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Mini-Review

Flavonoids in *Cannabis sativa*: Biosynthesis, Bioactivities, and Biotechnology

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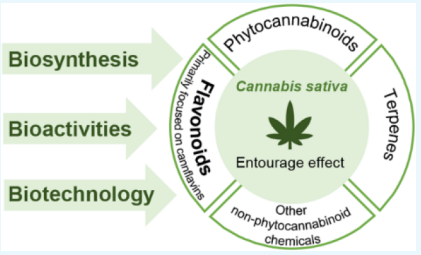
ABSTRACT: Although *Cannabis sativa* synthesizes a wide range of phytochemicals, much attention has been primarily given to two phytocannabinoids, Δ^9-tetrahydocannabinol (THC) and cannabidiol (CBD), due to their distinctive activities in humans. These bioactivities can be further enhanced through the interaction of THC and CBD with other phytocannabinoids or non-phytocannabinoid chemicals, such as terpenes and flavonoids, a phenomenon that is termed the entourage effect. Flavonoid metabolism in *C. sativa* and the entourage effect are currently understudied. This mini-review examines recent advances in the biosynthesis and bioactivities of cannflavins, which are prenylated (C5) and geranylated (C10) flavones that are relatively unique to *C. sativa*. We also discuss the rapidly developing omics tools that enable discoveries in flavonoid metabolism in *C. sativa* and manipulation of flavonoid production through biotechnology. These advances set the stage for interrogating the health benefits of *C. sativa* flavonoids, deciphering the contribution of flavonoids to the entourage effect, and developing drugs.



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1. INTRODUCTION

Cannabis sativa L. belongs to the *Cannabaceae* family that contains the genera *Cannabis* and *Humulus* (Hop), as well as eight genera that were previously classified as *Celtidaceae*.[1] In the formal botanical nomenclature of *C. sativa*, this single species of the *Cannabis* genus contains two subspecies, each with two varieties. These include *C. sativa* subsp. *sativa* var. *sativa*, *C. sativa* subsp. *sativa* var. *spontanea*, *C. sativa* subsp. *indica* var. *indica*, and *C. sativa* subsp. *indica* var. *kafiristanica*.[1] Aside from the botanical classification, it has been proposed that, instead of the commonly used designations of "cultivars" and "strains", *C. sativa* should be categorized as chemovars according to the chemical profiles of phytocannabinoids and terpenes in flowers.[2]

Among the chemicals produced in *C. sativa*, two phytocannabinoids, the psychoactive compound Δ^9-tetrahydocannabinol (THC) and the medicinally important, but nonpsychoactive, compound cannabidiol (CBD), have been intensively studied for their structures, biosynthesis, and biological activities. Additional phytocannabinoids, and other classes of plant chemicals, such as terpenes, flavonoids, and alkaloids, have also been identified in *C. sativa*.[3] These other plant chemicals exert synergistic effects to enhance the bioactivities of phytocannabinoids, known as "the entourage effect".[4] However, the underlying mechanisms of the entourage effect are not well understood. As such, studies on non-phytocannabinoid compounds, such as terpenes and flavonoids, are valuable for developing therapeutics in *C. sativa*.

More than 20 flavonoids have been identified in *C. sativa*, most of which are flavone (apigenin and luteolin) and flavonol (kaempferol and quercetin) aglycones and glycosides.[5,6] Interestingly, three prenylated/geranylated flavones, cannflavin A, B, and C, were isolated in *C. sativa* (Figure 1A). It is worth noting that, although cannflavins are often referred to as flavonoids unique to *C. sativa*, cannflavin A has also been identified in *Mimulus bigelovii*, a plant in the *Phrymaceae* family.[7] Since biosynthesis of the core flavonoid skeleton in plants and bioactivities of the common flavones and flavonols have been widely studied and reported, this mini-review will focus on the biosynthesis and bioactivities of the relatively unique cannflavins as well as the applications of *C. sativa* flavonoids.

