Table SI. The primer sequences for PCR amplifications.

| Gene | Sequences |
|---|---|
| Perp | F: 5'-GACCCCAGATGCTTGTTTTC-3' |
| | R: 5'-ACCAGGGAGATGATCTGGAA-3' |
| Adrb2 | F: 5'-GAGCACAAAGCCCTCAAGAC-3' |
| | R: 5'-GTTTTCGAAGAAGACCTGCG-3' |
| Chac1 | F: 5'-GACCATGAGGGCTGCACTTG-3' |
| | R: 5'-AGGAGCAGGGCCCAGGTAG-3' |
| Wnt6 | F: 5'-GGAGATATCCGTGCATTGGT-3' |
| | R: 5'-GTCCTGTAGATGGCCCAGAG-3' |
| β-actin | F: 5'-AGAGGGAAATCGTGCGTGAC-3' |
| | R: 5'-AGGCAGCTCATAGCTCTTCTCC-3' |

F, forward; R, reverse; Perp, tumor protein 53 apoptosis effector; Adrb2, adrenoceptor β2; chac1, cation transport regulator-like 1.

Table SII. Expression (fold change) of differentially expressed genes associated with aristolochic acid-induced early toxicity determined by microarray analysis.

| Probe set | Gene | Definition | GenBank accession no. | EntrezGene no. | Fold change |
|---|---|---|---|---|---|
| 1416034_at | CD24A | CD24a antigen | NM_009846 | 12484 | 2.40 |
| 1416120_at | RRM2 | Ribonucleotide reductase M2 | NM_009104 | 20135 | 2.45 |
| 1416271_at | PERP: | PERP, TP53 apoptosis effector | NM_022032 | 64058 | 4.38 |
| 1416340_a_at | MAN2B1 | Mannosidase 2, α B1 | BC005430 | 17159 | 2.49 |
| 1417439_at | CD248 | CD248 antigen, endosialin | NM_054042 | 70445 | -2.16 |
| 1417976_at | ADA | Adenosine deaminase | NM_007398 | 11486 | 3.54 |
| 1418184_at | CENPM | Centromere protein M | NM_025639 | 66570 | 2.31 |
| 1418203_at | PMAIP1 | Phorbol-12-myristate-13-acetate-induced protein 1 | NM_021451 | 58801 | 2.65 |
| 1418288_at | LPIN1 | Lipin 1 | NM_015763 | 14245 | 2.12 |
| 1419665_a_at | NUPR1 | Nuclear protein 1 | NM_019738 | 56312 | -2.85 |
| 1419666_x_at | NUPR1 | Nuclear protein 1 | NM_019738 | 56312 | -2.89 |
| 1420664_s_at | PROCR | Protein C receptor, endothelial | NM_011171 | 19124 | 3.67 |
| 1420773_at | DUB1 | Deubiquitinating enzyme 1 | NM_007887 | 13531 | 3.12 |
| 1422057_at | NODAL | Nodal | X70514 | 18119 | 2.87 |
| 1422851_at | HMGA2 | High mobility group AT-hook 2 | X58380 | 15364 | -2.39 |
| 1423108_at | SLC25A20 | Solute carrier family 25 (mitochondrial carnitine/acylcarnitine translocase), member 20 | AV008091 | 57279 | 2.25 |
| 1423109_s_at | SLC25A20 | Solute carrier family 25 (mitochondrial carnitine/acylcarnitine translocase), member 20 | AV008091 | 57279 | 2.53 |
