CLAIMS

What is claimed is:

1. An engineered variant of a cannabidiolic acid synthase (CBDAS) polypeptide comprising an amino acid sequence of SEQ ID NO:3 with one or more amino acid substitutions, wherein said one or more amino acid substitutions occurs at an amino acid selected from the group consisting of C12, F17, F18, S20, R31, N33, P43, L49, K50, L51, Q55, N56, N57, L59, M61, S62, V63, S66, L71, S75, I97, L98, S100, V103, T109, Q124, V125, I129, L132, S137, V149, W161, K165, E167, S170, L171, A172, Y175, C180, A181, H208, A235, A250, M256, K260, L268, H309, T310, F316, L326, G378, K389, E406, M412, L415, S428, L439, I445, N466, Y499, N527, P538, R541, H542, R543, and H544.

2. The engineered variant of claim 1, wherein the engineered variant comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:3.

3. The engineered variant of claim 1 or 2, wherein the engineered variant comprises at least one amino acid substitution in a signal polypeptide, a flavin adenine dinucleotide (FAD) binding domain, a berberine bridge enzyme (BBE) domain, or a combination of the foregoing.

4. The engineered variant of any one of claims 1-3, wherein the engineered variant comprises substitution of at least one surface exposed amino acid.

5. The engineered variant of any one of claims 1-4, wherein the engineered variant comprises at least one amino acid substitution at an amino acid selected from the group consisting of R31, P43, L49, K50, Q55, N56, N57, S62, S100, V103, T109, Q124, V125, L132, S137, H143, V149, W161, K165, E167, N168, S170, L171, A172, Y175, C180, A181, N196, H208, A235, M256, K260, L268, T310, F316, L326, G378, K389, S428, N466, Y499, N527, R541, H542, R543, and H544.

6. The engineered variant of any one of claims 1-5, wherein the engineered variant comprises at least one amino acid substitution at an amino acid selected from the group

consisting of L49, K50, N56, N57, V125, L132, V149, W161, K165, S170, L171, A172, N196, A235, K260, L268, T310, F316, L326, G378, S428, Y499, N527, R543, and H544.

7. The engineered variant of any one of claims 1-6, wherein the engineered variant comprises at least one amino acid substitution at an amino acid selected from the group consisting of N57, S170, A172, N196, A235, K260, and G378.

8. The engineered variant of any one of claims 1-6, wherein the engineered variant comprises amino acid substitution S170.

9. An engineered variant of a cannabidiolic acid synthase (CBDAS) polypeptide comprising an amino acid sequence of SEQ ID NO:3 with one or more amino acid substitutions, where the one or more amino acid substitutions are selected from the group consisting of C12F, F17M, F18T, F18W, S20G, R31Q, N33K, P43E, L49E, L49K, L49Q, K50T, L51I, Q55E, Q55P, N56E, N57D, N57E, L59E, M61H, M61S, M61W, S62N, S62Q, V63M, S66D, L71A, L71H, L71Q, S75D, S75E, I97V, L98V, S100A, V103A, V103F, T109V, Q124D, Q124E, Q124N, V125E, V125Q, I129V, L132M, S137G, H143D, V149I, W161K, W161R, W161Y, K165A, E167P, S170T, L171I, A172V, Y175F, C180A, A181V, N196Q, N196T, N196V, H208T, A235P, A250T, M256V, K260C, K260W, L268I, H309V, T310A, T310C, F316Y, L326I, G378T, G378S, K389E, E406K, M412Q, L415M, S428L, L439M, I445M, N466D, K474S, Y499M, Y499V, N527E, P538T, R541E, R541V, H542V, R543A, R543E, H544E, and H544D.

10. The engineered variant of claim 9, wherein the engineered variant comprises at least one amino acid substitution selected from the group consisting of R31Q, P43E, L49E, L49K, L49Q, K50T, Q55E, Q55P, N56E, N57D, S62Q, S100A, V103F, T109V, Q124D, Q124N, V125E, L132M, S137G, H143D, V149I, W161K, W161R, W161Y, K165A, E167P, N168S, S170T, L171I, A172V, Y175F, C180A, A181V, N196Q, N196T, N196V, H208T, A235P, M256V, K260C, K260W, L268I, T310A, T310C, F316Y, L326I, G378T, G378S, K389E, S428L, N466D, Y499M, Y499V, N527E, R541E, R541V, H542V, R543A, R543E, H544E, and H544D.

