

Cannabigerol and cannabichromene in *Cannabis sativa* L.

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In addition to delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), other phytocannabinoids, such as cannabigerol (CBG) and cannabichromene (CBC), also have beneficial effects on human health. A high content of CBG is found in plants with the B₀ genotype, whereas CBC is independent of the allelic chemotype locus B. In basic research models such as mice or rats, CBG has demonstrated anticancer properties, particularly against breast cancer. CBG has shown anti-inflammatory effects on murine colitis and on inflammatory bowel disease as well as stimulatory effects on the feeding behaviors of mice. It has also exhibited inhibition of aldose reductase, which is known to cause an accumulation of sorbitol and increase glucose levels in the blood, which may lead to diabetes. Cannabinoid CBC has also shown anti-inflammatory effects and reduced hypermobility in the gut and has displayed potential *in vitro* effect on adult neural stem progenitor cells. CBC also exerts modest analgesic properties in rodents, as well as anti-fungal, anti-bacterial, pro-apoptotic, and anti-proliferative effects in tumor cells.

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INTRODUCTION

Hemp (*Cannabis sativa* L.) is an important herbaceous species that has been used for textile fibers and rope, as a source of food, in medicine, and in agriculture for seeds, animal food, silage, fuel, and animal bedding (1). *C. sativa* originated in Central Asia. It contains unique phytochemicals that have many therapeutic effects in various diseases and disorders (1), with more than 500 phytochemicals having been detected in *C. sativa* to date (2). The most abundant among these are cannabinoids, terpenoids, steroids, flavonoids, lignans and alkaloids. The most important and well-known secondary metabolites are cannabinoids, terpenophenolic compounds unique to *Cannabis* (3). The most well-known cannabinoids are cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC), as well as cannabigerol (CBG) and cannabichromene (CBC). The highest proportion of cannabinoids are present in the plants' inflorescences and glandular trichomes (4).

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Cannabinoids have many beneficial effects on human health. THC is the psychoactive compound in *C. sativa*, whereas CBD, CBG, and CBC are non-psychoactive compounds (5). CBD has antinociceptive, anxiolytic, antipsychotic, antiinflammatory, and antioxidant effects (5). CBG and CBC are also claimed to have antibacterial effects, whereas THC stimulates appetite, reduces pain and spasticity while also functioning as a bronchodilator, neuroprotective antioxidant, and anti-inflammatory agent (6).

Different phenotypes of *C. sativa* are characterized by specific cannabinoid ratios; five major chemotypes have been described (7). In 1973, Small and Becksted (8) determined three chemotypes: (i) chemotype I (“drug” type), with a THC content over 0.3 % (usually higher than 0.5 %, however, it can also be over 20 %) and a CBD content lower than 0.5 %, (ii) chemotype II (intermediate type), with the CBD and THC ratio roughly equal and (iii) chemotype III (“fiber” type), with a higher CBD and THC content lower than 0.3 %. Later, in 1987, Fournier *et al.* (9) described two additional chemotypes: chemotype IV, with a prevalence of CBG (> 0.3 %) and CBD (< 0.5%) and chemotype V, with an undetectable content of cannabinoids. Cannabinoid content depends on many different factors, such as length of the day (10), UV light intensity (11), temperature (12), plant nutrition (13, 14), sex and the maturity of the plant (15).

The aim of this article is to summarize the literature data from investigations of cannabigerol and cannabichromene. Many studies on the health effects of CBD and THC have been made thus far, while only a few investigations have been devoted to CBG and CBC. Little is known about these non-psychoactive compounds (except CBD); thus, researchers still have great potential for further investigation.

THE BIOSYNTHETIC PATHWAY OF CBG AND CBC

To date, 113 different cannabinoids have been discovered (2). In plants, they appear in low concentrations except in rare chemotypes with a high CBG content (> 0.3 %). CBC constitutes about 0.3 % in *C. sativa*, but some varieties may contain significantly higher values (5). CBC was isolated in 1966 by Gaoni and Mechoulam (16). Cannabichromenic acid (CBCA), a precursor of CBC, predominates in young *C. sativa* plants, and its content decreases with maturation (1).

