Supplementary Material

# Supplementary Figures and Tables

## Supplementary Tables

Table S1 Peak area of top 100 substances

| Name | Formula | Molecular weight (Da) | CAS | RT [min] |
| --- | --- | --- | --- | --- |
| Flavonoids |
| Acacetin | C16H12O5 | 284.0685 | 480-44-4 | 7.1 |
| Chrysin | C15H10O4 | 254.0579 | 480-40-0 | 6.9 |
| 3-O-Methylquercetin | C16H12O7 | 316.0583 | 1486-70-0 | 5.4 |
| 2',3',4',5,7-Pentahydroxyflavone\* | C15H10O7 | 302.0427 | 480-16-0 | 5.2 |
| Tectochrysin | C16H12O4 | 268.0736 | 520-28-5 | 8.5 |
| Artocarpanone | C16H14O6 | 302.079 | 520-25-2 | 5.1 |
| Morin\* | C15H10O7 | 302.0427 | 480-16-0 | 4 |
| 3,5,7-Trihydroxyflavanone (Pinobanksin) | C15H12O5 | 272.0685 | 548-82-3 | 5.8 |
| Kaempferide (3,5,7-Trihydroxy-4'-methoxyflavone) | C16H12O6 | 300.0634 | 491-54-3 | 6.3 |
| 5,7,8-Tetrahydroxy-6-methoxyflavone | C16H12O6 | 300.0634 | - | 4.9 |
| 1,8-dihydroxy-2,6-dimethylxanthen-9-one | C15H12O4 | 256.0736 | - | 7 |
| 4',5-Dihydroxy-3,3',7-Trimethoxyflavone; Pachypodol\* | C18H16O7 | 344.0896 | 33708-72-4 | 7.6 |
| Ayanin (3',5-Dihydroxy-3,4',7-Trimethoxyflavone)\* | C18H16O7 | 344.0896 | 572-32-7 | 7.5 |
| 7,3',4'-Trihydroxyquercetin\* | C18H16O7 | 344.0896 | - | 7.4 |
| 6,7,8-Tetrahydroxy-5-methoxyflavone\* | C16H12O6 | 300.0634 | - | 6 |
| 2',4'-Dihydroxy-4-methoxychalcone; (E)-Cardamonin | C16H14O4 | 270.0892 | 19309-14-9 | 7.8 |
| Tenaxin I\* | C18H16O7 | 344.0896 | 86926-52-5 | 6.8 |
| Pinocembrin (Dihydrochrysin) | C15H12O4 | 256.0736 | 480-39-7 | 7 |
| Eupatilin (5,7-Dihydroxy-3',4',6-Trimethoxyflavone)\* | C18H16O7 | 344.0896 | 22368-21-4 | 6.7 |
| Pinostrobin | C16H14O4 | 270.0892 | 480-37-5 | 8.4 |
| 3',7-dihydroxy-4'-methoxyflavone\* | C16H12O5 | 284.0685 | 54867-60-6 | 4.9 |
| 3,5,4'-Trihydroxy-7-methoxyflavone (Rhamnocitrin)\* | C16H12O6 | 300.0634 | 569-92-6 | 5.8 |
| Galangin (3,5,7-Trihydroxyflavone) | C15H10O5 | 270.0528 | 548-83-4 | 7.1 |
| Diosmetin (5,7,3'-Trihydroxy-4'-methoxyflavone)\* | C16H12O6 | 300.0634 | 520-34-3 | 4.3 |
| 5,7,3',5'-tetrahydroxy-6-methylfavanone\* | C16H12O6 | 300.0634 | - | 5.7 |
| Prunetin-4'-O-glucoside(Prunitrin)\* | C22H22O10 | 446.1213 | 154-36-9 | 4.5 |
| (Z)-4,6-Dihydroxy-2-(4-Hydroxy-3-Methoxybenzylidene)-7-Methylbenzofuran-3(2h)-One\* | C17H14O6 | 314.079 | - | 7.2 |
| Tupichinol E\* | C17H14O6 | 314.079 | - | 7.3 |
| Chrysin-7-O-glucoside\* | C21H20O9 | 416.1107 | 31025-53-3 | 5.1 |
| Chrysin-5-O-glucoside (Toringin)\* | C21H20O9 | 416.1107 | 1329-10-8 | 5 |
| Hydroxygenkwanin | C16H12O6 | 300.0634 | 20243-59-8 | 6.5 |
| Wogonin (5,7-Dihydroxy-8-Methoxyflavone) | C16H12O5 | 284.0685 | 632-85-9 | 6.9 |
| Gerontoisoflavone A | C17H14O6 | 314.079 | - | 4.8 |
| 4'-Demethyleucomin glucoside\* | C22H22O10 | 446.1213 | - | 4.6 |
| (E)-7-O-β-D-glucopyranoside-5-hydroxy-3-(4'-hydroxybenzylidene)-chroman-4-one\* | C22H22O10 | 446.1213 | - | 4.6 |
| Rhamnetin; 3,5,3',4'-Tetrahydroxy-7-Methoxyflavone | C16H12O7 | 316.0583 | 90-19-7 | 6.2 |
| Norartocarpetin | C15H10O6 | 286.0477 | 520-30-9 | 5.6 |
