GENETICALLY MODIFIED PLANTS AND METHODS OF MAKING THE SAME

CROSS REFERENCE

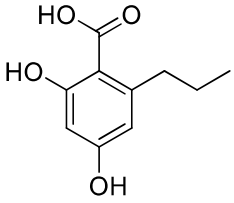
[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/909,094, filed October 1, 2019, which is entirely incorporated herein by reference.

BACKGROUND

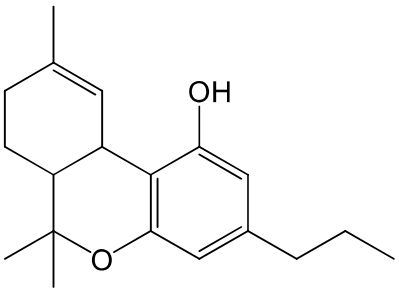
[0002] Naturally occurring components in cannabis may impact the efficacy of therapy and any potential side effects. Accordingly, cannabis plants having a modified therapeutic component(s) profile may be useful in the production of cannabis and/or may also be useful in the production of genetically modified cannabis providing a desired drug profile.

SUMMARY

[0002a] In one aspect, provided herein is a transgenic plant that comprises at least one genetic modification, wherein said genetic modification results in an increased level of the following compounds



(Divarinic acid (DA), Formula I) or a derivative or analog thereof; and

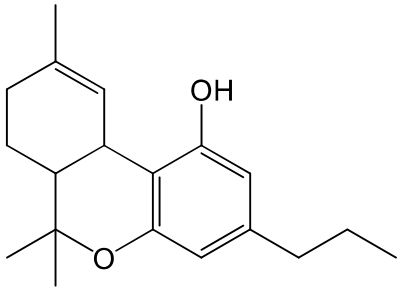


(Tetrahydrocannabivarin (THCV), Formula VI) or a derivative or analog thereof;

compared to a level of said compounds in a comparable plant lacking said genetic modification.

[0002b] In another aspect, provided herein is a pharmaceutical composition comprising an extract of said transgenic plant as described herein.

[0002c] In another aspect, provided herein is a transgenic plant that comprises at least one genetic modification, wherein said genetic modification results in at least about 50% more of a compound that is



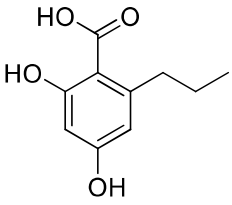
(Tetrahydrocannabivarin (THCV), Formula VI) or a derivative or analog thereof compared to a level of said compound in a comparable plant lacking said genetic modification.

[0002d] In another aspect, provided herein is a method of suppressing appetite in a subject, the method comprising administering an effective amount of the transgenic plant as described herein to the subject, thereby suppressing appetite in the subject.

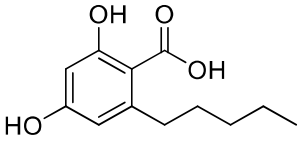
[0002e] In another aspect, provided herein is the pharmaceutical composition as described herein for use in therapy.

[0002f] In another aspect, provided herein is use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating a disease or condition in a subject, wherein the medicament is to be administered to the subject, thereby treating the disease or condition, wherein said disease or condition is selected from the group consisting of anorexia, emesis, pain, inflammation, multiple sclerosis, Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease, epilepsy, glaucoma, osteoporosis, schizophrenia, cardiovascular disorders, cancer, and obesity.

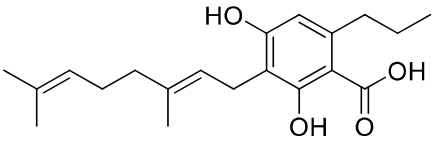
[0003] In one example, provided herein are transgenic plants that comprises at least one genetic modification, wherein said genetic modification results in an increased level of a compound of:

[0004] 

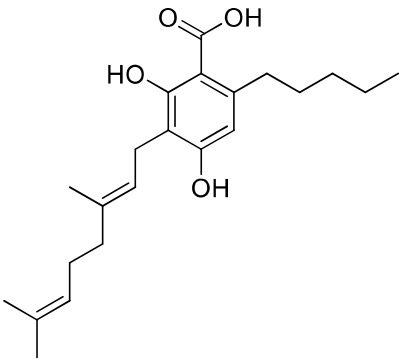
(Divarinic Acid, Formula I);

[0005] 

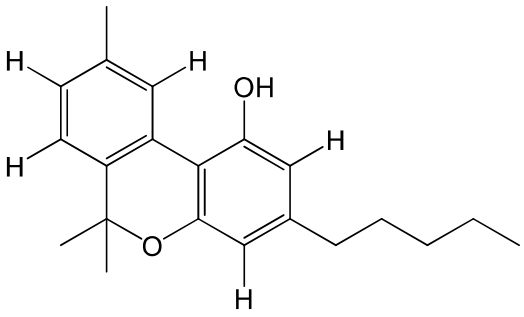
(Olivetolic Acid, Formula II);

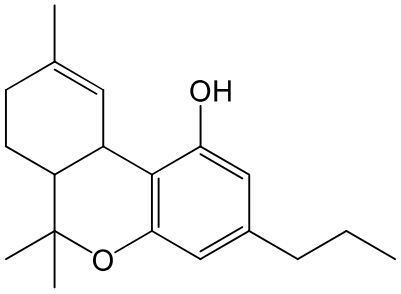
[0006] 

(Cannabigerovarinic Acid (CBGVA), Formula III);

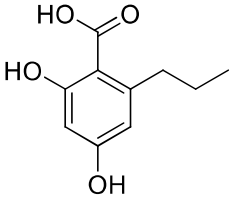
[0007] 

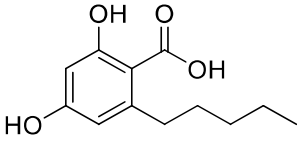
(Cannabigerolic acid (CBGA), Formula IV),

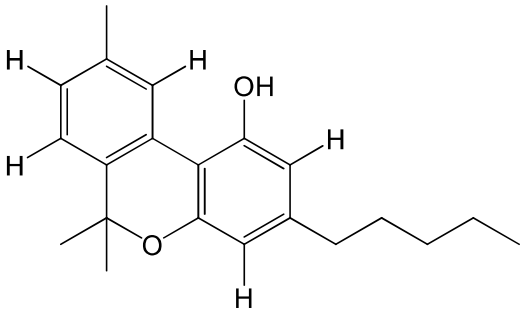
[0008]  (Cannabinol (CBN), Formula V); or

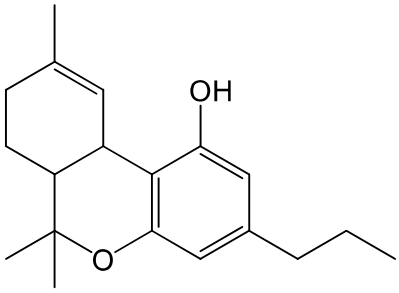
[0009]  (Tetrahydrocannabivarin (THCV), Formula VI); or a derivative or analog thereof, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0010] In another example, provided herein are transgenic plants that comprises at least one genetic modification, wherein said genetic modification results in an increased level of a compound of:

[0011]  (Divarinic Acid, Formula I);

[0012]  (Olivetolic Acid, Formula II);

[0013]  (Cannabinol (CBN), Formula V); or

[0014] 

(Tetrahydrocannabivarin (THCV), Formula VI); or a derivative or analog thereof, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0015] In some examples, said at least one genetic modification is in a promoter or enhancer sequence of a gene encoding a protein.

[0016] In some examples, said gene encodes a polyketide cyclase or a polyketide synthase.

[0017] In some examples, said polyketide cyclase is olivetolic acid cyclase.

[0018] In some examples, said polyketide synthase is olivetolic acid synthase.

[0019] In some examples, said at least one genetic modification increases expression of said protein compared to a comparable plant lacking said genetic modification.

[0020] In some examples, said at least one genetic modification increases activity of said promoter or enhancer.

[0021] In some examples, said at least one genetic modification results in an increased level of a compound of Formula II, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0022] In some examples, said at least one genetic modification results in an increased level of olivetolic acid compared to a comparable plant lacking said genetic modification.

[0023] In some examples, said transgenic plant comprises at least two genetic modifications, wherein each genetic modification is in a promoter or enhancer sequence of a gene encoding a protein.

[0024] In some examples, said transgenic plant comprises a genetic modification in a promoter or enhancer of a sequence of a gene encoding a polyketide cyclase and a genetic modification in a promoter or enhancer of a sequence of a gene encoding a polyketide synthase.

[0025] In some examples, said polyketide cyclase is olivetolic acid cyclase.

[0026] In some examples, said polyketide synthase is olivetolic acid synthase.

[0027] In some examples, said at least two genetic modifications increases expression of said olivetolic acid cyclase compared to a comparable plant lacking said at least genetic modification.

[0028] In some examples, said at least two genetic modifications increases expression of said olivetolic acid synthase compared to a comparable plant lacking said at least genetic modification.

[0029] In some examples, said at least two genetic modifications increases expression of said olivetolic acid synthase and olivetolic acid synthase compared to a comparable plant lacking said at least genetic modification.

[0030] In some examples, said at least two genetic modifications results in an increased level of a compound of Formula II, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0031] In some examples, said at least two genetic modifications results in an increased level of olivetolic acid compared to a comparable plant lacking said at least two genetic modification.

[0032] In some examples, said at least two genetic modifications increases activity of said promoters or enhancers.

[0033] In some examples, said gene encodes Geranyl-pyrophosphate—olivetolic acid geranyltransferase (GOT).

[0034] In some examples, said at least one genetic modification increases expression of Geranyl-pyrophosphate—olivetolic acid geranyltransferase (GOT) protein.

[0035] In some examples, said at least one genetic modification results in an increased level of a compound of Formula IV, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0036] In some examples, said at least one genetic modification results in an increased level of cannabigerolic acid (CBGA), compared to a comparable plant lacking said genetic modification.

[0037] In some examples, said at least one genetic modification increases activity of said promoter or enhancer.

[0038] In some examples, said at least one genetic modification is in a gene sequence that encodes a protein.

[0039] In some examples, said at least one genetic modification disrupts expression of said protein.

[0040] In some examples, said at least one genetic modification decreases expression of said protein compared to a comparable plant lacking said genetic modification.

