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REVIEW

A Review of Hemp As Food and Nutritional Supplement

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Abstract

The term "hemp" refers to *Cannabis sativa* cultivars grown for industrial purposes that are characterized by lower levels of tetrahydrocannabinol (THC), the active principle responsible for *Cannabis* psychotropic effects. Hemp is an extraordinary crop, with enormous social and economic value, since it can be used to produce food, textiles, clothing, biodegradable plastics, paper, paint, biofuel, and animal feed, as well as lighting oil. Various parts of the hemp plant represent a valuable source of food and ingredients for nutritional supplements. While hemp inflorescence is rich in nonpsychoactive, yet biologically active cannabinoids, such as cannabidiol (CBD), which exerts potent anxiolytic, spasmolytic, as well as anticonvulsant effects, hempseed has a pleasant nutty taste and represents a valuable source of essential amino acids and fatty acids, minerals, vitamins, and fibers. In addition, hempseed oil is a source of healthy polyunsaturated fatty acids, and hemp sprouts are rich in antioxidants. This review article aims to provide a comprehensive outlook from a multidisciplinary perspective on the scientific evidence supporting hemp beneficial properties when consumed as food or supplement. Marketing of hemp-derived products is subjected to diversified and complex regulations worldwide for several reasons, including the fact that CBD is also the active principal of pharmaceutical agents and that regulatory bodies in some cases ban *Cannabis* inflorescence regardless of its THC content. Some key regulatory aspects of such a complex scenario are also analyzed and discussed in this review article.

Keywords: cannabidiol; cannabinoids; *Cannabis*; hemp food; hemp

Introduction

Cannabis is a genus of flowering plants belonging to the family of Cannabaceae. According to some authors, the *Cannabis* genus includes three different species, such as *Cannabis sativa*, *C. indica*, and *C. ruderalis*.[1] Alternatively, it is considered as monospecific (*Cannabis sativa* L.) with two subspecies [*Cannabis sativa* L. subsp. *sativa* and *Cannabis sativa* L. subsp. *indica* (Lam.) E. Small & Cronq.] and four varieties [*Cannabis sativa* L. subsp. *sativa* var. *sativa*; *Cannabis sativa* L. subsp. *sativa* var. *spontanea* Vavilov; *Cannabis sativa* L. subsp. *indica* (Lam.) E. Small & Cronq. var. *indica*; and *Cannabis sativa* L. subsp. *indica* (Lam.) E. Small & Cronq., var. *kafiristanica* (Vavilov)].[2] Such a taxonomy was proposed by Small and Cronquist combining fruit morphology and (−)-trans-Δ9-tetrahydrocannabinol (THC) content.[2] *Cannabis* plants have been used for thousands of years for recreational, medicinal, or religious purposes.[3]

Currently, there are ∼147 million people worldwide who consume *Cannabis*, primarily because of its intoxicating properties mediated by THC.[4] Most people, who simply have knowledge of *Cannabis* as a recreational drug, ignore the enormous social, industrial, and economic value of "hemp." Hemp is the term used as opposed to "marijuana" to refer to *Cannabis* varieties characterized by lower THC levels and grown for industrial purposes.[5] Hemp is a versatile crop, which can be grown at high latitudes[6] and can

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be used to produce food, textiles, clothing, biodegradable plastics, paper, paint, biofuel, and animal feed, as well as lighting oil.[7] In 1938, the Popular Mechanics magazine defined hemp as "the new billion-dollar crop," with about 30,000 different products derived from the fiber and the stalk of plant.