| Quercetin-3,3'-dimethyl ether | C17H14O7 | 330.074 | 4382-17-6 | 6.5 |
| Azaleatin (5-O-Methylquercetin) | C16H12O7 | 316.0583 | 529-51-1 | 4.4 |
| Apigenin; 4',5,7-Trihydroxyflavone | C15H10O5 | 270.0528 | 520-36-5 | 5.7 |
| Loureirin D | C16H16O5 | 288.0998 | 119425-91-1 | 5.1 |
| Nevadensin | C18H16O7 | 344.0896 | 10176-66-6 | 7.1 |
| Drimiopsin C | C15H12O6 | 288.0634 | 773850-90-1 | 4.6 |
| Oroxin A | C21H20O10 | 432.1056 | 57396-78-8 | 4.7 |
| 2-Hydroxy-2,3-dihydrogenistein\* | C15H12O6 | 288.0634 | - | 4.9 |
| 3,7-dihydroxy-4'-methoxyflavone | C16H12O5 | 284.0685 | 54867-60-6 | 4.5 |
| Naringenin (5,7,4'-Trihydroxyflavanone) | C15H12O5 | 272.0685 | 480-41-1 | 5.5 |
| Xanthomicrol (5,4'-Dihydroxy-6,7,8-trimethoxyflavone)\* | C18H16O7 | 344.0896 | 16545-23-6 | 5 |
| Sophoricoside\* | C21H20O10 | 432.1056 | 152-95-4 | 4.4 |
| Phenolic acids |
| 2-Hydroxycinnamic acid\* | C9H8O3 | 164.0473 | 583-17-5 | 4.1 |
| α-Hydroxycinnamic Acid\* | C9H8O3 | 164.0473 | 5801-57-0 | 4.2 |
| Phenethyl caffeate | C17H16O4 | 284.1049 | 104594-70-9 | 7.1 |
| Ferulic acid | C10H10O4 | 194.0579 | 537-98-4 | 4 |
| 3,4-Dihydroxybenzoic acid (Protocatechuic acid)\* | C7H6O4 | 154.0266 | 99-50-3 | 2.5 |
| 2-(Formylamino)benzoic acid | C8H7NO3 | 165.0426 | 3342-77-6 | 3.8 |
| Caffeic aldehyde | C9H8O3 | 164.0473 | 141632-15-7 | 3.9 |
| Phenyl acetate | C8H8O2 | 136.0524 | 122-79-2 | 4.2 |
| 4-Hydroxybenzoic acid | C7H6O3 | 138.0317 | 99-96-7 | 3 |
| Ethyl caffeate | C11H12O4 | 208.0736 | 102-37-4 | 5.5 |
| Salicylic acid | C7H6O3 | 138.0317 | 69-72-7 | 3.1 |
| p-Coumaric acid | C9H8O3 | 164.0473 | 501-98-4 | 3.8 |
| Eugenol | C10H12O2 | 164.0837 | 97-53-0 | 4 |
| Dibutyl phthalate\* | C16H22O4 | 278.1518 | 84-74-2 | 9.6 |
| Phthalic anhydride | C8H4O3 | 148.016 | 85-44-9 | 9.7 |
| Methyl cumalate\* | C7H6O4 | 154.0266 | 6018-41-3 | 2.4 |
| 3,4-Dimethoxycinnamic acid | C11H12O4 | 208.0736 | 2316-26-9 | 4.9 |
| 2,5-Dihydroxybenzoic acid; Gentisic Acid\* | C7H6O4 | 154.0266 | 490-79-9 | 2.6 |
| 1,3-O-Di-p-Coumaroylglycerol | C21H20O7 | 384.1209 | - | 5.8 |
| Butyl isobutyl phthalate\* | C16H22O4 | 278.1518 | 17851-53-5 | 9.6 |
| Lipids |
| γ-Linolenic Acid\* | C18H30O2 | 278.2246 | 506-26-3 | 10.8 |
| α-Linolenic Acid\* | C18H30O2 | 278.2246 | 463-40-1 | 10.7 |
| Lyngbic acid | C15H28O3 | 256.2038 | 70607-97-5 | 7.3 |
| 2R-hydroxy-9Z,12Z,15Z-octadecatrienoic acid | C18H30O3 | 294.2195 | - | 9.4 |
| 3-Hydroxyoctadecanoic Acid | C18H36O3 | 300.2664 | 45261-96-9 | 10.2 |
| Choline Alfoscerate | C8H20NO6P | 257.1028 | 28319-77-9 | 0.8 |
| 9,12-Octadecadiynoic Acid | C18H28O2 | 276.2089 | 2012-14-8 | 9.2 |
| Stearic Acid | C18H36O2 | 284.2715 | 1957/11/4 | 10.8 |
| Octadeca-11E,13E,15Z-trienoic acid | C18H30O2 | 278.2246 | 25575-00-2 | 9.6 |
| 12(13)Ep-9-KODE | C18H30O4 | 310.2144 | 478931-82-7 | 7.7 |
| Others |
| Machilusolide D | C18H30O3 | 294.2195 | - | 9.3 |
| 6-Hydroxyrhein | C15H8O7 | 300.027 | - | 6 |
| 1,5-Dihydroxy-2,3-Dimethoxy-10-Methyl-9-Acridone | C16H15NO5 | 301.095 | - | 6.2 |