| 1423110_at | COLLA2 | Collagen, type I, α 2 | BF227507 | 12843 | -2.38 |
| 1423547_at<br>1435980_x_at | LYZ2 | Lysozyme 2 | AW208566 | 17105 | -3.85 |
| 1423608_at | ITM2A | Integral membrane protein 2A | BI966443 | 16431 | 2.84 |
| 1423627_at | NQOL | NAD(P)H dehydrogenase, quinone 1 | AV158882 | 18104 | 2.27 |
| 1423669_at | COLLA1 | Collagen, type I, α 1 | U08020 | 12842 | -2.29 |
| 1424131_at | COL6A3 | Collagen, type VI, α 3 | AF064749 | 12835 | -3.31 |
| 1425220_x_at | LOC100038935 | Hypothetical protein LOC100038935 | AF067062 | 1E+08 | 2.72 |
| 1425427_at | LOC639910 | Hypothetical protein LOC639910 | AF067058 | 639910 | 3.03 |
| 1425601_a_at | Rtkn | Rhotekin | BC013820 | 20166 | 2.18 |
| 1425615_a_at | PCK2 | Phosphoenolpyruvate carboxykinase 2 (mitochondrial) | BC010318 | 74551 | -2.46 |
| 1426584_a_at | SORd | Sorbitol dehydrogenase | BI143942 | 20322 | 2.7 |
| 1427126_at | HSPA1B | Heat shock protein 1B | M12573 | 15511 | 2.63 |
| 1427127_x_at | HSPA1B | Heat shock protein 1B | M12573 | 15511 | 2.57 |
| 1427479_at | BB287469, EG435337, EIFLA, GML6368, GM2056, GM4027, GM5039, GM5788, GM6804, GM8300, GM8332, LOC641136 | Eukaryotic translation initiation factor 1A pseudogene, predicted gene, EG435337, eukaryotic translation initiation factor 1A, eukaryotic translation initiation factor 1A pseudogene, predicted gene 2056, predicted gene 4027, eukaryotic translation initiation factor 1A pseudogene, predicted gene 5788, predicted gene 6804, predicted gene 8300, predicted gene 8332, similar to X-linked eukaryotic translation initiation factor 1A | AA413531 | 100039129 /// 100039226 /// 100042776 /// 13664 /// 266459 /// 435337 /// 544881 /// 544883 /// 627881 /// 641136 /// 666806 /// 666862 | 2.44 |
| 1427718_a_at | MDM2 | Transformed mouse 3T3 cell double minute 2 | X58876 | 17246 | 3.07 |
| 1427883_a_at | COL3A1 | Collagen, type III, α 1 | AW550625 | 12825 | -2.85 |
| 1429483_at | CALCOCO2 | Calcium binding and coiled-coil domain 2 | BG066947 | 76815 | 6 |
| 1431645_a_at | GDI2 | Guanosine diphosphate (GDP) dissociation inhibitor 2 | AK013104 | 14569 | 2.36 |
| 1433545_s_at | ACAD11, NPHP3: | Acyl-Coenzyme A dehydrogenase family, member 11, nephronophthisis 3 (adolescent) | BQ031255 | 102632 /// 74025 | 2.36 |