The precursors of cannabinoids have two biosynthetic pathways: (i) the polyketide pathway leading to olivetolic acid (OLA) and (ii) the plastidal 2-C-methyl-D-erythritol-4-phosphate (MEP) pathway leading to geranyl diphosphate (GPP) synthesis (17). CBGA (cannabigerolic acid) is formed from the alkylation of OLA with GPP (18). The main cannabinoids are biosynthesized in the form of carboxylic acids and can then be decarboxylated by drying and heating the harvested plants. CBG (CBGA) is the direct precursor of the primary cannabinoids such as THC(A), CBD(A) and CBC(A). There are also homologous compounds with propyl side-chains, which are biosynthesized from cannabigerovarin (CBGV); these include cannabivarichromene (CBCV), cannabidivarin (CBDV) and delta-9-tetrahydrocannabivarin (THCV) (4).

THE BIOLOGICAL ACTIVITIES OF CBG AND CBC

The cannabinoids CBG and CBC have different affinities for receptors in the human body. The most important cannabinoid receptors are CB1 and CB2 (19); they are part of the

human endocannabinoid system which regulates multiple processes in the human body. The endocannabinoid system is composed of neurotransmitters and metabolizing enzymes along with the receptors mentioned above (19). CB1 receptors are found in the central nervous system, especially in the basal ganglia, the hippocampus, the cortex, and the cerebellum, whereas CB2 receptors are found in peripheral regions. The binding of cannabinoids to these receptors has different effects: the binding to the CB1 receptor has a psychotropic effect (20), whereas binding to the CB2 receptor will result in an antiinflammatory effect. Besides CB1 and CB2, TRP (transient receptor potential) receptors are known. Their main task is to serve as ionotropic cannabinoid receptors. The TRP subfamilies are TRPV (transient receptor potential vanilloid), TRPA (transient receptor potential ankyrin), and TRPM (transient receptor potential melastatin) (21).

CBG was isolated from cannabis in 1964 by Gaoni and Mechoulam (22). Although it has a relatively weak agonistic effect at CB1 and CB2 receptors and an antagonistic effect at TRPV8, it stimulates cation channels from the TRP group (TRPV1, TRPV2, TRPA1, TRPA3, TRPV4) and α 2-adrenoceptor activity (23), which are important for pain sensation, heat sensitization and inflammation. CBG can also stimulate serotonin by binding to 5-HT_{1A} (5-hydroxytryptamine receptor subtype 1A) and CB1 receptors. CBG is also a relatively potent agonist for TRPM8 receptors, which can be important in prostate cancer, bladder pain, and detrusor overactivity. It can also have an antagonistic impact on serotonin 5-HT_{1A}, which is related to feelings of well-being and happiness (23). In 1982, Eisohly *et al.* (24) found that CBG also has a mild antifungal effect. CBG is found in the African *Helichrysum* species as well as in *C. sativa* (25).

There are CBC-rich *Cannabis* strains, which are the result of extensive cross-breeding (26). CBC has also been detected in *Rhododendron anthopogonoides*. It can interact with and stimulate the CB2 receptor by inhibition of endocannabinoid inactivation, but it has no activity on CB1 receptors (27). It also interacts with the TRP cation channels TRPA1, TRPV1-4, and TRPV8, which are involved in pain relief and inflammation (5). When binding with TRP1 receptors, CBC can stimulate an antinociceptive effect in the brain. TRP1 and CB2 are also known to be involved in the control of intestinal motility. CBC also activates TRPM8 receptors (28).

INHERITANCE OF CHEMICAL PHENOTYPES

Cannabigerol (CBG)

In 1987, Fournier *et al.* (9) described the fourth chemotype in *C. sativa*; this chemotype (IV) has a CBG content higher than 0.3 % and a CBD content lower than 0.5 %. As mentioned above, CBG is a direct precursor of THC (29), CBD (30) and CBC (16) (Fig. 1). The presence of the B_D allele in *C. sativa* leads to a higher CBD content, whereas the presence of the B_T allele leads to a higher THC content. CBG probably accumulates when the plant has a mutated allele called B₀ encoding for a defective synthase enzyme (31). Through selective breeding of *C. sativa* chemotypes, pure CBD plants have the B_D/B_D genotype (chemotype III), pure THC plants have the B_T/B_T genotype (chemotype I), and plants accumulating the CBG cannabinoid are presumed to have the B₀/B₀ genotype (chemotype IV). With cross breeding of CBG- prevalent and CBD-predominant plants, all of the resulting