11. The engineered variant of claim 10, wherein the engineered variant comprises at least one amino acid substitution selected from the group consisting of L49E, L49Q, K50T, N56E, N57D, V125E, L132M, V149I, W161R, K165A, S170T, L171I, A172V, N196Q, N196T, N196V,

A235P, K260W, K260C, L268I, T310A, T310C, F316Y, L326I, G378T, S428L, Y499M, Y499V, N527E, R543E, and H544E.

12. The engineered variant of claim 11, wherein the engineered variant comprises amino acid substitution S170T.

13. The engineered variant of any one of claims 9-12, wherein the engineered variant comprises an amino acid sequence with at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO:3.

14. The engineered variant of claim 9, wherein the engineered variant comprises an amino acid sequence selected from the group consisting of SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:84, SEQ ID NO:86, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:92, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:108, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:114, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, SEQ ID NO:178, SEQ ID NO:180, SEQ ID NO:182, SEQ ID NO:184, SEQ ID NO:186, SEQ ID NO:188, SEQ ID NO:190, SEQ ID NO:192, SEQ ID NO:194, SEQ ID NO:196, SEQ ID NO:198, SEQ ID NO:200, SEQ ID NO:202, SEQ ID NO:204, SEQ ID NO:206, SEQ ID NO:208, SEQ ID NO:210, SEQ ID NO:212, SEQ ID NO:214, SEQ ID NO:216, SEQ ID NO:218, SEQ ID NO:220, SEQ ID NO:222, SEQ ID NO:224, SEQ ID NO:226, SEQ ID NO:228, SEQ ID NO:230, SEQ ID NO:232, SEQ ID NO:234, SEQ ID NO:300, SEQ ID NO:302, and SEQ ID NO:304.

15. The engineered variant of claim 14, wherein the engineered variant comprises an amino acid sequence selected from the group consisting of SEQ ID NO:60, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:96, SEQ ID NO:116, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:124, SEQ ID NO:128, SEQ ID NO:130, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, SEQ ID NO:180, SEQ ID NO:182, SEQ ID NO:184, SEQ ID NO:186, SEQ ID NO:190, SEQ ID NO:192, SEQ ID NO:194, SEQ ID NO:196, SEQ ID NO:198, SEQ ID NO:200, SEQ ID NO:202, SEQ ID NO:206, SEQ ID NO:210, SEQ ID NO:214, SEQ ID NO:216, SEQ ID NO:218, SEQ ID NO:222, SEQ ID NO:224, SEQ ID NO:226, SEQ ID NO:228, SEQ ID NO:230, SEQ ID NO:232, and SEQ ID NO:234.

16. The engineered variant of claim 15, wherein the engineered variant comprises an amino acid sequence selected from the group consisting of SEQ ID NO:66, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:130, SEQ ID NO:136, SEQ ID NO:142, SEQ ID NO:146, SEQ ID NO:150, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:168, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:176, SEQ ID NO:182, SEQ ID NO:184, SEQ ID NO:186, SEQ ID NO:190, SEQ ID NO:192, SEQ ID NO:194, SEQ ID NO:196, SEQ ID NO:198, SEQ ID NO:206, SEQ ID NO:214, SEQ ID NO:216, SEQ ID NO:218, SEQ ID NO:230, and SEQ ID NO:232.

17. The engineered variant of claim 16, wherein the engineered variant comprises an amino acid sequence SEQ ID NO:156.

18. The engineered variant of any one of claims 1-17, wherein the engineered variant comprises an amino acid sequence of SEQ ID NO:3 with at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at

least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, or at least 30 amino acid substitutions.

19. The engineered variant of any one of claims 1-18, wherein the engineered variant comprises an amino acid sequence of SEQ ID NO:3 with 3 amino acid substitutions.

20. The engineered variant of any one of claims 1-19, wherein the engineered variant comprises at least one immutable amino acid in a flavin adenine dinucleotide (FAD) binding domain, a berberine bridge enzyme (BBE) domain, or a combination of the foregoing.

21. The engineered variant of claim 20, wherein the engineered variant comprises at least 15 immutable amino acids in the FAD binding domain.

22. The engineered variant of claim 20, wherein the engineered variant comprises at least 15 immutable amino acids in the BBE domain.