Table SII. Continued.

| Probe set | Gene | Definition | GenBank accession no. | EntrezGene no. | Fold change |
|---|---|---|---|---|---|
| 1434369_a_at | CRYAB | Crystallin, α B | AV016515 | 12955 | 2.50 |
| 1435980_x_at | WNT6 | Wingless-related MMTV integration site 6 | AV308073 | 22420 | 3.56 |
| 1436996_x_at | LYZ1 | Lysozyme 1 | AV066625 | 17110 | -3.12 |
| 1437302_at | ADRB2 | Adrenergic receptor, β 2 | AV083350 | 11555 | 4.39 |
| 1437345_a_at | BSCL2 | Bernardinelli-Seip congenital lipodystrophy 2 homolog (human) | BB223872 | 14705 | 2.17 |
| 1437851_x_at | RNPS1 | Ribonucleic acid binding protein S1 | BB214894 | 19826 | -3.44 |
| 1439332_at | DDIT4L | DNA-damage-inducible transcript 4-like | AV251625 | 73284 | 2.70 |
| 1439426_x_at | LYZ1 | Lysozyme 1 | AV058500 | 17110 | -3.55 |
| 1448182_a_at | CD24A | CD24a antigen | NM_009846 | 12484 | 2.20 |
| 1448194_a_at | H19 | H19 fetal liver mRNA | NM_023123 | 14955 | -3.11 |
| 1448326_a_at | CRABP1 | Cellular retinoic acid binding protein I | NM_013496 | 12903 | -2.28 |
| 1448416_at | MGP | Matrix Gla protein | NM_008597 | 17313 | -3.05 |
| 1448793_a_at | SDC4 | Syndecan 4 | BC005679 | 20971 | 2.95 |
| 1448823_at | CXCL12 | Chemokine (C-X-C motif) ligand 12 | BC006640 | 20315 | -2.84 |
| 1449106_at | GPX3 | Glutathione peroxidase 3 | NM_008161 | 14778 | 2.50 |
| 1449954_at | HYAL1, NAT6 | Hyaluronoglucosaminidase 1, N-acetyltransferase 6 | NM_008317 | 15586 /// 56441 | 3.99 |
| 1450017_at | CCNG1 | Cyclin G1 | BG065754 | 12450 | 2.56 |
| 1450627_at | ANK | Progressive ankylosis | NM_020332 | 11732 | -2.15 |
| 1450780_s_at | HMGA2 | High mobility group AT-hook 2 | X58380 | 15364 | -2.47 |
| 1450781_at | HMGA2 | High mobility group AT-hook 2 | X58380 | 15364 | -2.31 |
| 1451047_at | ITM2A | Integral membrane protein 2A | BI966443 | 16431 | 3.16 |
| 1451382_at | Chac1 | ChaC, cation transport regulator-like 1 (*E. coli*) | BC025169 | 69065 | -4.17 |
| 1451751_at | DDIT4L | DNA-damage-inducible transcript 4-like | AF335325 | 73284 | 2.67 |
| 1452318_a_at | HSPA1B | Heat shock protein 1B | M12573 | 15511 | 2.39 |
| 1452430_s_at | LOC100048559, SFRS1 | Similar to splicing factor, arginine/serine-rich 1 (splicing factor 2, alternate splicing factor), splicing factor, arginine/serine-rich 1 (ASF/SF2) | X66091 | 100048559 /// 110809 | 2.30 |
| 1455904_at | GAS5 | Growth arrest specific 5 | BI650268 | 14455 | -2.72 |
| 1456080_a_at | SERINC3 | Serine incorporator 3 | BM239368 | 26943 | 4.68 |
| 1428615_at | LPAR6 | Lysophosphatidic acid receptor 6 | AK008952 | 67168 | 3.23 |
| 1428705_at | 1700007K13RIK | RIKEN cDNA 1700007K13 gene | AK005731 | 69327 | 3.22 |
| 1433583_at | ZFP365 | Zinc finger protein 365 | AV327248 | 216049 | 2.42 |
| 1439630_x_at | SBSN | Suprabasin | AI844734 | 282619 | 3.61 |
| 1442334_at | GM13040, GM13043, GM13057 | Predicted gene 13040, predicted gene 13043, predicted gene 13057 | BB711873 | 100040854 /// 100040861 /// 545693 | 3.61 |
| 1444139_at | DDIT4L | DNA-damage-inducible transcript 4-like | BG797099 | 73284 | 2.83 |
| 1444529_at | EIF1A, GM8300 | Eukaryotic translation initiation factor 1A, predicted gene 8300 | BM197200 | 13664 /// 666806 | 2.30 |
| 1444583_at | NASP | Nuclear autoantigenic sperm protein (histone-binding) | AW741754 | 50927 | -2.22 |
| 1448470_at | FBP1 | Fructose bisphosphatase 1 | NM_019395 | 14121 | 9.24 |
| 1449088_at | FBP2 | Fructose bisphosphatase 2 | NM_007994 | 14120 | 6.43 |
| 1459897_a_at | SBSN | Suprabasin | AI507307 | 282619 | 4.00 |

Table SIII. Gene Ontology terms enriched by the DEGs associated with aristolochic acid-induced early toxicity in the category biological process.

