MICROORGANISMS AND METHODS FOR PRODUCING CANNABINOIDS AND CANNABINOID DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation application of International Application No. PCT/US2018/029668, filed April 27, 2018, which claims the benefit of U.S. Provisional Application No. 62/491,114, filed April 27, 2017, and U.S. Provisional Application No. 62/569,532, filed October 7, 2017, the contents of which are incorporated herein by reference in their entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

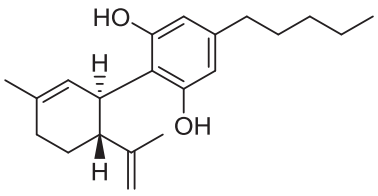
[0002] This invention was made with government support under Grant Numbers 1330914 and 1442724 awarded by the National Science Foundation. The government has certain rights in the invention.

REFERENCE TO A SEQUENCE LISTING

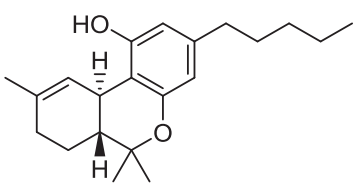
[0003] The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is DEMT_001_00WOSeqList_ST25_txt. The text file is about 673 KB, was created on April 25, 2018, and is being submitted electronically via EFS-Web.

INTRODUCTION

[0004] Plants from the genus *Cannabis* have been used by humans for their medicinal properties for thousands of years. In modern times, the bioactive effects of *Cannabis* are attributed to a class of compounds termed "cannabinoids," of which there are hundreds of structural analogs including tetrahydrocannabinol (THC) and cannabidiol (CBD). These molecules and preparations of *Cannabis* material have recently found application as therapeutics for chronic pain, multiple sclerosis, cancer-associated nausea and vomiting, weight loss, appetite loss, spasticity, and other conditions.



Cannabidiol / CBD



Tetrahydrocannabinol / THC / Dronabinol / Marinol

comprising one or more heterologous nucleic acids encoding a GOT polypeptide comprising an amino acid sequence having at least 65% sequence identity to SEQ ID NO:100.

[0011] In certain embodiments of any of the foregoing or following, the genetically modified host cell further comprises one or more heterologous nucleic acids encoding a tetraketide synthase (TKS) polypeptide and one or more heterologous nucleic acids encoding an olivetolic acid cyclase (OAC) polypeptide, or one or more heterologous nucleic acids encoding a fusion TKS and OAC polypeptide. In some embodiments, the TKS polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:11 or SEQ ID NO:76. In some embodiments, the OAC polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:10 or SEQ ID NO:78.

[0012] In certain embodiments of any of the foregoing or following, the genetically modified host cell further comprises one or more of the following: a) one or more heterologous nucleic acids encoding a polypeptide that generates an acyl-CoA compound or an acyl-CoA compound derivative; b) one or more heterologous nucleic acids encoding a polypeptide that generates GPP; or c) one or more heterologous nucleic acids encoding a polypeptide that generates malonyl-CoA. In some embodiments, the genetically modified host cell further comprises one or more heterologous nucleic acids encoding a polypeptide that generates an acyl-CoA compound or an acyl-CoA compound derivative, wherein the polypeptide that generates an acyl-CoA compound or an acyl-CoA compound derivative is an acyl-activating enzyme (AAE) polypeptide. In some embodiments, the AAE polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:90. In some embodiments, the AAE polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:92 or SEQ ID NO:149. In some embodiments, the genetically modified host cell further comprises one or more heterologous nucleic acids encoding a polypeptide that generates an acyl-CoA compound or an acyl-CoA compound derivative, wherein the polypeptide that generates an acyl-CoA compound or an acyl-CoA compound derivative is a fatty acyl-CoA ligase polypeptide. In some embodiments, the fatty acyl-CoA ligase polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:145 or SEQ ID NO:147. In some embodiments, the genetically modified host cell further comprises one or more heterologous nucleic acids encoding a polypeptide that generates an acyl-CoA compound or an acyl-CoA compound derivative, wherein the polypeptide that generates an acyl-CoA compound or an acyl-CoA compound derivative is a fatty acyl-CoA synthetase (FAA) polypeptide. In some embodiments, the FAA polypeptide comprises an amino acid sequence having at least 50%

polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:23, SEQ ID NO:24, or SEQ ID NO:115. In some embodiments, the genetically modified host cell further comprises one or more heterologous nucleic acids encoding an MK polypeptide. In some embodiments, the MK polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:64. In some embodiments, the genetically modified host cell further comprises one or more heterologous nucleic acids encoding a PMK polypeptide. In some embodiments, the PMK polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:62 or SEQ ID NO:205. In some embodiments, the genetically modified host cell further comprises one or more heterologous nucleic acids encoding a MVD polypeptide. In some embodiments, the MVD polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:66.

[0014] In certain embodiments of any of the foregoing or following, the genetically modified host cell further comprises one or more heterologous nucleic acids encoding a polypeptide that condenses two molecules of acetyl-CoA to generate acetoacetyl-CoA. In some embodiments, the polypeptide that condenses two molecules of acetyl-CoA to generate acetoacetyl-CoA is an acetoacetyl-CoA thiolase polypeptide. In some embodiments, the acetoacetyl-CoA thiolase polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:25.

[0015] In certain embodiments of any of the foregoing or following, the genetically modified host cell further comprises one or more heterologous nucleic acids encoding a pyruvate decarboxylase (PDC) polypeptide. In some embodiments, the PDC polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:117.

[0016] In certain embodiments of any of the foregoing or following, the genetically modified host cell is a eukaryotic cell. In some embodiments, the eukaryotic cell is a yeast cell. In some embodiments, the yeast cell is *Saccharomyces cerevisiae*. In some embodiments, the *Saccharomyces cerevisiae* is a protease-deficient strain of *Saccharomyces cerevisiae*. In some embodiments, the genetically modified host cell is a plant cell.

[0017] In certain embodiments of any of the foregoing or following, the genetically modified host cell is a prokaryotic cell.

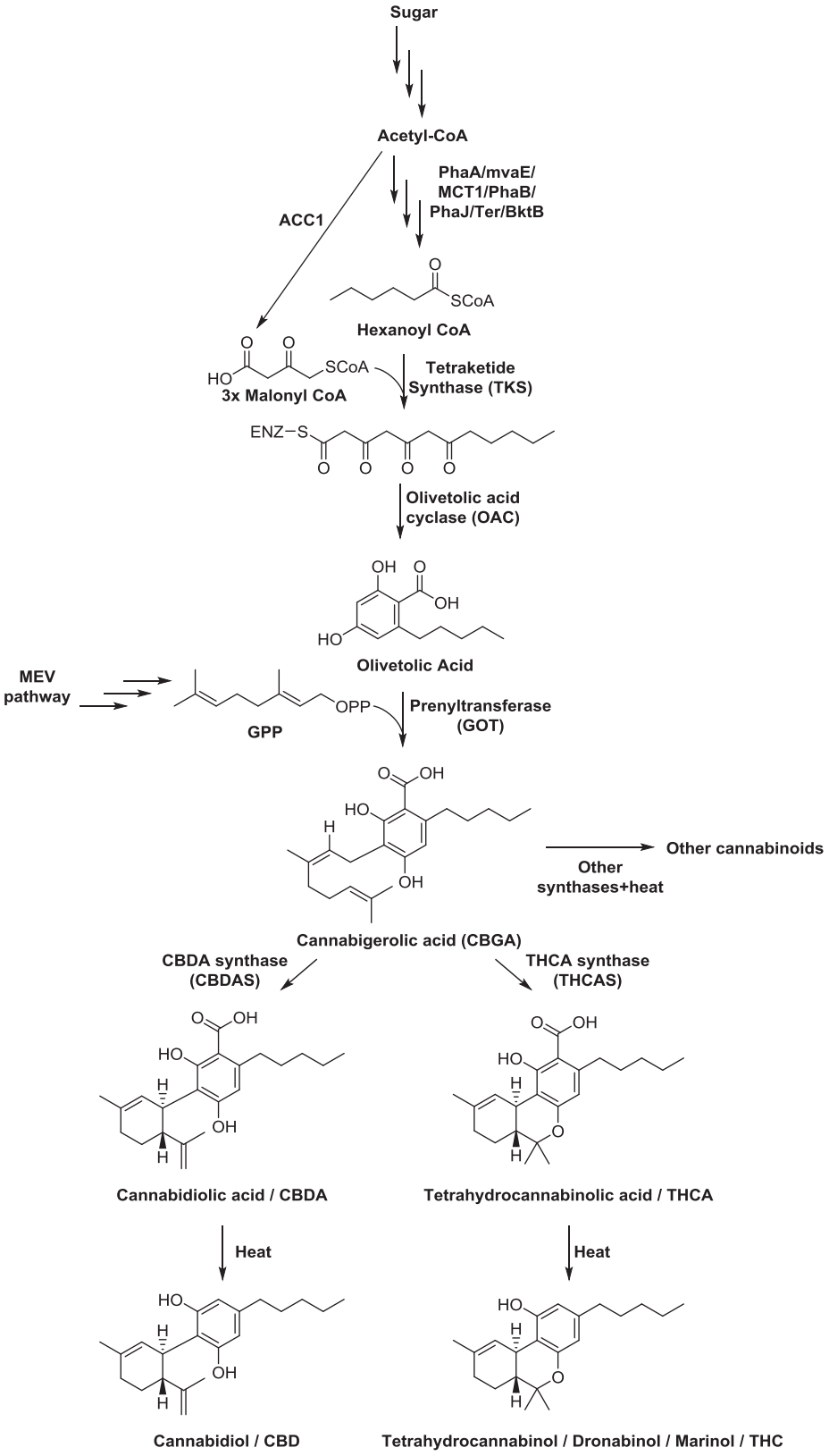
[0018] In certain embodiments of any of the foregoing or following, at least one of the one or more heterologous nucleic acids is integrated into the chromosome of the genetically modified host cell.