Over the past decades, to counteract its widespread use as a recreational drug, the authorities had banned cultivation of any variety of *Cannabis* without making a distinction based on the THC content, which severely and unfairly harmed the hemp industry. During the past few years most Western countries have recognized the incontrovertible economic, potential, and social value of industrial hemp and even promoted its cultivation through *ad hoc* legislative interventions, which have established a legal threshold for THC concentration in the dry plant material (e.g., 0.2% in the European Union).[8] In the United States, hemp is not considered as a controlled substance subject to Drug Enforcement Administration (DEA) regulation and can be produced according to the 2014 farm bill provision, although some aspects are still overseen by DEA, including the importation of viable seeds.[9]

Hempseeds and inflorescence are extensively used worldwide as source of food and supplement ingredients. Hemp inflorescence is rich in nonpsychoactive, yet biologically active cannabinoids, such as cannabidiol (CBD), which exerts potent anxiolytic, spasmolytic, as well as anticonvulsant effects, among others.[10]CBD nutritional supplements account for approximately one-third of the global 1.34 billion dollar market for CBD.[11] Hempseed has a pleasant nutty taste and represents a valuable source of essential fatty acids, minerals, vitamins, and fibers, as well as of essential amino acids contained in the highly digestible proteins edestin and albumin.[12] Hempseed oil is composed for its greater part (>90%) of polyunsaturated fatty acids[13] known for their beneficial effects against cardiovascular diseases, cancer, and inflammatory conditions.[14,15]

Hemp sprouts can also be consumed as food. Compared to hempseeds, hemp sprouts are characterized by higher content in total polyphenols, flavonoids, and flavonols, known for their positive cardiovascular and metabolic effects.[16] Besides the multiple potential advantages—most of which are yet to be proved in large prospective trials—associated with the hundreds of different compounds found in hemp, dietary consumption of hemp products may also carry potential risks for public health, mostly related to the excessive exposure to psychoactive and nonpsychoactive cannabinoids, that may be present as undesired contaminants[17] or may be purposely consumed in excessive and potentially harmful amounts. Presently, marketing of CBD-based dietary supplements, which is under intense debate in the scientific community,[18] is differently regulated in the United States, Europe, and the rest of the world.

The aim of this narrative review is to provide a comprehensive analysis of the available scientific evidence on the composition, nutritional properties, as well as safety of hemp consumed as food and nutritional supplements, with a focus on the related complex socio-economic and regulatory aspects.

Hemp Bioactive Compounds

The extensive research that has probably made *Cannabis* the most studied plant in human history has allowed to identify hundreds of different compounds with potential biological activity, including more than 120 terpenoids, 100 cannabinoids, 50 hydrocarbons, 34 glycosidic compounds, 27 nitrogenous compounds, 25 noncannabinoid phenols, 22 fatty acids, 21 simple acids, 18 amino acids, 13 simple ketones, 13 simple esters and lactones, 12 simple aldehydes, 11 proteins, glycoproteins, and enzymes, 11 steroids, 9 trace elements, 7 simple alcohols, 2 pigments, as well as vitamin K.[19]

Two recently published studies using an optimized method for chemical characterization of hemp identified 189 lipids, including 52 phospholipids and 80 sulfolipids,[20] and 147 compounds belonging to the classes of flavonoids, proanthocyanidins, and phenolic acids.[21] Nonpsychoactive cannabinoids reported in hemp include the abovementioned CBD, as well as cannabichromene (CBC), cannabigerol (CBG), cannabinol, cannabicyclol, cannabielsoin, cannabitriol, and others.[22] Part of their biological activity can be explained by the interaction with the endocannabinoid system, which includes two G protein-coupled cannabinoid receptors (CB1 and CB2) and two endogenous ligands (anandamide and 2-arachidonoylglycerol).[23,24]

The endocannabinoid system is physiologically involved in regulation of appetite, pain, mood, memory, inflammation, insulin sensitivity, as well as fat and energy metabolism, with a wide variety of potential therapeutic implications for treatment of pain, neuropsychiatric disorders, neurological diseases, and inflammatory bowel, which may benefit from CB1 activation, as well as for treatment of obesity, type 2 diabetes, and hepatic or kidney disorders, which may benefit from CB1 antagonism.[25]

