**Supplementary material**

**An Integrated Strategy to Discover the Quality Control Markers of Herbal Formulae of Danning Tablet with Anti-cholestasis Applications**

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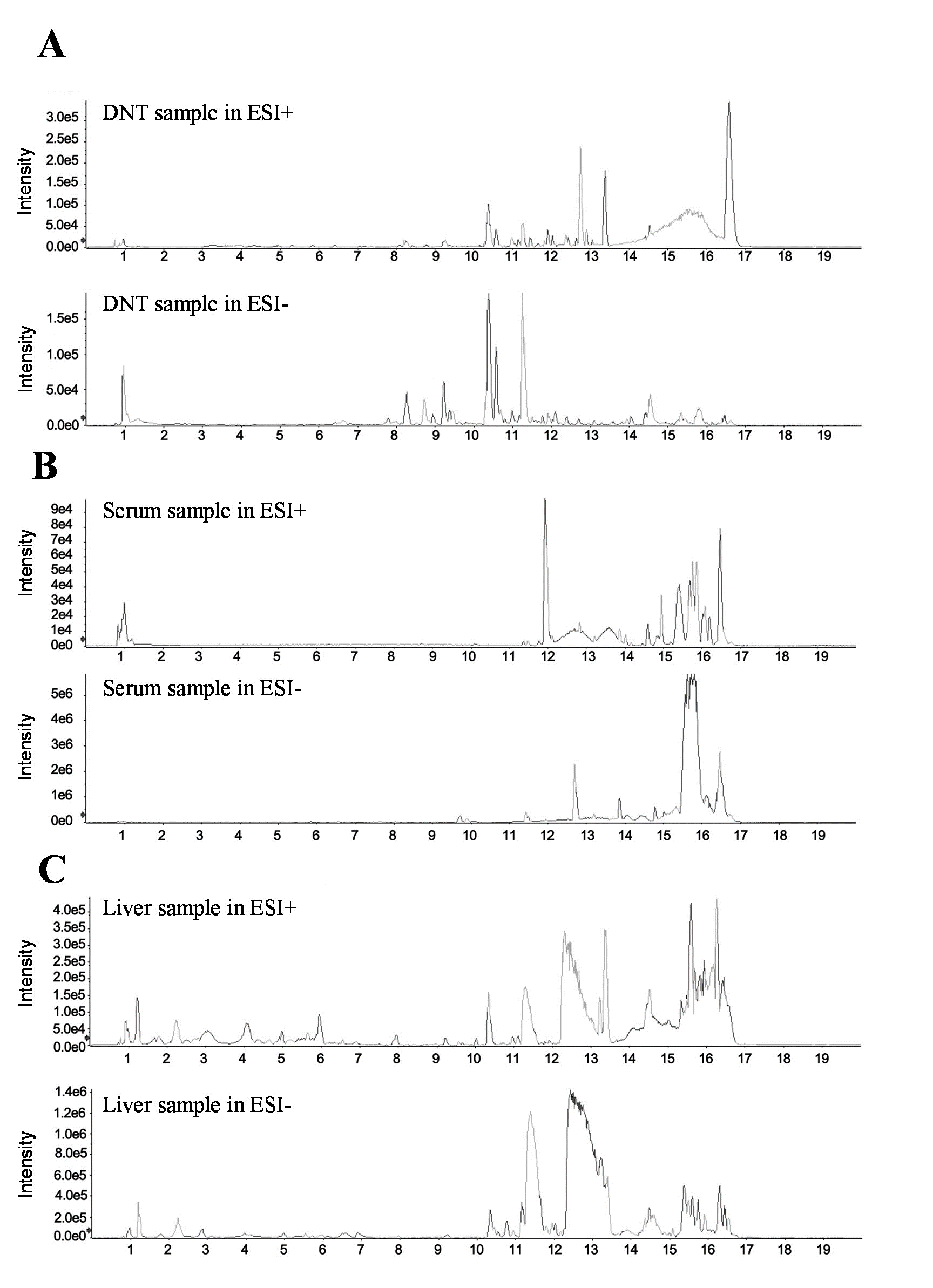
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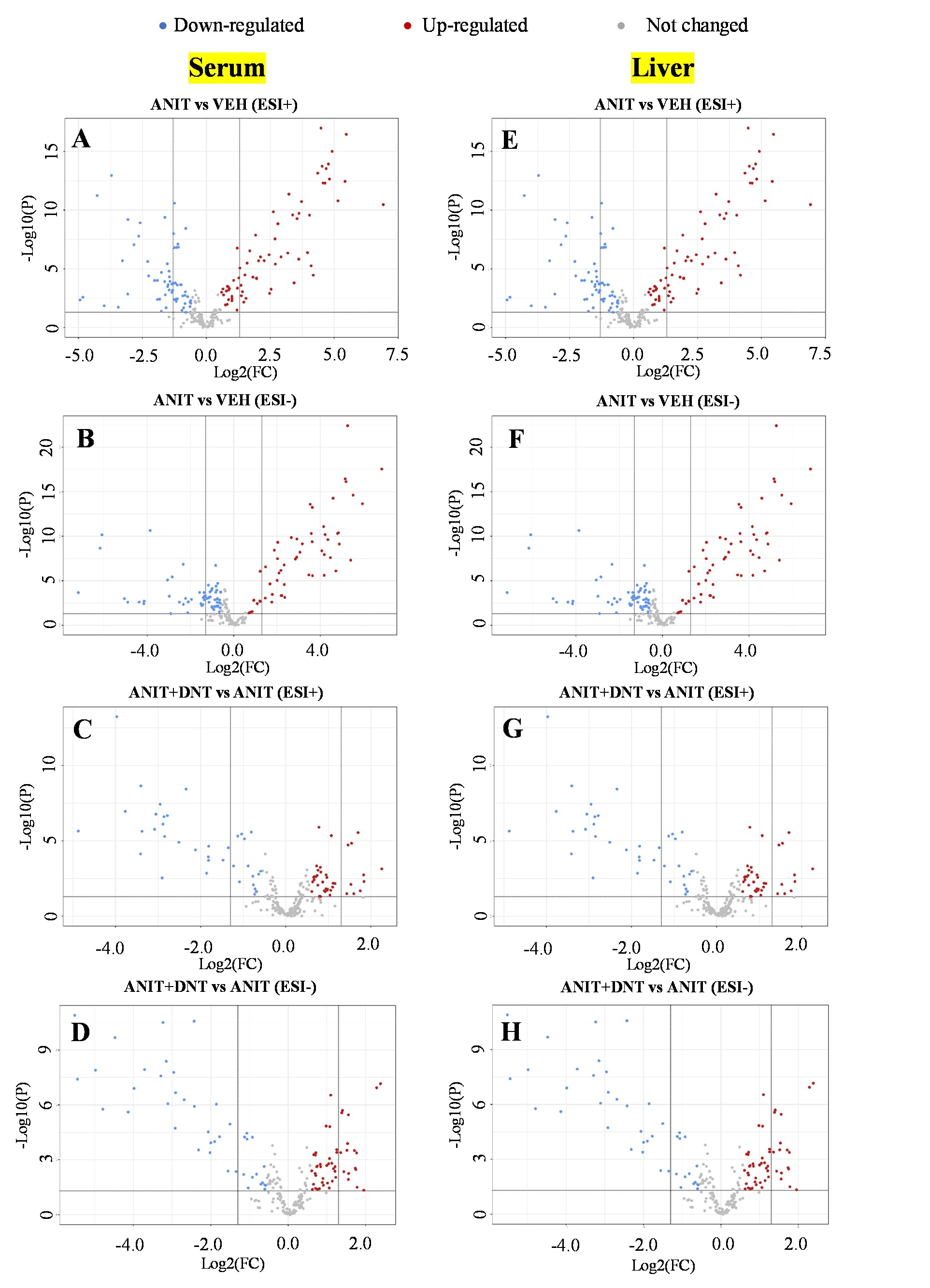
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