

-Supplemental material-

**Hepatotoxic pyrrolizidine alkaloids induce DNA damage response in rat liver in a
28 day feeding study**

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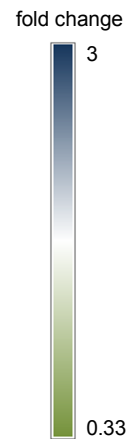
Table S1: Subset of 284 probe sets that are significantly different expressed among the treatment groups (one-way ANOVA, $q < 0.05$). Probe sets that are not significantly dysregulated compared to vehicle control as analyzed by post hoc-test ($q < 0.05$) are marked in gray.

gene symbol	fold change						entrez gene name
	echimidine	heliotrine	lasiocarpine	senecionine	senkirine	platyphylline	
<i>Cenpw</i>	1.16	1.17	1.15	1.77	1.31	1.03	centromere protein W
<i>Lig1</i>	1.09	1.08	1.03	1.23	1.15	1.03	DNA ligase 1
<i>Lig1</i>	1.09	1.10	1.02	1.25	1.16	1.02	DNA ligase 1
<i>Ethe1</i>	0.77	0.83	0.99	0.66	0.76	0.97	ETHE1, persulfide dioxygenase
<i>Aen</i>	1.22	1.41	1.28	1.26	1.30	1.00	apoptosis enhancing nuclease
<i>Ticrr</i>	1.17	1.11	1.07	1.36	1.24	1.01	TOPBP1 interacting checkpoint and replication regulator
<i>Prc1</i>	1.20	1.19	1.05	1.49	1.53	1.05	protein regulator of cytokinesis 1
<i>Rrm1</i>	1.18	1.21	1.03	1.52	1.39	1.09	ribonucleotide reductase catalytic subunit M1
<i>Wee1</i>	1.11	1.14	1.10	1.36	1.20	1.18	WEE1 G2 checkpoint kinase
<i>Acsm3</i>	0.79	0.57	0.77	0.79	0.69	0.89	acyl-CoA synthetase medium chain family member 3
<i>Loc100911413</i>	1.20	1.37	1.18	1.49	0.99	1.03	deleted in malignant brain tumors 1 protein-like
<i>Mgmt</i>	1.58	2.00	1.74	1.75	1.73	0.95	O-6-methylguanine-DNA methyltransferase
<i>Sptbn2</i>	1.01	1.06	1.00	1.07	1.00	0.89	spectrin beta, non-erythrocytic 2
<i>Aldh1A1</i>	2.81	5.20	3.28	3.61	2.84	0.98	aldehyde dehydrogenase 1 family member A1
<i>Fas</i>	1.40	1.64	1.43	1.65	1.42	0.92	Fas cell surface death receptor
<i>Ifit2</i>	1.55	1.29	1.25	1.49	1.42	1.14	interferon induced protein with tetratricopeptide repeats 2
<i>Kif11</i>	1.20	1.35	1.14	1.97	1.67	1.14	kinesin family member 11
<i>Loc100910701</i>	1.02	1.05	0.93	0.95	0.91	0.98	uncharacterized LOC100910701
<i>Fbxo5</i>	1.26	1.06	1.22	1.39	1.39	1.09	F-box protein 5
<i>Axl</i>	0.81	0.80	0.62	0.76	0.85	0.96	AXL receptor tyrosine kinase
<i>Fxyd5</i>	1.19	1.18	1.09	1.19	1.26	0.98	FXDY domain containing ion transport regulator 5
<i>Bax</i>	1.18	1.25	1.21	1.23	1.26	0.98	BCL2 associated X, apoptosis regulator
<i>E2f8</i>	1.20	1.24	1.17	1.45	1.36	1.00	E2F transcription factor 8

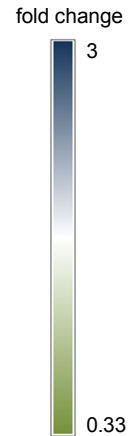




<i>Blm</i>	1.09	1.00	0.98	1.09	1.13	0.96	bloom syndrome RecQ like helicase