| Tri-p-coumaroyl Spermidine | C34H37N3O6 | 583.2677 | - | 5.2 |
| Erythro-Magnolignan B | C18H20O5 | 316.1311 | - | 5.4 |
| Betaine | C5H11NO2 | 117.079 | 107-43-7 | 0.8 |
| 4-Methylbenzaldehyde\* | C8H8O | 120.0575 | 104-87-0 | 4.2 |
| Chrysophanol-1-O-β-D-glucoside\* | C21H20O9 | 416.1107 | 4839-60-5 | 5.2 |
| 3-Methylbenzaldehyde\* | C8H8O | 120.0575 | 620-23-5 | 4.3 |
| 4-Hydroxyacetophenone | C8H8O2 | 136.0524 | 99-93-4 | 4 |
| 4-Guanidinobutyric acid | C5H11N3O2 | 145.0851 | 463-00-3 | 0.8 |
| 4-hydroxyphenyl acrylaldehyde | C9H8O3 | 164.0473 | - | 4 |
| 2,5-Dihydroxybenzaldehyde\* | C7H6O3 | 138.0317 | 1194-98-5 | 3.3 |
| Azelaic acid | C9H16O4 | 188.1049 | 123-99-9 | 4.4 |
| Protocatechualdehyde\* | C7H6O3 | 138.0317 | 139-85-5 | 3.3 |
| 6-Demethoxy-7-methylcapillarisin | C16H12O6 | 300.0634 | - | 7 |
| 3,8-Dihydroxy-1-methoxy-9,10-anthraquinone glucoside | C21H20O10 | 432.1051 | - | 4.9 |
| 4-Hydroxybenzaldehyde | C7H6O2 | 122.0368 | 123-08-0 | 3.7 |
| L-Lysine-Butanoic Acid | C10H22N2O4 | 234.158 | 80407-71-2 | 0.8 |
| D-Fructose 6-phosphate\* | C6H13O9P | 260.0297 | 643-13-0 | 1 |
| 3α,12β,15α,21β,24-pentahydroxyserratane | C30H50O8 | 538.3506 | - | 11.2 |

Table S2 Differential metabolite information between NC group and MC group

| Compound Name | VIP | Fold Change | M/Z | Trends | Formula | Precursor Type |
| --- | --- | --- | --- | --- | --- | --- |
| N-Acetyl-L-glutamine | 1.0265  | 1.5031  | 187.0709  | Up | C7H12N2O4 | [M-H]- |
| Nonadecanoic acid | 1.0895  | 1.3596  | 297.2775  | Up | C19H38O2 | [M-H]- |
| all-trans-Retinoic acid | 1.0909  | 1.7407  | 299.1996  | Up | C20H28O2 | [M-H]- |
| N-Formyl-L-glutamic acid | 1.0920  | 1.3083  | 176.0716  | Up | C6H9NO5 | [M+H]+ |
| Leucine | 1.1161  | 1.2942  | 130.0860  | Up | C6H13NO2 | [M-H]- |
| Daidzin | 1.1263  | 1.4459  | 397.2222  | Up | C21H20O9 | [M-H2O-H]- |
| Epinephrine | 1.1356  | 1.5181  | 184.0952  | Up | C9H13NO3 | [M+H]+ |
| D-Lyxose | 1.1470  | 1.9378  | 149.9935  | Up | C5H10O5 | [M]- |
| Linoleic acid | 1.1472  | 1.3652  | 280.2646  | Up | C18H32O2 | [M]+ |
| Chenodeoxycholic acid | 1.1537  | 1.5244  | 391.2826  | Up | C24H40O4 | [M-H]- |
| Oxalacetic acid | 1.1563  | 1.2943  | 112.9843  | Up | C4H4O5 | [M-H2O-H]- |
| 11Z-Eicosenoic acid | 1.1833  | 1.3554  | 310.2815  | Up | C20H38O2 | [M]- |
| N-Succinyl-L-citrulline | 1.2057  | 2.0296  | 276.1195  | Up | C10H17N3O6 | [M+H]+ |
| Vitamin K1 | 1.2126  | 2.6155  | 449.0934  | Up | C31H46O2 | [M-H]- |
| 8-Amino-7-oxononanoate | 1.2694  | 1.9029  | 188.1290  | Up | C9H17NO3 | [M+H]+ |
| Aminoadipic acid | 1.2783  | 1.5051  | 160.0606  | Up | C6H11NO4 | [M-H]- |
| Betaine | 1.2800  | 1.2157  | 118.0868  | Up | C5H11NO2 | [M+H]+ |
| (-)-Isopiperitenone | 1.2814  | 1.4502  | 150.1030  | Up | C10H14O | [M]+ |
| alpha-D-Ribose 1-phosphate | 1.3013  | 1.5744  | 229.0098  | Up | C5H11O8P | [M-H]- |
| 1-palmitoylglycerophosphocholine | 1.3026  | 1.5148  | 496.3419  | Up | C24H51NO7P | [M]+ |