2. BIOSYNTHESIS OF CANNFLAVINS IN *C. SATIVA*

The phenylpropanoid and flavonoid biosynthetic pathways build the core skeletons of flavonoids in *C. sativa* (Figure 1B).[3,8] Genes encoding two enzymes in the phenylpropanoid biosynthetic pathway, phenylalanine ammonia-lyase (PAL) and *p*-coumaroyl: CoA ligase (4CL), were isolated in *C. sativa* var. Futura by searching expressed sequence tags (ESTs) using homologous *PAL* and *4CL* sequences from other plants.[9] Conversion of *p*-coumaroyl CoA to luteolin (a flavone) encompasses condensation with three molecules of malonyl CoA to form naringenin chalcone by chalcone synthase (CHS),

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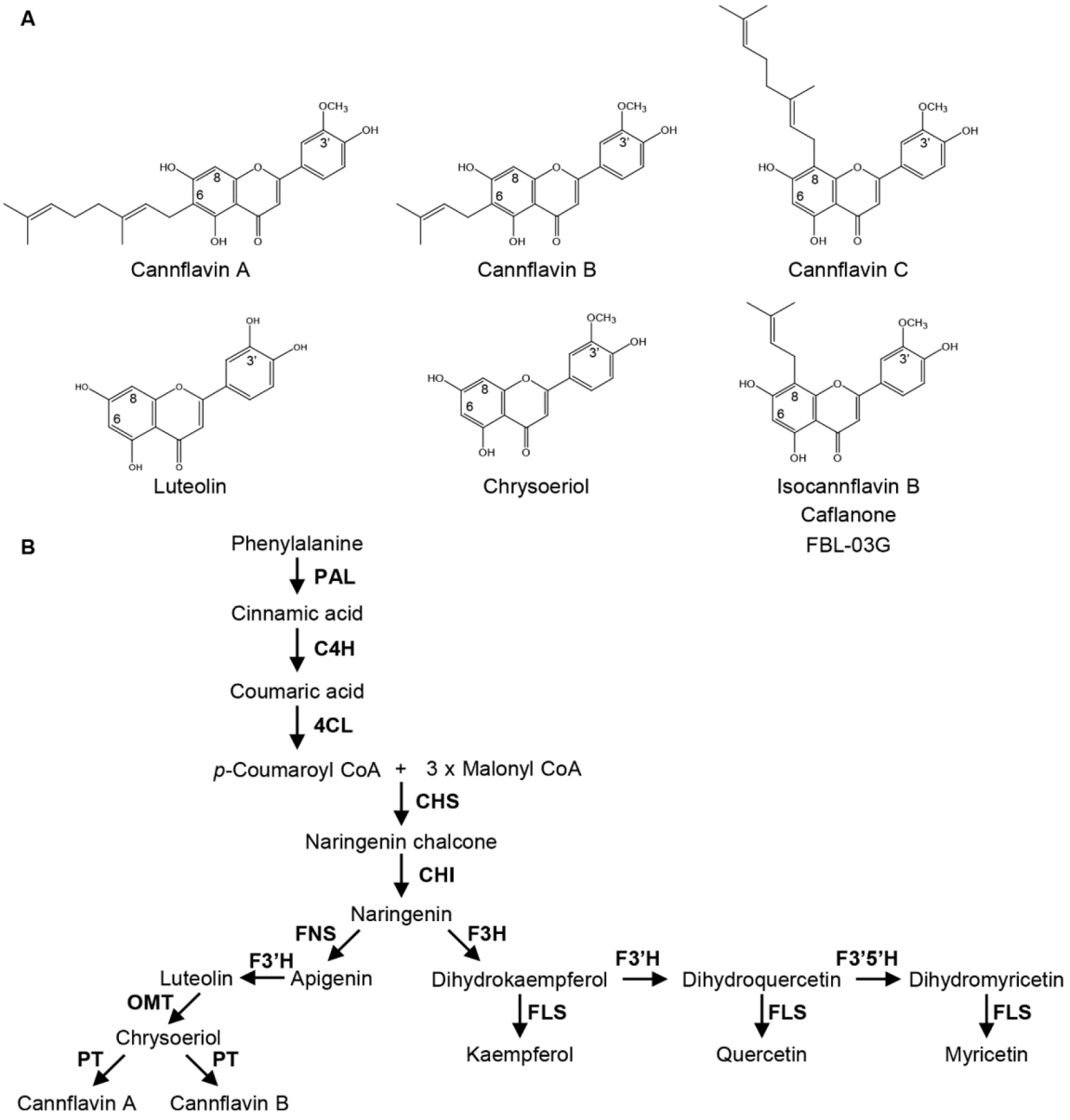

