**Supplementary Tables**

**Table S1**

**Table S1. The 8 Chinese herbal materials that make up CBFD.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **No.** | **Name** | **Medicinal part** | **Origin** | **Processing method** | **Manufacturer** | **Lot number** |
| 1 | Dioscoreae spongiosae rhizome | Dried rhizomes of *Dioscorea spongiosa* J. Q. Xi, M. Mizuno et W. L. Zhao of Nymphaeaceae | Zhejiang | Cut into slices | Anhui Jiayou Decoction Piece Co., Ltd. | 220701 |
| 2 | Plantaginis semen | Dried ripe seeds of *Plantago asiatica* L. of Plantaginaceae | Jiangxi | Fried dry with salted water | Anhui Hongkun Pharmaceutical Co., Ltd. | 210801 |
| 3 | Poria | Dried sclerotia of *Poria cocos* (Schw.) Wolf of Polyporaceae | Anhui | Peeled and cut into slabs | Anhui Cunzhen Decoction Piece Co., Ltd. | 220201 |
| 4 | Salviae miltiorrhizae radix et rhizoma | Dried roots and rhizomes of *Salvia miltiorrhiza* Bge. of Lamiaceae | Sichuan | Cut into slabs | Anhui Hongkun Pharmaceutical Co., Ltd. | 210501 |
| 5 | Phellodendri chinensis cortex | Dried barks of *Phellodendron chinense* Schneid. of Rutaceae | Sichuan | Cut into shreds | Jiangsu Huahong Pharmaceutical Technology Co., Ltd. | 220803 |
| 6 | Plumula nelumbinis | Dried germs and radicles in ripe seedsof *Nelumbo nucifera* Gaertn. of Nymphaeaceae | Hunan | Removed from lotus seeds and dried in the sun | Anhui Jiayou Decoction Piece Co., Ltd. | 210601 |
| 7 | Atractylodis macrocephalae rhizoma | Dried rhizomes of *Atractylodes macrocephala* Koidz. of Compositae | Zhejiang | Fried with bran | Anhui Cunzhen Decoction Piece Co., Ltd. | 211001 |
| 8 | Acori tatarinowii rhizoma | Dried rhizomes of *Acorus tatarinoxjuii* Schott of Dioscoreaceae | Sichuan | Cut into slabs | Anhui Hongkun Pharmaceutical Co., Ltd. | 210601 |

**Table S2**

**Table S2. The identified 4 chemical compounds from CBFD through GC-MS.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **No.** | **Name** | **Original source** | ***t*R (min)** | **Match** |
| 1 | α-acorenet | Acori tatarinowii rhizome | 20.534 | 586 |
| 2 | methyleugenol | 28.859 | 732 |
| 3 | γ-asarone | 36.092 | 684 |
| 4 | β-asarone | 38.529 | 693 |