| Glutathione | 1.3106  | 1.4247  | 307.0840  | Up | C10H17N3O6S | [M]+ |
| L-Lysine | 1.3194  | 1.2109  | 147.1128  | Up | C6H14N2O2 | [M+H]+ |
| Cyromazine | 1.3203  | 1.2239  | 166.0982  | Up | C6H10N6 | [M]+ |
| Sphingosine | 1.3411  | 1.2322  | 300.2905  | Up | C18H37NO2 | [M+H]+ |
| 17a-Estradiol | 1.3437  | 1.5440  | 272.1861  | Up | C18H24O2 | [M]+ |
| 3-Oxo-5beta-cholanate | 1.3696  | 2.4526  | 374.2745  | Up | C24H38O3 | [M]+ |
| beta-D-Fructose 6-phosphate | 1.3768  | 1.7495  | 259.0195  | Up | C6H13O9P | [M-H]- |
| 5,7-Dihydroxyflavone | 1.3829  | 1.8236  | 253.0492  | Up | C15H10O4 | [M-H]- |
| Pyroglutamic acid | 1.4002  | 1.4561  | 128.0350  | Up | C5H7NO3 | [M-H]- |
| Salicyluric acid | 1.4004  | 1.4589  | 194.0445  | Up | C9H9NO4 | [M-H]- |
| Succinic acid | 1.4017  | 1.6036  | 117.0549  | Up | C4H6O4 | [M-H]- |
| Thymidine | 1.4148  | 1.6883  | 223.0270  | Up | C10H14N2O5 | [M-H2O-H]- |
| Anserine | 1.4158  | 1.4991  | 240.1813  | Up | C10H16N4O3 | [M]+ |
| threo-3-Hydroxy-D-aspartate | 1.4279  | 1.2368  | 149.0233  | Up | C4H7NO5 | [M]+ |
| 8-HETE | 1.4416  | 1.4252  | 303.2325  | Up | C20H32O3 | [M+H-H2O]+ |
| Maltol | 1.4453  | 1.9528  | 127.0387  | Up | C6H6O3 | [M+H]+ |
| Picolinic acid | 1.4519  | 1.2227  | 123.0799  | Up | C6H5NO2 | [M]+ |
| Eicosapentaenoic Acid | 1.4532  | 1.4619  | 302.2157  | Up | C20H30O2 | [M]+ |
| 2-Deoxystreptamine | 1.4672  | 1.8398  | 163.1118  | Up | C6H14N2O3 | [M+H]+ |
| 4-Pyridoxic acid | 1.4712  | 3.2022  | 182.0438  | Up | C8H9NO4 | [M-H]- |
| 3-(3,4-Dihydroxy-5-methoxy)-2-propenoic acid | 1.4714  | 1.9878  | 193.0493  | Up | C10H10O5 | [M+H-H2O]+ |
| Citrulline | 1.4771  | 1.3425  | 174.0872  | Up | C6H13N3O3 | [M-H]- |
| Tridecanoic acid | 1.4879  | 2.3664  | 213.1846  | Up | C13H26O2 | [M-H]- |
| Indolepyruvate | 1.5269  | 1.2259  | 204.0664  | Up | C11H9NO3 | [M+H]+ |
| L-Isoleucine | 1.5343  | 1.6272  | 132.0533  | Up | C6H13NO2 | [M+H]+ |
| Coniferyl aldehyde | 1.5559  | 1.6004  | 178.0594  | Up | C10H10O3 | [M]+ |
| L-Carnitine | 1.5619  | 1.8189  | 162.0565  | Up | C7H15NO3 | [M+H]+ |
| Indoleacetaldehyde | 1.5974  | 1.6081  | 160.0767  | Up | C10H9NO | [M+H]+ |
| Vaccenic acid | 1.6087  | 1.3139  | 281.2434  | Up | C18H34O2 | [M-H]- |
| 13(S)-HpOTrE | 1.6375  | 2.6113  | 311.2225  | Up | C18H30O4 | [M+H]+ |
| 16-Hydroxy hexadecanoic acid | 1.6411  | 2.0129  | 271.2259  | Up | C16H32O3 | [M-H]- |
| Dodecanedioic acid | 1.6579  | 4.2965  | 229.1430  | Up | C12H22O4 | [M-H]- |
| Stearolic acid | 1.6795  | 2.8093  | 263.2380  | Up | C18H32O2 | [M+H-H2O]+ |
| Pipecolic acid | 1.6797  | 1.5311  | 130.0502  | Up | C6H11NO2 | [M+H]+ |
| Docosapentaenoic acid (22n-3) | 1.6868  | 1.7935  | 329.2476  | Up | C22H34O2 | [M-H]- |
| 5-Hydroxyindoleacetic acid | 1.7005  | 1.4096  | 191.1064  | Up | C10H9NO3 | [M]- |
| Pyridoxal phosphate | 1.7203  | 1.3265  | 247.1685  | Up | C8H10NO6P | [M]- |
| Hippuric acid | 1.7438  | 1.4943  | 180.0670  | Up | C9H9NO3 | [M+H]+ |
| Pantothenol | 1.7815  | 1.4419  | 206.1396  | Up | C9H19NO4 | [M+H]+ |