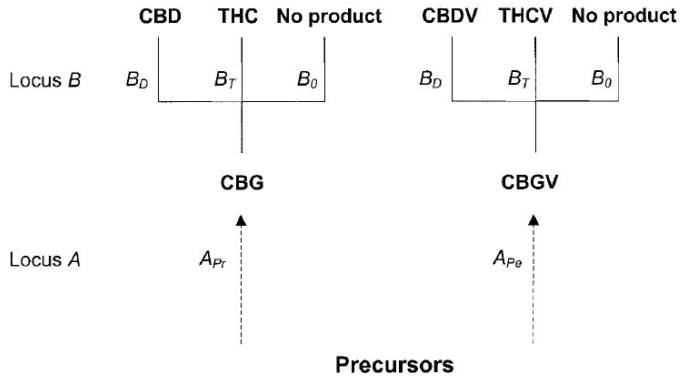


Fig. 1. Two separate loci (A and B) and CBG(V) precursor for conversion into CBD(V) and THC(V) and their encoding alleles (29).

generations will be strongly CBD- predominant (B_D/B_0 genotype), whereas cross-breeding of CBG-prevalent and THC-predominant plants results in offspring that are strongly THC-predominant (B_T/B_0 genotype) in the F1 generation. This occurs because of the interaction between the fully recessive B_0 allele with B_D or B_T . If plants have heterozygous B_D/B_T genotypes, they will have a mixed CBD/THC chemotype with ratios about 1:1 due to the similar conversion of CBG into CBD and THC. In 2005, Meijer and Hammond (32) have suggested that CBG can (in small amounts) convert to CBD, which suggests that the B_0 allele is a mutated form of B_D . Discoveries have been made that show that all CBG-predominant genotypes contain CBD in proportions of 10–15 %. THC-predominant plants (B_T/B_T or B_T/B_0 genotype) crossed with CBG-predominant plants (B_0/B_0 genotype) can display differentiation between B_T/B_0 and B_T/B_T genotypes in the F2 generation. This can happen because of the residual ability of the synthase that encodes the B_0 allele. As mentioned above, B_0 is fully recessive in interaction with the B_D and B_T alleles in heterozygous combination, and this is the reason for the differentiation of the B_T/B_0 and B_T/B_T genotypes.

Table I. Binding between cannabinoids and receptors and their impact on human health

Cannabinoid	Receptor	Health effect
	TRPV1, TRPV2, TRPA1, TRPA3, TRPV4 and $\alpha 2$ -adrenoceptor	Pain sensation, heat sensation, inflammation
CBG	Weak agonist CB1, CB2, 5HT _{1A}	Serotonin
	TRPM8	Prostate cancer, bladder pain, detrusor overactivity
	CB2	Inhibition of endocannabinoid inactivation
CBC	TRPA1	Antinociception
	TRPV1-4, TRPV8	Pain regulation, inflammation

Locus A encodes two different alleles: A_{pv} , which is the encoded propyl form of CBG, and A_{pe} , which is the encoded pentyl form of CBG (CBGV). CBG and CBGV are converted equally into the end-products THC(V) and CBD(V) encoded by locus B (31). With self-fertilization in monoecious populations of CBG-prevalent plants, a mutated B0 allele can become fixed in a few plants by repeated and frequent inbreeding (31).

Cannabichromene (CBC)

As mentioned above, CBG is a direct precursor of CBC (Fig. 2) (16). CBC is predominant in the juvenile phase and decreases in maturity. A high proportion of CBC is present in both CBD- and THC-predominant chemotypes but only in the phase of emergence, decreasing with aging. CBC-predominant plants can have a proportion of CBC up to 90 % in the phase of first true leaves, but this rapidly decreases to 1–5 %, the plant's final content of CBC, depending on the variety. Three possibilities of profile change exist for CBC synthase as *C. sativa* plants move from the juvenile phase to maturity. The first possibility is that CBC synthase activity is high in sessile trichomes, the second possibility is that different cannabinoid kinetic parameters influence synthases, and the third possibility is that CBC synthase is expressed only in the prolonged juvenile phase in plants with an ordinary low proportion of CBC (33).

