, anticonvulsant, antidiarrheal, appetite enhancer, anxiolytic, and sedative activities. The other indications of Cannabis are for the treatment of rabies, tetanus, cholera, and delirium tremens. The active principle of the plant lies in the plant's resinous glands. It is believed that 40% of the active compound, known as tetrahydrocannabinol (THC), is found in a hashish preparation used by wandering sects of India. In the "ganja" preparation, 26% of the THC compound is located in the dried flower heads commonly smoked in India's villages. The bhang drink preparation has about 10% of THC. Smoking was one of the best routes of administration, with a bioavailability of 18–50% across various studies. The plasma concentration of THC was triphasic, including an absorption phase with a half-time of 50 s, a slower distribution phase with a 40–80 min half-time, and notably a slower elimination of about 2 to 3 days. The slow clearance causes a risk for cumulative elevation in tissue concentration for regular smokers. The following sections discuss the various utility of Cannabis in India and are depicted in Fig. 1.

5.1 The Cultural Aspect of Cannabis in India

The eighteenth century text by M. Husain Khan has described its various preparations as an intoxicant, stimulant, and sedative (Kuddus et al. 2013). In Indian culture, the *Athara Veda* mentions the plant as one of the five sacred plants and says a guardian angel resides in its leaves. The *Vedas* refer to the plant as a "source of happiness," a "joy-giver," and "liberator." According to the Hindu scriptures, the Gods sent the hemp through compassion to attain delight, lose fear, and have sexual desires. Tradition has it that nectar (*amrita*) dropped from heaven and Cannabis sprouted from it. These nectars were consecrated especially to Lord Shiva; devotees of Shiva pour cannabis libations over the lingam (the Hindu Statue for praying) and offer him cannabis and datura drinks. It is also holy/consecrated to the most powerful Goddess "Kali" as well. Toward the end of the Durga Puja (a most popular festival in India), the main festival for her worship, it is customary to drink bowls of cannabis preparation and offer them to others (Dutt et al. 1877). In Madras (Currently

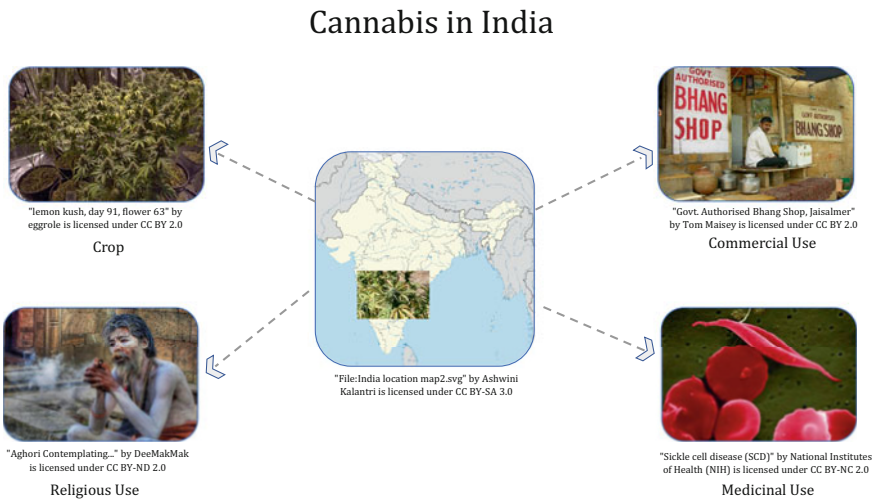

Fig. 1 Cannabis use in India

Chennai), Kama, the God of love, Shiva, and Kali are worshipped with imbibing's of Cannabis (Young and Kaplan 1969). In Bombay (currently Mumbai), it is Vishnu who receives the benefits of Cannabis. In each region, cannabis is given to the locally most favored form of God. Once the *amrita* appeared after the churning of the ocean, the demons tried to seize it. The Gods prevented this, which gave Cannabis the name Vijaya, meaning victory in commemoration of the auspicious event (Aldrich 1977). It is said to bestow supernatural influence and powers on the user, which can cause some religious users to engage in excessive consumption (Young and Kaplan 1969). Due to the popular Hindu religion, it was not uncommon for households to grow a plant or two to offer Cannabis to a passing sadhu (Touw 1981). It was even said to be smoked daily during devotional services (Fisher 2011). In Indian culture, the use of hemp in a non-secular manner was condemned and treated as wine was in Holy Communion to Christians.

North-East cultivates most of the Cannabis in India, and the north-east accounted for about 34% of all Cannabis seized throughout India in 2003. Cannabis is illicitly grown in Jammu & Kashmir, Himachal Pradesh, Manipur, Tamilnadu, Kerala, and Andhra Pradesh. Maharashtra and Gujarat are leading sources of hashish from among the Indian states. The illicit use of Cannabis, licensed for 'bhang' in some Indian states, in religious fests is still in practice, apart from approved medicinal and scientific purposes. The Indian governmental departments report increasing illicit cultivation, storage, trafficking, and seizure rates under the Narcotics Drugs and Psychotropic Substances Act, 1985 (NDPS Act). Some of the cultural uses of Cannabis in India are summarized in Table 2.