[0041] In some examples, said at least one genetic modification decreases expression of said protein by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, compared to a comparable plant lacking said genetic modification.

[0042] In some examples, said at least one genetic modification is in a gene sequence that encodes a tetrahydrocannabinolic acid synthase, a cannabidiolic acid synthase, or a cannabichromenic acid synthase.

[0043] In some examples, said transgenic plant comprises at least two genetic modifications each in a gene sequence that encodes a protein.

[0044] In some examples, said transgenic plant comprises at least two genetic modifications each in a different gene sequence that encode different proteins.

[0045] In some examples, said at least two genetic modifications disrupts expression of said proteins.

[0046] In some examples, said at least two genetic modifications decrease expression of said proteins compared to a comparable plant lacking said at least two genetic modifications.

[0047] In some examples, said at least two genetic modifications decrease expression of said proteins by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, compared to a comparable plant lacking said at least two genetic modifications.

[0048] In some examples, said at least two genetic modifications are in a gene sequence that encodes a tetrahydrocannabinolic acid synthase, a cannabidiolic acid synthase, or a cannabichromenic acid synthase.

[0049] In some examples, said transgenic plant that comprises a genetic modification in a promoter or enhancer sequence of a gene encoding a polyketide cyclase or a polyketide synthase, wherein said genetic modification in said promoter or enhancer increases expression of said polyketide cyclase or polyketide synthase, compared to a comparable plant lacking said genetic modificationin said promoter or enhancer sequence; a genetic disruption in a gene sequence that encodes a Tetrahydrocannabinolic acid synthase, a cannabidiolic acid synthase, or a cannabichromenic acid synthase, wherein said genetic disruption decreases expression of said tetrahydrocannabinolic acid synthase, cannabidiolic acid synthase, or cannabichromenic acid synthase; compared to a comparable plant lacking said genetic disruption in said gene sequence that encodes a Tetrahydrocannabinolic acid synthase, a cannabidiolic acid synthase, or a cannabichromenic acid synthase.

[0050] In some examples, said genetic modification in said promoter or enhancer increases expression of said polyketide cyclase or polyketide synthase by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, compared to a comparable plant lacking said genetic modification in said promoter or enhancer sequence.

[0051] In some examples, said genetic modification in said promoter or enhancer increases expression of said polyketide cyclase or polyketide synthase by at least 2 fold, 5 fold, 10 fold,

100 fold, 500 fold, 1000 fold, or 10000 fold compared to a comparable plant lacking said genetic modification in said promoter or enhancer sequence.

[0052] In some examples, said genetic disruption in said gene sequence that encodes a tetrahydrocannabinolic acid synthase, a cannabidiolic acid synthase, or a cannabichromenic acid synthase decreases expression of said tetrahydrocannabinolic acid synthase, cannabidiolic acid synthase, or cannabichromenic acid synthase by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, compared to a comparable plant lacking said genetic disruption in said gene sequence that encodes a tetrahydrocannabinolic acid synthase, a cannabidiolic acid synthase, or a cannabichromenic acid synthase.

[0053] In some examples, said genetic disruption in said gene sequence that encodes a tetrahydrocannabinolic acid synthase, a cannabidiolic acid synthase, or a cannabichromenic acid synthase decreases expression of said tetrahydrocannabinolic acid synthase, cannabidiolic acid synthase, or cannabichromenic acid synthase by at least 2 fold, 5 fold, 10 fold, 100 fold, 500 fold, 1000 fold, or 10000 fold, compared to a comparable plant lacking said genetic disruption in said gene sequence that encodes a tetrahydrocannabinolic acid synthase, a cannabidiolic acid synthase, or a cannabichromenic acid synthase.

[0054] In some examples, said wherein said at least one genetic modification results in an increased level of a compound of Formula II, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0055] In some examples, said wherein said at least one genetic modification results in an increased level of a compound of Formula IV, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0056] In some examples, said gene encodes tetrahydrocannabinolic acid synthase.

[0057] In some examples, said at least one genetic modification increases expression of said tetrahydrocannabinolic acid synthase compared to a comparable plant lacking said at least one genetic modification.

[0058] In some examples, said at least one genetic modification increases activity of said promoter or enhancer.

[0059] In some examples, said at least one genetic modification results in an increased level of a compound of Formula V, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0060] In some examples, said at least one genetic modification results in an increased level of cannabinol compared to a comparable plant lacking said genetic modification.

[0061] In some examples, said at least one genetic modification is in a gene sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase.

[0062] In some examples, said at least one genetic modification disrupts expression of said protein.

[0063] In some examples, said at least one genetic modification decreases expression of said protein compared to a comparable plant lacking said genetic modification.

[0064] In some examples, said at least one genetic modification decreases expression of said protein by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, compared to a comparable plant lacking said genetic modification.

[0065] In some examples, said at least one genetic modification decreases expression of said protein by at least 2 fold, 5 fold, 10 fold, 100 fold, 500 fold, 1000 fold, or 10000 fold, compared to a comparable plant lacking said genetic modification.

[0066] In some examples, said transgenic plant comprises a genetic modification in a promoter or enhancer sequence of a gene encoding a THC synthase, wherein said genetic modification in said promoter or enhancer increases expression of said THC synthase, compared to a comparable plant lacking said genetic modification in said promoter or enhancer sequence; and a genetic disruption in a gene sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase, wherein said genetic disruption decreases expression of said cannabidiolic acid synthase or said cannabichromenic acid synthase; compared to a comparable plant lacking said genetic disruption in said gene sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase.

[0067] In some examples, said genetic modificationin said promoter or enhancer increases expression of said THC synthase by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, compared to a comparable plant lacking said genetic modification in said promoter or enhancer sequence.

[0068] In some examples, said genetic modification in said promoter or enhancer increases expression of said THC synthase by at least 2 fold, 5 fold, 10 fold, 100 fold, 500 fold, 1000 fold, or 10000 fold compared to a comparable plant lacking said genetic modification in said promoter or enhancer sequence.

[0069] In some examples, said genetic disruption in said gene sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase decreases expression of said cannabidiolic acid synthase or said cannabichromenic acid synthase by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, compared to a comparable plant lacking said

genetic disruption in said gene sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase.

[0070] In some examples, said genetic disruption in said gene sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase decreases expression of said cannabidiolic acid synthase or said cannabichromenic acid synthase by at least 2 fold, 5 fold, 10 fold, 100 fold, 500 fold, 1000 fold, or 10000 fold, compared to a comparable plant lacking said genetic disruption in said gene sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase.

[0071] In some examples, said wherein said at least one genetic modification results in an increased level of a compound of Formula V, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0072] In some examples, said wherein said at least one genetic modification results in an increased level of a cannabinoil (CBN), compared to a level of said compound in a comparable plant lacking said genetic modification.

[0073] In some examples, said gene encodes THC synthase, olivetolate geranyltransferase (GOT), geranyl pyrophosphate synthase (GPPS), polyketide synthase, or divarinic acid cyclase.

[0074] In some examples, said gene encodes THC synthase.

[0075] In some examples, said gene encodes olivetolate geranyltransferase (GOT).

[0076] In some examples, said gene encodes geranyl pyrophosphate synthase (GPPS).

[0077] In some examples, said gene encodes polyketide synthase.

[0078] In some examples, said gene encodes divarinic acid cyclase.

[0079] In some examples, said at least one genetic modification increases expression of said protein compared to a comparable plant lacking said genetic modification.

[0080] In some examples, said at least one genetic modification increases activity of said promoter or enhancer.

[0081] In some examples, said at least one genetic modification results in an increased level of a compound of Formula I, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0082] In some examples, said at least one genetic modification results in an increased level of a compound of Formula II, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0083] In some examples, said at least one genetic modification results in an increased level of a compound of Formula III, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0084] In some examples, said at least one genetic modification results in an increased level of a compound of Formula VI, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0085] In some examples, said at least one genetic modification results in an increased level of a compound of Formula I, Formula II, Formula III, and Formula VI, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0086] In some examples, said at least one genetic modification results in an increased level of a compound of Formula III and Formula VI, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0087] In some examples, said at least one genetic modification results in an increased level of tetrahydrocannabivarinic Acid (THCVA) compared to a comparable plant lacking said genetic modification.

[0088] In some examples, said at least one genetic modification results in an increased level of cannabigerovarinic acid (CBGVA) compared to a comparable plant lacking said genetic modification.

[0089] In some examples, said transgenic plant comprises genetic disruption in a promoter or enhancer sequence of at least one, two, three, four, or five different genes, wherein said genes encode for olivetolate geranyltransferase (GOT), geranyl pyrophosphate synthase (GPPS), polyketide synthase, or divarinic acid cyclase.

[0090] In some examples, said transgenic plant comprises a genetic modification in a promoter or enhancer of a gene that encodes for olivetolate geranyltransferase (GOT), geranyl pyrophosphate synthase (GPPS), polyketide synthase, and divarinic acid cyclase.

[0091] In some examples, said genetic modifications increase expression of olivetolate geranyltransferase (GOT), geranyl pyrophosphate synthase (GPPS), polyketide synthase, and divarinic acid cyclase.

[0092] In some examples, said at least one genetic modification is in a gene sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase.

[0093] In some examples, said at least one genetic modification disrupts expression of said protein.

[0094] In some examples, said at least one genetic modification decreases expression of said protein compared to a comparable plant lacking said genetic modification.

[0095] In some examples, said at least one genetic modification decreases expression of said protein by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, compared to a comparable plant lacking said genetic modification.

[0096] In some examples, said at least one genetic modification decreases expression of said protein by at least 2 fold, 5 fold, 10 fold, 100 fold, 500 fold, 1000 fold, or 10000 fold, compared to a comparable plant lacking said genetic modification.

[0097] In some examples, said at least one genetic modification results in an increased level of a compound of Formula I, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0098] In some examples, said at least one genetic modification results in an increased level of a compound of Formula II, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0099] In some examples, said at least one genetic modification results in an increased level of a compound of Formula III, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0100] In some examples, said at least one genetic modification results in an increased level of a compound of Formula VI, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0101] In some examples, said at least one genetic modification results in an increased level of a compound of Formula I, Formula II, Formula III, and Formula VI, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0102] In some examples, said at least one genetic modification results in an increased level of a compound of Formula III and Formula VI, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0103] In some examples, said at least one genetic modification results in an increased level of tetrahydrocannabivarinic Acid (THCVA) compared to a comparable plant lacking said genetic modification.