CBD is biosynthesized as a carboxylic acid through the same metabolic pathway as THC, with the exception of the last chemical reaction that is catalyzed by CBD acid synthase instead of THC acid synthase.[26] CBD exerts a wide range of biological effects, including anticonvulsant, anxiolytic, anti-inflammatory, immune-modulating, and antineoplastic activity, as shown in multiple pre-clinical models. CBD dose-dependent anticonvulsant activity was also shown in a 4-aminopyridine model prepared using mouse hippocampal brain slices at concentrations ranging from 0.01 to 100 μM, as well as *in vivo* in a pentylenetetrazole model of generalized seizures, at doses of 1, 10, and 100 mg/kg.[27,28]

A potent anxiolytic effect of CBD has also been shown in pre-clinical models. In mice undergoing 2 weeks of chronic unpredictable stress, CBD repeated administration at the dose of 30 mg/kg exerted a potent anxiolytic effect through the CB1 cannabinoid receptor, as suggested by evidence of higher hippocampal anandamide levels associated with CBD administration and reversal of CBD effects through administration of a CB1-selective antagonist.[29]

Interestingly, CBD spectrum of biological activities includes immune-modulating and anti-inflammatory properties. In a mouse paw model of acute carrageenan-mediated inflammation, oral daily administration of CBD at doses ranging from 5 to 40 mg/kg for 3 days was able to reduce edema, prostaglandin E2 plasma levels, tissue cyclooxygenase activity, production of oxygen-derived free radicals, and nitric oxide after three doses of CBD.[30] Anti-inflammatory effects may be explained by inverse agonism activity toward the CB2 receptor,[31] which inhibits immune cell migration both in macrophages[32] and human neutrophils.[33] CBD may also exert potent and specific activity against neuroinflammation processes, which are involved in a number of neurodegenerative disorders.[34]

In an experimental murine multiple sclerosis model obtained through inducing autoimmune encephalomyelitis through immunization with myelin oligodendrocyte glycoprotein, CBD (5 mg/kg) administered for 3 days–3 weeks after myelin antigen administration at the time of disease onset was able to slow progression and reduce severity of the autoimmune encephalomyelitis. Clinical activity was accompanied by histologic evidence of diminished axonal damage and microglial activation and by *in vitro* evidence of decreased T cell proliferation in response to the myelin antigen.[35]

CBD also presents antineoplastic activity shown in several pre-clinical models. Among five different cannabinoids, including CBD, CBG, CBC, cannabidiol acid, and THC acid, CBD exhibited the strongest *in-vitro* antineoplastic activity in a panel of different cancer cell types, with an IC(50) between 6.0 and 10.6 μM.[36] The underlying mechanism of action may be mediated by CBD-induced production of reactive oxygen species and desensitization of transient receptor potential cation channel, subfamily A, member 1 (TRPA1),[36] which plays a critical role in maintaining cellular homeostasis in response to oxidative stress.[37]

TRPA1 is also desensitized by the strong agonistic activity exerted by another cannabinoid lacking psychotropic effects, CBC, which results in a potent anti-inflammatory effect, as shown in a mouse model of colitis induced by dinitrobenzene sulfonic acid.[38] CBG has also proven to reduce inflammation in an experimental murine model of colitis.[39] CBG may also reduce intraocular pressure, as shown after chronic topic administration to the eyes of cats.[40]

Terpenes found in hemp, which confer the typical aroma and flavor, may also exert multiple biologically relevant effects. β-Myrcene and limonene are among the most abundant terpenes in hemp. In a mouse model of osteoarthritis, myrcene showed meaningful anti-inflammatory activity in human chondrocytes.[41] *In vitro* studies also suggest that β-myrcene may be useful to treat pain through interaction with transient receptor potential cation channel subfamily V member 1 (TRPV1) channels.[42] Limonene may exert antiallergic activity.

