

## Biosynthetic Pathway and Medical Role of Cannabigerolic Acid

Yue Kang<sup>1</sup>, Jian Chi<sup>1</sup>, Yanjie Wang<sup>1</sup>, Xueyong Chi<sup>1</sup>, Quci Zhu<sup>1</sup>, Yuke Zhang<sup>1</sup>, Lingyan Dai<sup>2\*</sup>

<sup>1</sup>College of Life Science and Technology, Heilongjiang Bayi Agricultural University, Daqing 163319, China

<sup>2</sup>Professor, College of Life Science and Technology, Heilongjiang Bayi Agricultural University, Xinfeng Road 5#, Daqing City, Heilongjiang Province, 163319, China

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\*Corresponding author: Lingyan Dai

Professor, College of Life Science and Technology, Heilongjiang Bayi Agricultural University, Xinfeng Road 5#, Daqing City, Heilongjiang Province, 163319, China

### Abstract

### Review Article

Nowadays, the application of cannabinoids in various fields is gradually increasing, and more and more studies have been conducted on cannabigerolic acid, the basic compound produced by cannabis plants, which is produced by the reclamation of olivine acid and isopentenyl catalyzed by cannabis isopentenyl transferase. They are isoprenylated polyketone compounds derived from fatty acids and isoprenoid precursors. They are common receptors for all cannabinoid synthetases and have important effects on the production of cannabinoids. At the same time, CBGA also has certain medicinal value, which has certain efficacy in the treatment of diabetes, and glioblastoma, reducing neuroinflammation of neurodegenerative diseases and treating the side effects of chemotherapy, and will not produce psychotoxic side effects. This paper will describe the synthesis pathway and medical effects of cannabigerolic acid.

**Keywords:** *Cannabis sativa*, Cannabinoid, Cannabigerolic acid, Synthetic pathway, Medical role.

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## 1. INTRODUCTION

The application of plant components in medical treatment has a long history, and with the development of science and technology, people are increasingly recognizing the application value of natural compounds in plants in medicine 1. In recent years, more and more studies on the therapeutic effects of plant ingredients have been published in medical journals. At the same time, through the in-depth study of plants and their components, many plant components have been found to have therapeutic effects, so the application value of natural compounds contained in plants in medicine has been paid more and more attention 2. As a controversial plant - *Cannabis sativa*, the natural compounds in the plant have not only medicinal value but also paralytic and hallucinogenic effects. At present, 565 compounds have been identified from cannabis, including more than 300 cannabinoids, also known as cannabinoids, a group of terpenoid phenolic compounds found in cannabis plants, and naturally exist in the nervous and immune systems of animals 3. Among many cannabinoids, cannabigerolic acid (CBGA) is extremely important. CBGA exists in the trichome of cannabis flower, which has a protective effect on the growth of cannabis, triggers the targeted plant cell necrosis, and makes cannabis leaves get "pruned" to provide energy for the flower body.

Moreover, during the flowering of cannabis, CBGA can be converted into THCA, CBDA, and CBCA by its enzymes, and after decarboxylation of these three substances, the well-known three cannabinoids - THC, CBD, and CBC will be produced. Studies have found that CBGA has a good therapeutic effect in the treatment of glioblastoma, and its therapeutic effect is comparable to that of temozolomide, mitoxantrone, and fluoxetine 4. It also has a good effect on reducing tumor load and reducing neuroinflammation in neurodegenerative diseases 4. Many drugs, such as antidepressants, antipsychotics, antiepileptics, and blood pressure medications, contain cannabis **Error! Reference source not found.** Some studies have also found that CBGA has a good alleviating effect on the side effects of chemotherapy: it is significantly effective in reducing the tumor load of cancer patients and alleviating patients' nausea and vomiting; It can also relieve diarrhea problems caused by chemotherapy **Error! Reference source not found.** In addition, CBGA has also been found to be useful in the treatment of diabetes and some cardiovascular diseases.