The B_0/B_0 genotype offers an opportunity for breeding plants with high levels of CBC due to the completely obstructed CBG-THC and CBG-CBD pathways. As such, the CBC

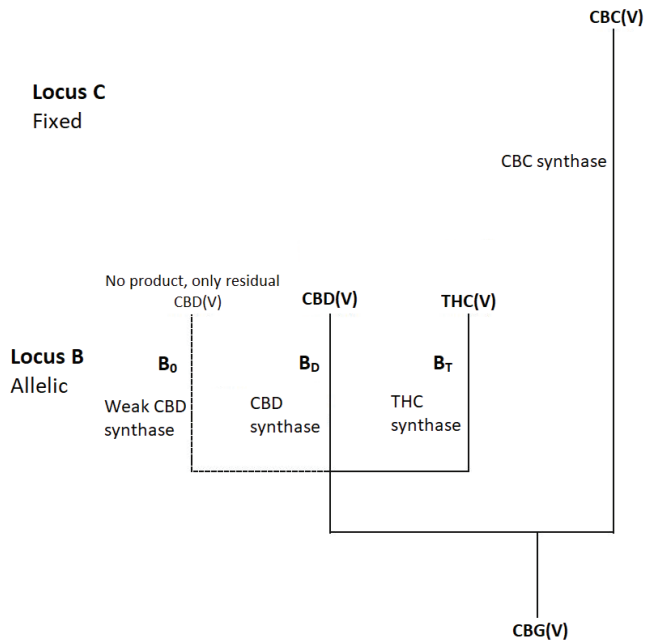


Fig. 2. Different conversions of CBG(V) and alleles for CBD(V), THC(V) and CBC(V) (31).

synthase is competing only against a weak CBD synthase. CBC synthase activity is a fixed trait in *C. sativa* plants, and it is not under the control of locus-B-like CBD- and THC-synthase activity (33).

In 2009, De Meijer and Hammond (33) discovered that the proportion of CBC in *C. sativa* increases with a reduction of light intensity, whereas the proportion of CBD, THC and CBG decreases with a reduction of light intensity.

HEALTH EFFECTS OF CBG AND CBC

Almost all biological properties of cannabinoids involve interactions with the endocannabinoid receptors in the human body. The endocannabinoid system plays a regulatory role in physiological processes including pain sensation, memory, appetite, mood, insulin content, inflammation, and fat and energy metabolism (27). It works as a large signaling system and is characterized by many endocannabinoid receptors, including CB1, CB2, anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Lipid mediators, called endocannabinoids, play a role in the endocannabinoid system in sharing enzymes and receptors with endocannabinoids and also have the ability to inactivate molecular targets and enzymes. Botanical drugs that contain cannabinoids stimulate endocannabinoid receptors and endocannabinoidome proteins (34).

As mentioned by Appendino *et al.* (35), preparations from *C. sativa* were extensively investigated in the 1950s as active topical antiseptic agents, but these studies were not entirely accurate. Later, in 2008, this group found that all major cannabinoids, including CBG and CBC, showed potent antimicrobial properties against multidrug-resistance (MDR) strains of *Staphylococcus aureus*, also to EMRSA-15 and EMRSA-16. Of all the cannabinoids, CBD and CBG showed the greatest impact on the resistance of these two strains of MRSA and were used for further research. Due to the role of phenolic hydroxyl which shows antibacterial properties, both, acetylation and methylation of the hydroxyl groups, had a negative effect on the activity against EMRSA. The minimum inhibitory concentration was higher than 100 $\mu\text{g mL}^{-1}$. The monophenols CBC and THC had also shown potent activity, whereas monomethylation of diphenols CBD and CBG had resulted in low antibacterial activity. CBD, CBG, and THC that were carboxylated had stronger antibacterial effects, while compounds with methylation of the carboxylic group had lower antibacterial potency. Low antibacterial properties were also displayed in compounds after the esterification of phenethyl alcohol. Phenolic acids have stronger antibacterial properties than the other compounds. Thus *C. sativa* represents an important source of antibacterial agents against MRSA and other pathogenic bacteria (35).