In an *in vitro* study conducted in human eosinophilic leukemia HL-60 clone 15 cells, limonene was capable of inhibiting reactive oxygen species production even at low concentrations (7.34 mmol/L), while at 14.68 mmol/L concentration limonene was able to decrease monocyte chemotactic protein-1 (MCP-1) synthesis, which suggests a potential clinical action against bronchial asthma,[43] as also confirmed by reduced allergic airway inflammation obtained with limonene inhalation in an experimental mouse model.[44] Another terpene found in hemp, β-Caryophyllene, has shown potent anxiolytic effects in mice.[45] Finally, cannaflavin A and B are two flavones with potent antioxidant activity found in hemp inflorescence that have shown to reduce prostaglandin E2 synthesis in cultures of human rheumatoid synovial cells[46] and may therefore provide anti-inflammatory effects in humans.[47]

Hemp Supplements

As a plant-derived, easily extractable, biologically active compound with large therapeutic index and

overall excellent safety profile, CBD is currently marketed both as a mainly hemp-derived dietary supplement, subjected to evolving legislation and regulatory actions, and as a drug, such as Epidiolex (CBD only) and Sativex (THC and CBD in 1:1 ratio), with specific approval indications worldwide.

Epidiolex is currently both European Medical Agency- and Food and Drug Administration approved against seizures associated with Lennox–Gastaut or Dravet syndrome in patients 2 years of age or older on the grounds of high quality scientific evidence from randomized controlled trials.[48,49] Concordantly with its biological activity discussed above and demonstrated in pre-clinical models, accumulating evidence from clinical trials suggests that CBD as a pharmaceutical agent has the potential to gain a number of additional indications for the treatment of sleep disorders, social phobia, post-traumatic stress syndrome, substance abuse and dependence, schizophrenia, bipolar disorder, depression, and Parkinson's disease.[50]

While CBD has been administered up to 6000 mg/day in phase I studies,[51] Epidiolex recommended that starting dose for the approved indications is 5 mg/kg, which can be increased up to 20 mg/kg/day.[52] Compared to placebo, Epidiolex has shown dose-dependent increased incidence of alanine aminotransferase elevations above thrice the upper limit of normal (13% vs. 1%, mainly in patients treated at the 20 mg/kg daily dose).[52] Dose-dependent CBD potential for inducing liver toxicity when administered at pharmacological doses is confirmed by pre-clinical experiences in the mouse model.[53]

In Epidiolex registrative trials, somnolence and sedation were reported in 34% and 27% of patients consuming 20 versus 10 mg/kg/day, while the risk of suicidal behavior associated with Epidiolex versus placebo was ~3.5 fold.[48] Decreased appetite, fatigue, diarrhea, transaminase elevation, rash, sleep disorders, as well as infections, were also reported in >10% of subjects treated with Epidiolex.[48] In view of the variety of potentially life-threatening adverse events, as well as of the recommended precautions and warnings, besides potential drug–drug interactions reported with CBD at pharmacological doses, the FDA has prohibited marketing of CBD as an ingredient for nutritional supplements,[18] which appears in contradiction with United States federal court ruling establishing that hemp-derived products, including those containing CBD, could be freely marketed under the 2014 Farm Bill.[54]

The scenario is also confusing in Europe, where CBD-containing products (e.g., CBD-enriched hemp oil) have been classified as novel foods because their use was not widespread in Europe before 1997,[55] which makes it mandatory to apply for authorization to place dietary CBD products on the market. One application requesting CBD to be authorized as a novel food with a daily intake of up to 130 mg or 1.86 mg/kg body weight has been filed by Cannabis Pharma, s.r.o. (Czech Republic) and remains currently pending.[56]

Despite such a regulatory and legislative confusion, the importance of the CBD issue from a public health perspective lies in its widespread self-administration without any medical supervision and wide availability as a supplement, with a market worth for retail sales of hemp-derived CBD products of $170 million in 2016 in the United States alone and a projected market worth of hemp-derived CBD of $22 billion in 2022.[57] Furthermore, in view of the lack of stringent controls of marketed products by the competent authorities, mislabeling of CBD supplements is frequent, which may represent a fraud for consumers, as well as pose a risk for their health.