CBD and less common cannabinoid species found at low levels in *Cannabis*; or cannabinoid derivatives or cannabinoid precursor derivatives. Bioproduction also enables synthesis of cannabinoids, cannabinoid derivatives, cannabinoid precursors, or cannabinoid precursor derivatives with defined stereochemistries, which is challenging to do using chemical synthesis.

[00136] The nucleic acids disclosed herein may include those encoding a polypeptide having at least one activity of a polypeptide present in the cannabinoid biosynthetic pathway, such as a GOT polypeptide (e.g., a CsPT4 polypeptide), responsible for the biosynthesis of the cannabinoid CBGA; a tetraketide synthase (TKS) polypeptide; an olivetolic acid cyclase (OAC) polypeptide; and a CBDA or THCA synthase polypeptide (see FIGS. 1 and 11). Nucleic acids disclosed herein may also include those encoding a polypeptide having at least one activity of a polypeptide involved in the synthesis of cannabinoid precursors. These polypeptides include, but are not limited to, polypeptides having at least one activity of a polypeptide present in the mevalonate pathway; polypeptides that generate acyl-CoA compounds or acyl-CoA compound derivatives (e.g., an acyl-activating enzyme polypeptide, a fatty acyl-CoA synthetase polypeptide, or a fatty acyl-CoA ligase polypeptide); polypeptides that generate GPP; polypeptides that generate malonyl-CoA; polypeptides that condense two molecules of acetyl-CoA to generate acetoacetyl-CoA, or pyruvate decarboxylase polypeptides (see FIGS. 1 and 11).

[00137] The disclosure also provides for generation of cannabinoid precursor derivatives or cannabinoid derivatives, as well as cannabinoids or precursors thereof, with polypeptides that generate acyl-CoA compounds or acyl-CoA compound derivatives. In certain such embodiments, genetically modified host cells disclosed herein are modified with one or more heterologous nucleic acids encoding a polypeptide that generates acyl-CoA compounds or acyl-CoA compound derivatives. These polypeptides may permit production of hexanoyl-CoA, acyl-CoA compounds, derivatives of hexanoyl-CoA, or derivatives of acyl-CoA compounds. In some embodiments, hexanoic acid or carboxylic acids other than hexanoic acid are fed to genetically modified host cells expressing a polypeptide that generates acyl-CoA compounds or acyl-CoA compound derivatives (e.g., are present in the culture medium in which the cells are grown) to generate hexanoyl-CoA, acyl-CoA compounds, derivatives of hexanoyl-CoA, or derivatives of acyl-CoA compounds. These compounds are then converted to cannabinoid derivatives or cannabinoid precursor derivatives, as well as cannabinoids or precursors thereof, via one or more polypeptides

1 and 11). Hexanoyl CoA derivatives, acyl-CoA compounds, or acyl-CoA compound derivatives may also be formed via such pathways and polypeptides.



Biosynthetic pathways to cannabinoids

[00148] GPP and hexanoyl-CoA may also be generated through pathways comprising polypeptides that condense two molecules of acetyl-CoA to generate acetoacetyl-CoA and pyruvate decarboxylase polypeptides that generate acetyl-CoA from pyruvate (see FIGS. 1 and 11). Hexanoyl CoA derivatives, acyl-CoA compounds, or acyl-CoA compound derivatives may also be formed via such pathways.

General Information

[00149] The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature: "*Molecular Cloning: A Laboratory Manual*," second edition (Sambrook et al., 1989); "*Oligonucleotide Synthesis*" (M. J. Gait, ed., 1984); "*Animal Cell Culture*" (R. I. Freshney, ed., 1987); "*Methods in Enzymology*" (Academic Press, Inc.); "*Current Protocols in Molecular Biology*" (F. M. Ausubel et al., eds., 1987, and periodic updates); "*PCR: The Polymerase Chain Reaction*," (Mullis et al., eds., 1994). Singleton et al., *Dictionary of Microbiology and Molecular Biology* 2nd ed., J. Wiley & Sons (New York, N.Y. 1994), and March, *Advanced Organic Chemistry Reactions, Mechanisms and Structure* 4th ed., John Wiley & Sons (New York, N.Y. 1992), provide one skilled in the art with a general guide to many of the terms used in the present application.

[00150] "Cannabinoid" or "cannabinoid compound" as used herein may refer to a member of a class of unique meroterpenoids found until now only in *Cannabis sativa*. Cannabinoids may include, but are not limited to, cannabichromene (CBC) type (e.g. cannabichromenic acid), cannabigerol (CBG) type (e.g. cannabigerolic acid), cannabidiol (CBD) type (e.g. cannabidiolic acid), Δ^9-trans-tetrahydrocannabinol (Δ^9 -THC) type (e.g. Δ^9-tetrahydrocannabinolic acid), Δ^8-trans-tetrahydrocannabinol (Δ^8 -THC) type, cannabicyclol (CBL) type, cannabielsoin (CBE) type, cannabinol (CBN) type, cannabinodiol (CBND) type, cannabitriol (CBT) type, cannabigerolic acid (CBGA), cannabigerolic acid monomethylether (CBGAM), cannabigerol (CBG), cannabigerol monomethylether (CBGM), cannabigerovarinic acid (CBGVA), cannabigerovarin (CBGV), cannabichromenic acid (CBCA), cannabichromene (CBC), cannabichromevarinic acid (CBCVA), cannabichromevarin (CBCV), cannabidiolic acid (CBDA), cannabidiol (CBD), cannabidiol monomethylether (CBDM), cannabidiol-C_4 (CBD-C_4), cannabidivarinic acid (CBDVA), cannabidivarin (CBDV), cannabidiorcol (CBD-C_1), Δ^9 –tetrahydrocannabinolic acid A (THCA-A), Δ^9 –tetrahydrocannabinolic acid B (THCA-B), Δ^9 –tetrahydrocannabinol (THC),

derivative. A genetically modified host cell of the present disclosure may be genetically modified with one or more heterologous nucleic acids disclosed herein encoding one or more polypeptides disclosed herein. Culturing of the genetically modified host cell in a suitable medium provides for synthesis of the cannabinoid, the cannabinoid derivative, the cannabinoid precursor, or the cannabinoid precursor derivative in a recoverable amount. In some embodiments, the genetically modified host cell of the disclosure produces a cannabinoid or a cannabinoid derivative.

[00220] The disclosure also provides nucleic acids, which can be introduced into microorganisms (e.g., genetically modified host cells), resulting in expression or overexpression of the one or more polypeptides, which can then be utilized *in vitro* (e.g., cell-free) or *in vivo* for the production of cannabinoids, cannabinoid derivatives, cannabinoid precursors, or cannabinoid precursor derivatives. In certain such embodiments, cannabinoids or cannabinoid derivatives are produced.

[00221] One or more polypeptides which can be utilized for the production of a cannabinoid, a cannabinoid derivative, a cannabinoid precursor, or a cannabinoid precursor derivative are disclosed herein, and may include, but are not limited to: one or more polypeptides having at least one activity of a polypeptide present in the cannabinoid biosynthetic pathway, such as, a GOT polypeptide, a CBDA or THCA synthase polypeptide, a TKS polypeptide, and an OAC polypeptide; one or more polypeptides having at least one activity of a polypeptide present in the mevalonate (MEV) pathway; a polypeptide that generates acyl-CoA compounds or acyl-CoA compound derivatives (e.g., an acyl-activating enzyme polypeptide, a fatty acyl-CoA synthetase polypeptide, or a fatty acyl-CoA ligase polypeptide); a polypeptide that generates GPP; a polypeptide that generates malonyl-CoA; a polypeptide that condenses two molecules of acetyl-CoA to generate acetoacetyl-CoA, and a pyruvate decarboxylase polypeptide. Additionally, polypeptides which can be utilized for the production of a cannabinoid, a cannabinoid derivative, a cannabinoid precursor, or a cannabinoid precursor derivative may be one or more polypeptides having at least one activity of a polypeptide present in the DXP pathway, instead of those of the MEV pathway.

[00222] Polypeptides which can be utilized for the production of a cannabinoid, a cannabinoid derivative, a cannabinoid precursor, or a cannabinoid precursor derivative may also include a hexanoyl-CoA synthase (HCS) polypeptide or one or more polypeptides that are part of a biosynthetic pathway that produces hexanoyl-CoA, including, but not limited to: a MCT1 polypeptide, a PaaH1 polypeptide, a Crt polypeptide, a Ter polypeptide, and a BktB

95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, at least 99.6%, at least 99.7%, at least 99.8%, at least 99.9%, or 100% sequence identity to SEQ ID NO:69.

Polypeptides that Generate Acetyl-CoA from Pyruvate, Nucleic Acids Comprising Said Polypeptides, and Genetically Modified Host Cells Expressing Said Polypeptides

[00442] In some embodiments, a genetically modified host cell of the present disclosure is genetically modified with one or more heterologous nucleic acids encoding a polypeptide that generates acetyl-CoA from pyruvate. Polypeptides that generate acetyl-CoA from pyruvate may include a pyruvate decarboxylase (PDC) polypeptide. In some embodiments, a genetically modified host cell of the present disclosure is genetically modified with one or more heterologous nucleic acids encoding a PDC polypeptide.

[00443] Exemplary PDC polypeptides disclosed herein may include a full-length PDC polypeptide, a fragment of a PDC polypeptide, a variant of a PDC polypeptide, a truncated PDC polypeptide, or a fusion polypeptide that has at least one activity of a PDC polypeptide.

