

CURRENT TRENDS AND FUTURE PROSPECTS OF MEDICINAL CANNABIS: AN UNDERUTILIZED ANCIENT ETHNOMEDICINAL PLANT FOR HUMAN WELLBEING

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Abstract- Medicinal Cannabis is one of the earliest herbs globally used as traditional medicine by the human being for million years ago. Medicinal Cannabis (*Cannabis sativa* L.) is a dioecious and an annual plant that belongs to Cannabaceae family. It has long history of cultivation for food, intoxicants & medicine, rope, paper, fiber, and oil extraction. Due to diverse therapeutic properties, it is legalized over 50 countries and cultivated as medicinal and recreational crop. This review was aimed at collecting information about medicinal cannabis ranging from traditional use to commercial utilization. This review article is based on gathering scientific literature from Google Scholar, Scopus, PubMed, Science Direct, Wiley Online Library, Taylor Francis and Springer with 95 documents including original articles, review articles, books and thesis from 1977 to 2022. It entails detailed discussion on medicinal uses linked with major secondary metabolites. Besides, cultivation practices are being discussed in detail for both controlled and indoor environmental conditions coupled with nutrients application. It can be concluded that much of the work need to be done for the validation of ethnobotanical claims by conducting detailed studies on exploring various phytocannabinoids regarding medicinal use through in vitro and in vivo activities and way forward for its commercial utilization.

Index Terms- Cannabinoids, CBD oil, Phytocannabinoids, Inflammation, Cultivation practices

I. INTRODUCTION

Hemp (*Cannabis sativa* L.) is dioecious, monotypic, erect and annual herbaceous plant belonged to family Cannabaceae. This species has diploid number of chromosomes ($2n=20$), with an estimated haploid genome of ~830 Mb [1]. The existing gene pool is reflection to be comprised predominantly of cultivated or specific populations, cultivars, and selection with a subsection having been subject to sheer choosy gradient toward phenotypes for precise end-uses [2] since many thousand years, cannabis had been grown in European countries from where it was domesticated to Africa, North America and now it is cultivated globally [3].

Cannabis has long history of domestication and one of the earliest most important crops [4]. It is versatile plant is cultivated for various purpose including fibers, food, oil, medicine, recreation and religious purposes since Millennia [5]. Its cultivation was started for textile and fiber from Egypt and Western Asia and afterward introduced in Europe and rest of the world. [6] As a medicine, it is popular in almost all region and religions. The plant is very hardy nature and can be grown in a variety of habitats and altitudes ranging from sea level to the alpine foothills of the Himalayas. Its geographic origin is believed to be from Central Asia that was expanded to East and South Asia and West to Europe [7,8].

Hemp is considered to be originated from china since 12 thousand years ago. Utilization and cultivation of hemp started from China [9]. Commercial market could get many positive products by the use of hemp plant. Hemp production was strictly banned in many countries of the world as it contained many drug contents in it. These contents are basically psychoactive in hemp plant [10]. Since the emergence of wonderful empires of Prussia, America and EU, hemp was grown throughout the times. Hemp industry became symbol of downfall as it is resembled to the marijuana plant [11]. Cannabis plant is mainly confused with marijuana and hashish. In contrast to this, marijuana, hashish and hemp contained THC compounds in it, which is thought to be major booster compounds in it. Hemp have very minute amount of THC as compared to hashish and marijuana [12].

Since many decades, hemp has been considered as a rising industry in UK, Canada and other countries of the world. Hemp has three varieties that grow up to length of 4 meter. This plant has global distribution including China, Europe and America. In the past, people

usually planted the hemp by insensitive manual labor [13]. Furthermore, as the technology progressed gradually, cultivation of hemp shifted from manual labor to the mechanized process. As hemp have very high socio-economic value, its cultivation can be beneficial in every aspect of life to raise the standard of living in textiles, construction, automobile industries and many other [14]. Scientists and Researchers of Pakistan have focus on research for molecular studies, environmental conditions necessary for the growth of hemp and to elaborate the difference between marijuana and hemp [15]. In the department of agriculture, hemp has several uses. Hemp can be considered to give a new lease of life in many sectors in the agriculture. Hemp is supposed to give new jobs and employment in agriculture engineering, textiles and construction companies [16]. Many different kinds of oils can be extracted from hemp by GC-MS techniques. The extracted oils may be different in their composition due to the presence of psychoactive compounds in it. Pakistan is an agro-based country and more research is needed for the complete investigation of this plant [17].