**Table S3**

**Table S3. The identified 49 chemical compounds from CBFD through UPLC-Q-Tof-MS/MS**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No.** | **Name** | ***t*R (min)** | **Original source** | **Formula** | **Molecular ion** | **Fragment ion** | **Ion form** | **ppm** | **Ref.** |
| **1** | *dl*-arginine | 3.186 | Dioscoreae spongiosae rhizoma | C6H14N4O2 | 175.1185 | 158.0905, 141.0657, 130.0968, 116.0705, 97.9662, 85.0760, 70.0646, 60.0553, 55.0540 | [M+H]+ | 2.8 | (Wang et al., 2022) |
| **2** | trigonelline | 3.644 | Dioscoreae spongiosae rhizoma | C7H7NO2 | 138.0546 | 114.1764, 110.0634, 97.9681, 94.0653, 92.0495, 81.9372, 78.0323 | [M+H]+ | 2.76 | (Wang et al., 2022) |
| **3** | gluconic acid | 3.647 | Dioscoreae spongiosae rhizoma | C6H12O7 | 191.0562 | 177.0385, 159.0315, 141.0187, 129.0191, 114.0317, 99.0095, 85.0304, 75.0092, 59.1040 | [M-H]- | 1.41 | (Wang et al., 2022) |
| **4** | sucrose | 3.815 | Plantaginis semen | C12H22O11 | 341.1091 | 179.0543, 179.0543, 161.0461, 131.0376, 119.0375, 101.0235, 89.0246, 71.0147, 59.0146 | [M-H]- | -0.66 | (Sun et al., 2022) |
| **5** | quinic acid | 3.983 | Phellodendri chinensis cortex | C7H12O6 | 191.0563 | 173.0449, 155.1743, 133.0810, 109.0276, 93.0368, 93.0368, 85.0297, 71.0142, 59.0145, 50.6972 | [M-H]- | -0.81 | (Sun et al., 2016) |
| Dioscoreae spongiosae rhizoma | (Wang et al., 2022) |
| **6** | valine | 4.409 | Dioscoreae spongiosae rhizoma | C5H11NO2 | 118.0862 | 72.0806, 55.0540 | [M+H]+ | 0.07 | (Wang et al., 2022) |
| **7** | *l*-(-)-malic acid | 4.509 | Dioscoreae spongiosae rhizoma | C4H6O5 | 133.0144 | 115.0041, 90.9258, 71.0144, 66.0946, 59.0163, 54.5186 | [M-H]- | -1.39 | (Wang et al., 2022) |
| **8** | citric acid | 5.842 | Plantaginis semen | C6H8O7 | 191.0196 | 157.7604, 129.0172, 111.0089, 87.0088, 85.0289, 85.0289, 67.0199, 57.0355 | [M-H]- | 0.56 | (Sun et al., 2022) |
| Dioscoreae spongiosae rhizoma | (Wang et al., 2022) |
| **9** | tyrosine | 6.775 | Atractylodis macrocephalae rhizoma | C9H11NO3 | 182.0808 | 162.9033, 152.9008, 147.0440, 141.9583, 136.0756, 123.0434, 119.0497, 112.2943, 107.0479, 97.9693, 91.0533 | [M+H]+ | 1.84 | (Huang et al., 2017) |
| **10** | *l*-norleucine | 7.532 | Dioscoreae spongiosae rhizoma | C6H13NO2 | 132.1016 | 121.9728, 95.9526, 86.0960, 69.0698, 57.0581 | [M+H]+ | 2.66 | (Wang et al., 2022) |
| **11** | norcoclaurine-4'-*O*-glucoside | 10.383 | Plumula nelumbinis | C22H27NO8 | 434.182 | 272.1308, 255.1037, 249.7883, 243.8881, 209.0940, 161.0590, 143.0498, 127.0414, 107.0496 | [M+H]+ | -2.53 | (Tian et al., 2018) |