| N-Acetyl-L-phenylalanine | 1.7890  | 1.9902  | 206.0806  | Up | C11H13NO3 | [M-H]- |
| S-Hexyl-glutathione | 1.8306  | 2.4558  | 391.2856  | Up | C16H29N3O6S | [M]+ |
| Aflatoxin B1 | 1.8920  | 1.5227  | 312.3632  | Up | C17H12O6 | [M]+ |
| Gluconic acid | 1.9915  | 3.7450  | 195.0493  | Up | C6H12O7 | [M-H]- |
| Ketoleucine | 2.0035  | 1.9690  | 131.0692  | Up | C6H10O3 | [M+H]+ |
| Methyleugenol | 2.0266  | 2.2088  | 179.1075  | Up | C11H14O2 | [M+H]+ |
| L-Leucine | 2.0417  | 1.8691  | 130.0861  | Up | C6H13NO2 | [M-H]- |
| Phenylethylamine | 2.0796  | 4.6136  | 121.0654  | Up | C8H11N | [M]- |
| S-Adenosylmethionine | 2.0960  | 2.5572  | 398.2404  | Up | C15H22N6O5S | [M]+ |
| Pyridoxamine | 2.1743  | 1.9452  | 169.0952  | Up | C8H12N2O2 | [M+H]+ |
| Heptanoic acid | 2.2482  | 2.1420  | 130.0654  | Up | C7H14O2 | [M]+ |
| Maleamate | 2.2636  | 2.4353  | 115.0030  | Up | C4H5NO3 | [M]- |
| 3-Methylxanthine | 1.0320  | 0.5221  | 149.0456  | Down | C6H6N4O2 | [M+H-H2O]+ |
| Mibefradil | 1.0847  | 0.7354  | 496.3038  | Down | C29H38FN3O3 | [M+H]+ |
| 2-Aminobenzoic acid | 1.0847  | 0.7492  | 137.0462  | Down | C7H7NO2 | [M]+ |
| D-beta-Phenylalanine | 1.0895  | 0.8204  | 166.0874  | Down | C9H11NO2 | [M+H]+ |
| L-Fucose | 1.0976  | 0.6340  | 165.1140  | Down | C6H12O5 | [M+H]+ |
| Azelaic acid | 1.1019  | 0.6483  | 171.0926  | Down | C9H16O4 | [M+H-H2O]+ |
| N-Acetylhistidine | 1.1028  | 0.6198  | 198.0856  | Down | C8H11N3O3 | [M+H]+ |
| Docosatetraenoyl Ethanolamide | 1.1217  | 0.6560  | 376.3195  | Down | C24H41NO2 | [M+H]+ |
| Biochanin A | 1.1319  | 0.7171  | 283.1678  | Down | C16H12O5 | [M-H]- |
| Iminoarginine | 1.1453  | 0.7389  | 172.0964  | Down | C6H12N4O2 | [M]- |
| Dihydrouracil | 1.1788  | 0.7124  | 115.0510  | Down | C4H6N2O2 | [M+H]+ |
| Adenosine | 1.1960  | 0.7392  | 268.1033  | Down | C10H13N5O4 | [M+H]+ |
| D-Ribose | 1.2088  | 0.8125  | 151.0363  | Down | C5H10O5 | [M+H]+ |
| D-synephrine | 1.2100  | 0.6903  | 168.0918  | Down | C9H13NO2 | [M+H]+ |
| Gamma-Tocotrienol | 1.2132  | 0.6782  | 410.3186  | Down | C28H42O2 | [M]+ |
| Cortisol | 1.2282  | 0.7446  | 361.1993  | Down | C21H30O5 | [M-H]- |
| Ergocalciferol | 1.2432  | 0.6833  | 396.3444  | Down | C28H44O | [M]+ |
| N-Acetylleucine | 1.2464  | 0.7342  | 174.1134  | Down | C8H15NO3 | [M+H]+ |
| 1-Methyladenosine | 1.2503  | 0.7645  | 281.1204  | Down | C11H15N5O4 | [M]- |
| Cortexolone | 1.2613  | 0.7285  | 346.3311  | Down | C21H30O4 | [M]+ |
| 3,4-Methylenedioxyamphetamine | 1.2696  | 0.4491  | 194.1188  | Down | C11H15NO2 | [M+H]+ |
| Taurine | 1.2898  | 0.8316  | 124.0066  | Down | C2H7NO3S | [M-H]- |
| (R)-Pantolactone | 1.3021  | 0.8088  | 131.5340  | Down | C6H10O3 | [M+H]+ |
| gamma-Aminobutyric acid | 1.3505  | 0.6805  | 103.0551  | Down | C4H9NO2 | [M]+ |
| D-Xylose | 1.3895  | 0.6839  | 151.0621  | Down | C5H10O5 | [M+H]+ |
| Retinol | 1.4425  | 0.6415  | 269.2271  | Down | C20H30O | [M+H-H2O]+ |
| Caryophyllene alpha-oxide | 1.4603  | 0.7965  | 221.1909  | Down | C15H24O | [M+H]+ |