American federal government enforced a ban on growing of cannabis due to presence of psychoactive compound (THC) that affects on the mental health of the people. The reason behind this ban was the resemblance in the genetics of hemp and marijuana. According to the Federal Law, cultivation of marijuana is strictly banned in USA. Presently, it is prohibited to grow hemp or marijuana in the United States by the federal law in contrast to this bill. A new act of 2014 showed a slight permission to cultivate hemp in different regions in USA [18]. This bill allows cultivation of hemp that can be obtained from hemp for producing range of products as shown in Fig. 1. Different universities have been permitted to cultivate hemp for source of knowledge and different educational and research purposes since 4 years. Some well reputed institutes are engaged in research on the pesticides and their impacts on hemp crop. Additionally, few institutes are engaged in research about economic policies and production on hemp crop [19]. This crop has potential to develop a stable promising industrial unit in country.

Materials and methods

Documents reported from 1977 to 2022 were considered, *Cannabis sativa* its synonymies were used as search terms in 5 databases. Duplicate documents were eliminated, registering 95 documents including original articles, review articles, books, and theses. Search terms were included “*Cannabis sativa*” OR “Cannabis” OR “Hemp” OR “Industrial hemp” OR “Medicinal hemp”

Results and Discussion

Distribution and history

China has common distribution of hemp that is essentially used in making paper, medicines, textiles and foods. Since ancient times, hemp was used by people for different purposes and become very important crop [20].



Fig. 1: Different Uses of the hemp plant

Since five thousand years, hemp was domesticated and interlinked with human beings [21]. In south Asia, hemp that has high THC contents is used for medicinal and frivolous activities. Hemp grown in low temperature, have low in THC contents that is used for making fiber and these hemp are used as source of diet as well [22]. Global multi-billion dollar industry has a strong share contributed

by hemp as it gives well foundations of it. It is the 5th most important crop after corn, soya beans, hay and wheat (Fig. 2). There is little work available on development and research on hemp plant as this was under restrictions under Federal laws. Due to Federal government restrictions very less research is reported [23]. But in recent era, few states of US have permitted for growth of cannabis formedicinal especially for manufacture of cannabidiol (CBD) [24].

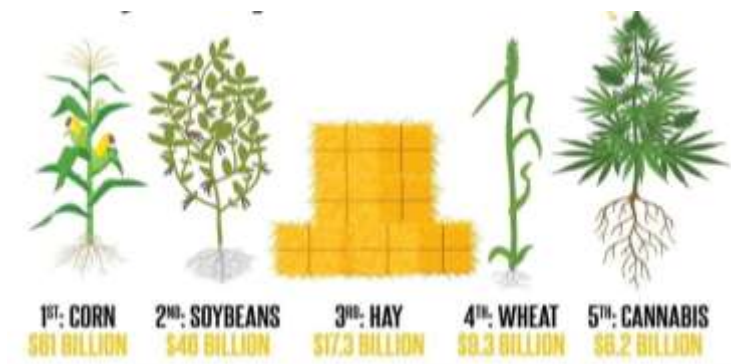


Fig 2: Cannabis is the fifth most valuable crop in the U.S., passing Cotton, Rice and Peanuts

Taxonomy of Cannabis

Cannabis has been identified with racemose inflorescence that is of compound type. This inflorescence have specific character with growth in monopodial in nature, apical meristem that is persistent in origin, or terminal undefined inflorescences in some orders [25]. The inflorescence is acropetal in succession where new flower are produced toward terminal position and older toward the base [26].

Reproduction system in cannabis

The hemp has separate male and female plant. Sometime, there is emergence of male flower with female flower. It enhances self-crossing in hemp plants. In addition to this, it leads to the development of feminized seeds [27]. Feminize seeds are valuable in medicinal purpose, which depend on CBD that is ultimately extracted from female plant [28]. Plant hormone especially ethylene is involved in sex expression. This hormone if suppressed stimulates maleness in plant [29].