Beak *et al.* (36) and Ligresti *et al.* (37) found CBG to have an important ability to reduce cell proliferation in tumoral cell lines in *in vitro* studies. It is very cytotoxic in high doses on carcinoma in mice and is also highly effective against breast cancer. CBG was demonstrated to have antidepressant effects in research animal models of rodents (37). CBG also has antiinflammatory effects on murine colitis, and it is assumed to be beneficial for patients affected by inflammatory bowel disease as well (1). It reduced colon mass/colon length ratio, which is an indicator of the inflammatory response, and had preventive and curative therapeutic effects; 30 mg per kg bm CBG reduced the rate of colon damage. The possible antioxidant effect of CBG in intestinal mucosa by reducing oxidative stress has also been studied.

In 2016, Brierley *et al.* (38) investigated the effects of CBG on the food intake and feeding behavior of male Lister hooded rats. They discovered that tests conducted for two hours showed CBG to be an appetite stimulant at a dose of 120–140 mg kg⁻¹ bm. This is the dose to increase appetite and food intake, but it is unrealistically high since it would mean almost 10 g of pure CBG for a 70-kg man. Previous research, done by Farrimond *et al.* (39) in 2012, showed that CBG at a dose of 0.176–17.60 mg kg⁻¹ bm had no significant impact on the feeding patterns of rats in a 4-h feeding test. CBG-induced hyperphagia may be a result of its potency as an antagonist of the α 2-adrenoceptor (38). Cannabinoids that act as CB1 receptor agonists showed limited clinical utility as appetite stimulants, however, there is a possibility that CBG induces hyperphagia. In contrast to studies done in the past, THC formulations resulted in the largest increase in food intake in the first hour of feeding, followed by a decrease in the second hour (39). Further investigations are needed for the evaluation of CBG as a therapeutic appetite stimulant.

In 2018, Smeriglio *et al.* (40) studied the inhibitory effects of non-psychoactive CBD and CBG cannabinoids on aldose reductase activity. They found that *C. sativa* CBD- and CBG-type extracts and their CBDA- and CBGA-rich fractions showed statistically significant inhibition of aldose reductase. Aldose reductase causes intercellular accumulation of sorbitol and increased glucose levels in the blood, which leads to diabetes. This study shows the ability of *C. sativa* to help prevent or treat diabetes and the complications related to this disease.

CBC is one of the non-psychoactive cannabinoids that shows antiinflammatory (5), analgesic and sedative (41) effects. It reduces hypermobility in the gut induced by croton oil (28). CBC in combination with THC has a greater antiinflammatory effect (5). It showed potential *in vitro* effects on adult neural stem progenitor cells (42), but the *in vivo* medical research needs to be done to account for various physiological and pathological variations.

In their review article, Izzo *et al.* (43) described a modest analgesic activity in rodents with CBC as well as pro-apoptotic and antiproliferative effects in tumor cell lines such as the human prostate carcinoma, human breast carcinoma, human gastric adenocarcinoma, human colorectal carcinoma and rat basophilic leukemia. CBC also had antifungal and antibacterial effects (44) and showed potent activity against *Staphylococcus aureus* strains, similar to the effects of CBG (18).

CONCLUSIONS

Besides THC and CBD, *C. sativa* has other phytocannabinoids such as CBG and CBC, which also have beneficial effects on human health. Little is known about these non-psychoactive cannabinoids. Research on the beneficial health effects of CBG and CBC has mostly been carried out on animals (rats and mice) and not yet in humans. Thus, studies on the effects of CBG and CBC in humans are needed in the future.

Abbreviations/acronyms/symbols. – AEA – anandamide, 2-AG – 2-arachidonoylglycerol, CB (1/2) – cannabinoid receptor, CBC – cannabichromene, CBCA – cannabichromenic acid, CBCV – cannabivarichromene, CBD – cannabidiol, CBDV – cannabidivarin, CBGA – cannabigerolic acid, CBG – cannabigerol, CBGV – cannabigerovarin, GPP – geranyl diphosphate, 5-HT1A – 5-hydroxytryptamine receptor subtype 1A, MDR – multidrug-resistance, MEP – methyl-D-erythritol-4-phosphate, MRSA – methicillin-resistant *Staphylococcus aureus*, OLA – olivetolic acid, PJC – prolonged juvenile

chemotype, THC – delta-9-tetrahydrocannabinol, THCV – delta-9-tetrahydrocannabivarin, TRP – transient receptor potential, TRPA – transient receptor potential ankyrin, TRPM – transient receptor potential melastatin, TRPV – transient receptor potential vanilloid.

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