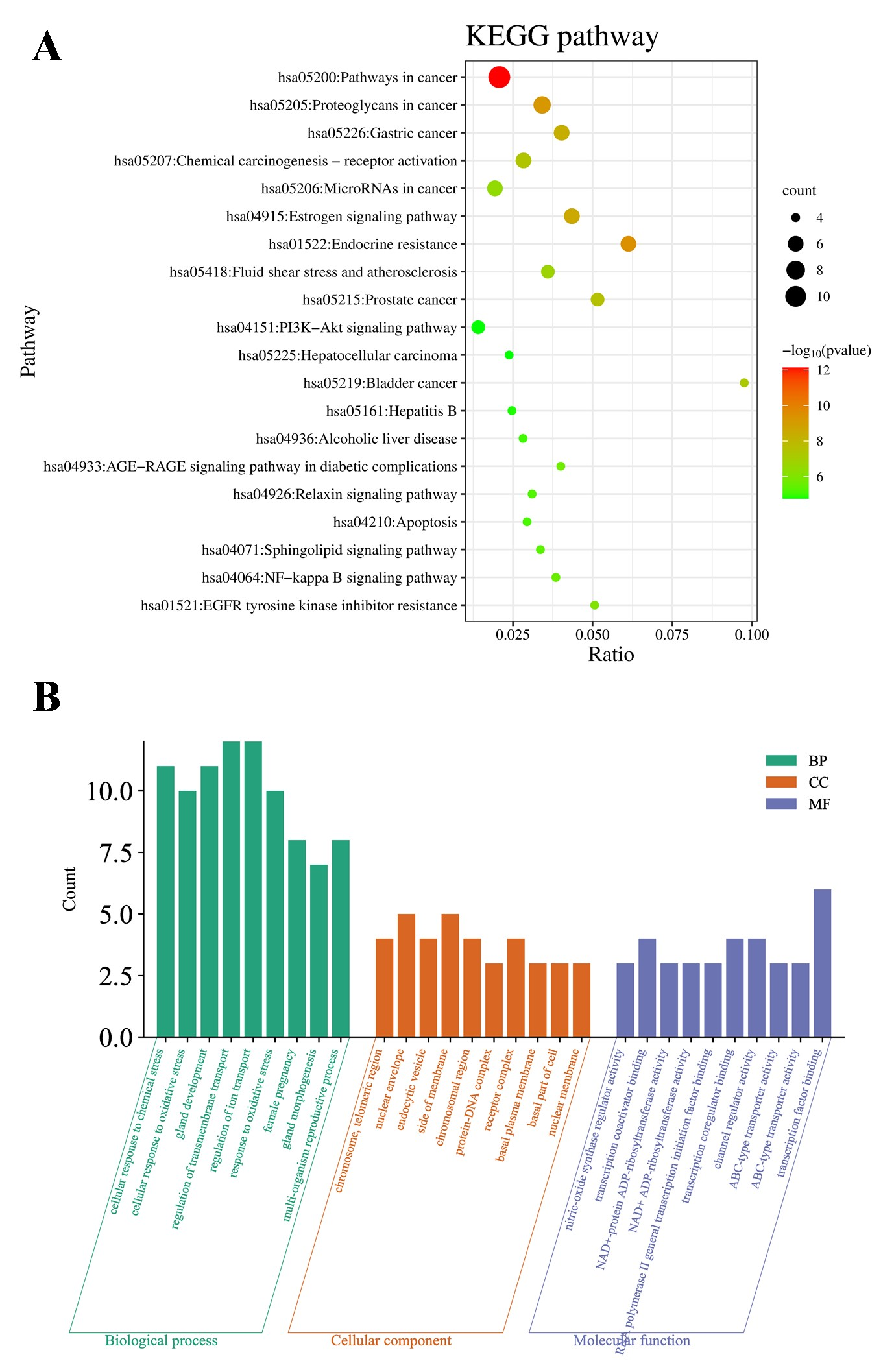
**Fig. S1** Typical UPLC-MS total ion chromatography of DNT sample (A), serum sample (B), and liver sample (C) in both of positive and negative ion modes.