| **12** | *l*-Phenylalanine | 11.044 | Dioscoreae spongiosae rhizoma | C9H11NO2 | 166.0859 | 149.0581, 131.0498, 120.0804, 107.0506, 103.0533, 99.9488, 93.0724, 80.0574, 74.0227 | [M+H]+ | 2.13 | (Wang et al., 2022) |
| **13** | lotusine | 11.231 | Plumula nelumbinis | C19H24NO3+ | 314.1749 | 269.1169, 240.1102, 237.0875, 209.0971, 107.0487 | [M]+ | 0.58 | (Lin et al., 2014) |
| **14** | argemexirine | 11.333 | Plumula nelumbinis | C17H19NO3 | 286.1436 | 255.0991, 237.0887, 182.0719, 161.0609, 143.1192, 123.0419, 107.0488 | [M+H]+ | 0.81 | (Tian et al., 2018) |
| **15** | danshensu | 11.336 | Salviae miltiorrhizae radix | C9H10O5 | 197.0454 | 17.0351, 135.0442, 123.0442 | [M-H]- | 0.84 | (Zhao et al., 2016) |
| **16** | norcoclaurine | 11.419 | Plumula nelumbinis | C16H17NO3 | 271.1208 | 255.1028, 227.0674, 161.0601, 145.0406, 123.0464, 107.0489 | [M+H]+ | 1.11 | (Lin et al., 2014) |
| **17** | nornuciferidine | 11.521 | Plumula nelumbinis | C18H19NO3 | 298.1437 | 283.1164, 268.1032, 254.1134, 238.1911, 229.6011, 211.0979, 177.0810, 151.0775, 116.7142, 107.0498 | [M+H]+ | 0.16 | (Lin et al., 2014) |
| **18** | geniposidic acid | 11.552 | Plantaginis semen | C16H22O10 | 373.1134 | 324.6423, 220.7105, 211.0600, 194.4166, 167.0701, 150.0650, 123.0438, 105.0340, 88.4443, 59.0150 | [M-H]- | 1.4 | (Sun et al., 2022) |
| **19** | liensinine | 12.101 | Plumula nelumbinis | C37H42N2O6 | 611.3144 | 580.2762, 489.2378, 206.1157 | [M+H]+ | -4.58 | (Lin et al., 2014) |
| **20** | phellodendrine | 12.251 | Phellodendri chinensis cortex | C20H24NO4+ | 342.1703 | 192.1010, 177.0780, 148.0875, 111.9748 | [M]+ | -1.07 | (Zhu et al., 2011) |
| **21** | *N*-methylisococlaurine | 12.522 | Plumula nelumbinis | C18H21NO3 | 300.1598 | 283.1381, 269.1150, 257.1170, 225.0937, 188.1038, 175.0765, 163.0715, 145.0670, 137.0594, 122.0676, 107.0489 | [M+H]+ | -1.18 | (Tian et al., 2018) |
| **22** | pronuciferine | 13.074 | Plumula nelumbinis | C19H21NO3 | 312.1595 | 282.1187, 269.1178, 254.0948, 206.1154 | [M+H]+ | -0.37 | (Lin et al., 2014) |
| **23** | *N*-methylcoclaurine | 13.139 | Plumula nelumbinis | C18H21NO3 | 300.1596 | 284.0602, 269.1228, 257.1217, 237.0891, 215.0163, 198.0466, 175.0740, 107.0480 | [M+H]+ | -0.65 | (Tian et al., 2018) |
| **24** | magnoflorine | 13.446 | Phellodendri chinensis cortex | C20H24NO4+ | 342.1705 | 297.1120, 265.0850, 237.0890, 196.0853 | [M]+ | -1.94 | (Zhu et al., 2011) |