## 2. Synthetic pathway of cannabigerolic acid

### 2.1 Synthesis of cannabigerolic acid

CBGA is a common receptor of all cannabinoid synthetase, and its content directly affects

the output of other cannabinoids, so the synthetic pathway of CBGA is particularly important **Error! Reference source not found.** CBGA is formed by isopentenyl condensation of geranyl diphosphate (GPP) and OLA catalyzed by prenyltransferase in *Cannabis sativa* **Error! Reference source not found.** The polyketide pathway and the plastidial 2-C-methyl-d-erythritol 4-phosphate (MEP) pathway are the main synthetic processes. Olivetolic acid (OLA) is produced through the polyketide pathway, while the geranyl diphosphate (GPP) is synthesized MEP pathway synthesises 7.

### 2.1.1 The polyketide pathway to synthesize oleic acid

Olivetolic acid (OLA) is a product of tetraketide synthase (TKS). Tetraketide synthase (TKS) is the first enzyme in the CBGA synthesis pathway. It catalyzes the condensation of caproyl-CoA with tri malonyl-CoA to form linear tetrone CoA intermediates. After this, olivetolic acid (OLA) was formed by olivetolic acid cyclase (OAC), which catalyzed the cyclization of the linear tetrone CoA intermediate 9.

### 2.1.2 The plastidial 2-C-methyl-d-erythritol 4-phosphate pathway to geranyl diphosphate

Geranyl diphosphate (GPP) is an isoprene compound that is a major precursor in the biosynthesis of cannabinoids and provides the monoterpene component in the biosynthesis of cannabinoids. Its molecular skeleton is formed by the condensation of two C5 terpenoid compounds, isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) 10.

The MEP pathway is an important pathway for the synthesis of terpenoids in plant plastids. The first step is to catalyze pyruvate and glyceraldehyde-3-phosphate to produce DXP (1-deoxyxylulose-5-phosphate) by DXS (deoxyxylulose-5-phosphate). DXP generates MEP under the action of DXR, MEP is continuously catalyzed by several enzymes, and finally, IPP and DMAPP are catalyzed by HDR. IPP and DMAPP are converted by IPP isomerase, which condensates to form GPP under the action of GPP synthetase **Error! Reference source not found.**

## 3. The medical value of ccannabinigerolic acid

### 3.1 Treatment of diabetes

If the PPAR does not function properly, people can develop conditions such as diabetes, high cholesterol, or triglycerides (dyslipidemia). In 2018, an Italian study showed that CBGA was able to activate PPAR receptors (peroxisome proliferator-activated receptors) and stimulate lipid metabolism, thereby reducing excessive lipid accumulation. At the same time, CBGA can stimulate the secretion of insulin and reduce blood sugar levels, thus reducing the development of diabetes. In addition, the study also found that CBGA can bind to ALR2 to control diabetes and its complications. Aldose reductase (ALR2) is a key enzyme in diabetes complications, and it is a

reductase produced by multiple cells. Since synthetic aldose reductase inhibitors (ARIs) are often associated with harmful side effects, the search for natural compound inhibitors has become a new and important topic 12.

CBGA has great research value in diabetes and cardiovascular diseases. However, no effective treatment has yet been developed. Therefore, efforts to develop new drugs should continue. In addition, the research on CBGA should be strengthened and its safety and efficacy should be emphasized.