**Fig. S2** Volcano plots of endogenous compounds highlights differentially expressed endogenous components in serum and liver samples of mice. (A-D) Volcano plots between VEH and ANIT groups both in positive and negative ion modes. (E-H) Volcano plots between ANIT and ANIT+DNT groups both in positive and negative ion modes. Differentially expressed endogenous components between groups were screened by the selection criteria of P<0.05 and fold change＞1.5.

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**Fig. S3** Hepatic mRNA expression of genes involved in bile acid biosynthesis and secretion in mice. Compared with the VEH (control) group, \*P <0.05, \*\*P <0.01, \*\*\*P <0.001; Compared with the ANIT (model) group, #P <0.05, ##P <0.01, ###P <0.001.



**Fig. S4** Possible mechanism for the anti-cholestatic effect of the DNT Q-markers. (A) KEGG pathway enrichment. The top 20 pathways are shown. (B) GO function enrichment analysis for BP, MF, CC. The top 10 significant terms (P < 0.05) are shown. X coordinate stands for enriched gene function, and Y coordinate stands for enriched gene number.

Table S1 Primers used for q-PCR.

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Gene | Forward | Reverse |
|
| 1 | *Fxr* | ATGTACCAGCCTGAGAACCC | CTCAGCGTGGTGATGGTTGA |
| 2 | *Shp* | AACATTCCAGGCACCCTTCT | GGTCACCTCAGCAAAAGCAT |
| 3 | *Cyp27a1* | TGAACGAGTACCACACCAGG | CATCAGACTATGGCGCAGGT |
| 4 | *Cyp8b1* | CTGGACAAGGGTTTTGTGCC | CCCGCATCCCCTTCAAGAAT |
| 5 | *Bsep* | TCTGACTCAGTGATTCTTCGCA | CCCATAAACATCAGCCAGTTGT |
| 6 | *Ntcp* | CCAGCAGCTCTGGAAAAAGGTA | AGAGTTCAGGCCATTAGGGG |
| 7 | *Tnf* | CGGGCAGGTCTACTTTGGAG | ACCCTGAGCCATAATCCCCT |
| 8 | *Esr1* | CCAGGCTTTGGGGACTTGAAT | GCAAGTTAGGAGCAAACAGGAG |
| 9 | *Egfr* | GCAATGTTCCCATCGCTGTC | CAGGTGTCTTTGCATGTGGC |
| 10 | *Akt1* | TGTTTCTACTGTGGGCAGCA | TGGTCGCGTCAGTCCTTAAT |
| 11 | *Gapdh* | GGCCGAGAATGGGAAGCTTGT | ACATACTCAGCACCGGCCTCA |

Table S2 Characterization of xenobiotic chemicals derived from DNT in mice with ANIT-induced cholestasis.