[00444] In some embodiments, the PDC polypeptide encoded by the one or more heterologous nucleic acids comprises the amino acid sequence set forth in SEQ ID NO:117. In some embodiments, the PDC polypeptide encoded by the one or more heterologous nucleic acids comprises the amino acid sequence set forth in SEQ ID NO:117, or a conservatively substituted amino acid sequence thereof. In some embodiments, the PDC polypeptide encoded by the one or more heterologous nucleic acids comprises an amino acid sequence having at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, or at least 75% amino acid sequence identity to SEQ ID NO:117. In some embodiments, the PDC polypeptide encoded by the one or more heterologous nucleic acids comprises an amino acid sequence having at least 80%, at least 81%, at least 82%, at least 83%, or at least 84% amino acid sequence identity to SEQ ID NO:117. In some embodiments, the PDC polypeptide encoded by the one or more heterologous nucleic acids comprises an amino acid sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, at least 99.6%, at least 99.7%, at least 99.8%, at least 99.9%, or 100% amino acid sequence identity to SEQ ID NO:117. In some embodiments, the PDC polypeptide encoded by the one or more heterologous nucleic acids comprises an amino acid sequence having at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,

geranyltransferase polypeptide can catalyze production of cannabigerolic acid from geranyl pyrophosphate and olivetolic acid in an amount at least ten times higher than a polypeptide comprising an amino acid sequence set forth in SEQ ID NO:82.

[00839] Embodiment III-2. A genetically modified host cell for producing a cannabinoid or a cannabinoid derivative, the genetically modified host cell comprising one or more heterologous nucleic acids encoding a geranyl pyrophosphate:olivetolic acid geranyltransferase polypeptide comprising an amino acid sequence having at least 65% sequence identity to SEQ ID NO:110.

[00840] Embodiment III-3. A genetically modified host cell for producing a cannabinoid or a cannabinoid derivative, the genetically modified host cell comprising one or more heterologous nucleic acids encoding a geranyl pyrophosphate:olivetolic acid geranyltransferase polypeptide comprising an amino acid sequence having at least 65% sequence identity to SEQ ID NO:100.

[00841] Embodiment III-4. The genetically modified host cell of any one of Embodiments III-1 to III-3, wherein the genetically modified host cell further comprises one or more heterologous nucleic acids encoding a tetraketide synthase (TKS) polypeptide and one or more heterologous nucleic acids encoding an olivetolic acid cyclase (OAC) polypeptide, or one or more heterologous nucleic acids encoding a fusion TKS and OAC polypeptide.

[00842] Embodiment III-5. The genetically modified host cell of Embodiment III-4, wherein the TKS polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:11 or SEQ ID NO:76.

[00843] Embodiment III-6. The genetically modified host cell of Embodiment III-4 or III-5, wherein the OAC polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:10 or SEQ ID NO:78.

[00844] Embodiment III-7. The genetically modified host cell of any one of Embodiments III-1 to III-6, wherein the genetically modified host cell further comprises one or more of the following: a) one or more heterologous nucleic acids encoding a polypeptide that generates an acyl-CoA compound or an acyl-CoA compound derivative; b) one or more heterologous nucleic acids encoding a polypeptide that generates geranyl pyrophosphate; or c) one or more heterologous nucleic acids encoding a polypeptide that generates malonyl-CoA.

[00845] Embodiment III-8. The genetically modified host cell of Embodiment III-7, wherein the genetically modified host cell further comprises one or more heterologous nucleic acids encoding a polypeptide that generates an acyl-CoA compound or an acyl-CoA

[00873] Embodiment III-36. The genetically modified host cell of Embodiment III-35, wherein the acetoacetyl-CoA thiolase polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:25.

[00874] Embodiment III-37. The genetically modified host cell of any one of Embodiments III-1 to III-36, wherein the genetically modified host cell further comprises one or more heterologous nucleic acids encoding a pyruvate decarboxylase (PDC) polypeptide.

[00875] Embodiment III-38. The genetically modified host cell of Embodiment III-37, wherein the PDC polypeptide comprises an amino acid sequence having at least 50% sequence identity to SEQ ID NO:117.

[00876] Embodiment III-39. The genetically modified host cell of any one of Embodiments III-1 to III-38, wherein the genetically modified host cell is a eukaryotic cell.

[00877] Embodiment III-40. The genetically modified host cell of Embodiment III-39, wherein the eukaryotic cell is a yeast cell.

[00878] Embodiment III-41. The genetically modified host cell of Embodiment III-40, wherein the yeast cell is *Saccharomyces cerevisiae*.

[00879] Embodiment III-42. The genetically modified host cell of Embodiment III-41, wherein the *Saccharomyces cerevisiae* is a protease-deficient strain of *Saccharomyces cerevisiae*.

[00880] Embodiment III-43. The genetically modified host cell of any one of Embodiments III-1 to III-39, wherein the genetically modified host cell is a plant cell.

[00881] Embodiment III-44. The genetically modified host cell of any one of Embodiments III-1 to III-38, wherein the genetically modified host cell is a prokaryotic cell.

[00882] Embodiment III-45. The genetically modified host cell of any one of Embodiments III-1 to III-44, wherein at least one of the one or more heterologous nucleic acids is integrated into the chromosome of the genetically modified host cell.

[00883] Embodiment III-46. The genetically modified host cell of any one of Embodiments III-1 to III-44, wherein at least one of the one or more heterologous nucleic acids is maintained extrachromosomally.

[00884] Embodiment III-47. The genetically modified host cell of any one of Embodiments III-1 to III-44, wherein two or more of the one or more heterologous nucleic acids are present in a single expression vector.

times higher than a polypeptide comprising an amino acid sequence set forth in SEQ ID NO:82.

[00910] Embodiment III-73. An isolated or purified nucleic acid encoding a polypeptide comprising an amino acid sequence having at least 65% sequence identity to SEQ ID NO:110.

[00911] Embodiment III-74. An isolated or purified nucleic acid encoding a polypeptide comprising an amino acid sequence having at least 65% sequence identity to SEQ ID NO:100.

[00912] Embodiment III-75. A vector comprising a nucleic acid encoding a geranyl pyrophosphate:olivetolic acid geranyltransferase polypeptide, wherein said geranyl pyrophosphate:olivetolic acid geranyltransferase polypeptide can catalyze production of cannabigerolic acid from geranyl pyrophosphate and olivetolic acid in an amount at least ten times higher than a polypeptide comprising an amino acid sequence set forth in SEQ ID NO:82.

[00913] Embodiment III-76. A vector comprising a nucleic acid encoding a polypeptide comprising an amino acid sequence having at least 65% sequence identity to SEQ ID NO:110.

[00914] Embodiment III-77. A vector comprising a nucleic acid encoding a polypeptide comprising an amino acid sequence having at least 65% sequence identity to SEQ ID NO:100.

[00915] Embodiment III-78. A method of making a genetically modified host cell for producing a cannabinoid or a cannabinoid derivative, comprising introducing one or more heterologous nucleic acids encoding a geranyl pyrophosphate:olivetolic acid geranyltransferase polypeptide, wherein said geranyl pyrophosphate:olivetolic acid geranyltransferase polypeptide can catalyze production of cannabigerolic acid from geranyl pyrophosphate and olivetolic acid in an amount at least ten times higher than a polypeptide comprising an amino acid sequence set forth in SEQ ID NO:82, into a host cell.

[00916] Embodiment III-79. A method of making a genetically modified host cell for producing a cannabinoid or a cannabinoid derivative, comprising introducing one or more heterologous nucleic acids encoding a geranyl pyrophosphate:olivetolic acid geranyltransferase polypeptide comprising an amino acid sequence having at least 65% sequence identity to SEQ ID NO:110 into a host cell.

[00917] Embodiment III-80. A method of making a genetically modified host cell for producing a cannabinoid or a cannabinoid derivative, comprising introducing one or more heterologous nucleic acids encoding a geranyl pyrophosphate:olivetolic acid geranyltransferase polypeptide comprising an amino acid sequence having at least 65% sequence identity to SEQ ID NO:100 into a host cell.

[00918] Embodiment III-81. A method of making a genetically modified host cell for producing a cannabinoid or a cannabinoid derivative, comprising introducing the vector of any one of Embodiments III-75 to III-77 into a host cell.

[00919] Provided in Table 1 are amino acid and nucleotide sequences disclosed herein. Where a genus and/or species is noted, the sequence should not be construed to be limited only to the specified genus and/or species, but also includes other genera and/or species expressing said sequence.