| Biological process term | Gene symbols | P-value | Trend of dysregulation |
|---|---|---|---|
| Positive regulation of intracellular signal transduction | Fgf1;Tek | 0.0002 | ↑ |
| Negative regulation of cysteine-type endopeptidase activity involved in apoptotic process | Wnt9a;Cryab;Hspa1b | 0.0006 | ↑<br>↑ |
| Positive regulation of heart rate | Scn3b;Ada | 0.0010 | ↑ |
| Positive regulation of focal adhesion assembly | Sdc4;Tek | 0.0010 | ↑ |
| Gluconeogenesis | Fbp1;Fbp2 | 0.0012 | ↑ |
| Positive regulation of smooth muscle contraction | Ada;Npnt | 0.0012 | ↑ |
| Positive regulation of sodium ion transport | Adrb2;Scn3b | 0.00143 | ↑ |
| Intrinsic apoptotic signaling pathway by p53 class mediator | Perp;Pmaip1 | 0.0016 | ↑ |
| Transmembrane transport | Tap1;Abcb1b;Slc26a2;<br>Slc25a31;Aqp3 | 0.0018 | ↑<br>↑ |
| Lung development | Tbx4;Fgf1;Ada | 0.0019 | ↑ |
| Metabolic process | Aldh1l2;Lyz1;Prkg1;<br>Lyz2;Pygl | $3.30 \times 10^{-5}$ | ↓<br>↓ |
| Cytolysis | Lyz1;Lyz2 | 0.0002 | ↓ |
| Defense response to Gram-negative bacterium | Lyz1;Lyz2 | 0.0004 | ↓ |
| Positive regulation of cell-substrate adhesion | Edil3;Ptn | 0.0005 | ↓ |
| Defense response to Gram-positive bacterium | Lyz1;Lyz2 | 0.0013 | ↓ |
| Forebrain development | Prkg1;Dclk1 | 0.0015 | ↓ |
| Steroid metabolic process | Vldlr;Cyp7b1 | 0.0017 | ↓ |
| Cholesterol metabolic process | Vldlr;Cyp7b1 | 0.0019 | ↓ |
| Neuron migration | Prkg1;Dclk1 | 0.0037 | ↓ |
| Negative regulation of mesenchymal cell proliferation | Ptn | 0.0046 | ↓ |

P-values refer to the enrichment.↑, upregulated DEGs; ↓, downregulated DEGs; DEG, differentially expressed gene.

Table SIV. Gene Ontology terms enriched by the differentially expressed genes associated with aristolochic acid-induced early toxicity in the categories cellular component and molecular function.

| Term | Gene symbols | P-value |
|---|---|---|
| Extracellular region | Sct;Ptx3;Fgf1;Lyz1;Lyz2;Ccl6;Fgfbp3;Sdc4;Cgref1; Tek;Npnt;Wnt9a;Edil3;Pm20d1;Mmp3;Ptn | $2.66 \times 10^{-5}$ |
| Rough endoplasmic reticulum lumen | Lyz1;Lyz2 | 0.0003 |
| Extracellular exosome | Aldh1l2;Aif1l;Fbp1;Cryab;Lyz1;Slc26a2;Procr;Lyz2; Pygl;Sdc4;Fbp2;Npnt;Akr1c18;Wnt9a;Edil3;Sord; Pm20d1;Aldh1l1;Pck2 | 0.0003 |
| Golgi cis cisterna | Lyz1;Lyz2 | 0.0005 |
| Mitochondrion | Perp;Aldh1l2;Tap1;Cryab;Abcb1b;Hspa1b;Pycr1; Slc25a31;Sord;Acaa1b;Mmp3;Aldh1l1;Pck2;Pmaip1 | 0.0005 |
| Microvillus | Lyz1;Lyz2;Tek | 0.0011 |
| Trans-Golgi network transport vesicle | Lyz1;Lyz2 | 0.0016 |
| Extracellular space | Sct;Ptx3;Fgf1;Lyz1;Ada;Lyz2;Ccl6;Vldlr;Wnt9a; Mmp3;Gabbr1 | 0.0016 |
| Costamere | Sdc4;Synm | 0.0019 |
| Cell surface | Cryab;Procr;Ada;Sdc4;Tek;Vldlr;Ptn | 0.0022 |
| Catalytic activity | Aldh1l2;Fbp1;Lyz1;Prkg1;Lyz2;Pygl;Fbp2;Acaa1b; Aldh1l1 | $2.52 \times 10^{-5}$ |
| Lysozyme activity | Lyz1;Lyz2 | 0.0005 |
| AMP binding | Fbp1;Pygl | 0.0009 |
| Aldehyde dehydrogenase activity | Aldh1l2;Aldh1l1 | 0.0020 |
| Oxidoreductase activity, acting on the aldehyde or oxo group of donors, NAD or NADP as acceptor | Aldh1l2;Aldh1l1 | 0.0022 |
| Structural constituent of eye lens | Cryab;Hspb6 | 0.0026 |
| Calcium ion binding | Cgref1;Aif1l;Npnt;Vldlr;Edil3;Mmp3 | 0.0078 |
| Growth factor binding | Fgfbp3;Tek | 0.0080 |
| ATPase activity, coupled to transmembrane movement of substances | Tap1;Abcb1b | 0.0080 |
| Heparin binding | Fgf1;Fgfbp3;Ptn | 0.0081 |