Compounds found in Hemp

The bioactive compounds specially CBD, CBN and CBG present in hemp plant are used in pharmaceutical industries and preparation of foods [30]. There are nearly 400 active compounds present in hemp. Cannabinoids are of crucial importance among all of these compounds [31]. There is different concentration of compounds present in hemp seed. Hemp oil has highest percentage among all compounds present in it. Seed oil 25-35 percent, carbohydrates 20-30 percent, omega 6 and omega 3 with 20-25 percent proteins. In addition to this, almost 50-70 percent fatty acid present in it [32]. In the treatment of fatal disorders like cancer, high blood pressure, high cholesterol level and sclerosis, hemp seed oil is found to be best remedial solution. Hemp oil have omega 3 and 6 which play important role in improving human health [33]. In the eradication of diseases and improvement of lipid metabolism, skin disorders and cardiovascular diseases, hemp seed has special antioxidants present [34]. Cannabis plant has a large amount of secondary metabolites present as alkaloids, flavonoids, glycoproteins and terpenoids. These compounds have antioxidant pharmaceutical properties present [35]. Cannabinoids present in cannabis plant have special production of compound named terpenophelics, which have excellent properties of medicinal [36]. Cannabis crop especially female flower have glandular trichomes that have secretory cells. These secretory cells have accumulation of phytocannabinoids. Female flower are avoided of pollination. If pollination occurs, the amount of secondary metabolites reduced in concentration [37]. Cannabis plant has confirmed pharmacological properties due to the presence of cannabidiol (CBD) and tetrahydrocannabinol (THC). These compounds have excellent properties of medicinal importance [38]. Female inflorescence has trichomes that have non- psychoactive compounds including CBD, their related acid and CBN [39].

Cannabis plant has active compound precursor as CBDA and CBGA. These compounds after natural decarboxylation give their predecessor as CBD and CBG respectively. This decarboxylation takes place either by light or temperature in the course of elongated storing process [40]. In addition to the properties of neuroprotection and anxiolytics, CBD have excellent remedies not only for anticholinesterases but also for antiemetic's [41]. Presence of flavonoids compounds in hemp is responsible for antioxidant properties [42]. Additionally, excellent nutraceutical properties are assumed to be related with hemp oil when it is taken as diet source [43]. The hemp oil has vital compounds like fatty acids, amino acids, vitamins and polysterols. In addition to above compounds α -linolenic acid is also present in minute concentration in hemp seed oil [44]. In the battle of disease of cancer, Cannabis plants have accumulation of certain chemicals in their trichomes. These are named as β -pinene, α -humulene, β -myrcene, and limonene (Table 1). These

compounds are member of sesquiterpenes and monoterpenes[45]. In the sector of medicine, cosmetics, agriculture, textiles and construction, hemp oil have numerous applications [46].

Table 1: Uses of some important compounds present in Hemp plant.

S. No.	Chemicals	Formula	Uses	REFERENCE S
1	linoleic acid (omega 6)	$C_{18}H_{32}O_2$	Treating symptoms of chronic diseases; strengthen Skin and hair growth, maintain bone health, regulate metabolism and maintain the reproductive system	[47]
2	α -linolenic acid (omega 3)	$C_{18}H_{30}O_2$	Help manage cholesterol, triglyceride, and blood pressure levels. Prevent depression, Parkinson's disease, and psychosis	[48]
3	Phytosterols	$C_{29}H_{50}O$	Enhance heart health. lower cholesterol levels by reducing cholesterol absorption	[34]
4	Tocopherols	$C_{55}H_{104}O$	Helps nervous and muscular system in working, helps anticoagulant proteins to stop blood clotting and boost up immune system	[49]
5	Glycoproteins	$C_{28}H_{47}N_5O_{18}$	Glycoproteins help for proper functioning of collagen and boost up immunity. It serves as lubricant in digestive track and secrete mucins in respiratory track	[33]

Phytocannabinoids

Cannabis plants possess chiefly cannabinoids named CBD and THC [50]. CBD is non- psychoactive compounds, hence recommended to be used as medicine; while, THC has abundance of psychoactive components and boost up [51]. CBD has attested to have a number of pharmacological properties (Table 2, Fig. 3), hence position amongst the utmost deliberate cannabinoids for its potential beneficial consumption in various disorders [52]. There are different strains of hemp that possibly will yield cannabinoids in the form of Cannabidiol (CBD) or tetrahydrocannabidiol (THC) [53]. There is slight difference between hemp and marijuana. Hemp has abundance of cannabidiol (CBD) while marijuana is rich in tetrahydrocannabidiol (THC). This difference is based on the concentration of THC. If it is below the 0.03 percent the plant will be considered hemp and if it crossed the figure of 0.03 percent it is considered as marijuana [54]. Moreover it must be clear between hemp and marijuana that is based on THC and CBD. Besides, taxonomist selected a new strain that is rich in CBG. In recent times this strain is known as industrial hemp [55].