Table 1: Amino acid and nucleotide sequences of the disclosure

SEQ ID	SEQUENCE
SEQ ID NO:1 hexanoyl-CoA synthetase (HCS) GenBank AFD33359 *Cannabis sativa*	MALELPHLLPYKLVKGQTLVAQAARAELASSSSSSVILKSNFINNNYIN YCNNNNNNERRLVVRRDWETMASSPSHSRNNNDIRTINHLRHVDSMA TMPSGAGKIPRLNAVILGEALATEENDLVFPTDEFSQQAHVPSPQKYLE MYKRSIEDPAGFWSEIASQFYWKQKWDDSVYSENLDVSKGRVNIEWF KGGITNICYNCLDKNVEAGLGDKIALYWEGNDTGFDDSLTYSQLLHK VCQLANYLKDMGVQKGDAVVIYLPMLLELPITMLACARIGAVHSVVF AGFSAESLSQRIIDCKPKVVITCNAVKRGPKIIHLKDIVDAALVESAKTG VPIDTCLVYENQLAMKRDITKWQDGRDIWWQDVIPKYPTECAVEWV DAEDPLFLLYTSGSTGKPKGVLHTTGGYMVYTATTFKYAFDYKPSDV YWCTADCGWITGHSYVTYGPLLNGASCIVFEGAPNYPDSGRCWDIVD KYKVTIFYTAPTLVRSLMRDGDEYVTRYSRKSLRILGSVGEPINPSAWR WFYNVVGDSRCPISDTWWQTETGGFMITPLPGAWPQKPGSATFPFFGV KPVIVDEKGVEIEGECSGYLCVKGSWPGAFRTLYGDYERYETTYFKPF TGYYFTGDGCSRDKDGYHWLTGRVDDVINVSGHRIGTAEVESALVSH PKCAEAAVVGIEHEVKGQAIYAFVTLVEGEPYSEELRKSLILSVRKQIG AFAAPERIHWAPGLPKTRSGKIMRRILRKIASGQLDELGDTSTLADPNV VEQLISLSNC
SEQ ID NO:2 RevS BAK64635.1| putative CoA ligase [Streptomyces sp. SN-593]	MELALPAELAPTLPEALRLRSEQQPDTVAYVFLRDGETPEETLTYGRL DRAARARAAALEAAGLAGGTAVLLYPSGLEFVAALLGCMYAGTAGA PVQVPTRRRGMERARRIADDAGAKTILTTTAVKREVEEHFADLLTGLT VIDTESLPDVPDDAPAVRLPGPDDVALLQYTSGSTGDPKGVEVTHANF RANVAETVELWPVRSDGTVVNWLPLFHDMGLMFGVVMPLFTGVPAY LMAPQSFIRRPARWLEAISRFRGTHAAAPSFAYELCVRSVADTGLPAG LDLSSWRVAVNGAEPVRWTAVADFTEAYAPAGFRPQAMCPGYGLAE NTLKLSGSPEDRPPTLLRADAAALQDGRVVPLTGPGTDGVRLVGSGVT VPSSRVAVVDPGTGTEQPAGRVGEIWINGPCVARGYHGRPAESAESFG ARIAGQEARGTWLRTGDLGFLHDGEVFVAGRLKDVVIHQGRNFYPQD IELSAEVSDRALHPNCAAAFALDDGRTERLVLLVEADGRALRNGGAD ALRARVHDAVWDRQRLRIDEIVLLRRGALPKTSSGKVQRRLARSRYL

SEQ ID	SEQUENCE
SEQ ID NO:114 Truncated 3-hydroxy-3-methyl-glutaryl-CoA reductase (tHMG1)	atgtccgatcaattagtcaagaccgaagtcaccaagaagtccttcaccgccccagttcaaaaagcctccactcca gtcttaactaacaagaccgttatttctggttccaaggttaagtctttatcctccgctcaatcctcctcttccggtccatc ttcttcttctgaagaagatgattcccgtgacattgagtccttggataagaaaatcagacctttggaagaattagaag ctttgttatcctctggtaatactaagcaattgaaaaacaaggaagttgctgctttggttattcacggtaaattacctttg tacgctttagagaagaagttaggtgacactacccgtgctgtcgccgttagaagaaaagctttgtctattttagctga ggcccctgttttggcttctgacagattaccatacaagaattacgattacgatagagttttcggtgcctgttgtgagaa cgttatcggttatatgccattaccagtcggtgttatcggtccattggttattgacggtacctcttaccacatcccaatg gctactactgaaggttgtttagtcgcctccgccatgagaggttgtaaggctatcaatgctggtggtggtgctactac cgtcttgactaaggatggtatgactagaggtccagttgtccgttttccaactttgaaaagatctggtgcttgtaagatt tggttggattctgaagaaggtcaaaatgccattaagaaggctttcaattccacctctagatttgccagattacaacat attcaaacctgtttagccggtgatttgttgttcatgagattcagaactactactggtgatgctatgggtatgaacatga tctctaagggtgtcgaatattctttaaaacaaatggttgaagagtatggttgggaagacatggaggtcgtctctgtct ctggtaactactgtactgataagaaaccagctgctatcaactggatcgaaggtcgtggtaagtctgttgttgccga agctactattccaggtgatgttgttagaaaggttttaaaatccgatgtctctgccttggttgagttgaacattgctaaa aacttggttggttctgctatggctggttctgtcggtggttttaatgcccatgccgccaacttagtcaccgccgttttctt agctttgggtcaagatccagctcaaaatgtcgaatcctccaactgtatcactttgatgaaagaggtcgacggtgac ttgcgtatctctgtttccatgccatctatcgaagttggtactatcggtggtggtactgttttggagccacaaggtgcta tgttggacttattgggtgttagaggtccacacgccactgctcctggtaccaacgccagacaattagctagaatcgt tgcctgtgccgtcttagctggtgagttgtctttatgtgctgccttagctgctggtcacttggtccaatcccacatgact cataacagaaagccagctgaacctaccaagcctaacaacttggatgccaccgatattaatcgtttaaaagatggtt ctgtcacttgcattaagtcctaa
SEQ ID NO:115 HMG-CoA synthase (Sc_ERG13) Saccharomyces sp.	MTELKKQKTAEQKTRPQNVGIKGIQIYIPTQCVNQSELEKFDGVSQGK YTIGLGQTNMSFVNDREDIYSMSLTVLSKLIKSYNIDTNKIGRLEVGTE TLIDKSKSVKSVLMQLFGENTDVEGIDTLNACYGGTNALFNSLNWIES NAWDGRDAIVVCGDIAIYDKGAARPTGGAGTVAMWIGPDAPIVFDSV RASYMEHAYDFYKPDFTSEYPYVDGHFSLTCYVKALDQVYKSYSKKA ISKGLVSDPAGSDALNVLKYFDYNVFHVPTCKLVTKSYGRLLYNDFRA NPQLFPEVDAELATRDYDESLTDKNIEKTFVNVAKPFHKERVAQSLIVP TNTGNMYTASVYAAFASLLNYVGSDDLQGKRVGLFSYGSGLAASLYS CKIVGDVQHIIKELDITNKLAKRITETPKDYEAAIELRENAHLKKNFKP QGSIEHLQSGVYYLTNIDDKFRRSYDVKK*
SEQ ID NO:116 Artificial HMG-CoA synthase (Sc_ERG13) nucleotide sequence	atgaccgaattgaagaagcaaaagactgctgaacaaaaaacccgtccacaaaatgttggtatcaagggtattca aatctacattccaactcaatgcgtcaaccaatctgaattggaaaaatttgatggtgtttctcaaggtaaatacactatt ggtttgggtcaaactaatatgtccttcgttaacgacagagaagatatttactccatgtccttgaccgtcttgtccaaat tgattaagtcttataatattgacaccaacaagatcggtagattggaagttggtactgaaactttgattgataagtctaa gtctgttaagtctgttttaatgcaattgttcggtgaaaatactgacgttgaaggtattgacactttgaacgcttgttacg gtggtactaatgctttatttaactctttgaactggattgaatccaacgcttgggacggtagagatgccattgtcgtttg tggtgacattgctatctatgacaagggtgccgctcgtccaactggtggtgctggtaccgttgctatgtggatcggt cctgacgccccaatcgtttttgattctgttcgtgcttcttacatggagcatgcttacgacttttataagccagactttac ctccgaatatccatacgtcgatggtcatttctctttgacctgctacgttaaagccttagatcaagtctacaagtcttact ccaagaaggccatttccaagggtttagtctccgatccagctggttccgatgctttaaacgttttaaagtacttcgatt acaacgtttttcatgtccctacttgtaaattggttaccaaatcttacggtagattattgtacaacgatttcagagctaat ccacaattatttccagaagtcgatgctgagttggctactagagattacgacgaatccttgaccgacaaaaatattga aaagacttttgttaacgttgctaagccatttcacaaagagagagttgcccaatctttgattgtcccaactaatactggt aatatgtatactgcttctgtttacgctgcctttgcttctttgttgaactatgtcggttctgacgacttacaaggtaagcgt gtcggtttgttctcctacggttccggtttggctgcctctttgtattcttgtaagattgtcggtgatgttcaacacatcatc aaggaattggatatcaccaataaattggccaagagaatcactgaaactcctaaagactatgaagctgctatcgaat tgagagaaaatgctcatttaaagaaaaactttaaaccacaaggttctattgaacacttgcaatccggtgtttactact taactaacatcgatgacaagttccgtagatcctacgacgtcaagaagtaa
SEQ ID NO:117 Pyruvate decarboxylase	MSYTVGTYLAERLVQIGLKHHFAVAGDYNLVLLDNLLLNKNMEQVY CCNELNCGFSAEGYARAKGAAAAVVTYSVGALSAFDAIGGAYAENLP VILISGAPNNNDHAAGHVLHHALGKTDYHYQLEMAKNITAAAEAIYT PEEAPAKIDHVIKTALREKKPVYLEIACNIASMPCAAPGPASALFNDEA