[0104] In some examples, said at least one genetic modification results in an increased level of cannabigerovarinic acid (CBGVA) compared to a comparable plant lacking said genetic modification.

[0105] In some examples, said transgenic plant comprises a genetic modification in a promoter or enhancer sequence of a gene encoding THC synthase, olivetolate geranyltransferase (GOT), geranyl pyrophosphate synthase (GPPS), polyketide synthase, or divarinic acid cyclase, wherein said genetic modification in said promoter or enhancer increases expression of said THC synthase, olivetolate geranyltransferase (GOT), geranyl pyrophosphate synthase (GPPS), polyketide synthase, or divarinic acid cyclase, compared to a comparable plant lacking said genetic modification in said promoter or enhancer sequence; and a genetic disruption in a gene

sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase, wherein said genetic disruption decreases expression of said cannabidiolic acid synthase or said cannabichromenic acid synthase; compared to a comparable plant lacking said genetic disruption in said gene sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase.

[0106] In some examples, said transgenic plant comprises a genetic modification in a promoter or enhancer sequence of at least one, two, three, four, or five different genes, wherein said genes encode for THC synthase, olivetolate geranyltransferase (GOT), geranyl pyrophosphate synthase (GPPS), polyketide synthase, or divarinic acid cyclase, wherein said genetic modification in said promoter or enhancer increases expression of said THC synthase, olivetolate geranyltransferase (GOT), geranyl pyrophosphate synthase (GPPS), polyketide synthase, or divarinic acid cyclase, compared to a comparable plant lacking said genetic modificationin said promoter or enhancer sequence; and a genetic disruption in at least one or two gene sequences that encode a cannabidiolic acid synthase or a cannabichromenic acid synthase, wherein said genetic disruption decreases expression of said cannabidiolic acid synthase or said cannabichromenic acid synthase; compared to a comparable plant lacking said genetic disruption in said gene sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase.

[0107] In some examples, said genetic modification in said promoter or enhancer increases expression of said THC synthase, olivetolate geranyltransferase (GOT), geranyl pyrophosphate synthase (GPPS), polyketide synthase, or divarinic acid cyclase by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, compared to a comparable plant lacking said genetic modification in said promoter or enhancer sequence.

[0108] In some examples, said genetic modification in said promoter or enhancer increases expression of said THC synthase, olivetolate geranyltransferase (GOT), geranyl pyrophosphate synthase (GPPS), polyketide synthase, or divarinic acid cyclase by at least 2 fold, 5 fold, 10 fold, 100 fold, 500 fold, 1000 fold, or 10000 fold compared to a comparable plant lacking said genetic modification in said promoter or enhancer sequence.

[0109] In some examples, said genetic disruption in said gene sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase decreases expression of said cannabidiolic acid synthase or said cannabichromenic acid synthase by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, compared to a comparable plant lacking said genetic disruption in said gene sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase.

[0110] In some examples, said genetic disruption in said gene sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase decreases expression of said cannabidiolic acid synthase or said cannabichromenic acid synthase by at least 2 fold, 5 fold, 10 fold, 100 fold, 500 fold, 1000 fold, or 10000 fold, compared to a comparable plant lacking said genetic disruption in said gene sequence that encodes a cannabidiolic acid synthase or a cannabichromenic acid synthase.

[0111] In some examples, said wherein said at least one genetic modification results in an increased level of a compound of Formula II, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0112] In some examples, said wherein said at least one genetic modification results in an increased level of a compound of Formula IV, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0113] In some examples, said at least one genetic modification results in an increased level of a compound of Formula I, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0114] In some examples, said at least one genetic modification results in an increased level of a compound of Formula II, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0115] In some examples, said at least one genetic modification results in an increased level of a compound of Formula III, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0116] In some examples, said at least one genetic modification results in an increased level of a compound of Formula VI, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0117] In some examples, said at least one genetic modification results in an increased level of a compound of Formula I, Formula II, Formula III, and Formula VI, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0118] In some examples, said at least one genetic modification results in an increased level of a compound of Formula III and Formula VI, compared to a level of said compound in a comparable plant lacking said genetic modification.

[0119] In some examples, said at least one genetic modification results in an increased level of tetrahydrocannabivarinic Acid (THCVA) compared to a comparable plant lacking said genetic modification.

[0120] In some examples, said at least one genetic modification results in an increased level of cannabigerovarinic acid (CBGVA) compared to a comparable plant lacking said genetic modification.

[0121] In some examples, said transgenic plant further comprises an increased amount of cannabigerol (CBG), derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said genetic modification.

[0122] The transgenic plant of claim 1 or 108, wherein said genetic modification comprises a genetic disruption that results in an increased expression of Formula II, or a derivative or analog thereof.

[0123] In some examples, said first group of genes comprises olivetolic acid cyclase (OAC) and olivetolic acid synthase (OLS).

[0124] In some examples, said genetic modification comprises a disruption of gene encoding prenyl-transferase, wherein said disruption results in an increased amount of prenyl-transferase compared to an amount of the same compound comparable control plant without said disruption.

[0125] In some examples, said prenyl-transferase is olivetolic acid geranyltransferase (GOT).

[0126] In some examples, said disruption is in a promoter region of said genes.

[0127] In some examples, said genetic modification comprises a disruption of a second of group of genes encoding CBCA synthase, CBDA synthase, and THCA synthase.

[0128] In some examples, said disruption results in a decreased amount of CBCA synthase, CBDA synthase, THCA synthase, derivatives or analogs thereof compared to an amount of the same compound of a comparable control plant without said disruption.

[0129] In some examples, said disruption is in a coding region of said genes.

[0130] In some examples, said transgenic plant comprises 10% more Formula IV measured by dry weight as compared to a comparable control plant without said modification.

[0131] In some examples, said transgenic plant comprises 25% more Formula IV measured by dry weight as compared to a comparable control plant without said modification.

[0132] In some examples, said transgenic plant comprises 35% more Formula IV measured by dry weight as compared to a comparable control plant without said modification.

[0133] In some examples, said transgenic plant comprises 50% more Formula IV measured by dry weight as compared to a comparable control plant without said modification.

[0134] In some examples, said transgenic plant comprises 10% less cannabichromenic acid (CBCA) measured by dry weight as compared to a comparable control plant without said modification.

[0135] In some examples, said transgenic plant comprises 10% less cannabidiolic acid (CBDA) measured by dry weight as compared to a comparable control plant without said modification.

[0136] In some examples, said transgenic plant comprises 10% less tetrahydrocannabinolic acid (THCA) measured by dry weight as compared to a comparable control plant without said modification.

[0137] In some examples, said transgenic plant comprises an increased amount of cannabinol (CBN), derivative or analog thereof compared to an amount of the same compound in a comparable control plant without said genetic modification.

[0138] In some examples, said genetic modification comprises a disruption of gene encoding THCA synthase.

[0139] In some examples, said disruption results in an increased amount of THCA synthase compared to an amount of the same compound in a comparable control plant without said disruption.

[0140] In some examples, said disruption is in a promoter region of said gene.

[0141] In some examples, said genetic modification comprises a disruption of genes encoding CBDA synthase and CBCA synthase respectively.

[0142] In some examples, said disruption results in decreased amount of CBDA synthase and CBCA synthase compared to a comparable control plant without said disruption.

[0143] In some examples, said disruption is in a coding region of said genes.

[0144] In some examples, said genetic modification comprises a disruption of a third group of genes, wherein said disruption results in increased UV absorption of said transgenic plant compared to a comparable control without said disruption.

[0145] In some examples, said transgenic plant comprises 10% more THC measured by dry weight as compared to a comparable control plant without said genetic modification.

[0146] In some examples, said transgenic plant comprises 25% more THC measured by dry weight as compared to a comparable control plant without said genetic modification.

[0147] In some examples, said transgenic plant comprises 35% more THC measured by dry weight as compared to a comparable control plant without said genetic modification.

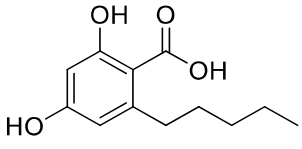
[0148] In some examples, said transgenic plant comprises 50% more THC measured by dry weight as compared to a comparable control plant without said genetic modification.

[0149] In some examples, said transgenic plant comprises 10% less CBCA measured by dry weight as compared to a comparable control plant without said genetic modification.

[0150] In some examples, said transgenic plant comprises 10% less CBDA measured by dry weight as compared to a comparable control plant without said genetic modification.

[0151] In some examples, said transgenic plant comprises an increased amount of tetrahydrocannabivarin (THCV), derivative or analog thereof compared to an amount of the same compound in a comparable control plant without said genetic modification.

[0152] In some examples, said genetic modification comprises a disruption of a first of group of genes, wherein said disruption results in an increased amount of Formula I, derivative or analog thereof.

[0153] In some examples, said genetic modification comprises a disruption of a second group of genes, wherein said disruption results in a decreased amount of 

, derivative or analog thereof.

[0154] In some examples, said second group of genes comprises OAC and OLS.

[0155] In some examples, said disruption is in a coding region of said genes.

[0156] In some examples, said genetic modification comprises a disruption of a THCA synthase.

[0157] In some examples, said disruption results in an increased amount of THCA synthase, derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said disruption.

[0158] In some examples, said disruption is in a promoter region of said genes.

[0159] In some examples, said genetic modification comprises a disruption of a third group of genes encoding CBCA synthase and CBDA synthase respectively.

[0160] In some examples, said disruption results in a decreased amount of CBCA synthase and CBDA synthase, derivatives or analogs thereof.

[0161] In some examples, said disruption is in a coding region of said genes.

[0162] In some examples, said transgenic plant comprises 10% more tetrahydrocannabivarin (THCV) measure by dry weight as compared to a comparable control plant without said modification.

[0163] In some examples, said transgenic plant comprises 25% more tetrahydrocannabivarin (THCV) measure by dry weight as compared to a comparable control plant without said modification.

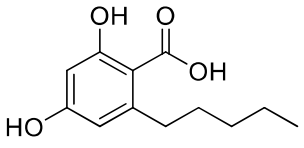
[0164] In some examples, said transgenic plant comprises 35% more tetrahydrocannabivarin (THCV) measure by dry weight as compared to a comparable control plant without said modification.