| Pyrimidodiazepine | 1.4925  | 0.7725  | 221.0931  | Down | C9H11N5O2 | [M]+ |
| L-Proline | 1.4969  | 0.7291  | 116.0718  | Down | C5H9NO2 | [M+H]+ |
| O-Acetylcarnitine | 1.5040  | 0.5768  | 205.1262  | Down | C9H18NO4 | [M+H]+ |
| Glyceric acid | 1.5191  | 0.4462  | 105.0186  | Down | C3H6O4 | [M-H]- |
| Phosphonoacetate | 1.5605  | 0.6344  | 140.0686  | Down | C2H5O5P | [M]+ |
| Chavicol | 1.6380  | 0.7135  | 135.0808  | Down | C9H10O | [M+H]+ |
| Cholesterol | 1.7058  | 0.6977  | 369.3524  | Down | C27H46O | [M+H-H2O]+ |
| N-Acetylglutamic acid | 1.7759  | 0.3948  | 190.0505  | Down | C7H11NO5 | [M+H]+ |
| 7,8-Diaminononanoate | 1.8504  | 0.8296  | 189.1647  | Down | C9H20N2O2 | [M+H]+ |
| L-Kynurenine | 1.8598  | 0.6290  | 209.0930  | Down | C10H12N2O3 | [M+H]+ |
| Sucrose | 1.9759  | 0.7405  | 343.2981  | Down | C12H22O11 | [M+H]+ |
| Antibiotic JI-20A | 1.9873  | 0.7142  | 482.3239  | Down | C19H39N5O9 | [M+H]+ |
| Ureidopropionic acid | 2.0573  | 0.6045  | 133.0614  | Down | C4H8N2O3 | [M+H]+ |

Table S3 Differential metabolite information between MC group and EEP group

| Compound Name | VIP | Fold Change | M/Z | Trends | Formula | Precursor Type |
| --- | --- | --- | --- | --- | --- | --- |
| m-Cresol | 1.2513  | 1.5897  | 109.1016  | Up | C7H8O | [M+H]+ |
| 1-Deoxy-D-xylulose | 1.6209  | 1.3998  | 117.0574  | Up | C5H10O4 | [M+H-H2O]+ |
| trans-Cinnamate | 1.4117  | 1.4441  | 131.0499  | Up | C9H8O2 | [M+H-H2O]+ |
| Anabasine | 1.7499  | 1.3469  | 144.9824  | Up | C10H14N2 | [M+H-H2O]+ |
| 4-Hydroxycinnamic acid | 1.1203  | 1.3127  | 146.9810  | Up | C9H8O3 | [M+H-H2O]+ |
| Allantoin | 1.2473  | 1.2190  | 158.0462  | Up | C4H6N4O3 | [M]+ |
| Aminoadipic acid | 1.1945  | 1.3550  | 160.0606  | Up | C6H11NO4 | [M-H]- |
| 3-(2-Hydroxyphenyl)propanoic acid | 2.0156  | 2.3171  | 167.0708  | Up | C9H10O3 | [M+H]+ |
| DL-Glycerol 1-phosphate | 1.6803  | 2.6921  | 171.0052  | Up | C3H9O6P | [M-H]- |
| D-Galactose | 1.8494  | 2.3476  | 181.0151  | Up | C6H12O6 | [M+H]+ |
| N-Succinyl-L-citrulline | 1.6085  | 1.7759  | 276.1195  | Up | C10H17N3O6 | [M+H]+ |
| Citric acid | 1.3674  | 1.3166  | 191.0177  | Up | C6H8O7 | [M-H]- |
| D-Glucuronic Acid | 1.1263  | 2.9108  | 195.1233  | Up | C6H10O7 | [M+H]+ |
| Indolelactic acid | 1.4903  | 1.9784  | 206.0824  | Up | C11H11NO3 | [M+H]+ |
| Capsidiol | 1.1840  | 2.5100  | 219.1756  | Up | C15H24O2 | [M+H-H2O]+ |
| Uridine | 1.1530  | 2.0054  | 243.0605  | Up | C9H12N2O6 | [M-H]- |
| beta-Alanyl-L-arginine | 1.3025  | 1.4170  | 245.1506  | Up | C9H19N5O3 | [M]+ |
| Alprenolol | 1.7472  | 2.7887  | 250.1787  | Up | C15H23NO2 | [M+H]+ |
| Docosatetraenoyl Ethanolamide | 1.0372  | 1.2061  | 376.3195  | Up | C24H41NO2 | [M+H]+ |
| Inosine | 1.0618  | 1.3092  | 267.0735  | Up | C10H12N4O5 | [M-H]- |
| gamma-Aminobutyric acid | 1.0873  | 1.2878  | 103.0551  | Up | C4H9NO2 | [M]+ |
| (R)-Pantolactone | 1.1080  | 1.2766  | 131.5340  | Up | C6H10O3 | [M+H]+ |