| No. | Name | Formula | Source | Mass (Da) | RT (min) | Fragment ions (relative abundance%) |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |
| 1 | eucomic acid | C11H12O6 | CF | 240.0634 | 7.3 | (ESI-)107.0490 (80%);133.0653 (40%);149.0599 (60%);177.0552 (80%);179.0344 (100%);195.0667 (20%);221.0451 (10%);239.0584 (100%) |
| 2 | isotachioside | C13H18O8 | PCRR | 302.1002 | 7.0 | (ESI-)101.0248 (65%);121.0275 (65%);139.0444 (35%);167.06 (65%);180.0623 (35%);195.0548 (65%);211.0862 (65%);223.0873 (35%);301.1246 (100%) |
| 3 | tachioside | C13H18O8 | PCRR | 302.1002 | 7.0 | (ESI-)101.0248 (65%);121.0275 (65%);139.0444 (35%);167.06 (65%);180.0623 (35%);195.0548 (65%);211.0862 (65%);223.0873 (35%);301.1246 (100%) |
| 4 | aloe emodin\* | C15H10O5 | RRR | 270.0529 | 12.4 | (ESI+)115.0539 (10%);141.0697 (15%);169.0646 (15%);173.06 (5%);197.0592 (55%);201.055 (10%);225.0546 (45%);229.05 (25%);271.0599 (100%)  (ESI-)182.0384 (10%);197.0616 (20%);210.033 (10%);225.057 (80%);241.0522 (35%);269.0479 (100%) |
| 5 | apigenin\* | C15H10O5 | PCRR | 270.0529 | 11.6 | (ESI+)115.0539 (10%);141.0697 (15%);169.0646 (15%);173.06 (5%);197.0592 (55%);201.055 (10%);225.0546 (45%);229.05 (25%);271.0599 (100%)  (ESI-)182.0384 (10%);197.0616 (20%);210.033 (10%);225.057 (80%);241.0522 (35%);269.0479 (100%) |
| 6 | emodin\* | C15H10O5 | RRR PCRR | 270.0529 | 14.5 | (ESI+)115.0539 (10%);141.0697 (15%);169.0646 (15%);173.06 (5%);197.0592 (55%);201.055 (10%);225.0546 (45%);229.05 (25%);271.0599 (100%)  (ESI-)182.0384 (10%);197.0616 (20%);210.033 (10%);225.057 (80%);241.0522 (35%);269.0479 (100%) |
| 7 | citreorosein | C15H10O6 | RRR PCRR | 286.0478 | 12.1 | (ESI+)199.0381 (5%);213.0555 (15%);223.0397 (5%);240.0418 (5%);241.0498 (25%);251.0359 (5%);258.0513 (5%);269.0449 (5%);287.0551 (100%)  (ESI-)195.0485 (5%);211.0411 (20%);224.0492 (5%);241.0518 (20%);225.0311 (5%);257.0475 (15%);268.0394 (10%);285.0427 (100%) |
| 8 | kaempferol\* | C15H10O6 | RRR PCRR CR CF | 286.0478 | 14.5 | (ESI+)199.0381 (5%);213.0555 (15%);223.0397 (5%);240.0418 (5%);241.0498 (25%);251.0359 (5%);258.0513 (5%);269.0449 (5%);287.0551 (100%)  (ESI-)195.0485 (5%);211.0411 (20%);224.0492 (5%);241.0518 (20%);225.0311 (5%);257.0475 (15%);268.0394 (10%);285.0427 (100%) |
| 9 | luteolin\* | C15H10O6 | CR | 286.0478 | 11.0 | (ESI+)199.0381 (5%);213.0555 (15%);223.0397 (5%);240.0418 (5%);241.0498 (25%);251.0359 (5%);258.0513 (5%);269.0449 (5%);287.0551 (100%)  (ESI-)195.0485 (5%);211.0411 (20%);224.0492 (5%);241.0518 (20%);225.0311 (5%);257.0475 (15%);268.0394 (10%);285.0427 (100%) |
| 10 | 13-hydroxygermacrone | C15H22O2 | CR | 234.1621 | 14.0 | (ESI+)123.0435 (5%);179.1059 (60%);219.1410 (5%);235.1698 (100%) |
| 11 | curcumanolide A | C15H22O2 | CR | 234.1621 | 14.0 | (ESI+)123.0435 (5%);179.1059 (60%);219.1410 (5%);235.1698 (100%) |
| 12 | curcumanolide B | C15H22O2 | CR | 234.1621 | 14.0 | (ESI+)123.0435 (5%);179.1059 (60%);219.1410 (5%);235.1698 (100%) |
| 13 | curcumenol | C15H22O2 | CR | 234.1621 | 14.0 | (ESI+)123.0435 (5%);179.1059 (60%);219.1410 (5%);235.1698 (100%) |
| 14 | curcumenone | C15H22O2 | CR | 234.1621 | 14.0 | (ESI+)123.0435 (5%);179.1059 (60%);219.1410 (5%);235.1698 (100%) |
| 15 | gajutsulactone A | C15H22O2 | CR | 234.1621 | 14.0 | (ESI+)123.0435 (5%);179.1059 (60%);219.1410 (5%);235.1698 (100%) |