[0165] In some examples, said transgenic plant comprises 50% more tetrahydrocannabivarin (THCV) measure by dry weight as compared to a comparable control plant without said modification.

[0166] In some examples, said transgenic plant comprises 10% less cannabichromevarin (CBCV) measure by dry weight as compared to a comparable control plant without said modification.

[0167] In some examples, said transgenic plant comprises 10% less cannabidivarin (CBDV) measure by dry weight as compared to a comparable control plant without said modification.

[0168] In some examples, said transgenic plant comprises a genetic modification, wherein said genetic modification results in an increased amount of cannabigerol (CBG), derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said genetic modification.

[0169] In some examples, said genetic modification comprises a disruption of a first group of genes, wherein said disruption results in an increased amount of 

, derivative or analog thereof.

[0170] In some examples, said first group of genes comprises olivetolic acid cyclase (OAC) and olivetolic acid synthase (OLS).

[0171] In some examples, said genetic modification comprises a disruption of gene encoding prenyl-transferase, wherein said disruption results in an increased amount of prenyl-transferase compared to a comparable control plant without said disruption.

[0172] In some examples, said prenyl-transferase is olivetolic acid geranyltransferase (GOT).

[0173] In some examples, said disruption is in a promoter region of said genes.

[0174] In some examples, said genetic modification comprises a disruption of a second of group of genes encoding CBCA synthase, CBDA synthase, and THCA synthase.

[0175] In some examples, said disruption results in a decreased amount of CBCA synthase, CBDA synthase, THCA synthase, derivatives or analogs thereof, compared to an amount of the same compound in a comparable control plant without said disruption.

[0176] In some examples, said disruption is in a coding region of said genes.

[0177] In some examples, said transgenic plant comprises 10% more Formula IV measured by dry weight as compared to a comparable control plant without said modification.

[0178] In some examples, said transgenic plant comprises 25% more Formula IV measured by dry weight as compared to a comparable control plant without said modification.

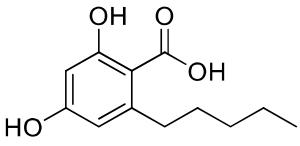
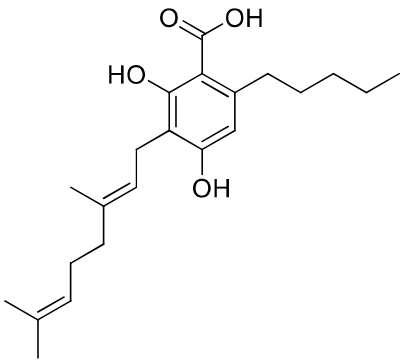
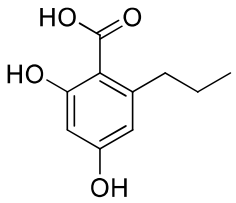
[0179] In some examples, said transgenic plant comprises 35% more Formula IV measured by dry weight as compared to a comparable control plant without said modification.

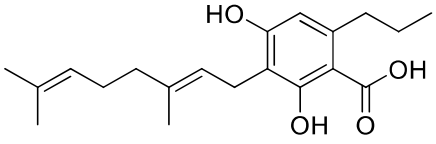
[0180] In some examples, said transgenic plant comprises 50% more Formula IV measured by dry weight as compared to a comparable control plant without said modification.

[0181] In some examples, said transgenic plant comprises 10% less cannabichromenic acid (CBCA) measured by dry weight as compared to a comparable control plant without said modification.

[0182] In some examples, said transgenic plant comprises 10% less cannabidiolic acid (CBDA) measured by dry weight as compared to a comparable control plant without said modification.

[0183] In some examples, said transgenic plant comprises 10% less tetrahydrocannabinolic acid (THCA) measured by dry weight as compared to a comparable control plant without said modification.

[0184] In one example, provided herein are genetically modified cells comprising a genetic modification, wherein said genetic modification results in an increased amount of  and , derivatives or analogs thereof, wherein said genetic modification does not result in a change of amount of  and



, derivatives or analogs thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0185] In some examples, said genetic modification further results in an increased amount of cannabigerol (CBG), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0186] In some examples, said genetic modification results in an increased amount of cannabinol (CBN), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0187] In some examples, said genetic modification results in an increased amount of tetrahydrocannabivarin (THCV), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0188] In some examples, said genetic modification comprises a disruption of gene encoding geranyl pyrophosphate synthase (GPPS), resulting in increased amount of geranyl pyrophosphate (GPP).

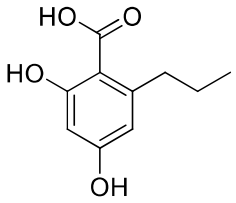
[0189] In some examples, genetic modification comprises a disruption of gene encoding polyketide synthase (PKS), resulting in increased amount of either Formula I or Formula II or both.

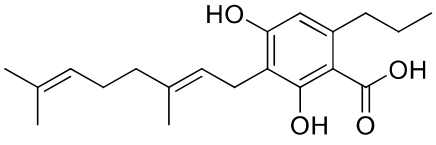
[0190] In some examples, the genetically modified cell is a plant cell, an algae cell, a agrobacterium cell, a E.coli cell, a yeast cell, an animal cell, or an insect cell.

[0191] In some examples, said genetically modified cell is a plant cell.

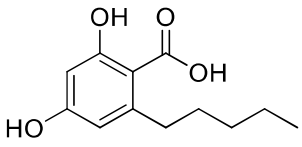
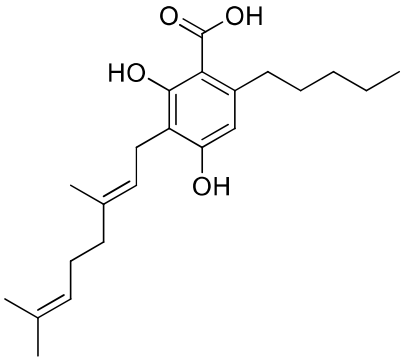
[0192] In some examples, said genetically modified cell is a cannabis plant cell.

[0193] In some examples, said genetically modified cell is a callus cell, a protoplast, an embryonic cell, a leaf cell, a seed cell, a stem cell, or a root cell.

[0194] In one example, provided herein are genetically modified cells comprising a genetic modification, wherein said genetic modification results in an increased amount of 

and 

, derivatives or analogs thereof, wherein

said genetic modification does not result in a change of amount of  and , derivatives or analogs thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0195] In some examples, said genetic modification further results in an increased amount of cannabigerol (CBG), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0196] In some examples, said genetic modification results in an increased amount of cannabinol (CBN), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0197] In some examples, said genetic modification results in an increased amount of tetrahydrocannabivarin (THCV), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0198] In some examples, said genetic modification comprises a disruption of gene encoding geranyl pyrophosphate synthase (GPPS), resulting in increased amount of geranyl pyrophosphate (GPP).

[0199] In some examples, genetic modification comprises a disruption of gene encoding polyketide synthase (PKS), resulting in increased amount of either Formula I or Formula II or both.

[0200] In some examples, the genetically modified cell is a plant cell, an algae cell, a agrobacterium cell, a E.coli cell, a yeast cell, an animal cell, or an insect cell.

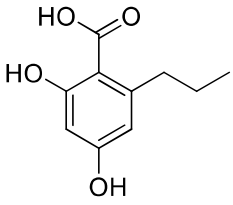
[0201] In some examples, said genetically modified cell is a plant cell.

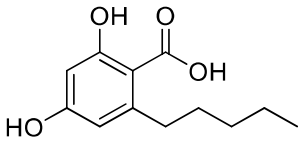
[0202] In some examples, said genetically modified cell is a cannabis plant cell.

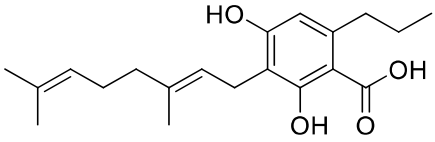
[0203] In some examples, said genetically modified cell is a callus cell, a protoplast, an embryonic cell, a leaf cell, a seed cell, a stem cell, or a root cell.

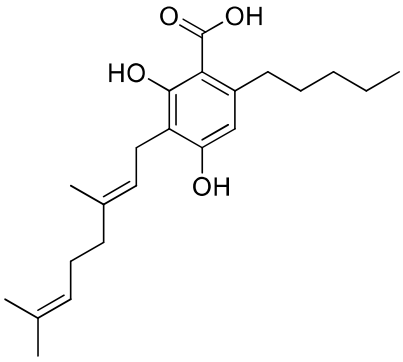
[0204] In some examples, said modification is integrated in the genome of said cell.

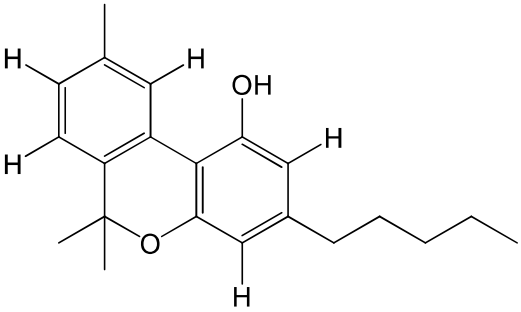
[0205] In one example, provided herein are compositions comprising an endonuclease or polynucleotide encoding said endonuclease capable of introducing a genetic modification, wherein said genetic modification results in an increased amount of a compound of:

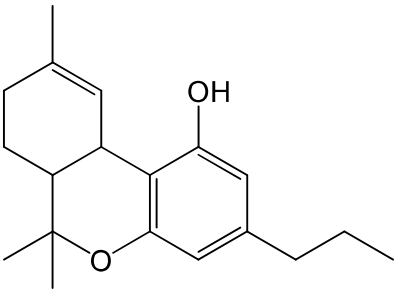
[0206]  (Formula I);

[0207]  (Formula II);

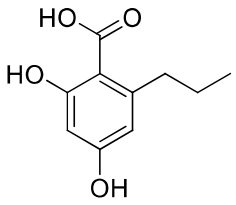
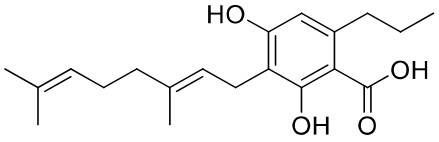
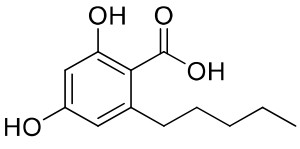
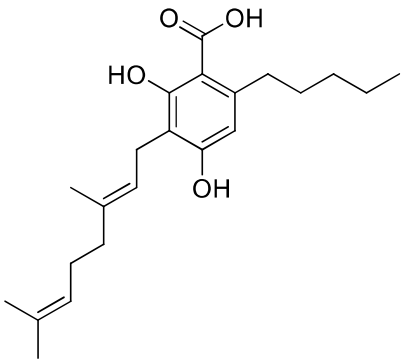
[0208]  (Formula III);

[0209]  (Formula IV),

[0210]  (Formula V); or

[0211]  (Formula VI); or derivatives or analogs thereof.