Figure 1. Flavonoids in *Cannabis sativa*. A. Chemical structures of cannflavins and selected flavones. Cannflavin A, B, and C are present in *C. sativa* tissues and isocannflavin B is chemically synthesized. B. Simplified scheme of reactions leading to flavone and flavonol biosynthesis in *C. sativa*. PAL, phenylalanine ammonia-lyase; C4H, cinnamate 4-hydroxylase; 4CL, *p*-coumaroyl: CoA ligase; CHS, chalcone synthase; CHI, chalcone isomerase; F3H, flavanone 3-hydroxylase; FNS, flavone synthase; F3′H, flavonoid 3′-hydroxylase; F3′5′H, flavonoid 3′5′-hydroxylase; FLS, flavonol synthase; OMT, *O*-methyltransferase; PT, prenyltransferase.

ring closure of naringenin chalcone to generate naringenin by chalcone isomerase (CHI), formation of apigenin from naringenin by flavone synthase (FNS), and 3-hydroxylation of apigenin to derive luteolin by flavonoid 3′-hydroxylase (F3′H) (Figure 1B). Based on their chemical structures, cannflavin A and B could be derived from luteolin through transferring a methyl group to the 3′-*O* position by a methyltransferase activity as well as a geranyl (C10) group (for cannflavin A) or a prenyl/dimethylallyl (C5) group (for cannflavin B) to the C_6-position by a prenyltransferase activity (Figure 1B). Candidate methyltransferases and prenyltransferases responsible for these reactions were identified from a draft *C. sativa* genome assembly based on sequence homology to previously characterized enzymes and phylogenetic analysis.[8] Upon functional characterization using purified recombinant proteins, it was shown that a regiospecific *O*-methyltransferase (*Cs*OMT21) methylates the 3′-*O* position of luteolin and forms chrysoeriol, and a prenyltransferase (*Cs*PT3) adds a geranyl or a prenyl group to chrysoeriol and produces cannflavin A and B.[8] However, the function of *Cs*OMT21 and *Cs*PT3 in cannflavin biosynthesis has not been demonstrated in a plant system.

To date, flavonoid identification in *C. sativa* has focused on plants that are grown under nonstressed conditions. While flavonoids are present in most tissues studied in *C. sativa*, including seedlings, leaves, flowers, and fruits, they are undetectable in roots and seeds.[9−11] In addition to the tissue-specific distribution, flavonoid profiles were also shown to vary in bracts during plant development.[11] As many flavonoids possess protective functions for plants, their production is responsive to environmental factors, which is also observed in *C. sativa*. For example, cannflavin A accumulation is determined not only by the genetic background, but as a response to

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temperature, solar radiation, rainfall, and humidity in the environment.[12] Moreover, higher elevation positively impacts the content of cannflavin A, B, and C in cloned (i.e., genetically identical) *C. sativa* plants grown at different altitudes.[13] With these observations taken into consideration, it is tempting to postulate that, aside from the flavonoids that have already been isolated in *C. sativa* tissues, some yet unidentified flavonoids may only be produced under specific environmental conditions, such as biotic and abiotic stresses. It is also possible that certain flavonoids only accumulate in significant quantities in specific *C. sativa* chemovars, such as cannflavin C that was isolated and identified from a high THC chemovar.[6] As such, unraveling the identity of additional flavonoids, particularly those unique to *C. sativa*, will facilitate a comprehensive understanding of the biosynthesis and functions of flavonoids in this important plant.