Table 2. Uses of CBD and THC in human disorders [56,57].

CBD	THC
Electrical disturbance in the brain (Seizures)	General pain
Inflammation of joints	Muscle tightness due to muscle contraction
Pain	Glaucoma
Mental disorders	Insomnia
Bowel diseases	Low appetite
Nausea	Nausea
Migraine	Anxiety
Depression	
Anxiety	

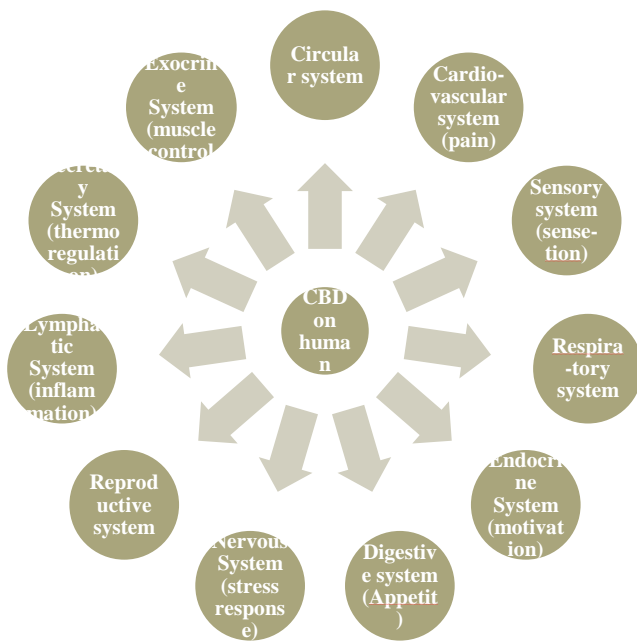


Fig.3. Effect of CBD on Human systems

Use of hemp seed oil

Cannabis oil have such balanced concentration of fatty acid that is highly recommended by World Health Organization Authority. The reason behind this suggestion is fatty acids in hemp that are in balanced composition. It is perfectly matched with the standard of FAO [58]. Hemp strains that are rich in cannabinoids are considered as most recommended varieties. Futura and Finola are two varieties that are selected for industrial purposes. These varieties produced discrete amount of seeds [59] to the best of our knowledge, there is no study regarding the evaluation of the comprehensive cannabinoid profile in this cannabis product. Our research group, and more recently other groups [60] study revealed that higher performance liquid chromatography technique is used for identification of different compounds present in cannabinoids in hemp. This method based on both exact mass and match of the fragmentation pattern (MS2) of pure analytical standards of the known cannabinoids. Exploiting HRMS technique, it is possible to define the comprehensive cannabinoid profile in commercial hemp seed oils in order to address their different nutraceutical properties to a specific cannabinoid. The present work is indeed focused on the identification and semi-quantification of the main and best known cannabinoids in commercially available hemp seed oils, CBD and THC, along with other “minor” cannabinoids, which contribute to the final

beneficial effects. A multivariate statistical analysis (MSA) was also carried out to highlight the significant differences among the commercial hemp seed oils [52].

Uses of CBD Oil

Cannabis plants have different types of cannabinoids present in it. It depends upon several factors and may vary from one strain to other. A unique cannabinoid known as cannabidiol (CBD) is less psychoactive in nature and is isomer of THC. Female flower of hemp have accumulation of cannabidiol [26]. Use of CBD boost up immune system and protect the nervous system from harm of fluctuations. In addition to this, CBD is found to be protective against cancer as it behaves as antioxidant (Fig. 4). It reduces the risk of production of free radicals of O₂. Cannabinoids are equally recommended for children for severe syndrome (autism, Dravet syndrome and ADHD) as well as for elderly ones (Parkinson’s disease, dementia and Alzheimer’s disease). CBD is used as effective remedy against cancer, epilepsy, lack of appetite, anxiety, and sleep disorders [61].