[0212] In one example, provided herein are compositions comprising an endonuclease or polynucleotide encoding said endonuclease capable of introducing a genetic modification,

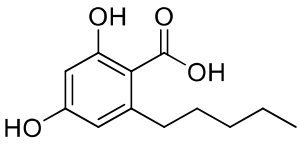
wherein said genetic modification results in an increased amount of  and , derivatives or analogs thereof, wherein said genetic modification does not result in a change of amount of  and , derivatives or analogs thereof, compared to a comparable control cell without said genetic modification.

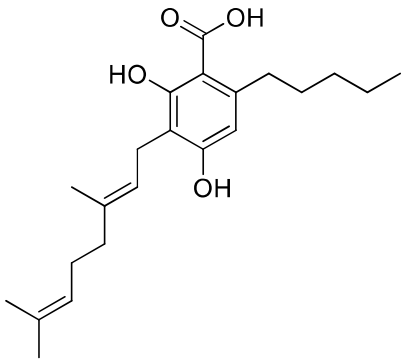
[0213] In some examples, said genetic modification further results in an increased amount of cannabigerol (CBG), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

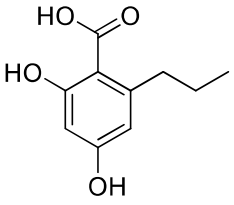
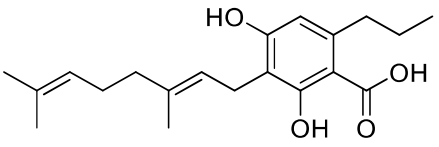
[0214] In some examples, said genetic modification results in an increased amount of cannabinol (CBN), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0215] In some examples, said genetic modification results in an increased amount of tetrahydrocannabivarin (THCV), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0216] In some examples, said modification is in a coding region of the THCAS gene.

[0217] In one example, provided herein are compositions comprising an endonuclease or polynucleotide encoding said endonuclease capable of introducing a genetic modification, wherein said genetic modification results in an increased amount of  and



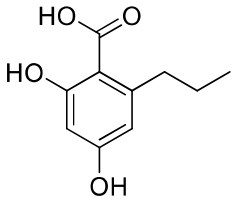
, derivatives or analogs thereof, wherein said genetic modification does not result in a change of amount of  and , derivatives or analogs thereof, compared to a comparable control cell without said genetic modification.

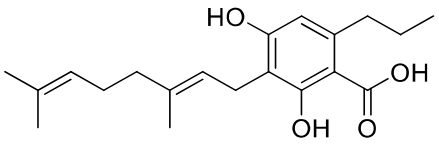
[0218] In some examples, said genetic modification further results in an increased amount of cannabigerol (CBG), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

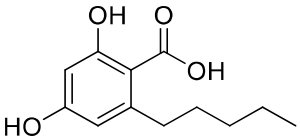
[0219] In some examples, said genetic modification results in an increased amount of cannabinol (CBN), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

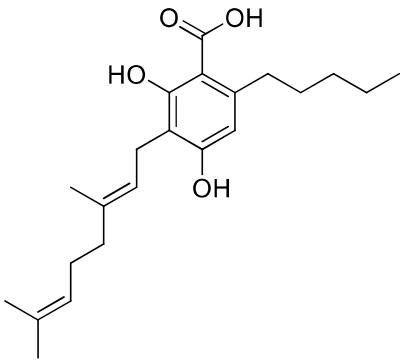
[0220] In some examples, said genetic modification results in an increased amount of tetrahydrocannabivarin (THCV), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0221] In some examples, said modification is in a coding region of the THCAS gene.

[0222] In one example, provided herein are compositions comprising an endonuclease or polynucleotide encoding said endonuclease capable of introducing a genetic modification, wherein said genetic modification results in an increased amount of  and



, derivatives or analogs thereof, wherein said genetic modification does not result in a change of amount of 

and 

, derivatives or analogs thereof, compared to a comparable control cell without said genetic modification.

[0223] In some examples, said genetic modification further results in an increased amount of cannabigerol (CBG), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0224] In some examples, said genetic modification results in an increased amount of cannabinol (CBN), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0225] In some examples, said genetic modification results in an increased amount of tetrahydrocannabivarin (THCV), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0226] In some examples, said modification is in a coding region of the THCAS gene.

[0227] In one example, provided herein are methods of making transgenic plants described herein.

[0228] In one example, provided herein are kits for genome editing comprising the composition described herein

[0229] In one example, provided herein are cells comprising the composition described herein.

[0230] In some examples, the genetically modified cell is a plant cell, an algae cell, a agrobacterium cell, a E.coli cell, a yeast cell, an insect cell, or an animal cell.

[0231] In some examples, said genetically modified cell is a plant cell.

[0232] In some examples, said genetically modified cell is a cannabis plant cell.

[0233] In some examples, said genetically modified cell is a callus cell, a protoplast, an embryonic cell, a leaf cell, a seed cell, a stem cell, or a root cell.

[0234] In one example, provided herein are plants comprising a cell described herein.

[0235] In one example, provided herein are pharmaceutical compositions comprising an extract of a transgenic plant described herein, a genetically modified cell described herein, a composition described herein, or a cell described herein.

[0236] In some examples, said method further comprises a pharmaceutically acceptable excipient, diluent, or carrier.

[0237] In some examples, said pharmaceutically acceptable excipient is a lipid.

[0238] In one example, provided herein are nutraceutical compositions comprising an extract of a transgenic plant described herein, a genetically modified described herein, a composition described herein, or a cell described herein.

[0239] In one example, provided herein are food supplement compositions comprising an extract of a transgenic plant described herein, a genetically modified described herein, a composition described herein, or a cell described herein.

[0240] In one example, provided herein are pharmaceutical compositions described herein, the nutraceutical compositions described herein, or the food supplements described herein in an oral form, a transdermal form, an oil formulation, an edible food, a food substrate, an aqueous dispersion, an emulsion, a solution, a suspension, an elixir, a gel, a syrup, an aerosol, a mist, a powder, a tablet, a lozenge, a gel, a lotion, a paste, a formulated stick, a balm, a cream, or an ointment.

[0241] In one example, provided herein are methods of treating a disease or condition comprising administering pharmaceutical composition, a nutraceutical composition, or a food supplement described herein.

[0242] In some examples, said disease or condition is selected from the group consisting of anorexia, emesis, pain, inflammation, multiple sclerosis, Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease, epilepsy, glaucoma, osteoporosis, schizophrenia, cardiovascular disorders, cancer, and obesity.

[0243] In one example, provided herein are transgenic plants comprising a genetic modification, wherein said genetic modification results in an increased amount of cannabinol (CBN), derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said genetic modification.

[0244] In some examples, said genetic modification comprises a disruption of gene encoding THCA synthase.

[0245] In some examples, said disruption results in an increased amount of THCA synthase compared to a comparable control plant without said disruption.

[0246] In some examples, said disruption is in a promoter region of said gene.

[0247] In some examples, said genetic modification comprises a disruption of genes encoding CBDA synthase and CBCA synthase respectively.

[0248] In some examples, said disruption results in decreased amount of CBDA synthase and CBCA synthase compared to a comparable control plant without said disruption.

[0249] In some examples, said disruption is in a coding region of said genes.

[0250] In some examples, said genetic modification comprises a disruption of a third group of genes, wherein said disruption results in increased UV absorption of said transgenic plant compared to a comparable control without said disruption.

[0251] In some examples, said transgenic plant comprises 10% more THC measured by dry weight as compared to a comparable control plant without said genetic modification.

[0252] In some examples, said transgenic plant comprises 25% more THC measured by dry weight as compared to a comparable control plant without said genetic modification.

[0253] In some examples, said transgenic plant comprises 35% more THC measured by dry weight as compared to a comparable control plant without said genetic modification.

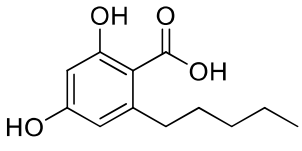
[0254] In some examples, said transgenic plant comprises 50% more THC measured by dry weight as compared to a comparable control plant without said genetic modification.

[0255] In some examples, said transgenic plant comprises 10% less CBCA measured by dry weight as compared to a comparable control plant without said genetic modification.

[0256] In some examples, said transgenic plant comprises 10% less CBDA measured by dry weight as compared to a comparable control plant without said genetic modification.

[0257] In one example, provided herein are transgenic plants comprising a genetic modification, wherein said genetic modification results in an increased amount of tetrahydrocannabivarin (THCV), derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said genetic modification.

[0258] In some examples, said genetic modification comprises a disruption of a first of group of genes, wherein said disruption results in an increased amount of Formula I, derivative or analog thereof.

[0259] In some examples, said genetic modification comprises a disruption of a second group of genes, wherein said disruption results in a decreased amount of 

, derivative or analog thereof.

[0260] In some examples, said second group of genes comprises OAC and OLS.

[0261] In some examples, said disruption is in a coding region of said genes.

[0262] In some examples, said genetic modification comprises a disruption of a THCA synthase.

[0263] In some examples, said disruption results in an increased level of THCA synthase, derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said disruption.

[0264] In some examples, said disruption is in a promoter region of said genes.

[0265] In some examples, said genetic modification comprises a disruption of a third group of genes encoding CBCA synthase and CBDA synthase respectively.

[0266] In some examples, said disruption results in a decreased amount of CBCA synthase and CBDA synthase, derivatives or analogs thereof.

[0267] In some examples, said disruption is in a coding region of said genes.

[0268] In some examples, said transgenic plant comprises 10% more tetrahydrocannabivarin (THCV) measure by dry weight as compared to a comparable control plant without said modification.