<i>Ddias</i>	1.33	1.48	1.31	2.08	1.59	1.15	DNA damage induced apoptosis suppressor
<i>Lyve1</i>	1.25	1.18	1.18	1.19	1.50	1.05	lymphatic vessel endothelial hyaluronan receptor 1
<i>Nupr1</i>	1.26	1.13	1.73	0.97	1.17	1.24	nuclear protein 1, transcriptional regulator
<i>Prss53</i>	1.11	1.04	1.09	0.91	1.08	1.07	protease, serine 53
<i>Mki67</i>	1.50	1.72	1.16	2.68	2.71	1.10	marker of proliferation Ki-67
<i>Adam8</i>	1.83	5.83	1.54	3.76	2.13	1.00	ADAM metallopeptidase domain 8
<i>Ccnd1</i>	1.02	1.14	0.90	1.47	1.13	0.81	cyclin D1
<i>Aldh1a7</i>	1.29	1.68	1.54	1.62	1.32	0.94	aldehyde dehydrogenase family 1, subfamily A7
<i>Fanci</i>	1.14	1.16	1.04	1.44	1.36	1.06	Fanconi anemia complementation group I
<i>Cd81</i>	1.09	1.21	1.15	1.04	1.17	1.08	CD81 molecule
<i>Arsb</i>	1.14	1.30	1.17	1.26	1.20	1.05	arylsulfatase B
<i>Dab2</i>	1.15	1.04	0.98	1.04	1.44	0.99	DAB2, clathrin adaptor protein
<i>Loc102554389</i>	1.18	0.94	1.00	1.10	1.01	1.24	zinc finger protein 862-like
<i>Plk4</i>	1.27	1.22	1.08	1.68	1.41	1.06	Polo like kinase 4
<i>Smc4</i>	1.10	1.24	0.97	1.63	1.46	1.10	structural maintenance of chromosomes 4
<i>Pdgfc</i>	1.13	1.37	1.21	1.24	1.19	0.82	platelet derived growth factor C
<i>Rab13</i>	1.16	1.22	1.11	1.19	1.17	0.95	RAB13, member RAS oncogene family
<i>Hist1h3g</i>	1.32	1.38	1.19	1.84	1.84	1.17	histone cluster 1 H3 family member g
<i>Phtf1</i>	0.84	0.88	0.83	0.88	0.82	0.91	putative homeodomain transcription factor 1
<i>Pde5a</i>	1.07	1.10	0.95	1.25	1.07	0.95	phosphodiesterase 5A
<i>Etnppl</i>	0.91	0.93	1.26	0.71	0.93	1.30	ethanolamine-phosphate phospho-lyase
<i>Cenpe</i>	1.19	1.21	1.06	1.43	1.49	1.01	centromere protein E
<i>Adgrl4</i>	1.23	1.07	1.07	1.12	1.54	0.97	adhesion G protein-coupled receptor L4
<i>Cenph</i>	1.06	1.11	1.07	1.24	1.13	1.05	centromere protein H
<i>Gzma</i>	0.70	0.80	0.63	0.58	0.56	0.87	granzyme A
<i>Lrrcc1</i>	1.24	1.15	1.05	1.44	1.38	1.03	leucine rich repeat and coiled-coil centrosomal protein 1
<i>Ccna2</i>	1.26	1.37	1.09	2.13	1.96	1.13	cyclin A2
<i>Igsf10</i>	1.02	0.92	0.93	1.11	1.08	0.92	immunoglobulin superfamily member 10
<i>Csf1</i>	1.15	1.02	1.00	1.20	1.20	0.96	colony stimulating factor 1
<i>Rgd1310209</i>	1.06	1.12	1.22	0.83	1.12	1.17	similar to KIAA1324 protein



<i>Loc102548573</i>	0.93	1.02	1.04	1.21	0.93	0.84	uncharacterized LOC102548573
<i>Loc102548789</i>	1.12	1.01	0.99	1.12	0.96	0.98	uncharacterized LOC102548789
<i>Map3k20</i>	1.16	1.23	1.16	1.22	1.15	1.01	mitogen-activated protein kinase kinase kinase 20