Difference between Hemp and Marijuana

Cannabis has two variants, hemp and marijuana. Both belong to the species common in them. But they have a difference in hemp and marijuana. The reason of difference is based on contents of tetrahydrocannabinoids. Marijuana contained THC range from 0.3 percent up to 15 percent, while in the case of hemp it must be lower than the 0.3 percent (Table 3). Advancement in technology has made possible the suppression of THC contents and increase in the concentration of CBD [62]. Industrialized hemp have very important role in the sector of textile and oils.

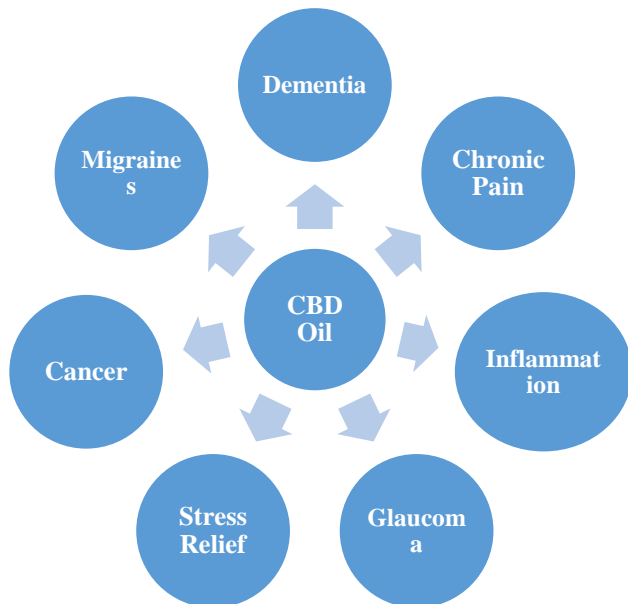


Fig. 4. Uses of CBD Oil against various diseases

Table 3: Difference between Hemp and marijuana [63].

Hemp	Marijuana
Higher CBD	Higher THC
THC: 0.3%	THC: 5-25%
Longer grow period	Shorter grow period
Legal in many countries	Legal in few countries
Medicinal uses	Medicinal uses
Industrial uses	Recreational uses
Non-Psychoactive	Psychoactive

Cultivation and growing conditions

Farming of the crop depends on the strain to be grown. In ordinary conditions, height of the crop can be up to 12 ft [64]. The height of the strains can be different; some are long with strong stem while some are short in stature. Although in the advancement of technology, even developed countries like China and France are growing hemp by traditional methods that were in use before 19 century [65]. Universities of USA have started their research on modern agricultural techniques and few of them are on their trail [66]. Certainly, these techniques significantly affect the yield. Since twenty century, hemp was known for its use in textile and no concept was there for extraction of its oil or CBD [67]. In first decade of twentieth century, new tools and techniques were developed to modernize textile industry. Literature data of 1970 showed the usage of modern tools and techniques for hemp cultivation [68].

Cannabis may grow at 13°C to 30°C. Above 30°C, THC contents may increase speedily. Hence it is necessary to control temperature in optimum range below 26°C [69]. Hemp grown in optimum temperature range gives complete structure. Hemp can be grown in northern as well as southern regions and could harvest according to time period of sowing [70]. Maturation time for hemp crop is 4 months [71]. In open fields, there is cultivation of one crop while in controlled condition it may give 4- 6 crop per year [72]. Hemp crop prefers deep and good-aerated soils having pH of 6, having appropriate moistness and nutrient holding capability [73].

Growing of hemp in Field

Human being cultivated hemp for over 6000 years before it was introduced in the United States [74]. Hemp has been grown across the world throughout time, from long-dead empires such as Prussia, to America and the rest of the world in 1937, to present day. Unfortunately, the association of hemp to marijuana was a major cause of the downfall of the hemp industry in the 1950s [75]. In recent years, hemp has become a re-emerging industry in the world. The hemp plant grows to about 3-4 m tall, has several varieties, and prospers across several environments within America, Europe, and China. The cultivation of hemp in the past was done by hand and harsh diligent labor [76]. Nowadays, the harvest of hemp is a mechanized process. The reintroduction of hemp growth can be beneficial for social and economic development in the countries, as this crop can be used as a source of fiber for textiles, rope, and other materials. Hemp can be used for many different things within the field of agriculture [16]. Hemp can be processed into oils and other byproducts, such as rope and textiles. As an agricultural-based society, we need to investigate the properties of this plant, the economic impact it can have on the agricultural system, and the benefits that its reintroduction can have on the textile industry [75]. Hemp can economically revitalize some parts of the agricultural industry and provide many new jobs to farmers and those in the textile industries [16]. Weed control is one of the many factors that can affect the growth of industrial hemp. Determining the best means of weed control is crucial for the future of this crop.