[0269] In some examples, said transgenic plant comprises 25% more tetrahydrocannabivarin (THCV) measure by dry weight as compared to a comparable control plant without said modification.

[0270] In some examples, said transgenic plant comprises 35% more tetrahydrocannabivarin (THCV) measure by dry weight as compared to a comparable control plant without said modification.

[0271] In some examples, said transgenic plant comprises 50% more tetrahydrocannabivarin (THCV) measure by dry weight as compared to a comparable control plant without said modification.

[0272] In some examples, said transgenic plant comprises 10% less cannabichromevarin (CBCV) measure by dry weight as compared to a comparable control plant without said modification.

[0273] In some examples, said transgenic plant comprises 10% less cannabidivarin (CBDV) measure by dry weight as compared to a comparable control plant without said modification.

[0274] In some examples, said genetic modification is conducted by an endonuclease.

[0275] In some examples, said genetic modification comprises an insertion, a deletion, a substitution, or a frameshift.

[0276] In some examples, said endonuclease comprises a CRISPR enzyme, TALE-Nuclease, transposon-based nuclease, Zinc finger nuclease, meganuclease, Mega-TAL or DNA guided nuclease.

[0277] In some examples, said DNA-guided nuclease comprises argonaute.

[0278] In some examples, said endonuclease is a CRISPR enzyme complexed with a guide polynucleotide that is complementary to a target sequence of at least one of genes encoding OAC, OLS, GOT, CBCA synthase, CBDA synthase, and THCA synthase.

[0279] In some examples, said target sequence is at least 18 nucleotides, at least 19 nucleotides, at least 20 nucleotides, at least 21 nucleotides, or at least 22 nucleotides in length.

[0280] In some examples, said target sequence is at most 17 nucleotides in length.

[0281] In some examples, said target sequence comprises a sequence selected from Table 2 or Table 3 or complementary thereof**.**

[0282] In some examples, said guide polynucleotide is a chemically modified.

[0283] In some examples, said guide polynucleotide is a single guide RNA (sgRNA).

[0284] In some examples, said guide polynucleotide is a chimeric single guide comprising RNA and DNA.

[0285] In some examples, said guide polynucleotide comprises a sequence selected from Table 2 or Table 3 or complementary thereof.

[0286] In some examples, said CRISPR enzyme is a Cas protein.

[0287] In some examples, the Cas protein comprises Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas5d, Cas5t, Cas5h, Cas5a, Cas6, Cas7, Cas8, Cas9, Cas10, Csy1 , Csy2, Csy3, Csy4, Cse1, Cse2, Cse3, Cse4, Cse5e, Csc1, Csc2, Csa5, Csn1, Csn2, Csm1, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx1S, Csf1, Csf2, CsO, Csf4, Csd1, Csd2, Cst1, Cst2, Csh1, Csh2, Csa1, Csa2, Csa3, Csa4, Csa5, C2c1, C2c2, C2c3, Cpf1, CARF, DinG, homologues thereof, or modified versions thereof.

[0288] In some examples, said Cas protein is Cas9.

[0289] In some examples, said Cas9 recognizes a canonical PAM.

[0290] In some examples, said Cas9 recognizes a non-canonical PAM.

[0291] In some examples, said guide polynucleotide binds said target sequence 3-10 nucleotides from of PAM.

[0292] In some examples, said CRISPR enzyme complexed with said guide polynucleotide is introduced into said transgenic plant by an RNP.

[0293] In some examples, said CRISPR enzyme complexed with said guide polynucleotide is introduced into said transgenic plant by a vector comprising a nucleic acid encoding said CRISPR enzyme and said guide polynucleotide.

[0294] In some examples, said vector is a binary vector or a Ti plasmid.

[0295] In some examples, said vector further comprises a selection marker or a reporter gene.

[0296] In some examples, said RNP or vector is introduced into said transgenic plant via electroporation, agrobacterium mediated transformation, biolistic particle bombardment, or protoplast transformation.

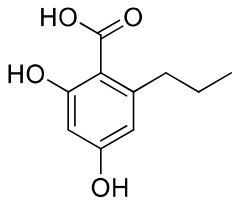
[0297] In some examples, said RNP or vector further comprising a donor polynucleotide.

[0298] In some examples, said donor polynucleotide comprises homology to sequences flanking said target sequence.

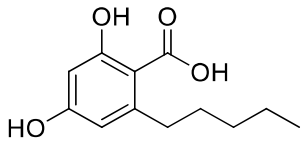
[0299] In some examples, said donor polynucleotide introduces a stop codon into at least one of genes encoding OAC, OLS, GOT, CBCA synthase, CBDA synthase, and THCA synthase.

[0300] In some examples, said donor polynucleotide further comprises a barcode, a reporter gene, or a selection marker.

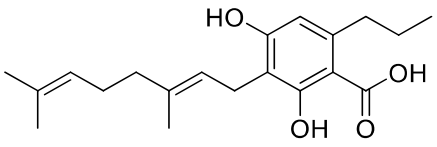
[0301] In one example, provided herein are methods for generating a transgenic plant, said method comprising: (a) contacting a plant cell with an endonuclease or a polypeptide encoding said endonuclease, wherein said endonuclease introduces a genetic modification resulting in an increased amount of a compound selected from:



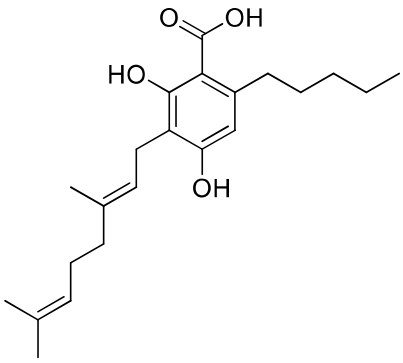
(Formula I);



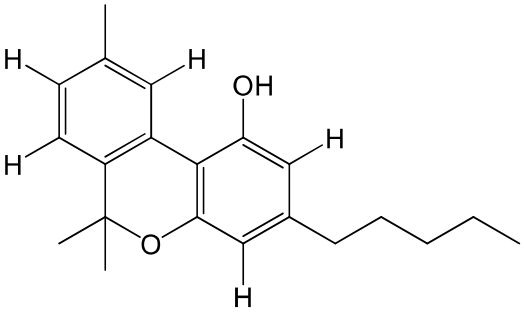
(Formula II);



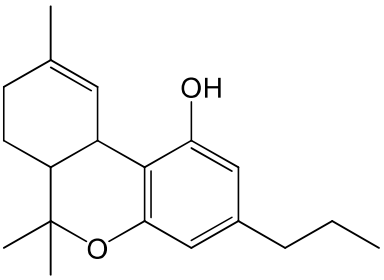
(Formula III);



(Formula IV);



(Formula V);



(Formula V1);

derivatives or analogs thereof, compared to an amount of the same compound in a comparable control plant without said genetic modification;

(b) culturing said plant cell in (a) to generate a transgenic plant.

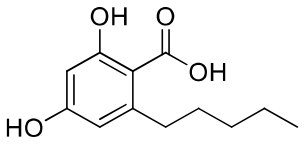
[0302] In some examples, said genetic modification comprises a disruption of gene encoding geranyl pyrophosphate synthase (GPPS), resulting in increased amount of geranyl pyrophosphate (GPP).

[0303] In some examples, said genetic modification comprises a disruption of gene encoding polyketide synthase (PKS), resulting in increased amount of either Formula I or Formula II or both.

[0304] In some examples, said contacting is via electroporation, agrobacterium mediated transformation, biolistic particle bombardment, or protoplast transformation.

[0305] In some examples, the method further comprises further comprising culturing said plant cell in (a) to generate a callus, a cotyledon, a root, a leaf, or a fraction thereof.

[0306] In some examples, said genetic modification results in an increased amount of cannabigerol (CBG), derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said genetic modification.

[0307] In some examples, said genetic modification comprises a disruption of a first group of genes, wherein said disruption results in an increased amount of 

, derivative or analog thereof.

[0308] In some examples, said first group of genes comprises olivetolic acid cyclase (OAC) and olivetolic acid synthase (OLS).

[0309] In some examples, said genetic modification comprises a disruption of gene encoding prenyl-transferase, wherein said disruption results in an increased amount of prenyl-transferase compared to an amount of the same compound in a comparable control plant without said disruption.

[0310] In some examples, said prenyl-transferase is olivetolic acid geranyltransferase (GOT).

[0311] In some examples, said disruption is in a promoter region of said genes.

[0312] In some examples, wherein said genetic modification comprises a disruption of a second of group of genes encoding CBCA synthase, CBDA synthase, and THCA synthase.

[0313] In some examples, said disruption results in a decreased amount of CBCA synthase, CBDA synthase, THCA synthase, derivatives or analogs thereof, compared to an amount of the same amount in a comparable control plant without said disruption.

[0314] In some examples, said disruption is in a coding region of said genes.

[0315] In some examples, said modification results in 10% more Formula IV measured by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0316] In some examples, said modification results in 25% more Formula IV measured by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0317] In some examples, said modification results in 35% more Formula IV measured by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0318] In some examples, said modification results in 50% more Formula IV measured by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0319] In some examples, said modification results in 10% less cannabichromenic acid (CBCA) measured by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0320] In some examples, said modification results in 10% less cannabidiolic acid (CBDA) measured by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0321] In some examples, said modification results in 10% less tetrahydrocannabinolic acid (THCA) measured by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0322] In some examples, said genetic modification results in an increased amount of cannabinol (CBN), derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said genomic modification.

[0323] In some examples, said genetic modification comprises a disruption of gene encoding THCA synthase.

[0324] In some examples, said disruption results in an increased amount of THCA synthase compared to an amount of the same amount in a comparable control plant without said disruption.

[0325] In some examples, said disruption is in a promoter region of said gene.

[0326] In some examples, said genetic modification comprises a disruption of genes encoding CBDA synthase and CBCA synthase respectively.

[0327] In some examples, said disruption results in decreased amount of CBDA synthase and CBCA synthase compared to an amount of the same compound in a comparable control plant without said disruption.

[0328] In some examples, said disruption is in a coding region of said genes.

[0329] In some examples, said genetic modification comprises a disruption of a third group of genes, wherein said disruption results in increased UV absorption of said transgenic plant compared to a comparable control without said disruption.

[0330] In some examples, said modification results in 10% more THC measured by dry weight in said transgenic plant as compared to a comparable control plant without said genetic modification.