23. The engineered variant of any one of claims 1-22, wherein the engineered variant comprises at least one immutable amino acid selected from the group consisting of A28, F34, L35, C37, L64, N70, P87, I93, C99, R108, R110, G112, E117, G118, S120, P126, F127, D131, D141, W148, G152, A153, L155, G156, E157, Y159, Y160, N163, A173, G174, C176, P177, T178, V179, G182, G183, H184, F185, G187, G188, G189, Y190, G191, P192, L193, R195, A201, D202, I205, D206, V210, G214, G223, D225, L226, F227, W228, R231, G234, S237, F238, G239, K245, I246, L248, V251, V259, Q276, F312, S313, L323, C341, F352, S354, F380, K381, I382, K383, D385, Y386, I391, G419, M422, I425, I430, P431, P433, H434, R435, G437, Y440, W443, Y444, I464, Y465, M468, T469, Y471, V472, P476, R484, N498, A502, N513, F514, K521, N528, F529, E533, Q534, and S535.

24. The engineered variant of claim 23, wherein the engineered variant comprises at least one immutable amino acid selected from the group consisting of C37, N70, I93, C99, E117, S120, F127, D131, G156, E157, Y159, G174, C176, G182, G183, F185, G187, G188, G189, Y190, G191, P192, R195, D202, D206, G214, W228, G234, F238, L248, Q276, S313, L323, S354, K381, K383, D385, G419, M422, R435, Y440, W443, Y444, Y471, P476, N513, F514, N528, and Q534.

25. The engineered variant of any one of claims 1-24, wherein the engineered variant produces cannabidiolic acid (CBDA) from cannabigerolic acid (CBGA) in a greater amount, as measured in mg/L or mM, than an amount of CBDA produced from CBGA by a cannabidiolic acid synthase polypeptide having an amino acid sequence of SEQ ID NO:3 under similar conditions for the same length of time.

26. The engineered variant of any one of claims 1-25, wherein the engineered variant produces cannabidiolic acid (CBDA) from cannabigerolic acid (CBGA) in an amount, as measured in mg/L or mM, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 150% at least 200%, at least 500%, or at least 1000% greater than an amount of CBDA produced from CBGA by a cannabidiolic acid synthase polypeptide having an amino acid sequence of SEQ ID NO:3 under similar conditions for the same length of time.

27. The engineered variant of any one of claims 1-26, wherein the engineered variant produces cannabidiolic acid (CBDA) from cannabigerolic acid (CBGA) in an increased ratio of CBDA over tetrahydrocannabinolic acid (THCA) compared to that produced by a cannabidiolic acid synthase polypeptide having an amino acid sequence of SEQ ID NO:3 under similar conditions for the same length of time.

28. The engineered variant of any one of claims 1-27, wherein the engineered variant produces CBDA from CBGA in a ratio of CBDA over THCA of about 11:1, about 11.5:1, about 12:1, about 12.5:1, about 13:1, about 13.5:1, about 14:1, about 14.5:1, about 15:1, about 15.5:1, about 16:1, about 16.5:1, about 17:1, about 17.5:1, about 18:1, about 18.5:1, about 19:1, about 19.5:1, about 20:1, about 25:1, about 30:1, about 35:1, about 40:1, about 45:1, about 50:1, about 60:1, about 70:1, about 80:1, about 90:1, about 100:1, about 150:1, about 200:1, about 500:1, or greater than about 500:1.

29. The engineered variant of any one of claims 1-28, wherein the engineered variant produces cannabidiolic acid (CBDA) from cannabigerolic acid (CBGA) in an increased ratio of CBDA over cannabichromenic acid (CBCA) compared to that produced by a cannabidiolic acid

synthase polypeptide having an amino acid sequence of SEQ ID NO:3 under similar conditions for the same length of time.

30. The engineered variant of any one of claims 1-29, wherein the engineered variant produces CBDA from CBGA in a ratio of CBDA over CBCA of about 11:1, about 11.5:1, about 12:1, about 12.5:1, about 13:1, about 13.5:1, about 14:1, about 14.5:1, about 15:1, about 15.5:1, about 16:1, about 16.5:1, about 17:1, about 17.5:1, about 18:1, about 18.5:1, about 19:1, about 19.5:1, about 20:1, about 25:1, about 30:1, about 35:1, about 40:1, about 45:1, about 50:1, about 60:1, about 70:1, about 80:1, about 90:1, about 100:1, about 150:1, about 200:1, about 500:1, or greater than about 500:1.