| 16 | gajutsulactone B | C15H22O2 | CR | 234.1621 | 14.0 | (ESI+)123.0435 (5%);179.1059 (60%);219.1410 (5%);235.1698 (100%) |
| 17 | procurcumenol | C15H22O2 | CR | 234.1621 | 14.0 | (ESI+)123.0435 (5%);179.1059 (60%);219.1410 (5%);235.1698 (100%) |
| 18 | 5-methoxyflavone | C16H12O3 | IR | 252.0787 | 12.2 | (ESI+)108.0204 (5%);136.0154 (5%);210.0678 (15%);237.0543 (15%);238.0625 (100%);253.0858 (30%) |
| 19 | 5,10-dihydroxy-2-methoxy-7-methylanthracene-1,4-dione | C16H12O5 | CR | 284.0685 | 11.9 | (ESI+)139.0533 (3%);168.0563 (15%);183.0793 (3%);196.0515 (15%);211.0746 (35%);224.0461 (5%);239.0698 (20%);242.0564 (35%);252.0441 (5%);285.074 (100%)  (ESI-)184.0543 (2%);212.0487 (5%);240.0449 (100%);268.0391 (2%);283.0635 (25%) |
| 20 | negletein | C16H12O5 | CRP | 284.0685 | 12.4 | (ESI+)139.0533 (3%);168.0563 (15%);183.0793 (3%);196.0515 (15%);211.0746 (35%);224.0461 (5%);239.0698 (20%);242.0564 (35%);252.0441 (5%);285.074 (100%)  (ESI-)184.0543 (2%);212.0487 (5%);240.0449 (100%);268.0391 (2%);283.0635 (25%) |
| 21 | physcion\* | C16H12O5 | RRR PCRR | 284.0685 | 11.9 | (ESI+)139.0533 (3%);168.0563 (15%);183.0793 (3%);196.0515 (15%);211.0746 (35%);224.0461 (5%);239.0698 (20%);242.0564 (35%);252.0441 (5%);285.074 (100%)  (ESI-)184.0543 (2%);212.0487 (5%);240.0449 (100%);268.0391 (2%);283.0635 (25%) |
| 22 | questin | C16H12O5 | PCRR | 284.0685 | 16.1 | (ESI+)139.0533 (3%);168.0563 (15%);183.0793 (3%);196.0515 (15%);211.0746 (35%);224.0461 (5%);239.0698 (20%);242.0564 (35%);252.0441 (5%);285.074 (100%)  (ESI-)184.0543 (2%);212.0487 (5%);240.0449 (100%);268.0391 (2%);283.0635 (25%) |
| 23 | wogonin\* | C16H12O5 | CR | 284.0685 | 11.9 | (ESI+)139.0533 (3%);168.0563 (15%);183.0793 (3%);196.0515 (15%);211.0746 (35%);224.0461 (5%);239.0698 (20%);242.0564 (35%);252.0441 (5%);285.074 (100%)  (ESI-)184.0543 (2%);212.0487 (5%);240.0449 (100%);268.0391 (2%);283.0635 (25%) |
| 24 | butyl phthalate | C16H22O4 | CR | 278.1519 | 14.3 | (ESI-)175.076 (50%);189.4915 (15%);191.1072 (75%);217.0864 (35%);235.1020 (34%);277.1453 (100%) |
| 25 | isobutyl phthalate | C16H22O4 | CR | 278.1519 | 14.3 | (ESI-)175.076 (50%);189.4915 (15%);191.1072 (75%);217.0864 (35%);235.1020 (34%);277.1453 (100%) |
| 26 | 3',4',5,7-tetramethoxyflavone | C19H18O6 | CRP CRPV | 342.1104 | 12.4 | (ESI+)153.0188 (3%);181.0129 (3%);285.0749 (25%);313.0690 (100%);328.0936 (15%);343.1158 (30%) |
| 27 | 3,5,7,4'-tetramethoxyflavone | C19H18O6 | CRP CRPV | 342.1104 | 12.4 | (ESI+)153.0188 (3%);181.0129 (3%);285.0749 (25%);313.0690 (100%);328.0936 (15%);343.1158 (30%) |
| 28 | 4',5,6,7-tetramethoxyflavone | C19H18O6 | CRP CRPV | 342.1104 | 12.4 | (ESI+)153.0188 (3%);181.0129 (3%);285.0749 (25%);313.0690 (100%);328.0936 (15%);343.1158 (30%) |
| 29 | demethyltangeretin | C19H18O7 | CRP CRPV | 358.1053 | 12.0 | (ESI+)257.0440 (3%);283.0599 (10%);311.0555 (10%);329.0653 (100%);344.0892 (20%);359.1117 (35%)  (ESI-)117.0343 (10%);176.9824 (5%);192.0073 (5%);207.031 (25%);241.0165 (5%);269.0119 (25%);284.0341 (15%);299.0591 (10%);312.0294 (25%);327.0541 (100%);342.0773 (20%);357.1007 (40%) |
| 30 | retusin | C19H18O7 | CRP | 358.1053 | 12.0 | (ESI+)257.0440 (3%);283.0599 (10%);311.0555 (10%);329.0653 (100%);344.0892 (20%);359.1117 (35%)  (ESI-)117.0343 (10%);176.9824 (5%);192.0073 (5%);207.031 (25%);241.0165 (5%);269.0119 (25%);284.0341 (15%);299.0591 (10%);312.0294 (25%);327.0541 (100%);342.0773 (20%);357.1007 (40%) |