[0331] In some examples, said modification results in 25% more THC measured by dry weight in said transgenic plant as compared to a comparable control plant without said genetic modification.

[0332] In some examples, said modification results in 35% more THC measured by dry weight in said transgenic plant as compared to a comparable control plant without said genetic modification.

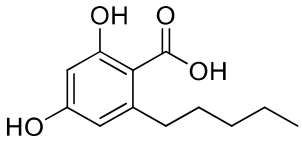
[0333] In some examples, said modification results in 50% more THC measured by dry weight in said transgenic plant as compared to a comparable control plant without said genetic modification.

[0334] In some examples, said modification results in 10% less CBCA measured by dry weight in said transgenic plant as compared to a comparable control plant without said genetic modification.

[0335] In some examples, said modification results in 10% less CBDA measured by dry weight in said transgenic plant as compared to a comparable control plant without said genetic modification.

[0336] In some examples, said genetic modification results in an increased amount of tetrahydrocannabivarin (THCV), derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said genomic modification.

[0337] In some examples, said genetic modification comprises a disruption of a first of group of genes, wherein said disruption results in an increased amount of Formula I, derivative or analog thereof.

[0338] In some examples, said genetic modification comprises a disruption of a second group of genes, wherein said disruption results in a decreased amount of 

, derivative or analog thereof.

[0339] In some examples, said second group of genes comprises OAC and OLS.

[0340] In some examples, said disruption is in a coding region of said genes.

[0341] In some examples, said genetic modification comprises a disruption of a THCA synthase.

[0342] In some examples, said disruption results in an increased amount of THCA synthase, derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said disruption.

[0343] In some examples, said disruption is in a promoter region of said genes.

[0344] In some examples, said genetic modification comprises a disruption of a third group of genes encoding CBCA synthase and CBDA synthase respectively.

[0345] In some examples, said disruption results in a decreased amount of CBCA synthase and CBDA synthase, derivatives or analogs thereof.

[0346] In some examples, said disruption is in a coding region of said genes.

[0347] In some examples, said modification results in 10% more tetrahydrocannabivarin (THCV) measure by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0348] In some examples, said modification results in 25% more tetrahydrocannabivarin (THCV) measure by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0349] In some examples, said modification results in 35% more tetrahydrocannabivarin (THCV) measure by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0350] In some examples, said modification results in 50% more tetrahydrocannabivarin (THCV) measure by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0351] In some examples, said modification results in 10% less cannabichromevarin (CBCV) measure by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

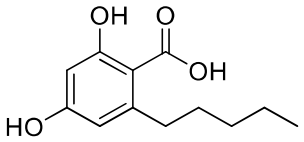
[0352] In some examples, said modification results in 10% less cannabidivarin (CBDV) measure by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0353] In one example, provided herein are methods for generating a transgenic plant, said method comprising: (a) contacting a plant cell with an endonuclease or a polypeptide encoding said endonuclease, wherein said endonuclease introduces a genetic modification resulting in an increased amount of cannabigerol (CBG), derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said genetic modification; (b) culturing said plant cell in (a) to generate a transgenic plant.

[0354] In some examples, said contacting is via electroporation, agrobacterium mediated transformation, biolistic particle bombardment, or protoplast transformation.

[0355] In some examples, the method further comprises culturing said plant cell in (a) to generate a callus, a cotyledon, a root, a leaf, or a fraction thereof.

[0356] In some examples, said genetic modification results in an increased amount of cannabigerol (CBG), derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said genetic modification.

[0357] In some examples, said genetic modification comprises a disruption of a first group of genes, wherein said disruption results in an increased amount of , derivative or analog thereof.

[0358] In some examples, said first group of genes comprises olivetolic acid cyclase (OAC) and olivetolic acid synthase (OLS).

[0359] In some examples, said genetic modification comprises a disruption of gene encoding prenyl-transferase, wherein said disruption results in an increased amount of prenyl-transferase compared to an amount of the same compound in a comparable control plant without said disruption.

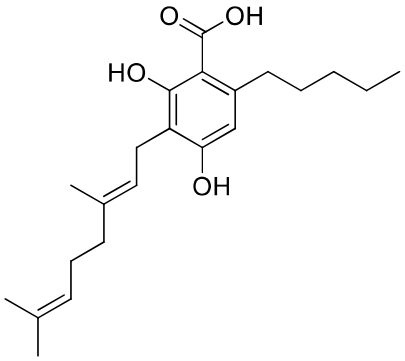
[0360] In some examples, said prenyl-transferase is olivetolic acid geranyltransferase (GOT).

[0361] In some examples, said disruption is in a promoter region of said genes.

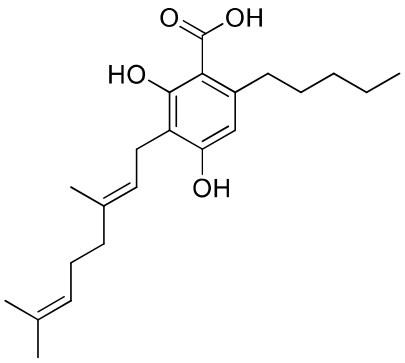
[0362] In some examples, said genetic modification comprises a disruption of a second of group of genes encoding CBCA synthase, CBDA synthase, and THCA synthase.

[0363] In some examples, said disruption results in a decreased amount of CBCA synthase, CBDA synthase, THCA synthase, derivatives or analogs thereof, compared to an amount of the same compound in a comparable control plant without said disruption.

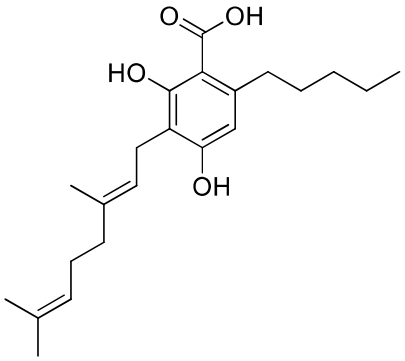
[0364] In some examples, said disruption is in a coding region of said genes.



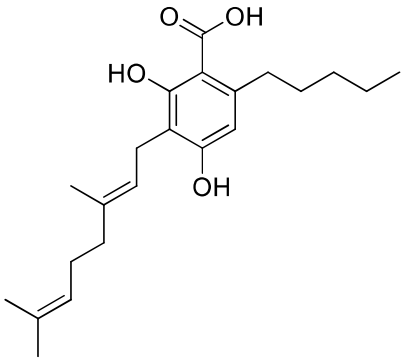
[0365] In some examples, said modification results in 10% more measured by dry weight in said transgenic plant as compared to a comparable control plant without said modification.



[0366] In some examples, said modification results in 25% more measured by dry weight in said transgenic plant as compared to a comparable control plant without said modification.



[0367] In some examples, said modification results in 35% more measured by dry weight in said transgenic plant as compared to a comparable control plant without said modification.



[0368] In some examples, said modification results in 50% more measured by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0369] In some examples, said modification results in 10% less cannabichromenic acid (CBCA) measured by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0370] In some examples, said modification results in 10% less cannabidiolic acid (CBDA) measured by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0371] In some examples, said modification results in 10% less tetrahydrocannabinolic acid (THCA) measured by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0372] In one example, provided herein are methods for generating a transgenic plant, said method comprising: (a) contacting a plant cell with an endonuclease or a polypeptide encoding said endonuclease, wherein said endonuclease introduces a genetic modification resulting in an increased amount of cannabinol (CBN), derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said genetic modification; (b) culturing said plant cell in (a) to generate a transgenic plant.

[0373] In some examples, said contacting is via electroporation, agrobacterium mediated transformation, biolistic particle bombardment, or protoplast transformation.

[0374] In some examples, the method further comprises culturing said plant cell in (a) to generate a callus, a cotyledon, a root, a leaf, or a fraction thereof.

[0375] In some examples, said genetic modification results in an increased amount of cannabinol (CBN), derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said genomic modification.

[0376] In some examples, said genetic modification comprises a disruption of gene encoding THCA synthase.

[0377] In some examples, said disruption results in an increased amount of THCA synthase compared to an amount of the same compound in a comparable control plant without said disruption.

[0378] In some examples, said disruption is in a promoter region of said gene.

[0379] In some examples, said genetic modification comprises a disruption of genes encoding CBDA synthase and CBCA synthase respectively.

[0380] In some examples, said disruption results in decreased amount of CBDA synthase and CBCA synthase compared to an amount of the same compound in a comparable control plant without said disruption.

[0381] In some examples, said disruption is in a coding region of said genes.

[0382] In some examples, said genetic modification comprises a disruption of a third group of genes, wherein said disruption results in increased UV absorption of said transgenic plant compared to a comparable control without said disruption.

[0383] In some examples, said modification results in 10% more THC measured by dry weight in said transgenic plant as compared to a comparable control plant without said genetic modification.

[0384] In some examples, said modification results in 25% more THC measured by dry weight in said transgenic plant as compared to a comparable control plant without said genetic modification.

[0385] In some examples, said modification results in 35% more THC measured by dry weight in said transgenic plant as compared to a comparable control plant without said genetic modification.

[0386] In some examples, said modification results in 50% more THC measured by dry weight in said transgenic plant as compared to a comparable control plant without said genetic modification.

[0387] In some examples, said modification results in 10% less CBCA measured by dry weight in said transgenic plant as compared to a comparable control plant without said genetic modification.

[0388] In some examples, said modification results in 10% less CBDA measured by dry weight in said transgenic plant as compared to a comparable control plant without said genetic modification.

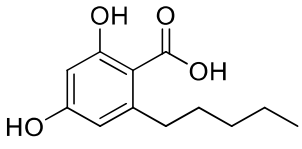
[0389] In one example, provided herein are methods for generating a transgenic plant, said method comprising: (a) contacting a plant cell with an endonuclease or a polypeptide encoding said endonuclease, wherein said endonuclease introduces a genetic modification resulting in an increased amount of tetrahydrocannabivarin (THCV), derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said genetic modification; (b) culturing said plant cell in (a) to generate a transgenic plant.

[0390] In some examples, said contacting is via electroporation, agrobacterium mediated transformation, biolistic particle bombardment, or protoplast transformation.

[0391] In some examples, the method further comprises culturing said plant cell in (a) to generate a callus, a cotyledon, a root, a leaf, or a fraction thereof.