Table 2 Traditional uses of Cannabis in India

Cultural use	• Holistic rituals • Obituaries • Religious function • Marriages • Christmas caroling party
Medicinal use	• Nutraceutical • Anti-inflammatory • Antispasmodic • Anticonvulsant • Antirheumatics • Antihistaminic • Sedative • AIDS wasting • Epilepsy • Neuropathic pain • Multiple sclerosis
Agriculture use	• Food • Fabric • Cotton • Fiber
Commercial use	• Business • Upholstery • Clothing • Economy • Biofuel • Green plastics
Recreational use	• Reduce stress • Banquet parties • Cocktail party • Pleasure • Personal enjoyment

5.2 The Medicinal Aspect of Cannabis in India

The use of Cannabis as medicine goes back far before 1000 B.C.E (Greden 1973). However, it was primarily used in a religious context. The initial application developed further and was used as a sedative, febrifuge, and cooling agent. Cannabis works as an antispasmodic, anticonvulsant, antirheumatics, antihistaminic and was even referred to as the "penicillin of ayurvedic medicine," indicating its wide array of use in infectious diseases (Young and Kaplan 1969). Cannabis is also a vermifuge and can be used against the venom of poisonous fish bites, scorpion stings, and even leprosy. When consuming cannabis for medical purposes, its different preparations (Charas, ganja, and Bhang) are almost exclusively taken orally. In the case of skin ailments, a poultice, most likely with fresh leaves, is applied externally to the affected area.

Cannabis has been used by many ethnic societies, including Uttaranchal in Northern India, where the plant is a part of the local culture (Aroonsrimorakot et al. 2020). The practice of consuming Cannabis has been linked to legends such

as *Vedas*, a sacred book of Hinduism. Cannabis has a history of use for neurologic conditions, including antispasmodic in epilepsy, convulsions and tetanus, treatment of paralysis, hemorrhoids, and a remedy for delirium during fever (Aroonsrimorakot et al. 2020).

Medicinal use of Hemp in India was never differentiated from religious service. In the text *Athara Veda,* it is referenced in overcoming enemies and evil forces, which may include physical and spiritual ills. Eventually, medicinal use became separated from religious use and could be fully explored without the secrecy and disreputability of religion. There are several different preparation methods: Bhang consists of dried leaves without the flower tops. Ganja has higher potency and is made of the female flowering plant tops that resin adheres to; the heaps of flower tops are then manually rolled or put into heaps trodden then dried in the sun, rolled, and dried again until sufficient resin has been pressed out the top. Typically rolled has generally higher quality and is used for medicinal purposes (Touw 1981). The use of Cannabis via animal products varies and has been traditionally used in honey, milk, and butter, more commonly ghee (clarified butter).

Medicinal Cannabis is often combined with other plants with phytotherapeutic benefits. However, there are many other beneficial ingredients that alleviate the same symptoms in these recipes. It is difficult to decipher the ingredients (bioactives) responsible for alleviating the symptoms. An Indian recipe used for aiding diarrhea, indigestion, cough, loss of appetite, and impotence is called "*Jatiiphaladi churna,"* which uses a mixture of nutmeg, cardamom, cinnamon, ginger, cumin, cloves, pepper, camphor, sandalwood, bamboo manna, sesame, javitri (*Myristica fragrans*) leaves, nagkesar (*Mesua* ferrea) flower, and Cannabis. Myrobalans (*Terminalia chebula*) are combined with an equal quantity of Bhang with twice as much sugar. The nutmeg, cardamom, cinnamon, ginger, cumin, cloves, pepper, camphor act as digestives, while the tannins in the myrobalans counteract diarrhea. Another recipe used for anti-diarrhea was a combination of Bhang, ghee (clarified butter), pepper, and poppy seeds (Chopra and Chopra 1957). A recipe used for soothing painful hemorrhoids is Bhang with turmeric, onion, and warm gingelly (*Sesamum indicum*) oil is applied externally.