SEQ ID	SEQUENCE
(Zm_PDC) *Zymomonas mobilis*	SDEASLNAAVEETLKFIANRDKVAVLVGSKLRAAGAEEAAVKFADAL GGAVATMAAAKSFFPEENPHYIGTSWGEVSYPGVEKTMKEADAVIAL APVFNDYSTTGWTDIPDPKKLVLAEPRSVVVNGIRFPSVHLKDYLTRL AQKVSKKTGALDFFKSLNAGELKKAAPADPSAPLVNAEIARQVEALLT PNTTVIAETGDSWFNAQRMKLPNGARVEYEMQWGHIGWSVPAAFGY AVGAPERRNILMVGDGSFQLTAQEVAQMVRLKLPVIIFLINNYGYTIEV MIHDGPYNNIKNWDYAGLMEVFNGNGGYDSGAGKGLKAKTGGELAE AIKVALANTDGPTLIECFIGREDCTEELVKWGKRVAAANSRKPVNKLL *
SEQ ID NO:118 Artificial pyruvate decarboxylase (Zm_PDC) nucleotide sequence	atgtcctacaccgttggtacctacttagctgagcgtttggtccaaatcggtttgaagcaccatttcgccgttgctggt gattacaacttggtcttgttagataatttattattgaacaagaacatggaacaagtctactgctgtaatgaattgaact gtggtttctctgctgaaggttatgctagagctaaaggtgccgctgccgctgttgtcacttactctgttggtgctttgtc tgccttcgacgctattggtggtgcttacgccgagaatttacctgttattttaatttctggtgcccctaacaataacgat catgctgctggtcatgttttacaccacgctttgggtaaaactgactaccattatcaattagagatggccaaaaacat caccgccgctgccgaggccatttacactccagaagaagccccagccaaaattgatcacgtcatcaaaaccgcc ttgagagagaaaaaacctgtttacttggaaatcgcctgtaatatcgcctctatgccttgcgccgctcctggtcctgc ttccgccttattcaacgatgaggcttctgatgaagcttccttaaacgctgctgttgaggagactttaaagttcatcgct aatagagataaggtcgctgttttagtcggttctaagttgcgtgctgccggtgccgaggaagctgctgttaaattcgc cgatgctttaggtggtgctgtcgccaccatggccgccgccaaatccttttccctgaagaaaacccacactacatc ggtacttcttggggtgaagtctcttacccaggtgtcgaaaagactatgaaggaagccgatgccgtcatcgccttg gccccagtttttaatgattattccaccactggttggactgatatcccagatcctaaaaagttagttttagccgagccta gatccgttgttgttaacggtattagattcccttccgttcacttgaaggattacttaactagattggctcaaaaggtttcc aagaagaccggtgctttggacttttcaaatctttgaacgccggtgagttaaagaaggccgcccctgctgacccat ctgctccattggttaacgctgagattgctagacaagtcgaagctttattgaccccaaacactaccgttatcgccgaa actggtgactcttggtttaatgctcaaagaatgaagttaccaaatggtgccagagttgagtacgaaatgcaatggg gtcatatcggttggtctgtcccagctgcttttggttatgctgttggtgcccctgagagaagaaacatcttgatggttg gtgacggttccttccaattgactgctcaagaagtcgctcaaatggttagattaaaattaccagtcatcatcttcttgat caataactacggttacactatcgaagtcatgattcacgatggtccttacaataatattaagaactgggactatgctg gtttgatggaagtctttaatggtaacggtggttacgattccggtgctggtaagggtttaaaggctaagactggtggt gaattagctgaagccattaaggttgccttggctaacaccgacggtcctactttaatcgaatgtttcattggtagaga ggattgtaccgaagagttagttaagtggggtaagagagttgccgctgctaattcccgtaagcctgtcaataaattg ttataa
SEQ ID NO:119 Truncated 3-hydroxy-3-methyl-glutaryl-CoA reductase (tHMG1)	atgcaattggtgaagactgaagtcaccaagaagtcttttactgctcctgtacaaaaggcttctacaccagttttaac caataaaacagtcatttctggatcgaaagtcaaaagtttatcatctgcgcaatcgagctcatcaggaccttcatcat ctagtgaggaagatgattcccgcgatattgaaagcttggataagaaaatacgtcctttagaagaattagaagcatt attaagtagtggaaatacaaaacaattgaagaacaaagaggtcgctgccttggttattcacggtaagttacctttgt acgctttggagaaaaaattaggtgatactacgagagcggttgcggtacgtaggaaggctctttcaattttggcaga agctcctgtattagcatctgatcgtttaccatataaaaattatgactacgaccgcgtatttggcgcttgttgtgaaaat gttataggttacatgccttgcccgttggtgttataggcccccttggttatcgatggtacatcttatcatataccaatggc aactacagagggttgtttggtagcttctgccatgcgtggctgtaaggcaatcaatgctggcggtggtgcaacaac tgttttaactaaggatggtatgacaagaggcccagtagtccgtttcccaactttgaaaagatctggtgcctgtaaga tatggttagactcagaagagggacaaaacgcaattaaaaaagcttttaactctacatcaagatttgcacgtctgca acatattcaaacttgtctagcaggagatttactcttcatgagatttagaacaactactggtgacgcaatgggtatgaa tatgatttctaagggtgtcgaatactcattaaagcaaatggtagaagagtatggctgggaagatatggaggttgtct ccgtttctggtaactactgtaccgacaaaaaaccagctgccatcaactggatcgaaggtcgtggtaagagtgtcg tcgcagaagctactattcctggtgatgttgtcagaaaagtgttaaaaagtgatgtttccgcattggttgagttgaaca ttgctaagaatttggttggatctgcaatggctgggtctgttggtggatttaacgcacatgcagctaatttagtgacag ctgttttcttggcattaggacaagatcctgcacaaaatgtcgaaagttccaactgtataacattgatgaaagaagtg gacggtgatttgagaatttccgtatccatgccatccatcgaagtaggtaccatcggtggtggtactgttctagaacc acaaggtgccatgttggacttattaggtgtaagaggcccacatgctaccgctcctggtaccaacgcacgtcaatt agcaagaatagttgcctgtgccgtcttggcaggtgaattatccttatgtgctgccctagcagccggccatttggttc aaagtcatatgacccacaacaggaaacctgctgaaccaacaaaacctaacaatttggacgccactgatataaatc gtttgaaagatgggtccgtcacctgcattaaatcctaa

Product	Strain	Titer (mg/L)	SD	n
CBGA	S49	55.7	9.3	8
CBGA	S50	22.9	7.0	8
CBGA	S90	67.5	2.8	4
CBGA	S91	63.5	4.2	4
CBGA	S78	38.5	2.5	4
CBGA	S80	37.5	1.8	4
CBGA	S81	32.1	5.8	4
CBGA	S82	35.1	7.0	4
CBGA	S83	35.1	2.6	4
CBGA	S84	36.4	3.5	4
CBGA	S85	34.4	4.3	4
CBGA	S86	36.6	1.8	4
CBGA	S87	32.2	4.9	4
CBGA	S88	40.9	1.4	4
CBGA	S89	39.3	2.7	4
CBGA	S94	59.6	7.9	8
CBGA	S95	58.5	9.2	8
CBGA	S97	72.9	5.5	8

Table 11: Constructs and strains used in the Examples

Strain (Constructs)	Parent Strain*	Polypeptide SEQ ID NOs (Nucleotide SEQ ID NOs)
S21 (FIGS. 29A and 29B)		Sc_tHMG1: SEQ ID NO:208 (SEQ ID NO:119) Sc_ERG13: SEQ ID NO:115 (SEQ ID NO:120) Sc_ERG10: SEQ ID NO:25 (SEQ ID NO:209) Sc_MVD1 (Sc_ERG19): SEQ ID NO:66 (SEQ ID NO:65) Sc_IDI1: SEQ ID NO:58 (SEQ ID NO:57) Zm_PDC: SEQ ID NO:117 (SEQ ID NO:118) Sc_ERG8: SEQ ID NO:205 (SEQ ID NO:204) Sc_ERG12: SEQ ID NO:64 (SEQ ID NO:206)
S29 (FIG. 86)	S21	Cs_PT4: SEQ ID NO:110 (SEQ ID NO:111) Sc_ERG20_mut: SEQ ID NO:60 (SEQ ID NO:161)
S31 (FIGS. 30A, 30B, and 30C)	S29	Cs_OAC: SEQ ID NO:10 (SEQ ID NO:163) Cs_TKS: SEQ ID NO:11 (SEQ ID NO:162) Cs_AAE1_v1: SEQ ID NO:90 (SEQ ID NO:164) Sc_FAA2: SEQ ID NO:169 (SEQ ID NO:168)
S34 (FIG. 85)	S29	Cs_CBDAS_co1: SEQ ID NO:88 (SEQ ID NO:167)
S35 (FIG. 31)	S29	Cs_CBDAS_t28: SEQ ID NO:151 (SEQ ID NO:152)

Strain (Constructs)	Parent Strain*	Polypeptide SEQ ID NOs (Nucleotide SEQ ID NOs)
S37 (FIG. 32)	S29	MBP_co1: SEQ ID NO:108 (SEQ ID NO:170) Cs_CBDAS_t28: SEQ ID NO:151 (SEQ ID NO:152) GS12: SEQ ID NO:172 (SEQ ID NO:171)
S38 (FIG. 33)	S29	Cs_CBDAS_t28: SEQ ID NO:151 (SEQ ID NO:152) GB1: SEQ ID NO:174 (SEQ ID NO:173) GS12: SEQ ID NO:172 (SEQ ID NO:171)
S39 (FIG. 34)	S29	Cs_CBDAS_t28: SEQ ID NO:151 (SEQ ID NO:152) Sc_MFalpha1_1-19: SEQ ID NO:176 (SEQ ID NO:175)
S41 (FIG. 35)	S29	Cs_CBDAS_t28: SEQ ID NO:151 (SEQ ID NO:152) Sc_MFalpha1_1-89: SEQ ID NO:178 (SEQ ID NO:177)
S42 (FIG. 36)	S29	Cs_CBDAS_t28: SEQ ID NO:151 (SEQ ID NO:152) DasherGFP: SEQ ID NO:180 (SEQ ID NO:179) GS12: SEQ ID NO:172 (SEQ ID NO:171)
S43 (FIG. 37)	S29	Cs_CBDAS_t28: SEQ ID NO:151 (SEQ ID NO:152) GS12: SEQ ID NO:172 (SEQ ID NO:171) ER1_tag: SEQ ID NO:182 (SEQ ID NO:181)
S44 (FIG. 38)	S29	Cs_CBDAS_t28: SEQ ID NO:151 (SEQ ID NO:152) GS12: SEQ ID NO:172 (SEQ ID NO:171) ER2_tag: SEQ ID NO:184 (SEQ ID NO:183)
S45 (FIG. 39)	S29	Cs_CBDAS_t28: SEQ ID NO:151 (SEQ ID NO:152) GS12: SEQ ID NO:172 (SEQ ID NO:171) PM1_tag: SEQ ID NO:186 (SEQ ID NO:185)
S46 (FIG. 40)	S29	Cs_CBDAS_t28: SEQ ID NO:151 (SEQ ID NO:152) GS12: SEQ ID NO:172 (SEQ ID NO:171) VC1_tag: SEQ ID NO:188 (SEQ ID NO:187)
S47 (FIG. 41)	S29	Cs_CBDAS_t28: SEQ ID NO:151 (SEQ ID NO:152)