31. The engineered variant of any one of claims 1-13, wherein the engineered variant comprises a truncation at an N-terminus, at a C-terminus, or at both the N- and C-termini.

32. The engineered variant of claim 31, wherein the truncated engineered variant comprises a signal polypeptide or a membrane anchor.

33. The engineered variant of claim 31 or 32, wherein the engineered variant lacks a native signal polypeptide.

34. A nucleic acid comprising a nucleotide sequence encoding an engineered variant of any one of claims 1-33.

35. A nucleic acid comprising a nucleotide sequence encoding an engineered variant of a cannabidiolic acid synthase (CBDAS) polypeptide comprising an amino acid sequence of SEQ ID NO:3 with one or more amino acid substitutions, wherein the nucleotide sequence is selected from the group consisting of SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:79, SEQ ID NO:81, SEQ ID NO:83, SEQ ID NO:85, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:95, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:107, SEQ ID NO:109, SEQ ID

NO:111, SEQ ID NO:113, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:181, SEQ ID NO:183, SEQ ID NO:185, SEQ ID NO:187, SEQ ID NO:189, SEQ ID NO:191, SEQ ID NO:193, SEQ ID NO:195, SEQ ID NO:197, SEQ ID NO:199, SEQ ID NO:201, SEQ ID NO:203, SEQ ID NO:205, SEQ ID NO:207, SEQ ID NO:209, SEQ ID NO:211, SEQ ID NO:213, SEQ ID NO:215, SEQ ID NO:217, SEQ ID NO:219, SEQ ID NO:221, SEQ ID NO:223, SEQ ID NO:225, SEQ ID NO:227, SEQ ID NO:229, SEQ ID NO:231, SEQ ID NO:233, SEQ ID NO:299, SEQ ID NO:301, and SEQ ID NO:303.

36. The nucleic acid of claim 34, wherein the nucleotide sequence is codon-optimized.

37. A vector comprising one or more nucleic acids of any one of claims 34-36.

38. A method of making a modified host cell for producing a cannabinoid or a cannabinoid derivative, the method comprising introducing one or more nucleic acids of any one of claims 34-36 or one or more vectors of claim 37 into a host cell.

39. A modified host cell for producing a cannabinoid or a cannabinoid derivative, wherein the modified host cell comprises one or more nucleic acids of any one of claims 34-36.

40. The modified host cell of claim 39, wherein the modified host cell comprises one or more heterologous nucleic acids comprising a nucleotide sequence encoding a geranyl pyrophosphate:olivetolic acid geranyltransferase (GOT) polypeptide.

41. The modified host cell of claim 40, wherein the GOT polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:17.

42. The modified host cell of claim 39, wherein the modified host cell comprises one or more heterologous nucleic acids comprising a nucleotide sequence encoding a NphB polypeptide.

43. The modified host cell of claim 42, wherein the NphB polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:294.

44. The modified host cell of any one of claims 39-43, wherein the modified host cell comprises one or more heterologous nucleic acids comprising a nucleotide sequence encoding a tetraketide synthase (TKS) polypeptide and one or more heterologous nucleic acids comprising a nucleotide sequence encoding an olivetolic acid cyclase (OAC) polypeptide.

45. The modified host cell of claim 44, wherein the TKS polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:19.

46. The modified host cell of claim 44 or 45, wherein the OAC polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:21 or SEQ ID NO:48.

47. The modified host cell of any one of claims 39-46, wherein the modified host cell comprises one or more heterologous nucleic acids comprising a nucleotide sequence encoding an acyl-activating enzyme (AAE) polypeptide.

48. The modified host cell of claim 47, wherein the AAE polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:23.

49. The modified host cell of any one of claims 39-48, wherein the modified host cell comprises one or more heterologous nucleic acids comprising a nucleotide sequence encoding:
a) a GOT polypeptide;
b) two to twelve copies of a TKS polypeptide;
c) two to twelve copies of an OAC polypeptide; and
d) one to eight copies of an AAE polypeptide,
wherein at least one of the one or more nucleic acids are integrated into the chromosome of the modified yeast host cell; and wherein at least one of the one or more nucleic acids are operably linked to an inducible promoter or a constitutive promoter.