<i>Slc43a1</i>	0.87	0.80	0.81	0.76	0.74	0.94	solute carrier family 43 member 1
<i>Kif18a</i>	1.15	1.21	1.07	1.52	1.46	1.04	kinesin family member 18A
<i>Ccdc34</i>	1.07	1.17	1.03	1.32	1.20	1.02	coiled-coil domain containing 34
<i>Kn1l</i>	1.26	1.50	1.07	2.07	1.93	1.07	kinetochore scaffold 1
<i>Rad51</i>	1.18	1.25	1.17	1.44	1.34	1.08	RAD51 recombinase
<i>Nusap1</i>	1.23	1.33	1.10	1.66	1.68	1.19	nucleolar and spindle associated protein 1
<i>Loc100911204</i>	1.14	1.37	1.03	1.85	1.70	1.02	protein CASC5-like
<i>Loc100911267</i>	1.14	1.32	1.17	1.59	1.42	1.05	DNA repair protein RAD51 homolog 1-like
<i>Dut</i>	1.18	1.31	1.13	1.37	1.26	1.02	deoxyuridine triphosphatase
<i>MacroD2</i>	0.95	0.96	1.00	0.90	0.96	1.02	MACRO domain containing 2
<i>Tpx2</i>	1.21	1.30	1.07	1.66	1.56	1.07	TPX2, microtubule nucleation factor
<i>Lbp</i>	1.19	1.07	1.07	1.55	1.14	1.10	lipopolysaccharide binding protein
<i>Myb12</i>	1.35	1.72	1.48	1.65	1.38	1.00	MYB proto-oncogene like 2
<i>Ube2C</i>	1.12	1.16	1.04	1.33	1.29	1.04	ubiquitin conjugating enzyme E2 C
<i>Ntsr1</i>	0.85	0.83	0.79	0.84	0.90	1.17	neurotensin receptor 1
<i>Fcna</i>	0.74	0.69	0.66	0.71	0.74	0.94	ficolin A
<i>Rpl35</i>	1.10	1.03	1.09	0.99	1.06	1.10	ribosomal protein L35
<i>Rbm43</i>	1.11	1.07	1.06	1.17	1.08	0.98	RNA binding motif protein 43
<i>Rcn1</i>	1.20	1.11	1.04	1.25	1.33	0.97	reticulocalbin 1
<i>Arhgap11a</i>	1.23	1.40	1.00	1.67	1.86	1.13	Rho GTPase activating protein 11A
<i>Myef2</i>	1.08	1.07	0.99	1.25	1.16	0.97	myelin expression factor 2
<i>Spp12a</i>	1.01	1.05	0.94	1.11	1.07	1.10	Ssignal peptide peptidase like 2A
<i>Ncaph</i>	1.20	1.33	1.12	1.53	1.43	1.07	non-SMC condensin I complex, subunit H
<i>Ckap2l</i>	1.12	1.05	1.03	1.17	1.19	0.97	cytoskeleton associated protein 2 like
<i>Rrbp1</i>	0.94	0.94	0.87	0.96	0.95	0.85	ribosome binding protein 1
<i>E2f1</i>	1.06	1.11	1.10	1.23	1.07	1.02	E2F transcription factor 1
<i>Sipi (Includes Others)</i>	0.95	0.91	0.66	0.72	0.84	0.95	secretory leukocyte peptidase inhibitor
<i>Pltp</i>	0.74	0.68	0.56	0.68	0.79	0.99	phospholipid transfer protein



<i>Rbm33</i>	1.00	1.06	0.89	1.00	1.06	0.99	RNA binding motif protein 33
<i>Cav2</i>	1.10	1.00	0.98	1.31	1.08	0.92	caveolin 2
<i>Arf5</i>	1.05	0.99	1.12	0.89	0.97	1.05	ADP ribosylation factor 5
<i>Exoc4</i>	1.05	1.16	1.02	1.19	1.23	0.96	exocyst complex component 4
<i>Akr1b10</i>	1.14	1.05	1.12	1.08	1.46	0.97	aldo-keto reductase family 1 member B10
<i>Mad2l1</i>	1.08	1.13	0.96	1.49	1.22	1.01	mitotic arrest deficient 2 like 1