| 31 | bonanzin | C19H18O8 | CRP | 374.1002 | 12.7 | (ESI+)197.0069 (5%);302.0412 (3%);327.0482 (35%);330.0353 (5%);345.0596 (100%);360.0844 (20%);375.1064 (90%)  (ESI-)185.0246 (5%);193.0156 (5%);201.0198 (5%);229.0145 (3%);241.0162 (5%);257.0114 (5%);285.0059 (10%);300.0294 (10%);313.0004 (15%);328.0247 (55%);343.0484 (100%);358.0702 (50%);373.095 (40%) |
| 32 | quercetagetin-3,5,6,3'-tetramethyl ether | C19H18O8 | IR | 374.1002 | 12.7 | (ESI+)197.0069 (5%);302.0412 (3%);327.0482 (35%);330.0353 (5%);345.0596 (100%);360.0844 (20%);375.1064 (90%)  (ESI-)185.0246 (5%);193.0156 (5%);201.0198 (5%);229.0145 (3%);241.0162 (5%);257.0114 (5%);285.0059 (10%);300.0294 (10%);313.0004 (15%);328.0247 (55%);343.0484 (100%);358.0702 (50%);373.095 (40%) |
| 33 | 5-demethylnobiletin | C20H20O8 | CRP CRPV | 388.1159 | 13.4 | (ESI+)197.0076 (5%);316.0588 (5%);328.0939 (5%);341.0647 (55%);343.0446 (3%);359.0742 (100%);374.099 (35%);389.1212 (70%) |
| 34 | 7-hydroxy-3,5,6,3',4'-pentamethoxyflavone | C20H20O8 | CRPV | 388.1159 | 13.4 | (ESI+)197.0076 (5%);316.0588 (5%);328.0939 (5%);341.0647 (55%);343.0446 (3%);359.0742 (100%);374.099 (35%);389.1212 (70%) |
| 35 | monohydroxy-pentamethoxyflavone | C20H20O8 | CRP | 388.1159 | 10.6 | (ESI+)197.0076 (5%);316.0588 (5%);328.0939 (5%);341.0647 (55%);343.0446 (3%);359.0742 (100%);374.099 (35%);389.1212 (70%) |
| 36 | 5,4'-dihydroxy-3,6,7,8,3'-pentamethoxyflavone | C20H20O9 | CRP | 404.1108 | 11.5 | (ESI-)148.0172 (3%);163.0391 (5%);200.0069 (3%);215.0334 (3%);231.0356 (5%);245.0987 (3%);270.0546 (5%);287.0259 (5%);299.9921 (5%);315.0167 (20%);330.0391 (20%);343.0116 (45%);358.0358 (90%);373.0582 (100%);388.0818 (80%);403.1 (85%) |
| 37 | graminones B | C21H22O8 | IR | 402.1315 | 12.8 | (ESI+)183.0283 (5%);211.0231 (10%);258.0519 (3%);301.0693 (10%);313.0707 (10%);327.0839 (25%);329.0632 (5%);330.0726 (25%);355.0789 (35%);373.089 (100%);403.1357 (40%) |
| 38 | nobiletin\* | C21H22O8 | CRP CRPV | 402.1315 | 12.6 | (ESI+)183.0283 (5%);211.0231 (10%);258.0519 (3%);301.0693 (10%);313.0707 (10%);327.0839 (25%);329.0632 (5%);330.0726 (25%);355.0789 (35%);373.089 (100%);403.1357 (40%) |
| 39 | isovanilline | C8H8O3 | IR | 152.04734 | 7.8 | (ESI+)109.0272 (50%);110.0353 (100%);111.0777 (50%);125.0566 (100%);153.0477 (50%) |
| 40 | vanillin | C8H8O3 | CR | 152.04734 | 7.8 | (ESI+)109.0272 (50%);110.0353 (100%);111.0777 (50%);125.0566 (100%);153.0477 (50%) |
| 41 | ethyl 4-hydroxybenzoate | C9H10O3 | IR | 166.06299 | 12.9 | (ESI+)121.0273 (100%);123.0799 (3%);139.0376 (5%);149.0589 (20%);167.0699 (3%) |
| 42 | paeonol | C9H10O3 | CRPV CR | 166.06299 | 12.9 | (ESI+)121.0273 (100%);123.0799 (3%);139.0376 (5%);149.0589 (20%);167.0699 (3%) |
| 43 | 4-acetylbenzoic acid | C9H8O3 | CRP CRPV | 164.04734 | 12.7 | (ESI+)107.0474 (3%);109.0624 (15%);119.0489 (20%);123.044 (100%);137.0595 (20%);147.0452 (5%);165.0543 (20%) |
| 44 | 4-hydroxycinnamic acid | C9H8O3 | RRR CRP IR | 164.04734 | 12.7 | (ESI+)107.0474 (3%);109.0624 (15%);119.0489 (20%);123.044 (100%);137.0595 (20%);147.0452 (5%);165.0543 (20%) |
| 45 | luteolin-7-glucoside | C21H20O11 | PCRR | 448.38000 | 11.1 | (ESI-)206.0340;268.0378;285.0387;379.2104;447.0925 |