Ayurvedic physicians in India commonly consider Cannabis to be "pittala" or "bile," which is one of the three pillars in Ayurvedic medicine (Russo 2005). Pitta rules the activating, heating, and metabolic functions in the liver (Touw 1981). In general, a pittalla drug is used to generate fire or heat and activate the liver specifically. Due to the above aspect, the therapeutic use is indicated for conditions of heat and dryness, and later deactivation is considered more of a side effect of prolonged therapy (Dymock et al. 1893). One of the earliest medical works, "*Sushruta Samhita*" (an ancient Sanskrit text on medicine and surgery), provided the first direct evidence of cannabis use and was deemed anti-phlegmatic because of its expectorant and suppressant mechanisms (Dutt et al. 1877). An anti-phlegmatic in the sense of Ayurvedic medicine would also enliven the imagination and flow of thought by removing the "phlegm." With protracted use, it must be noted that it can lead from initial exhilarant and aphrodisiac effect to a sedative one with melancholy, loss of memory, indigestion, weight loss, and impotence (Touw 1981).

India began to use Cannabis as a sedative in cases of mania and hysteria with success, generally, in disorders of the nervous system. Charas, ganja, and their extracts were used (Datta and Mukerji 1952). Majum is another common Indian recipe made of Bhang, typically combined with milk, ghee (clarified butter), flour, and sugar. This was medicinally consumed for a sedative purpose to aid insomnia, and it was as effective as opium. Cannabis is highly effective in its neuralgic properties, commonly used for sciatica, facial neuralgia, migraine headaches, regular headaches, and those that accompany malaria during the paroxysms. Its anti-inflammatory properties are notable enough that it is said to be of use to any pain caused by inflammation or inflammatory disease, including the pain of broken bones (Touw 1981). It can be applied to areas with broken bones, generally combined with other herbs for a phytotherapeutic effect (Jain 1967). Topical anesthesia and general anesthesia have even been achieved with Cannabis (Chopra and Chopra 1957). The anticonvulsant and antispasmodic properties of Cannabis are astounding. They can be used in everything from simple stomach cramps to tetanus, epilepsy, and rabies to infantile epilepsy when mixed with belladonna (Nadkarni and Nadkarni 1954; O'Shaughnessy 1843). Another way cannabis is used in respiratory ailments is to calm coughs, including asthma, whooping cough, bronchitis, while decreasing the pain (Nadkarni and Nadkarni 1954; Young and Kaplan 1969). Similar to the remedies for neural ailments, Charas is the preferred form of Cannabis in respiratory diseases.

Another medicinal use of Cannabis is to regulate excessive salivation. Cases of decreased appetite, indigestion, colic, nausea, and insufficient weight gain would be treated with a bhang drink containing magnum, made with milk or ghee to obtain the benefits of the fat-soluble and water-soluble substances (Young and Kaplan 1969). It is not very commonly used for constipation, but there have been instances reported. It is more commonly used in diarrhea. It was also used in severe diseases, such as cholera. If taken early in treatment, Cannabis is said to have an action similar to opium (Dymock et al. 1893). Cannabis was used in diseases and problems in the urogenital and reproductive tract, such as cystitis, urethritis, orchitis, hydrocele, and dysmenorrhea. It helped aid in pain-free or nearly pain-free childbirth (Dymock et al. 1893). Cannabis displays many anti-spasmatic properties, but the use during labor strengthens uterine contractions almost as efficiently as ergot, but with less persistent action (Greden 1973). It is also used to stop uterine hemorrhage as well (Dymock et al. 1893). Culturally, Cannabis was a known aphrodisiac and believed to have allowed one to feel the pleasures of life, so it was commonly given for incontinence of sperm and helped provide ejaculation control (Chopra and Chopra 1957).

Further medical uses include gram-positive antibacterial effects; however, it loses its potency when in the blood serum (Kabelik et al. 1960). Fresh leaf powder or juice would be sprinkled into wounds, sores, and externally on the eye and ear for infections (Nadkarni and Nadkarni 1954; Young and Kaplan 1969). Fresh juice of Cannabis exhibits the vermifuge properties of Cannabis. It is used topically and orally for ear and eye worms and relieves lice and dandruff with topical application (Chopra and Chopra 1957; Nadkarni and Nadkarni 1954; Young and Kaplan 1969). Cannabis use is banned today in India except for Bhang as it is an exception to the

NDS Act due to its deeply religious and cultural ties. Cannabis is thought commonly as a "motivational drug"; however, Cannabis is widely used by the poor working class to give them endurance while they work (Young and Kaplan 1969). The consumption of Cannabis increased to 50% during the harvest season, making the statement of Cannabis being "a motivational drug" less convincing (Chopra and Chopra 1957). Additionally, Cannabis was used in the veterinary setting to help fight fatigue in bullocks. The most common medicinal uses of Cannabis in India are summarized in Table 2.