3. BIOACTIVITIES OF CANNFLAVINS

Besides the antioxidative effects that cannflavins share with many other flavonoids, a relatively well-studied bioactivity for cannflavins is their anti-inflammatory properties. An intriguing observation was first reported in 1981, showing that compounds present in a phytocannabinoid-free extract of *C. sativa* leaves could be involved in the production or release of prostaglandin E2 (PGE2) in mice.[14] Further work showed that cannflavins in ethanolic extracts of *C. sativa* leaves inhibited 12-*O*-tetradecanoylphorbol-13-acetate (TPA; a proinflammatory agent)-induced PGE2 production in cultured human rheumatoid synovial cells.[15] Chemical structures of cannflavin A and B were subsequently solved using nuclear magnetic resonance (NMR) and demonstrated to be prenylated/geranylated flavones.[16] More recently, it was shown in *in vitro* enzyme assays that cannflavin A and B exert anti-inflammatory activities by inhibiting the microsomal PGE2 synthase-1 and the 5-lipoxygenase activities, leading to reduced PGE2 and leukotriene production, respectively.[17] Cannflavin A and B show promise as an anti-inflammatory therapeutic agent because they were about 30 times more effective than aspirin in inhibiting PGE2 release when assayed in human rheumatoid cells.[16] An additional advantage is that cannflavin A only weakly inhibits cyclooxygenases (COXs) COX-1 and COX-2, and therefore can circumvent the adverse side effects exhibited by COX inhibitors (anti-inflammatory drugs), such as gastrointestinal erosion.[17]

The neuroprotective role of cannflavin A was explored in neuronal PC12 cells.[18] At 10 μM or lower concentrations, cannflavin A enhanced the viability of neuronal PC12 cells against amyloid β (Aβ)-induced cytotoxicity by reducing $A\beta_{1-42}$ aggregation and fibril formation.[18] Anticancer activities were reported for a synthetic 8-prenylated isomer of cannflavin B, isocannflavin B (FBL-03G; caflanone) (Figure 1A). Isocannflavin B suppressed the proliferation of estrogen-dependent T47-D human breast cancer cells through a G0/G1 cell cycle arrest.[19] It also increased apoptosis in two pancreatic cancer cell lines Panc-02 and Ptf1/p48-Cre (KPC).[20] Treatment with isocannflavin B caused a delay in both local and metastatic tumor progression and increased survival in mice with pancreatic cancer.[20] These reports suggest the potential of isocannflavin B as an anticancer drug, though translational studies should be undertaken to determine its activities in humans.

A combination of *in vitro* bioassays and *in silico* molecular docking analysis established antiparasitic activities of cannflavins. Cannflavin A (IC_{50} = 4.5 μg/mL) and cannflavin B (IC_{50} = 5 μg/mL) exhibited moderate anti-leishmanial activities against a culture of *Leishmania donovani* promastigotes.[6] The bioassay results were corroborated by strong docking energy (−144.0 kJ/mol) of cannflavin A to one of the protein targets in *L. donovani*, *Leishmania pteridine* reductase 1.[21] Besides *L. donovani*, cannflavin A also showed moderate inhibitory activity against the parasite *Trypanosoma brucei brucei* with an IC_{50} value of 1.9 μg/mL.[7] The mechanistic basis for the antiparasitic effects of cannflavins remains to be elucidated.

To date, only molecular docking/computational analysis has been employed to evaluate the antiviral activities of cannflavins. Cannflavin A showed a relatively high binding affinity (−9.7 kcal/mol) and high reactivity (energy gap between highest occupied molecular orbital and lowest unoccupied molecular orbital = 0.114 kcal/mol) against HIV-1 protease, an enzyme that renders human immunodeficiency viruses (HIV) infectious, as determined by the density functional theory (DFT) analysis.[22] A molecular docking study of multiple protein targets of Dengue virus revealed cannflavin A as a strong docking ligand (docking energy = −125.7 kJ/mol) for the Dengue virus envelope protein.[23] Cannflavin A is also among the phytochemicals that are predicted to show efficient docking to the helicase (RNA site) (−131.7 kJ/mol), helicase (ATP site) (−134.6 kJ/mol), methyltransferase (−126.9 kJ/mol), and RNA-dependent RNA polymerase (−120.3 kJ/mol) of Zika virus.[24] Although the computational analysis suggests cannflavins as potential antiviral drug leads, further empirical evidence is still needed to precisely determine their bioactivities.