| **25** | isoliensinine | 13.858 | Plumula nelumbinis | C37H42N2O6 | 611.3141 | 608.6758, 580.2691, 568.2757, 489.7262, 475.2158, | [M+H]+ | -4.04 | (Lin et al., 2014) |
| **26** | 4'-methyl-*N*-methylcoclaurine | 15.726 | Plumula nelumbinis | C19H23NO3 | 314.1758 | 283.1322, 271.1310, 252.1144, 212.1091, 194.1216, 178.0938, 165.0898, 151.0771, 145.0610, 133.0666, 121.0668, 107.0486 | [M+H]+ | -2.2 | (Lin et al., 2014) |
| **27** | armepavine | 16.165 | Plumula nelumbinis | C19H23NO3 | 314.1758 | 282.1515, 269.1160, 237.0913, 210.1006, 188.1070, 163.0784, 121.0628, 107.0506 | [M+H]+ | -2.27 | (Lin et al., 2014) |
| **28** | menisperine | 16.492 | Phellodendri chinensis cortex | C21H26NO4+ | 356.1862 | 311.1285, 297.6463, 279.1022, 178.0809, 123.7979, 58.0669 | [M]+ | -1.43 | (Zhu et al., 2011) |
| **29** | neferine | 16.602 | Plumula nelumbinis | C38H44N2O6 | 625.3297 | 594.2824, 489.2359, 297.1123, 206.1202 | [M+H]+ | -3.92 | (Lin et al., 2014) |
| **30** | 6-demethyl-4'-methyl-*N*-methylcoclaurine | 17.491 | Plumula nelumbinis | C18H21NO3 | 300.159 | 269.1198, 192.1012, 177.0881, 131.0493, 121.0642, 107.0482 | [M+H]+ | 1.62 | (Tian et al., 2018) |
| **31** | tetrahydropalmatine | 17.501 | Phellodendri chinensis cortex | C21H25NO4 | 356.1856 | 343.6519, 225.0168, 192.1008, 177.0517, 94.0653 | [M+H]+ | 0.19 | (Zhu et al., 2011) |
| **32** | *N*‑methyltetrahydrocolumbamine | 17.501 | Phellodendri chinensis cortex | C21H26NO4+ | 356.1856 | 338.6157, 192.1049, 177.0723 | [M]+ | 0.08 | (Sun et al., 2016) |
| **33** | oxyberberine | 17.688 | Phellodendri chinensis cortex | C20H17NO5 | 352.1179 | 337.0952, 321.0341, 308.0848 | [M+H]+ | 0.02 | (Zhu et al., 2011) |
| **34** | columbamine | 18.595 | Phellodendri chinensis cortex | C20H20NO4+ | 338.1395 | 323.1141, 309.0953, 294.1119, 278.4820, 262.0878, 157.0613 | [M]+ | -2.15 | (Zhu et al., 2011) |
| **35** | berberrubine | 18.734 | Phellodendri chinensis cortex | C19H16NO4+ | 322.1084 | 307.0882, 269.9327, 147.0464 | [M]+ | -1.3 | (Zhu et al., 2011) |
| **36** | lithospermic acid | 18.83 | Salviae miltiorrhizae radix | C27H22O12 | 537.1013 | 358.3200, 339.0492, 321.0374, 295.0594, 265.4712, 253.0449, 222.3262, 205.0226, 185.0171, 104.7366 | [M-H]- | 4.68 | (Zhao et al., 2016) |
| **37** | berberine | 19.313 | Phellodendri chinensis cortex | C20H24NO4+ | 336.1234 | 321.0995, 306.0764, 292.0972, 278.0817 | [M]+ | -1.18 | (Zhu et al., 2011) |