Strain (Constructs)	Parent Strain*	Polypeptide SEQ ID NOs (Nucleotide SEQ ID NOs)
		PEX8_tag: SEQ ID NO:190 (SEQ ID NO:189)
S49 (FIGS. 42A, 42B, and 42C)	S29	Cs_OAC: SEQ ID NO:10 (SEQ ID NO:163) Cs_TKS: SEQ ID NO:11 (SEQ ID NO:162) Cs_AAE1_v1: SEQ ID NO:90 (SEQ ID NO:164) Cs_AAE_v1: SEQ ID NO:90 (SEQ ID NO:164)
S50 (FIGS. 43A, 43B, and 43C)	S29	Cs_OAC: SEQ ID NO:10 (SEQ ID NO:163) Cs_TKS: SEQ ID NO:11 (SEQ ID NO:162) Sc_FAA2: SEQ ID NO:169 (SEQ ID NO:168)
S51 (FIGS. 44A, 44B, and 44C)	S29	Cs_OAC: SEQ ID NO:10 (SEQ ID NO:163) Cs_TKS: SEQ ID NO:11 (SEQ ID NO:162)
S78 (FIG. 45)	S51	Cs_AAE1_v1: SEQ ID NO:90 (SEQ ID NO:164) Cs_AAE_v1: SEQ ID NO:90 (SEQ ID NO:164) GB1: SEQ ID NO:174 (SEQ ID NO:173)
S80 (FIG. 46)	S51	Cs_AAE3: SEQ ID NO:92 (SEQ ID NO:166)
S81 (FIG. 47)	S51	Cs_AAE3_Ctrunc: SEQ ID NO:149 (SEQ ID NO:150)
S82 (FIG. 48)	S51	Sc_FAA1: SEQ ID NO:192 (SEQ ID NO:191) FAA1: SEQ ID NO:192 (SEQ ID NO:191)
S83 (FIG. 49)	S51	Sc_FAA2: SEQ ID NO:169 (SEQ ID NO:168)
S84 (FIG. 50)	S51	Sc_FAA2_Ctrunc: SEQ ID NO:194 (SEQ ID NO:193)
S85 (FIG. 51)	S51	Sc_FAA2_Cmut: SEQ ID NO:196 (SEQ ID NO:195) Sc_FAA2: SEQ ID NO:169 (SEQ ID NO:168)
S86 (FIG. 52)	S51	Sc_FAA3: SEQ ID NO:198 (SEQ ID NO:197)
S87 (FIG. 53)	S51	Sc_FAA4: SEQ ID NO:200 (SEQ ID NO:199)
S88 (FIG. 54)	S51	Cs_AAE1_v1: SEQ ID NO:90 (SEQ ID NO:164) Sc_ACC1_act: SEQ ID NO:207 (SEQ ID NO:201)
S89 (FIG. 55)	S51	Sc_FAA2: SEQ ID NO:169 (SEQ ID NO:168) Sc_ACC1_act: SEQ ID NO:207 (SEQ ID NO:201)
S90 (FIGS. 56A, 56B, and 56C)	S29	Cs_OAC: SEQ ID NO:10 (SEQ ID NO:163) Cs_TKS: SEQ ID NO:11 (SEQ ID NO:162) Cs_AAE1_v1: SEQ ID NO:90 (SEQ ID NO:164)

Strain (Constructs)	Parent Strain*	Polypeptide SEQ ID NOs (Nucleotide SEQ ID NOs)
		Cs_AAE_v1: SEQ ID NO:90 (SEQ ID NO:164)
S91 (FIGS. 57A, 57B, and 57C)	S29	Cs_OAC: SEQ ID NO:10 (SEQ ID NO:163) Cs_TKS: SEQ ID NO:11 (SEQ ID NO:162) Sc_FAA2: SEQ ID NO:169 (SEQ ID NO:168)
S94 (FIG. 58)	S31	Cs_PT4_full: SEQ ID NO:110 (SEQ ID NO:111)
S95 (FIG. 59)	S31	GB1: SEQ ID NO:174 (SEQ ID NO:173) Cs_OAC: SEQ ID NO:10 (SEQ ID NO:163)
S97 (FIG. 60)	S31	Cs_OAC: SEQ ID NO:10 (SEQ ID NO:163) Cs_TKS: SEQ ID NO:11 (SEQ ID NO:162) GS12: SEQ ID NO:172 (SEQ ID NO:171)
S104 (FIG. 61)	S21	Cs_PT4: SEQ ID NO:110 (SEQ ID NO:111) Ag_GPPS: SEQ ID NO:133 (SEQ ID NO:134) GB1: SEQ ID NO:174 (SEQ ID NO:173)
S108 (FIG. 62)	S21	Cs_PT4: SEQ ID NO:110 (SEQ ID NO:111) Hb_GPPS: SEQ ID NO:143 (SEQ ID NO:144) GB1: SEQ ID NO:174 (SEQ ID NO:173)
S112 (FIG. 63)	S21	Cs_PT4: SEQ ID NO:110 (SEQ ID NO:111) Cs_GPPS_NTrunc: SEQ ID NO:127 (SEQ ID NO:128)
S114 (FIG. 64)	S21	Cs_PT4: SEQ ID NO:110 (SEQ ID NO:111) Pa_GPPS_NTrunc: SEQ ID NO:131 (SEQ ID NO:132)
S115 (FIG. 65)	S21	Cs_PT4: SEQ ID NO:110 (SEQ ID NO:111) Ag_GPPS_NTrunc: SEQ ID NO:203 (SEQ ID NO:202)
S116 (FIG. 66)	S21	Cs_PT4: SEQ ID NO:110 (SEQ ID NO:111) Pb_GPPS_NTrunc: SEQ ID NO:135 (SEQ ID NO:136)
S118 (FIG. 67)	S21	Cs_PT4: SEQ ID NO:110 (SEQ ID NO:111) Es_GPPS_NTrunc: SEQ ID NO:139 (SEQ ID NO:140)
S123 (FIG. 68)	S29	Cs_THCAS_full: SEQ ID NO:155 (SEQ ID NO:156)
S147 (FIG. 69)	S21	Cs_PT4t: SEQ ID NO:100 (SEQ ID NO:224) Sc_ERG20_mut: SEQ ID NO:60 (SEQ ID NO:161)
S164 (FIG. 70)	S21	Cs_PT1: SEQ ID NO:82 (SEQ ID NO:220)

Strain (Constructs)	Parent Strain*	Polypeptide SEQ ID NOs (Nucleotide SEQ ID NOs)
		Sc_ERG20_mut: SEQ ID NO:60 (SEQ ID NO:161)
S165 (FIG. 71)	S21	CsPT1_t75: SEQ ID NO:223 (SEQ ID NO:222) Sc_ERG20_mut: SEQ ID NO:60 (SEQ ID NO:161)
S166 (FIG. 72)	S21	CsPT4_t112: SEQ ID NO:211 (SEQ ID NO:210) Sc_ERG20_mut: SEQ ID NO:60 (SEQ ID NO:161)
S167 (FIG. 73)	S21	CsPT4_t131: SEQ ID NO:213 (SEQ ID NO:212) Sc_ERG20_mut: SEQ ID NO:60 (SEQ ID NO:161)
S168 (FIG. 74)	S21	CsPT4_t142Cs_PT4: SEQ ID NO:215 (SEQ ID NO:214) Sc_ERG20_mut: SEQ ID NO:60 (SEQ ID NO:161)
S169 (FIG. 75)	S21	CsPT4_t166: SEQ ID NO:217 (SEQ ID NO:216) Sc_ERG20_mut: SEQ ID NO:60 (SEQ ID NO:161)
S170 (FIG. 76)	S21	CsPT4_t186: SEQ ID NO:219 (SEQ ID NO:218) Sc_ERG20_mut: SEQ ID NO:60 (SEQ ID NO:161)

* If a strain has a parent strain, it is a child strain. All of the constructs present in the parent strain are also all present in the child strain.

[00966] While the present disclosure has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the disclosure. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present disclosure. All such modifications are intended to be within the scope of the claims appended hereto.

CLAIMS

What is claimed is:

1. A genetically modified yeast cell for producing a cannabinoid or a cannabinoid derivative, the genetically modified yeast cell comprising one or more heterologous nucleic acids integrated into a chromosome of the genetically modified yeast cell and encoding a geranyl pyrophosphate:olivetolic acid geranyltransferase polypeptide comprising an amino acid sequence having at least 85% sequence identity to SEQ ID NO:110 or SEQ ID NO:100.

2. The genetically modified yeast cell of claim 1, wherein the genetically modified yeast cell further comprises one or more heterologous nucleic acids integrated into a chromosome of the genetically modified yeast cell and encoding a tetraketide synthase (TKS) polypeptide and one or more heterologous nucleic acids integrated into a chromosome of the genetically modified yeast cell and encoding an olivetolic acid (OAC) polypeptide, or one or more heterologous nucleic acids integrated into a chromosome of the genetically modified yeast cell and encoding a fusion TKS and OAC polypeptide.