<i>Uroc1</i>	0.96	0.99	1.04	0.87	0.98	1.10	urocanate hydratase 1
<i>Fancd2</i>	1.13	1.16	1.00	1.49	1.32	0.99	Fanconi anemia complementation group D2
<i>Emp1</i>	1.06	0.98	1.02	1.09	1.31	1.03	epithelial membrane protein 1
<i>Nos3</i>	1.03	0.97	0.98	0.96	1.10	0.94	nitric oxide synthase 3
<i>Abcb1b</i>	2.62	6.75	3.36	5.92	3.33	0.76	ATP-binding cassette, sub-family B (MDR/TAP), member 1B
<i>Abcb1</i>	1.26	1.35	1.22	1.53	1.24	0.94	ATP binding cassette subfamily B member 1
<i>Mktn1</i>	0.89	0.90	0.88	0.90	0.85	0.93	makorin ring finger protein 1
<i>Inmt</i>	0.63	0.52	0.94	0.43	0.62	0.86	indolethylamine N-methyltransferase
<i>Herc6</i>	1.10	1.26	0.91	1.61	1.22	0.99	HECT and RLD domain containing E3 ubiquitin protein ligase family member 6
<i>Celc4f</i>	0.66	0.59	0.46	0.68	0.63	0.85	C-type lectin domain family 4 member F
<i>Rad18</i>	1.05	1.12	1.04	1.24	1.18	1.06	RAD18, E3 ubiquitin protein ligase
<i>C1s</i>	1.03	1.06	0.92	1.20	1.01	0.97	complement C1s
<i>Klra5 (Includes Others)</i>	1.08	1.12	1.05	1.07	1.12	0.96	killer cell lectin-like receptor, subfamily A, member 5
<i>Klra2</i>	1.27	1.32	1.10	1.35	1.26	0.96	killer cell lectin-like receptor, subfamily A, member 2
<i>Klrc2/Klrc3</i>	0.82	0.89	0.74	0.78	0.80	0.91	killer cell lectin-like receptor subfamily C, member 2
<i>Mybl1</i>	1.66	2.81	1.58	3.67	2.07	0.82	MYB proto-oncogene like 1
<i>Ccne2</i>	1.21	1.30	1.14	1.86	1.54	1.16	cyclin E2
<i>Pip4p2</i>	1.07	1.23	1.07	1.21	1.12	0.99	phosphatidylinositol-4,5-bisphosphate 4-phosphatase 2
<i>Melk</i>	1.11	1.13	1.08	1.29	1.24	1.02	maternal embryonic leucine zipper kinase
<i>Smc2</i>	1.08	1.24	0.97	1.70	1.48	1.08	structural maintenance of chromosomes 2
<i>Stil</i>	1.17	1.23	1.07	1.54	1.45	1.02	STIL, centriolar assembly protein
<i>Clspn</i>	1.12	1.16	1.10	1.27	1.22	1.04	claspin
<i>Stmn1</i>	1.25	1.29	1.10	1.55	1.50	1.03	stathmin 1
<i>Sdhb</i>	1.04	0.97	1.05	0.92	0.96	0.99	succinate dehydrogenase complex iron sulfur subunit B



<i>Pm20d2</i>	0.78	0.89	0.87	0.79	0.80	0.93	peptidase M20 domain containing 2
<i>Loc100360453</i>	1.01	1.07	0.91	1.35	1.14	1.02	chromobox homolog 3-like
<i>Klf4</i>	1.10	1.08	1.03	1.12	1.14	0.95	kruppel like factor 4
<i>Astn2</i>	0.93	0.98	0.98	0.90	0.83	0.95	astrotactin 2
<i>Loc100362895</i>	1.01	1.12	1.04	1.33	1.10	0.96	heat shock protein 1, alpha-like
<i>Tinagl1</i>	1.07	1.02	1.05	0.92	1.17	0.96	tubulointerstitial nephritis antigen like 1
<i>C1qc</i>	0.87	0.80	0.70	0.82	0.83	0.98	complement C1q C chain
<i>Zmpste24</i>	1.00	1.08	1.03	1.09	1.08	1.12	zinc metallopeptidase STE24