| **38** | palmatine | 19.35 | Phellodendri chinensis cortex | C21H22NO4+ | 352.1551 | 336.1256, 320.1253, 308.1331, 293.1066, 170.4812 | [M]+ | -2.29 | (Zhu et al., 2011) |
| **39** | nuciferine | 19.92 | Plumula nelumbinis | C19H21NO2 | 296.1644 | 281.0519, 265.1212, 250.0967, 234.1005, 226.0588, 153.9114, 116.3793 | [M+H]+ | 0.45 | (Tian et al., 2018) |
| **40** | isosalvianolic acid A | 20.015 | Salviae miltiorrhizae radix | C26H22O10 | 493.1124 | 408.4466, 336.3408, 313.0834, 295.0610, 249.0601, 197.0460, 185.0238, 159.0463, 135.0440, 109.0299 | [M-H]- | 3.41 | (Ruan et al., 2012) |
| **41** | salvianolic acid B | 20.578 | Salviae miltiorrhizae radix | C36H30O16 | 717.1445 | 519.0916, 339.0496, 321.0395, 279.0264 | [M-H]- | 2.3 | (Zhao et al., 2016) |
| 20.517 | 741.1439 | 697.1133, 626.7821, 543.0925, 519.0140, 362.0396 | [M+Na]+ | -1.61 |
| **42** | rosmarinic acid | 21.147 | Salviae miltiorrhizae radix | C18H16O8 | 359.0772 | 197.0458, 179.0357, 161.0257, 143.9998, 135.0414, 108.7632 | [M-H]- | 0.52 | (Zhao et al., 2016) |
| **43** | salvianolic acid L | 22.464 | Salviae miltiorrhizae radix | C36H30O16 | 717.1449 | 656.9713, 562.4101, 519.0940, 493.1181, 423.0126, 340.0500, 321.0457 | [M-H]- | 1.91 | (Zhao et al., 2016) |
| **44** | salvianolic acid A | 23.566 | Salviae miltiorrhizae radix | C26H22O10 | 493.113 | 314.0721, 295.0602, 277.0574, 239.0697, 223.7416, 197.0422, 185.0227, 159.0452, 151.0376, 137.0507 | [M-H]- | 1.73 | (Ruan et al., 2012) |
| **45** | (15*Z*)-9,12,13-trihydroxy-15-octadecenoic acid | 27.39 | Dioscoreae spongiosae rhizoma | C18H34O5 | 329.2328 | 294.2357, 229.1433, 211.1311, 171.1017, 127.1149, 99.0813, 68.6939 | [M-H]- | 1.85 | (Wang et al., 2022) |
| **46** | cryptotanshinone | 32.047 | Salviae miltiorrhizae radix | C19H20O3 | 297.1489 | 279.1366, 269.1533, 251.1431, 206.1018, 128.0618 | [M+H]+ | -1.19 | (Zhao et al., 2016) |
| 32.074 | 319.1311 | 131.0205 | [M+Na]+ | -2.35 |
| **47** | tanshinone IIA | 32.663 | Salviae miltiorrhizae radix | C19H18O3 | 317.1151 | 220.0396 | [M+Na]+ | -1.02 | (Zhao et al., 2016) |
| 32.681 | 295.1329 | 277.1232, 266.0914, 249.1267, 235.0774, 207.0830, 178.0804, 159.9626 | [M+H]+ | -0.08 |
| **48** | palmitic acid | 34.555 | Dioscoreae spongiosae rhizoma | C16H32O2 | 255.2325 | 237.2171, 222.5188, 156.1686, 129.1926 | [M-H]- | 1.72 | (Wang et al., 2022) |
| **49** | bis (2-ethylhexyl) phthalate | 34.811 | Dioscoreae spongiosae rhizoma | C24H38O4 | 391.2846 | 213.0305, 167.0351, 149.0221, 129.3323, 71.0860, 57.0710 | [M+H]+ | -0.61 | (Wang et al., 2022) |