P-values refer to the enrichment.

Table SV. Pathways enriched by the differentially expressed genes associated with aristolochic acid-induced early toxicity.

| Pathway | Gene symbols | P-value | -log10 (P-value) |
|---|---|---|---|
| Salivary secretion | Adrb2;Lyz2;Lyz1;Prkg1 | 0.0006 | 3.2399 |
| Fructose and mannose metabolism | Fbp1;Fbp2;Sord | 0.0007 | 3.1654 |
| Biosynthesis of antibiotics | Fbp1;Pycr1;Fbp2;Acaa1b;Pck2 | 0.0038 | 2.4232 |
| Glycolysis/Gluconeogenesis | Fbp1;Fbp2;Pck2 | 0.0042 | 2.3818 |
| One carbon pool by folate | Aldh1l2;Aldh1l1 | 0.0043 | 2.3621 |
| Insulin signaling pathway | Pygl;Fbp1;Fbp2;Pck2 | 0.0048 | 2.3173 |
| Pentose phosphate pathway | Fbp1;Fbp2 | 0.0099 | 2.0030 |
| Primary immunodeficiency | Ada;Tap1 | 0.0131 | 1.8815 |
| Glucagon signaling pathway | Pygl;Fbp1;Pck2 | 0.0136 | 1.8678 |
| ABC transporters | Tap1;Abcb1b | 0.0215 | 1.6669 |
| AMPK signaling pathway | Fbp1;Fbp2;Pck2 | 0.0242 | 1.6159 |
| Regulation of lipolysis in adipocytes | Adrb2;Prkg1 | 0.0326 | 1.4865 |
| p53 signaling pathway | Perp;Pmaip1 | 0.0421 | 1.3757 |
| cGMP-PKG signaling pathway | Adrb2;Slc25a31;Prkg1 | 0.0494 | 1.3060 |
| Rheumatoid arthritis | Tek;Mmp3 | 0.0599 | 1.2228 |
| PPAR signaling pathway | Acaa1b;Pck2 | 0.0599 | 1.2228 |
| Antigen processing and presentation | Tap1;Hspa1b | 0.0611 | 1.2137 |
| Steroid hormone biosynthesis | Akr1c18;Cyp7b1 | 0.0663 | 1.1786 |
| ECM-receptor interaction | Sdc4;Npnt | 0.0676 | 1.1701 |
| Primary bile acid biosynthesis | Cyp7b1 | 0.0777 | 1.1094 |

Adrb2, adrenoceptor β 2; Fbp1, fructose-1,6-bisphosphatase 1; Fbp2, fructose-1,6-bisphosphatase 2; Pmaip1, phorbol-12-myristate-13-acetate-induced protein 1; Perp, tumor protein 53 apoptosis effector.