3. The genetically modified yeast cell of claim 2, wherein the TKS polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:11 and the OAC polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:10.

4. The genetically modified yeast cell of any one of claims 1-3, wherein the genetically modified yeast cell further comprises one or more of the following:

a) one or more heterologous nucleic acids encoding a polypeptide that generates an acyl-CoA compound or an acyl-CoA compound derivative; or

b) one or more heterologous nucleic acids encoding a polypeptide that generates geranyl pyrophosphate.

5. The genetically modified yeast cell of claim 4, wherein the genetically modified yeast cell further comprises one or more heterologous nucleic acids encoding a polypeptide that generates an acyl-CoA compound or an acyl-CoA compound derivative and wherein the polypeptide that generates an acyl-CoA compound or an acyl-CoA compound

derivative is an acyl-activating enzyme (AAE) polypeptide, a fatty acyl-CoA ligase polypeptide, or a fatty acyl-CoA synthetase (FAA) polypeptide.

6. The genetically modified yeast cell of claim 5, wherein the AAE polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:90, SEQ ID NO:92 or SEQ ID NO:149; the fatty acyl-CoA ligase polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:145 or SEQ ID NO:147; and

the FAA polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:169, SEQ ID NO:192, SEQ ID NO:194, SEQ ID NO:196, SEQ ID NO:198, or SEQ ID NO:200.

7. The genetically modified yeast cell of claim 4, wherein the genetically modified yeast cell further comprises one or more heterologous nucleic acids encoding a polypeptide that generates geranyl pyrophosphate and wherein the polypeptide that generates geranyl pyrophosphate is a geranyl pyrophosphate synthetase (GPPS) polypeptide.

8. The genetically modified host cell of claim 7, wherein the GPPS polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:60.

9. The genetically modified yeast cell of any one of claims 1-8, wherein the genetically modified yeast cell further comprises one or more of the following:

a) one or more heterologous nucleic acids encoding a HMG-CoA synthase (HMGS) polypeptide;

b) one or more heterologous nucleic acids encoding a 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGR) polypeptide;

c) one or more heterologous nucleic acids encoding a mevalonate kinase (MK) polypeptide;

d) one or more heterologous nucleic acids encoding a phosphomevalonate kinase (PMK) polypeptide;

e) one or more heterologous nucleic acids encoding a mevalonate pyrophosphate decarboxylase (MVD) polypeptide; or

f) one or more heterologous nucleic acids encoding a isopentenyl diphosphate isomerase (IDI) polypeptide.

10. The genetically modified yeast cell of claim 9, wherein the genetically modified yeast cell further comprises one or more heterologous nucleic acids encoding an IDI polypeptide.

11. The genetically modified yeast cell of claim 10, wherein the IDI polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:58.

12. The genetically modified yeast cell of claim 9, wherein the genetically modified yeast cell further comprises one or more heterologous nucleic acids encoding an HMGR polypeptide and wherein the HMGR polypeptide is a truncated HMGR polypeptide.

13. The genetically modified yeast cell of claim 12, wherein the HMGR polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:115 and the truncated HMGR polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:208.

14. The genetically modified yeast cell of claim 9, wherein the genetically modified yeast cell further comprises one or more heterologous nucleic acids encoding an MK polypeptide and one or more heterologous nucleic acids encoding a PMK polypeptide.

15. The genetically modified yeast cell of claim 14, wherein the MK polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:64 the PMK polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:205.

16. The genetically modified yeast cell of claim 9, wherein the genetically modified yeast cell further comprises one or more heterologous nucleic acids encoding a MVD polypeptide.

17. The genetically modified yeast cell of claim 16, wherein the MVD polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:66.

18. The genetically modified yeast cell of claim 9, wherein the genetically modified yeast cell further comprises one or more heterologous nucleic acids encoding a polypeptide that condenses two molecules of acetyl-CoA to generate acetoacetyl-CoA and wherein the polypeptide that condenses two molecules of acetyl-CoA to generate acetoacetyl-CoA is an acetoacetyl-CoA thiolase polypeptide.

19. The genetically modified yeast cell of claim 18, wherein the acetoacetyl-CoA thiolase polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:25.

20. The genetically modified yeast cell of any one of claims 1-19, wherein the yeast cell is *Saccharomyces cerevisiae*.

21. The genetically modified yeast cell of claim 1, wherein the genetically modified yeast cell further comprises one or more heterologous nucleic acids encoding a cannabinoid synthase polypeptide, wherein the cannabinoid synthase polypeptide is a tetrahydrocannabinolic acid (THCA) synthase polypeptide or a cannabidiolic acid (CBDA) synthase polypeptide.

22. The genetically modified yeast cell of claim 21, wherein the THCA synthase polypeptide comprises an amino acid sequence having at least 85% sequence identity to NO:155 and the CBDA synthase polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:88 or SEQ ID NO:151.

23. The genetically modified yeast cell of claim 1, wherein the genetically modified yeast cell further comprises one or more of the following:

a) one or more heterologous nucleic acids encoding a polypeptide that generates an acyl-CoA compound or an acyl-CoA compound derivative;

b) one or more heterologous nucleic acids encoding a polypeptide that generates geranyl pyrophosphate;

c) one or more heterologous nucleic acids encoding a HMG-CoA synthase (HMGS) polypeptide;

d) one or more heterologous nucleic acids encoding a 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGR) polypeptide;

e) one or more heterologous nucleic acids encoding a mevalonate kinase (MK) polypeptide;

f) one or more heterologous nucleic acids encoding a phosphomevalonate kinase (PMK) polypeptide;

g) one or more heterologous nucleic acids encoding a mevalonate pyrophosphate decarboxylase (MVD) polypeptide;

h) one or more heterologous nucleic acids encoding a isopentenyl diphosphate isomerase (IDI) polypeptide;

i) one or more heterologous nucleic acids encoding a polypeptide that condenses two molecules of acetyl-CoA to generate acetoacetyl-CoA, wherein the polypeptide that condenses two molecules of acetyl-CoA to generate acetoacetyl-CoA is an acetoacetyl-CoA thiolase polypeptide; or

j) one or more heterologous nucleic acids encoding a tetraketide synthase (TKS) polypeptide and one or more heterologous nucleic acids encoding an olivetolic acid cyclase (OAC) polypeptide, or one or more heterologous nucleic acids encoding a fusion TKS and OAC polypeptide.

24. A genetically modified yeast that produces a cannabinoid or cannabinoid derivative, wherein the yeast cell is genetically modified with:

a) one or more heterologous nucleic acids integrated into a chromosome of the genetically modified yeast cell and encoding a tetraketide synthase (TKS) polypeptide;

b) one or more heterologous nucleic acids integrated into a chromosome of the genetically modified yeast cell and encoding an olivetolic acid cyclase (OAC) polypeptide;

c) one or more heterologous nucleic acids integrated into a chromosome of the genetically modified yeast cell and encoding a prenyltransferase polypeptide; and

d) at least one of

i) one or more heterologous nucleic acids encoding an ERG 8 polypeptide;

ii) one or more heterologous nucleic acids encoding an ERG 10 polypeptide;

iii) one or more heterologous nucleic acids encoding an ERG 12 polypeptide; and

iv) one or more heterologous nucleic acids encoding an ERG 13 polypeptide.

25. A genetically modified yeast cell that produces a cannabinoid or cannabinoid derivative, wherein the yeast cell is genetically modified with:

a) one or more heterologous nucleic acids integrated into a chromosome of the genetically modified yeast cell and encoding a fusion polypeptide comprising a tetraketide synthase (TKS) polypeptide and an olivetolic acid cyclase (OAC) polypeptide; and

b) one or more heterologous nucleic acids integrated into a chromosome of the genetically modified yeast cell and encoding a prenyltransferase polypeptide.

26. The genetically modified yeast cell of claim 24 or 25, wherein the prenyltransferase polypeptide is a geranyl pyrophosphate olivetolic acid geranyltransferase (GOT) polypeptide.

27. The genetically modified yeast cell of claim 26, wherein the geranyl pyrophosphate olivetolic acid geranyltransferase (GOT) polypeptide has at least 85% sequence identity to SEQ ID NO: 12.

28. The genetically modified yeast cell of any of claims 24 to 27, wherein the yeast cell is further genetically modified with:

a) one or more heterologous nucleic acids encoding a tetrahydrocannabinolic acid (THCA) synthase polypeptide or a cannabidiolic acid (CBDA) synthase polypeptide;

b) one or more heterologous nucleic acids encoding one or more polypeptides that generate geranyl pyrophosphate;

c) one or more heterologous nucleic acids encoding one or more polypeptides that generate hexanoyl-CoA or derivatives thereof; and

d) one or more heterologous nucleic acids encoding one or more polypeptides that generate malonyl-CoA.

29. The genetically modified yeast cell of claim 24 or 25, wherein the TKS polypeptide and OAC polypeptide exist in a fusion polypeptide.

30. The genetically modified yeast cell of claim 29, wherein the TKS-OAC fusion polypeptide has at least 85% sequence identity to SEQ ID NO: 80.

31. The genetically modified yeast cell of claim 27, wherein the one or more polypeptides that generate malonyl-CoA comprise an acetyl-CoA carboxylase-1 (ACC1) polypeptide.

32. The genetically modified yeast cell of claim 28, wherein the one or more polypeptides that generate hexanoyl-CoA or derivatives thereof comprise a hexanoyl-CoA synthetase (HCS) polypeptide.