In a study involving 88 CBD liquid products, including oil and vaporization liquid, marketed by 31 different companies, CBD median levels were 9.45 mg/mL (range 0.10–655.27 mg/mL), which was lower compared to the median labeled concentration of 15.00 mg/mL (range 1.33–800.00). CBD-containing oil to be consumed orally was inaccurately labeled in 55% of cases.[58] The FDA has sent warning letters to several companies requesting them to stop claiming that their CBD products may treat or even cure serious diseases, including cancer.[59]

The widespread use of CBD products has been poorly investigated. One study recruited 2409 individuals who participated in an online survey designed to assess the reasons, risks, and modalities behind CBD consumption.[60] Approximately a third of participants reported some nonserious adverse event, with the most frequently occurring adverse events being dry mouth (11.12%), euphoria (6.43%), hunger (6.35%), red eyes (2.74%), and sedation/fatigue (1.78%). Among the 1483 users who reported using CBD to treat a medical condition, which most frequently included pain, anxiety, depression, and sleep disorders, approximately one-third of participants stated that CBD alone could manage their medical condition by itself.

Importantly, ~40% of participants were motivated to consume CBD as part of a healthy lifestyle. Despite its numerous limitations, including the lack of data

regarding the dose consumed and timing of consumption, as well as the absence of a control group, this study has the merit to capture consumers' motivations behind CBD use, which is essential to direct further research and investigations, as well as regulatory interventions.

Despite the large consumption of CBD as a nutritional supplement, evidence from pre-clinical and clinical studies exploring the effects of CBD as a dietary ingredient is scarce to nonexisting. In one pre-clinical study conducted in eight dogs and eight cats,[61] CBD administered at the daily dose of 4 mg/kg for 12 weeks did not cause any alteration in complete blood count or serum chemistry, with the exception of one cat showing persistent abnormalities in alanine aminotransferase levels. Dogs presented few adverse events, including loose stool and vomiting occurring for $<5\%$ of the observation time, while cats showed multiple adverse events, including licking and head shaking, observed for 35.4% and 25.2% of the observation time, respectively.

In a small interventional prospective trial, including 12 individuals receiving up to 90 mg of single oral doses of CBD and assessed for cardiovascular and cognitive functions after CBD consumption, increased cerebral perfusion and reduced blood pressure compared with baseline were reported in a subgroup of participants receiving 90 mg CBD, without any clinically evident adverse events or laboratory alteration in blood count, inflammation, or metabolic markers.[62]

Although adequate trials assessing CBD effects when administered as nutritional supplement in large populations and for a prolonged period of time are lacking, the clinical evidence summarized here allows to hypothesize that the acceptable dose for supplementation in adults may be comprised between the total dose of 5–10 mg/day, obtained by roughly estimating CBD exposure through historic use patterns based on the available data on smoked *Cannabis*[63] and the pharmacological total daily doses >350 mg a day, that is, in the range of 50–100 mg a day. This may represent the dose range for testing CBD hemp supplements as part of a healthy diet.

The need for further research is becoming more compelling as multinational companies such as Coca-Cola are planning to supplement some of their products with CBD,[64] which will expand the variety of CBD-supplemented food and beverages—as an example, a Californian company is marketing CBD-supplemented wine,[65] while New York-based company Sovereign Vines has produced a wine with special tastes and flavors of hemp.

Hemp Food

Hemp has been a valuable source of food for mankind for millennia, as shown by the hempseeds found in tombs dating back to the third millennium before Christ in China, where roasted hempseed can still be bought on the street as snacks.[66] Although hemp leaves, sprouts, and flowers can be consumed as a raw food by preparing juices and salads,[67] hempseeds represent the most common part of the hemp plant to be consumed as food. The true seed is an achene, enveloped by a subtle and hard pericarp, and matures 3–6 weeks after the fertilization of female flower.[68] Hempseeds provide $\sim$500–600 Kcal/100 g of product and are composed of approximately one-fourth of proteins, one-fourth of carbohydrates, and one-third of fat,[69] with some significant variations among different genotypes.[70]

Hempseeds are rich in polyunsaturated fatty acids, which also vary among different genotypes. One study of seven different hempseed cultivars ("Bialobrzeskie," "Felina 32," "Tygra 75," "Futura 27," "Santhica," "Fedora 17," and "Finola") showed that "Finola" had the highest content of γ linolenic and α-linolenic acids and the lowest content in oleic acid and saturated fatty acids, such as palmitic and stearic acids.[70]