<i>Fam49a</i>	1.32	1.91	1.53	1.72	1.48	0.90	family with sequence similarity 49 member A
<i>Nrcam</i>	1.38	2.31	1.64	1.65	1.60	0.91	neuronal cell adhesion molecule
<i>Rnf144a</i>	0.82	0.83	0.87	0.77	0.79	0.93	ring finger protein 144A
<i>Atp6v1d</i>	1.21	1.63	1.26	1.47	1.30	1.06	ATPase H ⁺ transporting V1 subunit D
<i>Ndufb1</i>	0.98	1.01	1.07	1.06	1.06	1.14	NADH:ubiquinone oxidoreductase subunit B1
<i>Hsp90aa1</i>	1.04	1.27	1.07	1.37	1.14	1.09	heat shock protein 90 alpha family class A member 1
<i>Hsp90aa1</i>	1.05	1.29	1.07	1.41	1.16	1.13	heat shock protein 90 alpha family class A member 1
<i>Mok</i>	1.27	1.49	1.40	1.32	1.35	0.93	MOK protein kinase
<i>Pros1</i>	0.92	1.01	0.97	0.98	0.97	1.01	protein S
<i>Cyp4f22</i>	1.23	1.21	1.12	1.17	1.30	0.96	cytochrome P450 family 4 subfamily F member 22
<i>Stac3</i>	0.67	0.60	0.67	0.54	0.62	0.81	SH3 and cysteine rich domain 3
<i>Atad2</i>	1.20	1.32	0.99	1.81	1.66	1.16	ATPase family, AAA domain containing 2
<i>Gtse1</i>	1.12	1.13	1.11	1.32	1.28	1.04	G2 and S-phase expressed 1
<i>Cfd</i>	0.77	0.75	0.76	0.74	0.75	0.97	complement factor D
<i>Timp3</i>	0.80	0.94	0.94	0.85	0.76	1.00	TIMP metallopeptidase inhibitor 3
<i>Cenpm</i>	1.06	1.14	1.10	1.12	1.08	0.99	centromere protein M
<i>Krt79</i>	0.91	1.03	1.00	1.06	0.89	0.94	keratin 79
<i>Csad</i>	1.30	1.21	0.85	1.15	1.29	1.02	cysteine sulfinic acid decarboxylase
<i>Gpt</i>	1.03	0.91	1.11	0.77	0.88	1.06	glutamic--pyruvic transaminase
<i>Casp12</i>	0.99	1.05	0.88	1.55	0.93	0.97	caspase 12
<i>Thyn1</i>	1.23	1.41	1.17	1.34	1.21	0.94	thymocyte nuclear protein 1
<i>Mcam</i>	1.15	1.03	1.08	1.03	1.33	0.95	melanoma cell adhesion molecule
<i>Pclaf</i>	1.25	1.45	1.20	2.05	1.74	1.09	PCNA clamp associated factor

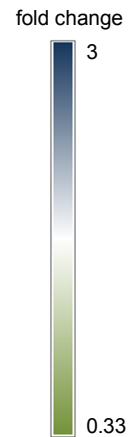
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<i>Anxa2</i>	1.30	1.12	1.09	1.32	1.44	1.02	annexin A2
<i>Ttk</i>	1.19	1.35	1.07	1.85	1.73	1.10	TTK protein kinase
<i>Topbp1</i>	1.11	1.12	0.99	1.28	1.19	1.06	DNA topoisomerase II binding protein 1
<i>Kif15</i>	1.15	1.23	1.11	1.31	1.35	1.02	kinesin family member 15
<i>Cep295</i>	1.08	1.10	1.03	1.12	1.17	0.98	centrosomal protein 295
<i>Spc24</i>	1.04	1.06	1.03	1.13	1.16	0.99	SPC24, NDC80 kinetochore complex component
<i>Anln</i>	1.09	1.14	1.04	1.32	1.31	1.05	anillin actin binding protein
<i>Jam3</i>	1.34	1.87	1.49	1.64	1.43	0.98	junctional adhesion molecule 3
<i>Tbcel</i>	0.97	0.95	0.91	1.09	0.95	1.03	tubulin folding cofactor E like
<i>Kif23</i>	1.10	1.12	1.09	1.26	1.27	1.05	kinesin family member 23