Growing in controlled conditions

The majority of medical *C. sativa* crop growing occurs in controlled conditions, such as greenhouses and indoor facilities that use soilless cultivation systems such as Rockwool and Coco peat substrates irrigated with nutrients solution with synthetic fertilizers [77]. In combination, the use of artificial lights is becoming gradually popular as a means to reduce high temperature and energy limitations requirements [78]. Mostly researcher and cultivators of *C. sativa* uses a variety of soilless cultivation systems, including nutrient film technique, hand watering organic pot systems and conventional Rockwool with drip irrigation [79]. These systems have various root zones: the presence of oxygen, movement of water, and availability of mineral nutrients can differ significantly, subject to the physicochemical properties of the substrates used and agronomical management practices [80,81]. Despite the importance of root zone management to the success of many greenhouse crops [82, 83, 84, 85], it is often overlooked as an important factor affecting *C. sativa*. In a recent meta-analysis by [86], describing cultivation factors that affect *C. sativa*, it is suggested that some root zone factors, such as pot-size and fertilization, can significantly influence *C. sativa* yield and potency. Furthermore, recent studies have found that root zone macro-nutrients can alone influence *C. sativa* inflorescence yield and phytocannabinoid contents [87, 88]. *C. sativa* like other flowering crops is suggested to have increased P and K demands during the flowering stage of growth in both soil and soilless systems [87, 89]. When *C. sativa* was grown in a potting mixture, supplemented with 15% more N, P, and K than that supplied in a conventional fertigation, total yield of crop increased considerably, indicating potential nutrient inadequacy of one or more elements. While the nutrient requirements and stoichiometry have been minimally investigated in hemp, the nutritional requirements of drug-type *C. sativa* cultivars, particularly in controlled environments, remains almost entirely unknown [87].

Effects of nutrients on the growth and yield of cannabis

Nutrient running is a main aspect that affects development and growth of plants. Specially, Nitrogen is the most important nutrient required by plants. It is taken as macronutrient and has the role in metabolism and development as it is constituents of protein. Nitrogen is needed for development and maintenance of chlorophyll in hemp crop [90]. For economic stability and cannabinoid profile are highly dependent on macronutrient (Nitrogen, Potassium, Phosphorus) and micronutrients (Calcium, molybdenum, Zinc, Iron, Manganese) and continuous supply of these nutrients [91]. The details of the nutrition on various plant parts are shown in Table 4.

Hemp plant metabolic development and growth is highly dependent on mineral nutrition [92]. The application of the suitable nutritional dealings including organic fertilizers, complements, and biostimulants is therefore a vigorous feature of medicinal plant production comprising medicinal cannabis [93].

Table 4: Effect of nutrients on phytocannabinoids on different parts of plant.

Name of nutrient	Effect on plant part	Effect on secondary metabolites
Nitrogen	Inflorescence	Increases CBG
Phosphorus	Inflorescence	Lowered CBD and CBT
NPK	Flower	Lowered CBN
NPK	Leaf	Did not effect
Humic acid	Flower	Lowered CBD, THC and CBG
NPK	Middle of the plant	Increases THC and THCv
NPK	Top of the plant	Increase CBG and CBC

This table showed the effect on nutrients on CBD contents in hemp. CBD productions as a result on application of nutrients were more concentrated in inflorescence of female flower as compared to leaves or stem [94]. Further studies showed that CBD concentration was more in upper most parts than lower parts [95].

Conclusions

Hemp has long history of ethnobotanical use. CBD and THC are two important compounds which possess variety of medicinal properties. CBD being non narcotic metabolite is gaining popularity in treating cancer, epilepsy, glaucoma, migraine, inflammation and arthritis as well as other chronic diseases. This review discussed detailed its economic and benefit along with cultivation practices in hydroponic as well as field conditions.

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