**Table S4**

Table S4. Screening target proteins interacted with bioactives of CBFD from SEA and ATP.

Please refer to Table S4.csv

**Table S5**

Table S5. Screening target proteins connected to BPH from DiGeNet and GeneCards OMIM databases.

Please refer to Table S5.csv

**Table S6**

**Table S6. Target proteins in 20 signaling pathways enrichment related to BPH.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| KEGG ID | Description | Target Proteins | Corresponding components | False Discovery Rate |
| hsa04915 | Estrogen signaling pathway | AKT1, AKT2, ESR1, ESR2, JUN,  MAPK1, MMP2, MMP9, NOS3 | 6-demethy-4'-methyl-N-methylcoclaurine,  l-Phenylalanine, liensinine, armepavine | 7.71495E-06 |
| hsa01522 | Endocrine resistance | AKT1, AKT2, ESR1, ESR2,  JUN, MAPK1, MMP2, MMP9 | phellodendrine, N-methylisococlaurine, N-methylcoclaurine,  l-Phenylalanine, liensinine, armepavine, 6-demethy-4'-methyl-N-methylcoclaurine | 7.71495E-06 |
| hsa05207 | Chemical carcinogenesis - receptor activation | AKT1, AKT2, CYP1A1, CYP1B1, ESR1,  ESR2, JUN, MAPK1, PPARA, STAT3 | 6-demethy-4'-methyl-N-methylcoclaurine,  N-methylisococlaurine, N-methylcoclaurine, armepavine | 1.58756E-05 |
| hsa05417 | Lipid and atherosclerosis | AKT1, AKT2, CYP1A1, JUN, MAPK1,  MMP3, MMP9, NOS3, PPARG, STAT3 | l-phenylalanine, magnoflorine,  6-demethy-4'-methyl-N-methylcoclaurine | 1.58756E-05 |
| hsa04022 | cGMP-PKG signaling pathway | ADRA1A, ADRA1B, ADRA1D, ADRA2B,  AKT1, AKT2, MAPK1, NOS3, PDE5A | menisperine, liensinine, nornuciferidine, N-methylisococlaurine,  N-methylcoclaurine, magnoflorine, l-Phenylalanine, 6-demethy-4'-methyl-N-methylcoclaurine | 1.58756E-05 |
| hsa04926 | **Relaxin signaling pathway** | AKT1, AKT2, JUN, MAPK1,  MMP2, MMP9, NOS2, NOS3 | l-phenylalanine, 6-demethy-4'-methyl-N-methylcoclaurine,  menisperine, magnoflorine, liensinine | 2.15291E-05 |
| hsa05418 | Fluid shear stress and atherosclerosis | AKT1, AKT2, DUSP1, JUN,  MMP2, MMP9, NOS3, NQO1 | l-phenylalanine, 6-demethy-4'-methyl-N-methylcoclaurine,  argemexirine | 3.26206E-05 |
| hsa04933 | AGE-RAGE signaling pathway in diabetic complications | AKT1, AKT2, JUN, MAPK1,  MMP2, NOS3, STAT3 | menisperine, l-phenylalanine, magnoflorine,  6-demethy-4'-methyl-N-methylcoclaurine | 3.81432E-05 |
| hsa04917 | Prolactin signaling pathway | AKT1, AKT2, ESR1,  ESR2, MAPK1, STAT3 | 6-demethy-4'-methyl-N-methylcoclaurine, N-methylisococlaurine,  N-methylcoclaurine, menisperine, liensinine, armepavine | 6.14582E-05 |
| hsa04668 | TNF signaling pathway | AKT1, AKT2, JUN, MAPK1,  MMP3, MMP9, PTGS2 | l-phenylalanine, 6-demethy-4'-methyl-N-methylcoclaurine,  tetrahydropalmatine, palmitic acid, magnoflorine, liensinine | 6.55019E-05 |
| hsa04080 | Neuroactive ligand-receptor interaction | ADRA1A, ADRA1B, ADRA1D, ADRA2B,  CHRM2, CHRM3, CNR1, DRD2, THRB, TRPV1, TSPO | nuciferine, nornuciferidine, menisperine | 9.68314E-05 |
| hsa05142 | Chagas disease | ACE, AKT1, AKT2, JUN, MAPK1, NOS2 | l-phenylalanine, 6-demethy-4'-methyl-N-methylcoclaurine,  armepavine, N-methylcoclaurine, N-methylisococlaurine | 0.000352336 |
| hsa04066 | HIF-1 signaling pathway | AKT1, AKT2, MAPK1, NOS2, NOS3, STAT3 | l-phenylalanine, menisperine, 6-demethy-4'-methyl-N-methylcoclaurine,  dl-arginine, liensinine, l-norleucine, magnoflorine, palmitic acid, tyrosine | 0.000479502 |
| hsa05145 | Toxoplasmosis | AKT1, AKT2, ALOX5, MAPK1, NOS2, STAT3 | l-phenylalanine, menisperine, palmitic acid, oxyberberine,  magnoflorine, 6-demethy-4'-methyl-N-methylcoclaurine | 0.000493276 |
| hsa05415 | Diabetic cardiomyopathy | ACE, AKT1, AKT2, MMP2,  MMP9, NOS3, PPARA | l-phenylalanine, 6-demethy-4'-methyl-N-methylcoclaurine,  bis(2-ethylhexyl)phthalate, tyrosine | 0.001396234 |
| hsa05205 | Proteoglycans in cancer | AKT1, AKT2, ESR1, MAPK1, MMP2, MMP9, STAT3 | menisperine, magnoflorine, l-phenylalanine,  6-demethy-4'-methyl-N-methylcoclaurine | 0.001419276 |
| hsa04024 | cAMP signaling pathway | AKT1, AKT2, CHRM2, DRD2,  JUN, MAPK1, PPARA | 6-demethy-4'-methyl-N-methylcoclaurine, armepavine, l-phenylalanine,  menisperine, N-methylcoclaurine, N-methylisococlaurine, palmitic acid | 0.001788288 |
| hsa05208 | Chemical carcinogenesis - reactive oxygen species | AKT1, AKT2, CYP1A1,  CYP1B1, JUN, MAPK1, NQO1 | 6-demethy-4'-methyl-N-methylcoclaurine, methyleugenol,  palmatine, tetrahydropalmatine, β-Asarone, γ-Asarone | 0.001826584 |
| hsa05206 | MicroRNAs in cancer | ABCB1, CYP1B1, EZH2, HDAC1,  MAPK1, MMP9, PTGS2, STAT3 | tetrahydropalmatine, liensinine, γ-asarone, β-asarone, pronuciferine, palmitic acid, palmatine,  methyleugenol, magnoflorine, l-phenylalanine, 6-demethy-4'-methyl-N-methylcoclaurine | 0.002223825 |
| hsa04020 | Calcium signaling pathway | ADRA1A, ADRA1B, ADRA1D,  CHRM2, CHRM3, NOS2, NOS3 | nuciferine, 4'-methyl-N-methylcoclaurine,  6-demethy-4'-methyl-N-methylcoclaurine, nornuciferidine | 0.002328889 |