<i>Zwilch</i>	1.30	1.33	1.16	1.76	1.69	1.20	zwilch kinetochore protein
<i>Loc102546846</i>	1.25	1.03	1.00	0.99	1.01	0.98	uncharacterized LOC102546846
<i>Acpp</i>	0.77	0.77	0.91	0.68	0.83	0.87	acid phosphatase, prostate
<i>Cmtm8</i>	1.17	1.11	1.23	1.07	1.10	1.04	CKLF like MARVEL transmembrane domain containing 8
<i>Gnmt/Loc100911564</i>	0.81	0.84	0.94	0.69	0.75	0.89	glycine N-methyltransferase
<i>Gnmt/Loc100911564</i>	0.80	0.83	0.94	0.68	0.74	0.88	glycine N-methyltransferase
<i>Klc4</i>	1.01	0.96	1.00	0.89	0.95	1.00	kinesin light chain 4
<i>Cenpq</i>	1.20	1.32	1.16	1.79	1.43	1.10	centromere protein Q
<i>Map4K4</i>	1.08	1.03	0.94	1.12	1.20	0.91	mitogen-activated protein kinase kinase kinase kinase 4
<i>Inpp1</i>	1.18	1.21	1.07	1.35	1.11	0.96	inositol polyphosphate-1-phosphatase
<i>Aox4</i>	0.84	0.86	0.78	0.79	0.82	0.94	aldehyde oxidase 4
<i>Cd28</i>	1.13	1.09	1.09	1.04	1.42	1.09	CD28 molecule
<i>Alkbh7</i>	1.05	1.05	1.05	0.90	0.96	1.07	AlkB homolog 7
<i>Uhrf1</i>	1.18	1.18	1.16	1.33	1.34	1.03	ubiquitin like with PHD and ring finger domains 1
<i>Mcm3</i>	1.13	1.31	1.09	1.54	1.34	1.09	minichromosome maintenance complex component 3
<i>Gsta1</i>	1.17	1.31	1.28	1.21	1.25	1.13	glutathione S-transferase alpha 1
<i>Gsta1</i>	1.19	1.38	1.32	1.29	1.29	1.16	glutathione S-transferase alpha 1
<i>Nhej1</i>	1.12	1.18	1.21	1.11	1.13	0.92	non-homologous end joining factor 1
<i>Hjurp</i>	1.17	1.10	1.07	1.25	1.17	1.00	holliday junction recognition protein
<i>Ndc80</i>	1.25	1.37	1.06	1.79	1.72	1.12	NDC80, kinetochore complex component
<i>Tyms</i>	1.32	1.61	1.30	1.82	1.65	1.09	thymidylate synthetase



<i>Heph</i>	1.21	1.28	1.09	1.14	1.14	1.01	hephaestin
<i>Kif4A</i>	1.17	1.21	1.04	1.40	1.44	1.02	kinesin family member 4A
<i>Gria3</i>	1.45	1.99	1.46	1.55	1.69	1.00	glutamate ionotropic receptor AMPA type subunit 3
<i>Loc100912524/Rgd1565862</i>	0.98	0.87	1.03	0.79	0.94	1.03	similar to Spindlin-like protein 2 (SPIN-2)
<i>Eda2r</i>	2.40	4.78	2.80	3.54	4.18	1.00	ectodysplasin A2 receptor
<i>Ercc6l</i>	1.24	1.25	1.40	1.39	1.49	1.21	ERCC excision repair 6 like, spindle assembly checkpoint helicase
<i>Il13ra2</i>	1.31	1.13	1.01	1.31	1.52	0.99	interleukin 13 receptor subunit alpha 2
<i>Mpv17</i>	0.95	0.96	1.02	0.98	0.91	1.10	MPV17, mitochondrial inner membrane protein
<i>Adam19</i>	1.06	1.03	1.05	1.02	1.24	0.97	ADAM metalloproteinase domain 19
<i>Aurkb</i>	1.14	1.19	1.11	1.45	1.31	1.06	aurora kinase B
<i>Ankfy1</i>	0.96	0.95	0.86	1.06	1.04	0.96	ankyrin repeat and FYVE domain containing 1