To investigate the microbial metabolism of cannflavins, cannflavin A and B were fermented with *Mucor ramannianus* (ATCC 9628) and *Beauveria bassiana* (ATCC 13144), which resulted in 6″*S*,7″-dihydroxycannflavin A, 6″*S*,7″-dihydroxycannflavin A 7-sulfate, and 6″*S*,7″-dihydroxycannflavin A 4′-*O*-α-L-rhamnopyranoside from cannflavin A, and cannflavin B 7-*O*-β-D-4′″-*O*-methylglucopyranoside and cannflavin B 7-sulfate from cannflavin B.[25] However, these microbial transformed metabolites do not possess the antimicrobial and antiparasitic activities reported for cannflavin A and B.[25]

Whether and how the geranylation and prenylation at C6 of cannflavin A and B and at C8 of cannflavin C and isocannflavin B (differentially) contribute to their anti-inflammatory, neuroprotective, anticancer, antiparasitic, and antiviral activities should be further investigated. Insights into the structure−function relationship of these prenylated/geranylated flavones will inform the effective development of therapeutics. Furthermore, microbial degradation products of cannflavins in humans need to be elucidated to better understand drug metabolism and biological functions of cannflavins in humans.

4. BIOTECHNOLOGY OF *C. SATIVA* FLAVONOIDS

Molecular and genetic studies in *C. sativa* have lagged behind many other plant species due to its historically prohibited status. However, the advancements in omics methods and the availability of genome and transcriptome sequences in the public domain have largely facilitated molecular studies in *C. sativa*. A draft genome of cultivated *C. sativa* was released in 2011, although it was not assembled to the chromosomal level.[26] Recently, a high-quality (scaffold size = 83 Mb; N_{50} = 513.57 kb) reference genome of a wild *C. sativa* variety was obtained using PacBio, a single-molecule real-time sequencing technology, and Hi-C, a next-generation sequencing technology for chromosome conformation capture.[27] With the assistance of transcriptome sequencing, 38,828 protein-coding genes were delineated, over 98% of which were functionally annotated.[27] In the past few

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years, there have also been increasing efforts in sequencing the transcriptomes of multiple chemovars and wild *C. sativa*. As of January 2021, 59 *C. sativa*-related bioprojects (sets of experimental data) have been registered in the National Center for Biotechnology Information (NCBI) Sequence Read Archive (SRA) database, a repository of high-throughput sequencing data. Of these bioprojects, 37 contain genome or transcriptome sequences of plant materials. These bioprojects aim to discover genes responsible for the biosynthesis of *C. sativa* phytochemicals, to elucidate the evolution and genetic diversity of *C. sativa* accessions, or to examine changes in transcriptomes when *C. sativa* plants are exposed to abiotic stresses. These sequencing data collectively are invaluable for gene discovery, biological application, and genetic improvement of *C. sativa*.

Indeed, the utility of *C. sativa* genome sequences has already been demonstrated in cloning genes encoding the prenyltransferase and methyltransferase enzymes for cannflavin biosynthesis.[8] On the other hand, transcriptome data that are publicly available or generated in individual research groups will be useful for elucidating the flavonoid biosynthetic and regulatory genes using gene coexpression analysis. In addition to transcriptomic analysis, integrated analysis of transcriptome, metabolome, and proteome data can be utilized to reveal genes responsible for the spatial and temporal distribution of flavonoids in *C. sativa* regulated by plant development and/or the environment. Because it is an integral part of the complex metabolic network, understanding the control of flavonoid production will have implications in the accumulation of phytocannabinoids and other non-phytocannabinoid chemicals in *C. sativa*. Moreover, understanding the control of stress-induced flavonoids will facilitate the development of environmentally resilient *C. sativa* plants.