Hempseed proteins represent a valuable source of sulfur-containing amino acid methionine and cystine and provide high quantities of arginine, an essential amino acid with beneficial cardiovascular properties. Accumulating evidence supporting the antihypertensive effect of hydrolyzed hempseed proteins, possibly mediated by inhibition of angiotensin-converting enzyme and renin,[71] provided the rationale for an ongoing human trial testing hemp protein powder as an antihypertensive nutritional intervention.[72]

This trial is going to enroll 35 individuals showing systolic blood pressure >130 mmHg or elevated diastolic blood pressure ≤ 110 mmHg, who will be randomized to a dietary intervention consisting of either 25 g of casein or 25 g of hempseed protein or 22.5 g of hempseed protein added with 2.5 g of hempseed protein hydrolysate derived enriched with bioactive peptides.[72] Finally, as little as 50 mg of hempseeds can cover 50–100% of the recommended daily intake of several minerals, including copper, magnesium, and zinc, and provide $>100\%$ of the daily recommended dose of vitamins A, D, and E.[73]

Hempseeds can also be used to make flour and oil with valuable nutritional properties. In one study, flour of hemp "Fedora" contains moisture, protein, lipids, carbohydrates, and ash in the proportion of 7.9 ± 0.9, 30.7 ± 1.2, 13.6 ± 1.9, 41.6 ± 2.5, and 6.2 ± 0.5%, respectively, with a high content of total polyphenols quantified with the Folin–Ciocalteu method (744 ± 29 gallic acid equivalents).[74] Up to 10% of flour obtained from hempseed added to wheat flour did not affect dough stability and dough strength, but improved the nutritional value of the final product by increasing the levels of proteins and minerals.[75] In another study, the addition of hemp flour to starch to make gluten-free bread was associated with improvement in palatability in terms of flavor and color, as well as in the nutritional value, with increased levels of fibers and proteins.[76] Crackers made from hemp flour have also improved nutritional value.[77]

Hempseed oil is the most commonly used edible hemp derivative, with potential uses also in the cosmetic industry as a sun cream due to its capacity to absorb UV rays and its high content in vitamin E (100 mg/100 mL).[78] Hempseed oil consists of > 800% unsaturated fats with an established cardioprotective effect such as linoleic acid (18:2 omega-6) and α-linolenic acid (18:3 omega-3), which are found in hemp oil at an optimal ratio of 2/3:1.[74,79] Of note, despite the nutritional value of a balanced content in omega-6:omega-3 fatty acids, most commercially available cooking oils are selected to have a low content in omega-3 fatty acids to improve their stability, as omega-3 fatty acids rapidly turn rancid because of the presence of three double bonds.[80]

In one study evaluating the composition of hempseed oil derived from seven cultivars, including "Novosadska," "Secuieni," "Beniko," "Felina 34," "Futura 75," "Tiborszállási," and "Carmagnola Seleccionata," the total amount of unsaturated fatty acids was 82–86%, with 51.9–55.7% of linoleic acid and 12.3–15.3% of α-linolenic acid, while γ-linolenic acid, which is involved in inflammatory processes,[81] ranged from 0.8% in domestic "Novosadska" cultivar to 2.46% in "Beniko".[82] Hempseed oil also has a high antioxidant capacity due to its content in phenols and flavonoids, with 267.5 ± 8.84 mg of gallic acid equivalents and 2780.4 mg ± 133.06 of quercetin equivalents in 100 g of fresh cold-pressed hempseed oil from "Finola" cultivar,[83] while β-caryophyllene and myrcene have been found at concentrations of 740 and 160 mg/L, respectively.[84]

With its pleasant, nutty-favored taste, with somewhat of a bitter aftertaste,[85] hempseed oil may be used in cooking as a replacement for olive oil, which has established benefits for cardiovascular health.[86] Small quantities of hempseed oil (2 g/day) did not produce any effect in plasma levels of total cholesterol, high and low density cholesterol, triglycerides, nor did it induce any effect in terms of platelet aggregation and levels of circulating inflammatory markers in a trial[87] in a 12-week trial, including 86 healthy participants. These results were confirmed in another trial enrolling 36 children with primary hyperlipidemia, who did not show any improvement in their lipid profile after consuming 3 g of hempseed oil.[88]