50. The modified host cell of any one of claims 39-49, wherein the modified host cell comprises one or more of the following: a) one or more heterologous nucleic acids comprising a nucleotide sequence encoding a HMG-CoA synthase (HMGS) polypeptide; b) one or more heterologous nucleic acids comprising a nucleotide sequence encoding a truncated 3-hydroxy-3-methyl-glutaryl-CoA reductase (tHMGR) polypeptide; c) one or more heterologous nucleic acids comprising a nucleotide sequence encoding a mevalonate kinase (MK) polypeptide; d) one or more heterologous nucleic acids comprising a nucleotide sequence encoding a phosphomevalonate kinase (PMK) polypeptide; e) one or more heterologous nucleic acids comprising a nucleotide sequence encoding a mevalonate pyrophosphate decarboxylase (MVD1) polypeptide; and f) one or more heterologous nucleic acids comprising a nucleotide sequence encoding a isopentenyl diphosphate isomerase (IDI1) polypeptide.

51. The modified host cell of claim 50, wherein the IDI1 polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:25.

52. The modified host cell of claim 50 or 51, wherein the tHMGR polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:27.

53. The modified host cell of any one of claims 50-52, wherein the HMGS polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:29.

54. The modified host cell of any one of claims 50-53, wherein the MK polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:39.

55. The modified host cell of any one of claims 50-54, wherein the PMK polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:37.

56. The modified host cell of any one of claims 50-55, wherein the MVD1 polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:33.

57. The modified host cell of any one of claims 39-56, wherein the modified host cell comprises one or more heterologous nucleic acids comprising a nucleotide sequence encoding an acetoacetyl-CoA thiolase polypeptide.

58. The modified host cell of claim 57, wherein the acetoacetyl-CoA thiolase polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:31.

59. The modified host cell of any one of claims 39-58, wherein the modified host cell comprises one or more heterologous nucleic acids comprising a nucleotide sequence encoding a pyruvate decarboxylase (PDC) polypeptide.

60. The modified host cell of claim 59, wherein the PDC polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:35.

61. The modified host cell of any one of claims 39-60, wherein the modified host cell comprises one or more heterologous nucleic acids comprising a nucleotide sequence encoding a geranyl pyrophosphate synthetase (GPPS) polypeptide.

62. The modified host cell of claim 61, wherein the GPPS polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:41.

63. The modified host cell of any one of claims 39-62, wherein the modified host cell comprises one or more heterologous nucleic acids comprising a nucleotide sequence encoding a KAR2 polypeptide.

64. The modified host cell of claim 63, wherein the KAR2 polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:5.

65. The modified host cell of claim 63 or 64, wherein the modified host cell comprises two or more heterologous nucleic acids comprising a nucleotide sequence encoding a KAR2 polypeptide.

66. The modified host cell of any one of claims 39-65, wherein the modified host cell comprises one or more heterologous nucleic acids comprising a nucleotide sequence encoding a PDI1 polypeptide.

67. The modified host cell of claim 66, wherein the PDI1 polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:9.

68. The modified host cell of any one of claims 39-67, wherein the modified host cell comprises one or more heterologous nucleic acids comprising a nucleotide sequence encoding an IRE1 polypeptide.

69. The modified host cell of claim 68, wherein the IRE1 polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:11 or SEQ ID NO:296.

70. The modified host cell of any one of claims 39-69, wherein the modified host cell comprises one or more heterologous nucleic acids comprising a nucleotide sequence encoding an ERO1 polypeptide.

71. The modified host cell of claim 70, wherein the ERO1 polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:7.

72. The modified host cell of any one of claims 39-71, wherein the modified host cell comprises one or more heterologous nucleic acids comprising a nucleotide sequence encoding a FAD1 polypeptide.

73. The modified host cell of claim 72, wherein the FAD1 polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:298.

74. The modified host cell of any one of claims 39-73, wherein the modified host cell comprises a deletion or downregulation of one or more genes encoding a PEP4 polypeptide.

75. The modified host cell of any one of claims 39-74, wherein the modified host cell comprises a deletion or downregulation of one or more genes encoding a ROT2 polypeptide.

76. The modified host cell of any one of claims 39-75, wherein the modified host cell is a eukaryotic cell.

77. The modified host cell of claim 76, wherein the eukaryotic cell is a yeast cell.

78. The modified host cell of claim 77, wherein the yeast cell is *Saccharomyces cerevisiae*.

79. The modified host cell of claim 78, wherein the *Saccharomyces cerevisiae* is a protease-deficient strain of *Saccharomyces cerevisiae*.