<i>Myo1c</i>	1.04	0.98	0.97	1.01	1.13	0.96	myosin IC
<i>Atad5</i>	1.08	1.15	1.07	1.34	1.25	0.99	ATPase family, AAA domain containing 5
<i>Rpl19</i>	1.16	1.21	1.19	1.19	1.16	1.07	ribosomal protein L19
<i>Hmmr</i>	1.16	1.41	1.00	2.14	1.75	1.16	hyaluronan mediated motility receptor
<i>Ccng1</i>	1.43	2.04	1.61	1.91	1.59	0.99	cyclin G1
<i>Gabrg2</i>	1.11	1.02	1.19	1.03	0.98	1.07	gamma-aminobutyric acid type A receptor gamma2 subunit
<i>Loc103693330/Loc103693430</i>	1.08	1.05	1.11	1.01	1.08	1.24	up-regulated during skeletal muscle growth protein 5-like
<i>Tmem88</i>	1.11	1.01	1.14	1.05	1.36	0.98	transmembrane protein 88
<i>Shbg</i>	1.05	0.99	1.06	0.89	1.00	0.98	sex hormone binding globulin
<i>Chrne</i>	1.27	1.15	1.16	0.95	1.18	1.09	cholinergic receptor nicotinic epsilon subunit
<i>Sez6</i>	0.88	0.76	0.86	0.76	0.86	0.86	seizure related 6 homolog
<i>Slnf13</i>	1.05	0.98	0.86	1.01	1.13	0.95	schlafen family member 13
<i>Top2a</i>	1.30	1.52	1.00	2.64	2.35	1.16	DNA topoisomerase II alpha
<i>Brca1</i>	1.16	1.12	0.97	1.39	1.32	1.02	BRCA1, DNA repair associated
<i>Lgals3bp</i>	1.24	1.44	1.05	1.38	1.42	0.97	galectin 3 binding protein
<i>Spag5</i>	1.05	1.10	0.98	1.21	1.17	0.98	sperm associated antigen 5
<i>Olf209</i>	1.00	1.09	1.12	1.20	1.05	0.96	olfactory receptor 209
<i>Hmgb2 (Includes Others)</i>	1.21	1.25	1.11	1.46	1.42	0.99	high mobility group box 2
<i>Gcsam</i>	0.78	0.91	0.72	0.72	0.77	0.89	germinal center associated signaling and motility
<i>Cd80</i>	1.16	1.11	1.11	1.26	1.51	0.96	CD80 molecule



<i>Golgb1</i>	0.86	0.87	0.84	0.93	0.96	0.85	golgin B1
<i>Loc102553356</i>	1.77	1.57	1.58	1.13	1.70	1.13	uncharacterized LOC102553356
<i>Loc680825</i>	0.81	0.74	0.73	0.74	0.79	0.93	hypothetical protein LOC680825
<i>Kntc1</i>	1.18	1.30	1.11	1.54	1.51	1.07	kinetochore associated 1
<i>Oasl2</i>	1.10	1.16	0.89	1.16	1.17	0.95	2'-5' oligoadenylate synthetase-like 2
<i>Acmsd</i>	0.72	0.76	0.93	0.99	0.89	1.16	aminocarboxymuconate semialdehyde decarboxylase
<i>Loc102555796</i>	1.13	1.14	1.18	1.04	1.01	1.13	uncharacterized LOC102555796
<i>Kdm5b</i>	0.83	0.86	0.78	0.85	0.88	0.84	lysine demethylase 5B
<i>Ube2t</i>	1.11	1.20	1.12	1.21	1.23	1.07	ubiquitin conjugating enzyme E2 T
<i>Kif14</i>	1.07	1.02	1.03	1.16	1.10	0.99	kinesin family member 14
<i>Sh2d1b</i>	1.06	1.29	0.99	1.25	1.16	1.02	SH2 domain containing 1B
<i>Cd244</i>	1.01	1.09	0.90	1.02	0.98	0.90	CD244 molecule
<i>Exo1</i>	1.06	1.11	1.05	1.15	1.19	1.00	exonuclease 1