Interestingly, daily consumption of 30 mL hempseed versus flaxseed oil was associated with an improvement in the total cholesterol to high density lipoprotein cholesterol ratio[89] in another small trial enrolling 14 individuals. In another controlled, randomized single-blind crossover study, 20 participants with atopic dermatitis were instructed to consume 30 mL of olive versus hempseed oil during a 20 week period. Importantly, consumption of hempseed oil resulted in subjective decreases in both skin dryness and itchiness along with reduced use of topical medications, while this effect was not reported for olive oil. Although limited, these results suggest that hempseed oil can be part of a diet with potential health advantages. Finally, hemp sprouts may also represent an attractive functional food due to their content in flavonoids and flavanols,[90] although clinical trials exploring palatability and potential benefits associated with their consumption are lacking.

Future Directions

Hemp potential as an extraordinary source of supplement ingredients and a healthy food remains largely to be investigated in adequately powered clinical trials. FDA position to consider hemp-derived CBD as a drug only with prohibition to market it as a supplement appears as a legitimate safeguard against uncontrolled use of an active principal approved as a drug, which carries the risk of serious adverse events, drug–drug interaction, and cannot and should not be used without medical supervision.

Nevertheless, we believe that CBD is likely to be safely consumed as a nutritional supplement up to a dose of 1–2 mg/kg, as also reported in the position paper by European Industrial Hemp Association.[91] Unfortunately, while data regarding the effects associated with very high doses of CBD (up to 6000 mg/day)

for short periods,[51] data obtained in population studies with a double-blind design and with sufficient power to capture even infrequent adverse effects are currently lacking unfortunately.

Regulatory agencies are allowed to err on the side of prudence provided that sufficient impulse is given to the design and conduction of such clinical studies. Prohibition of CBD marketing as a supplement ingredient within certain dose limits may limit consumers' right to have access to a naturally occurring substance obtained from THC-free hemp, which can be freely marketed. In contrast, interventions aimed at guaranteeing hemp-derived food safety are compulsory. After analyzing the cannabinoid profile by a liquid chromatography method coupled to high-resolution mass spectrometry in 10 commercially available organic hempseed oils, Citti et al.[92] reported noninsignificant concentrations of THC and CBD besides other 30 cannabinoids, which is probably due to contamination of seeds with inflorescence, as cannabinoids are not found in hempseeds.

The Zoo-Prophylactic Institute of Southern Italy (IZSM) is the first public Italian Institution operating under the supervision of the Italian Ministry of Health and with jurisdiction over food safety to provide assessment of THC content in food and hemp products in Accredia-certified internal laboratories, with enormous implications for public health and hemp law enforcement (www.reica.org). A large, IZSM-sponsored observational study, the HEMPEDOCLE study, is going to recruit ~900 Cannabis users, including 600 individuals who consume hemp-derived *Cannabis* products as food or supplement. This trial is going to prove or disprove safety of dietary hemp products and measure subsequent cannabinoid exposure in participating subjects.

Conclusions

Hemp use in the food and supplement industry is predicted to expand in the coming years as demand grows, with enormous social, economic, and sanitary implications. Legislative and regulatory interventions should aim at encouraging adequate clinical research to prove or disprove safety of hemp-derived products, which has not been done so far independently by the industry or by the scientific community.

Authors' Contributions

P.C., C.B., G.C., and A.G. drafted the article. All authors equally contributed to literature search and critical revision for important intellectual content and finally approved the article.

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Abbreviations Used

CBC = cannabichromene
CBD = cannabidiol
CBG = cannabigerol
DEA = Drug Enforcement Administration
FDA = Food and Drug Administration
IZSM = The Zoo-prophylactic Institute of Southern Italy
THC = tetrahydrocannabinol
TRPA1 = transient receptor potential cation channel, subfamily A, member 1