The bioactivities of cannflavins and other flavonoids make them a desirable bioproduct that will require the biosynthesis of a large amount of flavonoids for downstream applications. However, flavonoids are present at low levels in *C. sativa* tissues grown under normal conditions. Overexpressing the biosynthetic and regulatory genes of flavonoids can potentially increase their accumulation in *C. sativa*, though it is currently challenging to transform and propagate *C. sativa* plants. To this end, cell suspension and hairy root tissue cultures and heterologous expression systems have been developed for *C. sativa*, which can be utilized for the production of flavonoids and functional genomics of flavonoid metabolism.[28]

5. FUTURE PERSPECTIVES

Non-phytocannabinoid constituents of *C. sativa* are a rapidly growing area of research that holds great promise. Future studies should further investigate how flavonoid metabolism in *C. sativa* responds to various biotic and abiotic stresses, facilitating the discovery of regulatory factors, e.g., transcription factors and miRNAs, to further enhance flavonoid accumulation. The isolation and characterization of cannflavin biosynthetic genes pave the way for reconstructing the entire pathway in plant cultures or heterologous systems, e.g. bacteria and yeast, for manufacturing cannflavins. Additional considerations should be given to increasing the overall carbon flux to the flavonoid pathway in *C. sativa* by overexpressing upstream biosynthetic genes in a plant system or feeding of substrates in heterologous expression systems. Overall, scaling up cannflavin production is crucial for studying drug metabolism in preclinical drug development and clinical studies to elucidate the clinically relevant bioactivities of *C. sativa* flavonoids and interrogate the entourage effect in *C. sativa*.

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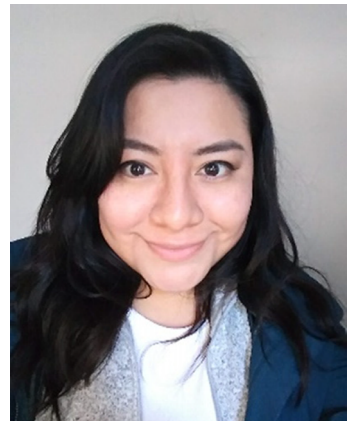
Notes

The authors declare no competing financial interest.

Biographies



Johanna L. Bautista is a Ph.D. student in the Plant Biology Program at the University of California, Davis, under the supervision of Prof. Dr. Li Tian. Her research interest is mainly the study of the metabolic regulation of phenolic compounds from medicinal plants. She received her bachelor's degree from California State University, Los Angeles.

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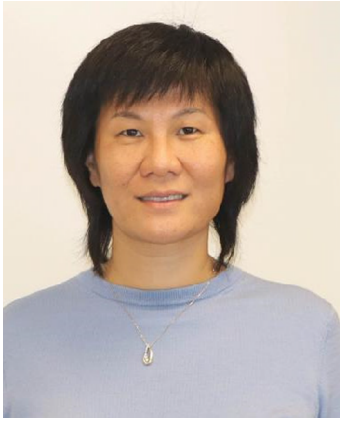
focuses on carotenoid metabolism and provitamin A biofortification in wheat.



Li Tian received her Ph.D. in Plant Biology at Michigan State University and obtained postdoctoral training in natural product biochemistry at the Samuel Roberts Noble Foundation. She joined the faculty at the University of California, Davis in 2008. She is currently an Associate Professor in the Department of Plant Sciences and a member of the Food for Health Institute. Her research group is interested in understanding how phytonutrients (e.g., phenolics) are made in plants using molecular, genetic, and biochemical tools. They also examine how accumulation of phytonutrients in plants is controlled by different factors under various environmental conditions. Their long-term goal is to apply the knowledge obtained from these investigations to improve the nutritional value and agronomic performance of crop plants.

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