### 3.2 Treatment of epilepsy

Epilepsy is a recurrent malfunction of the central nervous system caused by the excessive firing of neurons in the brain and is the second most common disease of the nervous system, affecting about 50 million people worldwide. Using a mouse model of Dravet syndrome (*Scn1a*<sup>+/-</sup> mouse model), Anderson and colleagues found that cannabinoids play a significant role in preventing hyperthermia-induced seizures **Error! Reference source not found.** The study focused on seven cannabinoids (cannabinol, cannabidiol, tetrahydrocannabinol, isocannabinoid, dihydrocannabinol, cannabidiol, and THC). In addition to cannabidiol, four other cannabinoids have been shown to have a significant effect on the anticonvulsant effect in mouse models, with cannabinol acid (CBGA) being considered the most potent cannabinoid in this model **Error! Reference source not found.**

It is important to note that the study did not directly compare the effectiveness of CBGA and CBD in preventing heat-induced seizures, but both are effective in reducing seizures. In this study, Anderson and colleagues showed that when CBGA is used as an adjunct treatment, it can enhance the anticonvulsant effects of clobazam. This finding makes it possible for cannabinoids such as CBGA to be combined with the current "gold standard" treatment for this type of epilepto **Error! Reference source not found.**

### 3.3 Anti-inflammatory and analgesic

Inflammation is a common response to tissue damage caused by mechanical injury or pathogen infection, with clinical manifestations of swelling, fever, redness, and pain 16, 17. Inflammation consists of two responses: acute inflammation, which occurs immediately and is non-specific, and chronic inflammation, which occurs later and is specific 18. Acute inflammatory responses begin with an injury to tissues and are characterized by the release of endogenous pro-inflammatory mediators (chemokines and cytokines), resulting in changes in vascular flow and permeability, and activation of locally resident cells such as mast cells, macrophages, and monocytes, followed by polymorphonuclear leukocytes 18. If not addressed, persistent reactions can lead to chronic

inflammation and subsequent tissue damage. The way to block its ongoing response is to release anti-inflammatory mediators in place of pro-inflammatory mediators to suppress inflammation and begin repair **Error! Reference source not found.** The release of proinflammatory mediators is regulated by calcium-dependent signaling mechanisms that activate a variety of transcription factor pathways, the most important of which is the Ca<sup>2+</sup> inflow mechanism, the store-operated calcium entry (SOCE), which is a key mechanism in the activation of T cells and most immune cells.

Malika Faouzi *et al.* examined the effects of several cannabinoids and cannabis extracts on SOCE as possible anti-inflammatory analgesic treatments. The results showed that the inhibition of several cannabinoids on SOCE was dose-dependent. Among these substances, CBGA had the best effect, IC<sub>50</sub> was submicromolar (IC<sub>50</sub>=530 nm) 20.

To examine what channels CBGA affects SOCE by inhibiting, they used whole-cell patchy clamp electrophysiological recordings to measure calcium release-activated calcium (CRAC) currents (I<sub>CRAC</sub>) in Jurkat NFAT cells. This experiment was performed by infusing the cytoplasm with 50 μm IP<sub>3</sub> to consume Ca<sup>2+</sup> stores via IP<sub>3</sub>R and trigger the CRAC current I<sub>CRAC</sub>. The results confirmed that CBGA regulates SOCE in T cells by inhibiting CRAC channels. A novel mechanism of action for CBGA and possibly other cannabinoids, and also reveals a novel and potent inhibitor of CRAC channels, a highly sought-after pharmacological target in drug development for multiple inflammatory diseases 20.

#### 4. CONCLUSION

CBGA has great potential in the treatment of these diseases. In recent years, people have paid more and more attention to the development of natural drugs, more and more research on CBGA, and the synthetic pathway of CBGA is clearer. However, cannabis cultivation is restricted in many countries, and only a few countries in the world have legalized cannabis cultivation, such as the United States, Canada, Australia, and New Zealand. In China, the only areas where industrial hemp can be grown legally are Heilongjiang and Yunnan. It is very difficult to obtain a large amount of CBGA by growing cannabis, at present, CBGA has been successfully synthesized *in vitro* by constructing engineering bacteria. However, more pharmacological experiments are needed before CBGA can be used in clinical treatment. Future research should also focus on increasing the yield of CBGA and clinical studies of drugs for the treatment of diseases.

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