**Table S7**

**Table S7. Toxicological properties of the 3 key bioactives with good binding affinities on the relevant target protein in molecular docking.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameters** | **Compound Name** | | |
| **6-Demethyl-4'-methyl-*N*-methylcoclaurine** | **Isoliensinine** | **Liensinine** |
| Human ether-a-go-go-related gene inhibition | 0.7049  Weak inhibitor | 0.7237  Weak inhibitor | 0.7237  Weak inhibitor |
| Ames toxicity | 0.5615  Non Ames toxic | 0.6547  Non Ames toxic | 0.6547  Non Ames toxic |
| Acute oral toxicity (c) | 0.6250  III | 0.7554  III | 0.7554  III |
| Carcinogenicity (three-class) | 0.7175  Non-required | 0.6795  Non-required | 0.6795  Non-required |
| Rat acute toxicity | 2.6377 | 2.5197 | 2.5197 |

**Table S8**

**Table S8. LD50 of liensinine and isoliensinine administered orally to mice**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Compounds | Group | Dosage, mg/kg | Numbers of animals | Dead animals | Mortality,  % | LD50/Confidence limit, mg/kg |
| Liensinine | 1 | 4800 | 10 | 10 | 100 | 2619.9  (2245.7–3056.6) |
| 2 | 3600 | 10 | 8 | 80 |
| 3 | 2700 | 10 | 5 | 50 |
| 4 | 2025 | 10 | 3 | 30 |
| 5 | 1519 | 10 | 0 | 0 |
| Isoliensinine | 1 | 3600 | 10 | 10 | 100 | 1886.3  (1565.7–2272.6) |
| 2 | 2700 | 10 | 7 | 70 |
| 3 | 2025 | 10 | 6 | 60 |
| 4 | 1519 | 10 | 3 | 30 |
| 5 | 1139 | 10 | 1 | 10 |