| Catechin | 1.5583  | 1.6163  | 289.0700  | Up | C15H14O6 | [M-H]- |
| Epiandrosterone | 1.0656  | 1.2914  | 288.9504  | Up | C19H30O2 | [M-H]- |
| 1-Methyladenosine | 1.3195  | 1.3458  | 281.1204  | Up | C11H15N5O4 | [M]- |
| Antibiotic JI-20A | 1.2728  | 1.2449  | 482.3239  | Up | C19H39N5O9 | [M+H]+ |
| Ergocalciferol | 1.3155  | 1.6074  | 396.3444  | Up | C28H44O | [M]+ |
| Corticosterone | 1.9976  | 3.0597  | 347.2205  | Up | C21H30O4 | [M+H]+ |
| (4Z,7Z,10Z,13Z,16Z,19Z)-Docosahexaenoic acid ethyl ester | 1.5894  | 2.4738  | 357.2785  | Up | C24H36O2 | [M+H]+ |
| Nitrendipine | 1.8242  | 1.9334  | 361.1401  | Up | C18H20N2O6 | [M+H]+ |
| 11-Dehydro-thromboxane B2 | 1.5942  | 2.1704  | 369.2254  | Up | C20H32O6 | [M+H]+ |
| Caryophyllene alpha-oxide | 1.6995  | 1.3725  | 221.1909  | Up | C15H24O | [M+H]+ |
| LysoPA(16\_0\_0\_0) | 1.1889  | 1.4152  | 409.2322  | Up | C19H39O7P | [M-H]- |
| Sucrose | 1.9588  | 1.3122  | 343.2981  | Up | C12H22O11 | [M+H]+ |
| N-Acetylhistidine | 2.1185  | 2.5661  | 198.0856  | Up | C8H11N3O3 | [M+H]+ |
| alpha-D-Ribose 1-phosphate | 1.0622  | 0.7881  | 229.0098  | Down | C5H11O8P | [M-H]- |
| S-Adenosylmethionine | 1.0085  | 0.7781  | 398.2404  | Down | C15H22N6O5S | [M]+ |
| Coniferyl aldehyde | 1.1302  | 0.7315  | 178.0594  | Down | C10H10O3 | [M]+ |
| L-Isoleucine | 1.2030  | 0.7382  | 132.0533  | Down | C6H13NO2 | [M+H]+ |
| Vitamin K1 | 1.2001  | 0.4476  | 449.0934  | Down | C31H46O2 | [M-H]- |
| 4-Hydroxyphenylacetaldehyde | 1.1392  | 0.7007  | 136.0488  | Down | C8H8O2 | [M]+ |
| Tyramine | 1.4884  | 0.3622  | 137.0828  | Down | C8H11NO | [M]+ |
| Spermidine | 1.1068  | 0.7770  | 143.9148  | Down | C7H19N3 | [M-H]- |
| Cyromazine | 1.1977  | 0.8258  | 166.0982  | Down | C6H10N6 | [M]+ |
| 3-Hydroxyanthranilic acid | 1.8255  | 0.5461  | 152.0344  | Down | C7H7NO3 | [M-H]- |
| 2-Amino-4-nitrotoluene | 1.3152  | 0.5906  | 153.0664  | Down | C7H8N2O2 | [M+H]+ |
| D-Xylitol | 1.5483  | 0.6832  | 153.0773  | Down | C5H12O5 | [M+H]+ |
| 2,3-Butanediol | 1.3600  | 0.6677  | 155.1079  | Down | C4H10O2S2 | [M+H]+ |
| Pipecolic acid | 1.3665  | 0.7325  | 130.0502  | Down | C6H11NO2 | [M+H]+ |
| 3,4-Dihydroxyphenylglycol | 1.8763  | 0.4832  | 171.0643  | Down | C8H10O4 | [M+H]+ |
| 3-Dehydroshikimate | 2.1835  | 0.4689  | 171.9922  | Down | C7H8O5 | [M]+ |
| Tetrahydrodipicolinate | 1.2960  | 0.7855  | 172.0763  | Down | C7H9NO4 | [M+H]+ |
| N-Formyl-L-glutamic acid | 1.5808  | 0.5686  | 176.0716  | Down | C6H9NO5 | [M+H]+ |
| D-Fructose | 1.0068  | 0.7760  | 181.0868  | Down | C6H12O6 | [M+H]+ |
| myo-Inositol | 1.1704  | 0.4827  | 181.0149  | Down | C6H12O6 | [M+H]+ |
| Undecanoic acid | 1.6958  | 0.7476  | 186.9568  | Down | C11H22O2 | [M+H]+ |
| 3-Indoleacrylate | 1.6326  | 0.4416  | 188.0714  | Down | C11H9NO2 | [M+H]+ |
| Methyl (indol-3-yl)acetate | 1.8146  | 0.6479  | 189.0791  | Down | C11H11NO2 | [M]+ |
| Kynurenic acid | 1.3136  | 0.6862  | 190.0868  | Down | C10H7NO3 | [M+H]+ |
| Quinate | 1.4097  | 0.6464  | 191.0550  | Down | C7H12O6 | [M-H]- |