Note: \* were confirmed with chemical standard references.

Table S3 The modeling and predictive abilities of OPLS-DA models.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameters | ESI+ data | | ESI- data | |
| ANIT vs Control | ANITESI+DNT vs ANIT | ANIT vs Control | ANITESI+DNT vs ANIT |
| Serum |  |  |  |  |
| R2Y | 0.993 | 0.990 | 0.992 | 0.997 |
| Q2 | 0.954 | 0.803 | 0.960 | 0.953 |
| Liver |  |  |  |  |
| R2Y | 0.997 | 0.988 | 0.997 | 0.993 |
| Q2 | 0.962 | 0.960 | 0.971 | 0.931 |

Table S4 The detailed endogenous metabolite identification information.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| No. | | m/z (Da) | tR(min) | Metabolites | Formula | Class |
|  |
| ESI- | 1 | 145.1 | 0.8 | L-Glutamine | C5H10N2O3 | Amino acid |  |
| 2 | 172.1 | 8.2 | I-Acetyl-L-leucine | C8H15NO3 | Amino acid derivatives |  |
| 3 | 277.2 | 13.5 | Octadecatrienoic acid | C18H30O2 | Fatty acid |  |
| 4 | 279.2 | 15.6 | Linoleate | C18H32O2 | Fatty Acyls |  |
| 5 | 281.2 | 14.3 | (11E) -Octadecenoic acid | C18H34O2 | Fatty acid |  |
| 6 | 301.2 | 12.2 | Icosapentaenoic acid | C20H30O2 | Fatty acid |  |
| 7 | 303.2 | 15.5 | Arachidonate | C20H32O2 | Fatty acid |  |
| 8 | 307.3 | 16.1 | Icosadienoic acid | C20H36O2 | Fatty acid |  |
| 9 | 464.3 | 13.6 | Glycocholate | C26H43NO6 | Amino acid |  |
| 10 | 802.6 | 15.6 | PC (P-18:0) | C44H86NO9P | Phosphatidylcholine |  |
| 11 | 829.6 | 18.2 | SM(d20:1/PGF1alpha) | C45H87N2O9P | Sphingomyelin |  |
| 12 | 515.7 | 11.6 | Taurocholic acid | C26H45NO7S | Bile acid |  |
| 13 | 456.6 | 12.2 | Glycocholic acid | C26H43NO6 | Bile acid |  |
| 14 | 499.7 | 13.9 | Taurochenodeoxycholic acid | C26H45NO6S | Bile acid |  |
| ESI+ | 1 | 132.1 | 2.5 | L-Isoleucine | C6H13NO2 | Amino acid |  |
| 2 | 166.1 | 4.1 | L-Phenylalanine | C9H11NO2 | Amino acid |  |
| 3 | 169.0 | 1.8 | Urate | C5H4N4O3 | Purine |  |
| 4 | 188.1 | 5.9 | Tryptophan | C11H12N2O2 | Amino acid |  |
| 5 | 203.1 | 0.9 | Adipoylglycine | C8H13NO5 | Amino acid derivatives |  |
| 6 | 498.3 | 15.4 | Taurallocholic acid | C26H45NO7S | Bile acids |  |
| 7 | 524.4 | 15.6 | LysoPC (18:0) | C26H54NO7P | Phosphatidylcholine |  |
| 8 | 782.6 | 16.0 | PA (22:1(13Z)) | C45H83O8P | Phosphatidic acid |  |
| 9 | 782.6 | 16.1 | PE (P-18:1(9Z)) | C45H84NO7P | Phospholipids |  |
| 10 | 784.6 | 16.6 | PC (22:4(7Z,10Z,13Z,16Z)) | C48H86NO7P | Phosphatidylcholine |  |
| 11 | 784.6 | 16.5 | SM (d18:2(4E,14Z)) | C43H79N2O7P | Sphingomyelin |  |
| 12 | 785.6 | 14.9 | PA (20:2(11Z,14Z)) | C45H85O8P | Phosphatidic acid |  |

Table S5 Potential biomarkers in serum responsible for the protective effect of DNT against ANIT-induced injury in mice.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| No. | RT (min) | Identification | Mass accuracy (ppm) | Fold change | |
| ANIT/ Control | ANIT+DNT /ANIT |
| 1 | 11.6 | taurocholic acid | -3.6 | 24.98 ↑ | 0.45 ↓ |
| 2 | 12.2 | glycocholic acid | 0.2 | 4.01 ↑ | 0.62 ↓ |
| 3 | 13.9 | taurochenodeoxycholic acid | -1.1 | 5.31 ↑ | 0.51 ↓ |

↑ indicates up-regulated in mice while ↓ means down-regulated in mice.

Table S6 Potential biomarkers in liver responsible for the protective effect of DNT against ANIT-induced injury in mice.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| No. | RT (min) | Identification | Mass accuracy (ppm) | Fold change | |
| ANIT/ Control | ANIT+DNT /ANIT |
| 1 | 11.6 | taurocholic acid | 0.7 | 4.13 ↑ | 0.66 ↓ |
| 2 | 12.2 | glycocholic acid | -0.7 | 22.53 ↑ | 0.53 ↓ |
| 3 | 13.9 | taurochenodeoxycholic acid | 0.1 | 4.36 ↑ | 0.54 ↓ |

↑ indicates up-regulated in mice while ↓ means down-regulated in mice.