[0392] In some examples, said genetic modification results in an increased amount of tetrahydrocannabivarin (THCV), derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said genomic modification.

[0393] In some examples, said genetic modification comprises a disruption of a first of group of genes, wherein said disruption results in an increased amount of Formula I, derivative or analog thereof.

[0394] In some examples, said genetic modification comprises a disruption of a second group of genes, wherein said disruption results in a decreased amount of 

, derivative or analog thereof.

[0395] In some examples, said second group of genes comprises OAC and OLS.

[0396] In some examples, said disruption is in a coding region of said genes.

[0397] In some examples, said genetic modification comprises a disruption of a THCA synthase.

[0398] In some examples, said disruption results in an increased amount of THCA synthase, derivative or analog thereof, compared to an amount of the same compound in a comparable control plant without said disruption.

[0399] In some examples, said disruption is in a promoter region of said genes.

[0400] In some examples, said genetic modification comprises a disruption of a third group of genes encoding CBCA synthase and CBDA synthase respectively.

[0401] In some examples, said disruption results in a decreased amount of CBCA synthase and CBDA synthase, derivatives or analogs thereof.

[0402] In some examples, said disruption is in a coding region of said genes.

[0403] In some examples, said modification results in 10% more tetrahydrocannabivarin (THCV) measure by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0404] In some examples, said modification results in 25% more tetrahydrocannabivarin (THCV) measure by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0405] In some examples, said modification results in 35% more tetrahydrocannabivarin (THCV) measure by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0406] In some examples, said modification results in 50% more tetrahydrocannabivarin (THCV) measure by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0407] In some examples, said modification results in 10% less cannabichromevarin (CBCV) measure by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0408] In some examples, said modification results in 10% less cannabidivarin (CBDV) measure by dry weight in said transgenic plant as compared to a comparable control plant without said modification.

[0409] In some examples, said genetic modification is conducted by an endonuclease.

[0410] In some examples, said genetic modification comprises an insertion, a deletion, a substitution, or a frameshift.

[0411] In some examples, said endonuclease comprises a CRISPR enzyme, TALE-Nuclease, transposon-based nuclease, Zinc finger nuclease, meganuclease, Mega-TAL or DNA guided nuclease.

[0412] In some examples, said DNA-guided nuclease comprises argonaute.

[0413] In some examples, said endonuclease is a CRISPR enzyme complexed with a guide polynucleotide that is complementary to a target sequence of at least one of genes encoding OAC, OLS, GOT, CBCA synthase, CBDA synthase, and THCA synthase.

[0414] In some examples, said target sequence is at least 18 nucleotides, at least 19 nucleotides, at least 20 nucleotides, at least 21 nucleotides, or at least 22 nucleotides in length.

[0415] In some examples, said target sequence is at most 17 nucleotides in length.

[0416] In some examples, said target sequence comprises a sequence selected from Table 2 or Table 3 or complimentary thereof.

[0417] In some examples, said guide polynucleotide is a chemically modified.

[0418] In some examples, said guide polynucleotide is a single guide RNA (sgRNA).

[0419] In some examples, said guide polynucleotide is a chimeric single guide comprising RNA and DNA.

[0420] In some examples, said guide polynucleotide comprises a sequence selected from Table 2 or Table 3 or complimentary thereof.

[0421] In some examples, said CRISPR enzyme is a Cas protein.

[0422] In some examples, said Cas protein comprises Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas5d, Cas5t, Cas5h, Cas5a, Cas6, Cas7, Cas8, Cas9, Cas10, Csy1 , Csy2, Csy3, Csy4, Cse1, Cse2, Cse3, Cse4, Cse5e, Csc1, Csc2, Csa5, Csn1, Csn2, Csm1, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx1S, Csf1, Csf2, CsO, Csf4, Csd1, Csd2, Cst1, Cst2, Csh1, Csh2, Csa1, Csa2, Csa3, Csa4, Csa5, C2c1, C2c2, C2c3, Cpf1, CARF, DinG, homologues thereof, or modified versions thereof.

[0423] In some examples, said Cas protein is Cas9.

[0424] In some examples, said Cas9 recognizes a canonical PAM.

[0425] In some examples, said Cas9 recognizes a non-canonical PAM.

[0426] In some examples, said guide polynucleotide binds said target sequence 3-10 nucleotides from of PAM.

[0427] In some examples, said CRISPR enzyme complexed with said guide polynucleotide is introduced into said transgenic plant by an RNP.

[0428] In some examples, said CRISPR enzyme complexed with said guide polynucleotide is introduced into said transgenic plant by a vector comprising a nucleic acid encoding said CRISPR enzyme and said guide polynucleotide.

[0429] In some examples, said vector is a binary vector or a Ti plasmid.

[0430] In some examples, said vector further comprises a selection marker or a reporter gene.

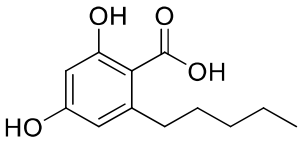
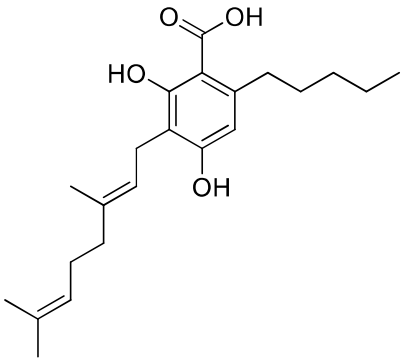
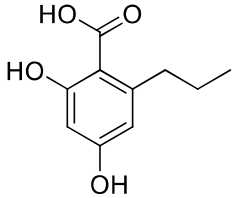
[0431] In some examples, said RNP or vector is introduced into said transgenic plant via electroporation, agrobacterium mediated transformation, biolistic particle bombardment, or protoplast transformation.

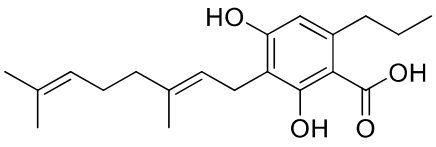
[0432] In some examples, said RNP or vector further comprising a donor polynucleotide.

[0433] In some examples, said donor polynucleotide comprises homology to sequences flanking said target sequence.

[0434] In some examples, said donor polynucleotide introduces a stop codon into at least one of genes encoding OAC, OLS, GOT, CBCA synthase, CBDA synthase, and THCA synthase.

[0435] In some examples, said donor polynucleotide further comprises a barcode, a reporter gene, or a selection marker.

[0436] In one example, provided herein are genetically modified cell comprising a genetic modification, wherein said genetic modification results in an increased amount of  and , derivatives or analogs thereof, wherein said genetic modification does not result in a change of amount of  and



, derivatives or analogs thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0437] In some examples, said genetic modification further results in an increased amount of cannabigerol (CBG), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0438] In some examples, said genetic modification results in an increased amount of cannabinol (CBN), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0439] In some examples, said genetic modification results in an increased amount of tetrahydrocannabivarin (THCV), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0440] In some examples, said genetic modification comprises a disruption of gene encoding geranyl pyrophosphate synthase (GPPS), resulting in increased amount of geranyl pyrophosphate (GPP).

[0441] In some examples, genetic modification comprises a disruption of gene encoding polyketide synthase (PKS), resulting in increased amount of either Formula I or Formula II or both.

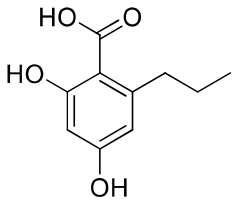
[0442] In some examples, the genetically modified cell is a plant cell, an algae cell, a agrobacterium cell, a E.coli cell, a yeast cell, an animal cell, or an insect cell.

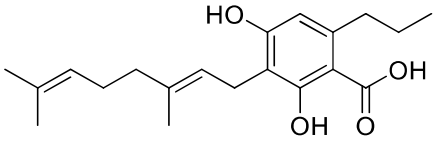
[0443] In some examples, said genetically modified cell is a plant cell.

[0444] In some examples, said genetically modified cell is a cannabis plant cell.

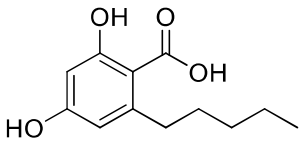
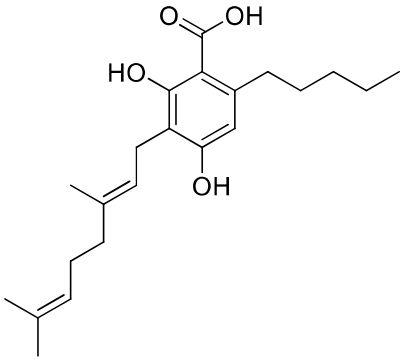
[0445] In some examples, said genetically modified cell is a callus cell, a protoplast, an embryonic cell, a leaf cell, a seed cell, a stem cell, or a root cell.

[0446] In some examples, said modification is integrated in the genome of said cell.

[0447] In one example, provided herein are genetically modified cell comprising a genetic modification, wherein said genetic modification results in an increased amount of 

and 

, derivatives or analogs thereof, wherein

said genetic modification does not result in a change of amount of  and , derivatives or analogs thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0448] In some examples, said genetic modification further results in an increased amount of cannabigerol (CBG), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0449] In some examples, said genetic modification results in an increased amount of cannabinol (CBN), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0450] In some examples, said genetic modification results in an increased amount of tetrahydrocannabivarin (THCV), derivative or analog thereof, compared to an amount of the same compound in a comparable control cell without said genetic modification.

[0451] In some examples, said genetic modification comprises a disruption of gene encoding geranyl pyrophosphate synthase (GPPS), resulting in increased amount of geranyl pyrophosphate (GPP).

[0452] In some examples, genetic modification comprises a disruption of gene encoding polyketide synthase (PKS), resulting in increased amount of either Formula I or Formula II or both.

[0453] In some examples, the genetically modified cell is a plant cell, an algae cell, a agrobacterium cell, a E.coli cell, a yeast cell, an animal cell, or an insect cell.

[0454] In some examples, said genetically modified cell is a plant cell.

[0455] In some examples, said genetically modified cell is a cannabis plant cell.

[0456] In some examples, said genetically modified cell is a callus cell, a protoplast, an embryonic cell, a leaf cell, a seed cell, a stem cell, or a root cell.

[0457] In some examples, said modification is integrated in the genome of said cell.