80. The modified host cell of any one of claims 39-79, wherein at least one of the one or more nucleic acids are integrated into the chromosome of the modified host cell.

81. The modified host cell of any one of claims 39-80, wherein at least one of the one or more nucleic acids are operably-linked to an inducible promoter.

82. The modified host cell of any one of claims 39-80, wherein at least one of the one or more nucleic acids are operably-linked to a constitutive promoter.

83. A method of producing a cannabinoid or a cannabinoid derivative, the method comprising:

a) culturing a modified host cell of any one of claims 39-82 in a culture medium.

84. The method of claim 83, wherein the method comprises:

b) recovering the produced cannabinoid or cannabinoid derivative.

85. The method of claim 83 or 84, wherein the culture medium comprises a carboxylic acid.

86. The method of claim 85, wherein the carboxylic acid is an unsubstituted or substituted C_3-C_{18} carboxylic acid.

87. The method of claim 86, wherein the unsubstituted or substituted C_3-C_{18} carboxylic acid is an unsubstituted or substituted hexanoic acid.

88. The method of any one of claims 83-87, wherein the culture medium comprises olivetolic acid or an olivetolic acid derivative.

89. The method of any one of claims 83-88, wherein the cannabinoid is cannabidiolic acid, cannabidiol, cannabidivarinic acid, or cannabidivarin.

90. The method of any one of claims 83-89, wherein the culture medium comprises a fermentable sugar.

91. The method of any one of claims 83-90, wherein the culture medium comprises a pretreated cellulosic feedstock.

92. The method of any one of claims 83-91, wherein the culture medium comprises a non-fermentable carbon source.

93. The method of claim 92, wherein the non-fermentable carbon source comprises ethanol.

94. The method of any one of claims 83-93, wherein the cannabinoid or the cannabinoid derivative is produced in an amount of more than 100 mg/L culture medium.

95. A method of screening an engineered variant of a cannabidiolic acid synthase (CBDAS) polypeptide comprising an amino acid sequence of SEQ ID NO:3 with one or more amino acid substitutions, the method comprising:

a) dividing a population of host cells into a control population and a test population;

b) co-expressing in the control population a CBDAS polypeptide having an amino acid sequence of SEQ ID NO:3 and a comparison cannabinoid synthase polypeptide, wherein the CBDAS polypeptide having an amino acid sequence of SEQ ID NO:3 can convert cannabigerolic acid (CBGA) to a first cannabinoid, cannabidiolic acid (CBDA), and the comparison cannabinoid synthase polypeptide can convert the same CBGA to a different second cannabinoid;

c) co-expressing in the test population the engineered variant and the comparison cannabinoid synthase polypeptide, wherein the engineered variant may convert CBGA to the same first cannabinoid, cannabidiolic acid (CBDA), as the CBDAS polypeptide having an amino acid sequence of SEQ ID NO:3, and wherein the comparison cannabinoid synthase polypeptide

can convert the same CBGA to the second cannabinoid and is expressed at similar levels in the test population and in the control population;

d) measuring a ratio of the first cannabinoid, cannabidiolic acid (CBDA), over the second cannabinoid produced by both the test population and the control population; and

e) measuring an amount, in mg/L or mM, of the first cannabinoid produced by both the test population and the control population;

wherein the cannabinoid synthase polypeptide is a tetrahydrocannabinolic acid synthase polypeptide; wherein the tetrahydrocannabinolic acid synthase polypeptide comprises an amino acid sequence having at least 85% sequence identity to SEQ ID NO:44;

wherein the second cannabinoid is tetrahydrocannabinolic acid (THCA); and

wherein:

(i) the test population is identified as comprising an engineered variant having improved *in vivo* performance compared to the cannabidiolic acid synthase polypeptide having an amino acid sequence of SEQ ID NO:3, wherein improved *in vivo* performance is demonstrated by an increase in the ratio of the first cannabinoid over the second cannabinoid produced by the test population compared to that produced by the control population under similar culture conditions for the same length of time; and/or

(ii) the test population is identified as comprising an engineered variant having improved *in vivo* performance compared to the cannabidiolic acid synthase polypeptide having an amino acid sequence of SEQ ID NO:3 by producing the first cannabinoid in a greater amount, as measured in mg/L or mM, by the test population compared to the amount produced by the control population under similar culture conditions for the same length of time.