| Diaminopimelic acid | 1.5357  | 0.5530  | 191.0404  | Down | C7H14N2O4 | [M+H]+ |
| Scopoletin | 1.0714  | 0.4148  | 193.0493  | Down | C10H8O4 | [M+H]+ |
| 3-Methyl-L-tyrosine | 1.4378  | 0.8262  | 195.1024  | Down | C10H13NO3 | [M]+ |
| Procollagen 5-hydroxy-L-lysine | 1.8283  | 0.2637  | 197.8068  | Down | C7H13N3O3R2 | [M-H]- |
| Docosapentaenoic acid (22n-3) | 1.5777  | 0.7806  | 329.2476  | Down | C22H34O2 | [M-H]- |
| 3-(3,4-Dihydroxy-5-methoxy)-2-propenoic acid | 1.7788  | 0.4057  | 193.0493  | Down | C10H10O5 | [M+H-H2O]+ |
| L-Carnitine | 1.7964  | 0.7434  | 162.0565  | Down | C7H15NO3 | [M+H]+ |
| Myristoleic acid | 1.1270  | 0.8121  | 209.1908  | Down | C14H26O2 | [M+H-H2O]+ |
| Succinic acid | 2.0029  | 0.8183  | 117.0549  | Down | C4H6O4 | [M-H]- |
| N-Acetyl-D-glucosamine | 1.5346  | 0.8183  | 221.1532  | Down | C8H15NO6 | [M]- |
| Deoxyuridine | 1.4537  | 0.8015  | 228.1962  | Down | C9H12N2O5 | [M]+ |
| 13(S)-HpOTrE | 1.9691  | 0.2328  | 311.2225  | Down | C18H30O4 | [M+H]+ |
| Palmitic acid | 1.4579  | 0.6201  | 256.2619  | Down | C16H32O2 | [M]+ |
| Genistein | 1.1169  | 0.2813  | 270.1696  | Down | C15H10O5 | [M]- |
| N2-gamma-Glutamylglutamine | 1.5031  | 0.8277  | 274.1025  | Down | C10H17N3O6 | [M-H]- |
| Oleic acid | 1.2504  | 0.6443  | 282.2795  | Down | C18H34O2 | [M]+ |
| (6Z)-Octadecenoic acid | 1.6644  | 0.5983  | 282.2800  | Down | C18H34O2 | [M]+ |
| 3-Methylxanthine | 1.1633  | 0.8198  | 149.0456  | Down | C6H6N4O2 | [M+H-H2O]+ |
| Octadecanamide | 1.1217  | 0.6210  | 284.2957  | Down | C18H37NO | [M+H]+ |
| Hexadecanedioate | 1.0508  | 0.8205  | 285.2047  | Down | C16H30O4 | [M-H]- |
| Indoleglycerol phosphate | 1.8360  | 0.4102  | 288.0749  | Down | C11H14NO6P | [M+H]+ |
| 9,10-Dihydroxystearate | 1.8181  | 0.4167  | 299.2587  | Down | C18H36O4 | [M+H-H2O]+ |
| Sphinganine | 1.1597  | 0.7519  | 302.3054  | Down | C18H39NO2 | [M+H]+ |
| Ribose 1,5-bisphosphate | 2.0143  | 0.6099  | 309.1713  | Down | C5H12O11P2 | [M-H]- |
| Pergolide | 1.6957  | 0.1837  | 314.1839  | Down | C19H26N2S | [M]+ |
| 1-Arachidonoylglycerol | 1.3190  | 0.5514  | 361.2747  | Down | C23H38O4 | [M+H-H2O]+ |
| O-Acetylcarnitine | 1.5024  | 0.3501  | 205.1262  | Down | C9H18NO4 | [M+H]+ |
| Myriocin | 1.4851  | 0.5475  | 402.2860  | Down | C21H39NO6 | [M+H]+ |
| 3beta,5beta-Ketodiol | 1.1046  | 0.7803  | 417.3359  | Down | C27H44O3 | [M+H]+ |
| Lanosterin | 1.3166  | 0.7935  | 425.2539  | Down | C30H50O | [M-H]- |
| Galactosylsphingosine | 1.6828  | 0.4198  | 461.3255  | Down | C24H47NO7 | [M]+ |
| 3-Epiecdysone | 1.4271  | 0.3086  | 464.2840  | Down | C27H44O6 | [M]+ |
| L-Olivosyl-oleandolide | 2.2581  | 0.6106  | 517.3112  | Down | C26H44O10 | [M+H]+ |
| L-Oleandrosyl-oleandolide | 1.5910  | 0.6045  | 530.3212  | Down | C27H46O10 | [M]+ |
| Avermectin A1b aglycone | 1.1084  | 0.7072  | 567.3269  | Down | C34H48O8 | [M+H-H2O]+ |

## Supplementary Figures



**Supplementary Figure 1** The total ion current chromatogram of the propolis ethanol extract