5.3 The Agricultural Aspect of Cannabis in India

Cannabis grows wild throughout the country, and its cultivation is widespread from the north to the south. Still, it has never been officially accounted for due to the lack of surveys conducted in the country (Chouvy 2019). Cannabis is illegal in the Charas and ganja form, and an offender can be sentenced to up to 20 years imprisonment. However, *Bhang* can be produced and sold by government-authorized premises under the NDPS Act of 1985 (Sinha and Fogla 2020). The NDPS Act was put into place 24 years after India agreed to join the global fight against narcotic drugs, signing the United Nations Single Convention on Narcotic drugs bringing a new prohibition era. The controversy surrounding the cannabis plant is prevalent in the taxonomic nomenclature of the plant. Cannabis was first described as a monotypic genus by Linnaeus. However, there is a common debate that it is a polytypic genus by Lamarck, who proposed the two species: *Cannabis indica and Cannabis sativa,* and later a third subspecies was hypothesized as *C. ruderalis* (Clarke and Merlin 2016). In an attempt to settle this debate, molecular genetics were used, but due to the limited knowledge on the Cannabis genetic and experimental data, the question was still left unresolved. Sawler and colleagues, states "the inaccuracy of reported ancestry in marijuana likely stems from the predominately clandestine nature of cannabis growing and breeding over the past century" (Sawler et al. 2015). Due to the restricted nature of the cannabis plant, it is only allowed to be grown in the districts of Almora, Garhwal, and Nainital, with a small extent in Kashmir and Travancore. Different varieties of the plant are grown based on the desired end product (Table 2). For example, varieties grown for medicine are small, multi-branched with smaller dark leaves. The plants grown for fibers typically have longer stalks that branch very little and yield small quantities of seed. Plants grown for the seed oil are smaller, mature earlier, and produce large quantities of seed (Kuddus et al. 2013).

5.4 Commercial Aspect of Cannabis in India

Under the NDPS Act, certain regions are allowed to cultivate Hemp for Bhang because of its sociocultural roots, medicinal purposes, and textile uses which the government regulates. The economic case for cannabis decriminalization in India, its legalization, and fair and just regulation is a logically strong one, given the fact that India is a constitutionally proclaimed welfare state (Gautam 2020). They mention the steady flow of income needed to run a state and meet its constitutional obligations, which Cannabis could provide. The cannabis market could be turned into that reliable, steady stream of income for the state. The United States has recreational cannabis use in 12+ states. Since the selling of recreational Cannabis in the USA, an estimated 5.8 billion dollars in tax revenue has occurred since 2014. Thus, one may safely conclude that the cannabis market has been a reliable tax base (Gautam 2020). This is valid because the plant's native status in India's commercial opportunities for growth is endless, thus bringing more income to the local economies. There would be an increase in revenue to the state there would create an entirely new trade market. There would be an increased need for farmers, manufacturers, and many other jobs related to the cannabis industry. It would also create more.

revenue for the farmers and state via income and other commercial taxes. During the hippie era, the Indian cannabis market exploded. The need for cultivation increased, and the profits increased as the market grew. Until dealer's licenses were revoked on 16 July 1973, there was an approximate loss of $100,000 in state tax revenues, not including the profit loss of farmers and dealers. Some of the uses of Cannabis in India are summarized in Table 2.

5.5 Recreational Use of Cannabis in India

Cannabis is the most commonly used illicit psychoactive substance in India. Like they were mentioned earlier, during times of harvest, consumption increases. It is common among laborers, such as farmers and fishermen, to use cannabis preparations to alleviate fatigue and increase their physical strength in stressful situations (Balhara et al. 2020). Traditionally Hindu yogis have used Cannabis to aid in deepening their meditations, and male devotees use Cannabis as a symbol of fellowship in their frequent *bhajan.* Aldrich states that at the beginning of the ceremony, a potent cannabis preparation is consumed, with the peak effects of the drug not felt until about an hour into the meditation practice (Aldrich 1977). This method is also used in tantric ceremony practices to create a state of bliss. The role played by Cannabis in the tantric ceremony, or Kundalini yogi, allows the worshipers to feel their divinity within and without themselves (Aldrich 1977). It has also been said that those who are too old to work in the fields anymore stay home and consume ganja to help pass the time. Some of the recreational uses of Cannabis in India are summarized in Table 2.

6 Conclusion

The ancient and traditional Indian medicinal systems have constantly promoted global wellness and healthcare in the past and expect to play a crucial critical role in the future. The Indian medicinal system has most of its roots/origin from India. However, few have come from foreign origins and have been embraced and integrated into the Indian culture as the "Indian Systems of Medicine." India has the distinct honor and excellence of having variously accepted and established medicinal systems. Ayurveda, Homoeopathy Naturopathy, Siddha, Unani, and Yoga are considered the "Indian Systems of Medicine." For thousands of years, Indians have used Cannabis for treating headaches and migraines, gastrointestinal disorders, generalized or localized pain, easing childbirth, clearing phlegm, sharpening the appetite, digestion, well-being, curing insomnia, and relieving pain dysentery, anemia, weight loss, and for coughing. Currently, doctors of India are advocating for increased research regarding the efficacy of cannabinoids in cancer patients.

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