33. The genetically modified yeast cell of claim 28, wherein the one or more polypeptides that generate geranyl pyrophosphate comprise a geranyl pyrophosphate synthetase (GPPS) polypeptide.

34. The genetically modified yeast cell of claim 33, wherein the GPPS polypeptide is a heterodimeric polypeptide comprising a GPPS large subunit polypeptide and a GPPS small subunit polypeptide.

35. The genetically modified yeast cell of claim 28, wherein the one or more polypeptides that generate hexanoyl-CoA or derivatives thereof comprise a MCT1 polypeptide, a PaaH1 polypeptide, a PhaB polypeptide, a PhaJ polypeptide, a Crt polypeptide, a Ter polypeptide, and/or a BktB polypeptide.

36. The genetically modified yeast cell of any one of the preceding claims, wherein at least one of the heterologous nucleic acids is operably linked to an inducible promoter.

37. The genetically modified yeast cell of any one of claims 24-36, wherein the yeast cell is *Saccharomyces cerevisiae.*

38. The genetically modified yeast cell of claim 23, wherein the genetically modified yeast cell further comprises one or more heterologous nucleic acids encoding a polypeptide that generates an acyl-CoA compound or an acyl-CoA compound derivative and wherein the polypeptide that generates an acyl-CoA compound or an acyl-CoA compound derivative is an acyl-activating enzyme (AAE) polypeptide, a fatty acyl-CoA ligase polypeptide, or a fatty acyl-CoA synthetase (FAA) polypeptide.

39. The genetically modified yeast cell of claim 38, wherein the AAE polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:90, SEQ ID NO:92 or SEQ ID NO:149; the fatty acyl-CoA ligase polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:145 or SEQ ID NO:147; and the FAA polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:169, SEQ ID NO:192, SEQ ID NO:194, SEQ ID NO:196, SEQ ID NO:198, or SEQ ID NO:200.

40. The genetically modified yeast cell of any of claims 23, 28, and 33, wherein the GPPS polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:60.

41. The genetically modified yeast cell of claim 23, wherein the IDI polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:58.

42. The genetically modified yeast cell of claim 23, wherein the genetically modified yeast cell further comprises one or more heterologous nucleic acids encoding an HMGS polypeptide and one or more heterologous nucleic acids encoding a HMGR polypeptide and wherein the HMGR polypeptide is a truncated HMGR polypeptide.

43. The genetically modified yeast cell of claim 42, wherein the HMGS polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:115 and the truncated HMGR polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:208.

44. The genetically modified yeast cell of claim 23, wherein the genetically modified yeast cell further comprises one or more heterologous nucleic acids encoding an MK polypeptide and one or more heterologous nucleic acids encoding a PMK polypeptide.

45. The genetically modified yeast cell of claim 23, wherein the MK polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:64 and the PMK polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:205.

46. The genetically modified yeast cell of claim 23, wherein the MVD polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:66.

47. The genetically modified yeast cell of claim 23 or 24, wherein the TKS polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:11 and the OAC polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:10.

48. The genetically modified yeast cell of claim 23 or 25, wherein the TKS-OAC fusion polypeptide has at least 85% sequence identity to SEQ ID NO: 80.

49. The genetically modified yeast cell of claim 24, wherein the ERG 8 polypeptide has at least 85% sequence identity to SEQ ID NO: 62, the ERG 10 polypeptide has at least 85% sequence identity to SEQ ID NO: 25, the ERG 12 polypeptide has at least 85% sequence identity to SEQ ID NO: 64, and/or the ERG 13 polypeptide has at least 85% sequence identity to SEQ ID NO: 24.

50. The genetically modified yeast cell of claim 28, wherein the THCA synthase polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:155 and the CBDA synthase polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:88 or SEQ ID NO:151.

51. The genetically modified yeast cell of claim 31, wherein the ACC1 polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:9.

52. The genetically modified yeast cell of claim 32, wherein the HCS polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:1, SEQ ID NO: 2, SEQ ID NO: 3, or SEQ ID NO: 4.

53. The genetically modified yeast cell of claim 35, wherein the MCT1 polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 42, the PaaH1 polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 18 or SEQ ID NO: 46, the PhaB polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 94, the PhaJ polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 96, the Crt polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:19 or SEQ ID NO: 48, the Ter polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 20 or SEQ ID NO: 50, and/or the BktB polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 21 or SEQ ID NO: 44.

54. A method of producing a cannabinoid or a cannabinoid derivative in a genetically modified yeast cell, the method comprising:

a) culturing the genetically modified host cell of any one of claims 1-53 in a suitable medium; and

b) recovering the produced cannabinoid or cannabinoid derivative.

55. The method of claim 54, wherein the suitable medium comprises a carboxylic acid, hexanoic acid, olivetolic acid or an olivetolic acid derivative.

56. The method of claim 54 or 55, wherein the cannabinoid is cannabigerolic acid, cannabigerolic acid monomethylether (CBGAM), cannabigerol, cannabigerol monomethylether, Δ^9-trans-tetrahydrocannabinol, Δ^9-tetrahydrocannabinolic acid, Δ^9-tetrahydrocannabinol, Δ^8-tetrahydrocannabinolic acid, Δ^9-tetrahydrocannabinolic acid A, Δ^9-tetrahydrocannabinolic acid B, Δ^9-tetrahydrocannabinolic acid-C_4, Δ^9-tetrahydrocannabinol-C_4, Δ^9-tetrahydrocannabivarinic acid, Δ^9-tetrahydrocannabivarin, Δ^9-tetrahydrocannabiorcolic acid, Δ^9-tetrahydrocannabiorcol, Δ^7-cis-iso-tetrahydrocannabivarin, Δ^9-tetrahydrocannabinol, Δ^8-tetrahydrocannabinolic acid, Δ^8-trans-tetrahydrocannabinol, Δ^8-tetrahydrocannabinol, cannabidiolic acid, cannabidiol, cannabichromenic acid,

cannabichromene, cannabinolic acid, cannabinol, cannabidiol monomethylether (CBDM), cannabidiol-C_4 (CBD-C_4), cannabidiorcol (CBD-C_1), cannabitriol, cannabichromenic acid, cannabichromene, cannabinolic acid, cannabinol, cannabinol methylether, cannabinol-C4, cannabinol-C2, cannabicyclovarin, cannabielsoic acid A, cannabielsoic acid B, cannabidivarinic acid, cannabidivarin, tetrahydrocannabivarinic acid, tetrahydrocannabivarin, cannabichromevarinic acid, cannabichromevarin, cannabigerovarinic acid, cannabigerovarin, cannabicyclolic acid, cannabicyclol, cannabielsoinic acid, cannabielsoin, cannabicitranic acid, or cannabicitran.

57. A method of making a genetically modified yeast cell for producing a cannabinoid or a cannabinoid derivative, comprising introducing one or more heterologous nucleic acids encoding a geranyl pyrophosphate:olivetolic acid geranyltransferase polypeptide comprising an amino acid sequence having at least 85% sequence identity to SEQ ID NO:110 or SEQ ID NO:100 into the genetically modified yeast cell.

58. A method of producing a cannabinoid or a cannabinoid derivative, the method comprising use of a geranyl pyrophosphate:olivetolic acid geranyltransferase (GOT) polypeptide comprising an amino acid sequence having at least 85% sequence identity to SEQ ID NO:110 or SEQ ID NO:100.

59. The method of claim 58, wherein the GOT polypeptide comprises the amino acid sequence of SEQ ID NO:110 or SEQ ID NO:100.

60. The method of claim 58, wherein the cannabinoid is cannabigerolic acid, cannabigerolic acid monomethylether (CBGAM), cannabigerol, cannabigerol monomethylether, Δ^9-trans-tetrahydrocannabinol, Δ^9-tetrahydrocannabinolic acid, Δ^9-tetrahydrocannabinolic acid A, Δ^9-tetrahydrocannabinolic acid B, Δ^9-tetrahydrocannabinolic acid-C_4, Δ^9-tetrahydrocannabinol-C_4, Δ^9-tetrahydrocannabivarinic acid, Δ^9-tetrahydrocannabivarin, Δ^9-tetrahydrocannabiorcolic acid, Δ^9-tetrahydrocannabiorcol, Δ^7-cis-iso-tetrahydrocannabivarin, Δ^9-tetrahydrocannabinol, Δ^8-tetrahydrocannabinolic acid, Δ^8-trans-tetrahydrocannabinol, Δ^8-tetrahydrocannabinol, cannabidiolic acid, cannabidiol, cannabidiol monomethylether (CBDM), cannabidiol-C_4 (CBD-C_4), cannabidiorcol (CBD-C_1), cannabitriol, cannabichromenic acid, cannabichromene, cannabinolic acid, cannabinol, cannabinol methylether, cannabinol-C4, cannabinol-C2, cannabidivarinic acid,

cannabidivarin, tetrahydrocannabivarinic acid, tetrahydrocannabivarin, cannabichromevarinic acid, cannabichromevarin, cannabigerovarinic acid, cannabigerovarin, cannabicyclolic acid, cannabicyclol, cannabicyclovarin, cannabielsoic acid A, cannabielsoic acid B, cannabielsoinic acid, cannabielsoin, cannabicitranic acid, or cannabicitran.

61. The method of claim 58, wherein the method comprises mixing of the GOT polypeptide with a prenyl group acceptor molecule and a prenyl group donor molecule.

62. The method of claim 61, wherein the prenyl group acceptor molecule is olivetolic acid or an olivetolic acid derivative and the prenyl group donor molecule is geranyl pyrophosphate (GPP) or a GPP derivative.

63. The method of claim 62, wherein the prenyl group acceptor molecule is olivetolic acid and the prenyl group donor molecule is GPP.