<i>Loc690147</i>	1.19	1.43	1.18	1.34	1.29	0.93	similar to Epoxide hydrolase 1 (Microsomal epoxide hydrolase) (Epoxide hydratase)
<i>Kiss1</i>	1.13	1.05	1.18	0.96	1.06	1.05	KiSS-1 metastasis-suppressor
<i>Slamf7</i>	0.87	0.96	0.82	0.83	0.93	1.00	SLAM family member 7
<i>Ephx1</i>	1.21	1.51	1.29	1.39	1.39	1.01	epoxide hydrolase 1
<i>Cenpf</i>	1.06	1.08	0.95	1.30	1.27	0.96	centromere protein F
<i>Dtl</i>	1.23	1.32	1.16	1.67	1.54	1.05	denticleless E3 ubiquitin protein ligase homolog
<i>Cr1l</i>	1.19	1.43	1.29	1.32	1.27	1.02	complement C3b/C4b receptor 1 like
<i>Gbp6</i>	1.18	1.29	0.92	1.46	1.23	1.03	guanylate binding protein family member 6
<i>Hsd17b13</i>	0.95	0.97	1.04	0.88	0.95	1.01	hydroxysteroid 17-beta dehydrogenase 11
<i>Hsd17b13</i>	1.33	1.49	1.52	1.21	1.35	1.27	hydroxysteroid 17-beta dehydrogenase 13
<i>Ugt2b17</i>	1.40	1.34	1.69	1.05	1.33	1.11	UDP glucuronosyltransferase family 2 member B17
<i>Sgcb</i>	1.16	1.55	1.27	1.53	1.38	1.05	sarcoglycan beta
<i>Qdpr</i>	0.98	0.89	1.01	0.86	0.90	1.02	quinoid dihydropteridine reductase
<i>Man2b2</i>	1.10	1.14	1.02	1.15	1.10	0.95	mannosidase alpha class 2B member 2
<i>Bmp3</i>	1.12	1.06	1.11	1.03	1.64	1.01	bone morphogenetic protein 3
<i>Dck</i>	1.07	1.19	1.04	1.36	1.27	1.06	deoxycytidine kinase
<i>Kit</i>	1.13	1.08	1.05	1.00	1.43	0.96	KIT proto-oncogene receptor tyrosine kinase

fold change



<i>Tacc3</i>	1.12	1.12	1.02	1.28	1.21	1.04	transforming acidic coiled-coil containing protein 3
<i>Loxl2</i>	1.09	0.99	0.98	1.05	1.24	0.94	lysyl oxidase like 2
<i>Pcdh17</i>	1.19	1.03	1.06	1.14	1.44	0.99	protocadherin 17
<i>Wdhd1</i>	1.07	1.11	0.92	1.14	1.17	0.97	WD repeat and HMG-box DNA binding protein 1
<i>Dlgap5</i>	1.14	1.12	1.00	1.54	1.32	1.01	DLG associated protein 5
<i>Ndrp2</i>	0.94	0.94	0.97	0.86	0.92	1.00	NDRG family member 2
<i>Ebpl</i>	1.14	1.12	1.19	1.12	1.21	1.16	emopamil binding protein like
<i>Esco2</i>	1.30	1.26	1.13	2.37	1.95	1.16	establishment of sister chromatid cohesion N-acetyltransferase 2
<i>Cdca2</i>	1.15	1.14	1.04	1.35	1.26	1.02	cell division cycle associated 2
<i>Loc102549099</i>	1.38	1.81	1.66	1.54	1.52	1.04	uncharacterized LOC102549099
<i>Diaph3</i>	1.27	1.45	1.11	1.70	1.78	1.04	diaphanous related formin 3
<i>Il17rd</i>	1.31	2.80	1.77	2.00	1.38	0.85	interleukin 17 receptor D
<i>Chdh</i>	1.01	0.93	1.09	0.87	0.98	1.03	choline dehydrogenase
<i>Loc102553008</i>	0.87	0.77	0.87	0.55	0.82	1.10	uncharacterized LOC102553008
<i>Nrg1</i>	1.14	1.70	1.26	1.62	1.20	0.91	neuregulin 1
<i>Ckap2</i>	1.62	2.08	1.25	3.12	2.34	1.14	cytoskeleton associated protein 2
<i>Loc100360260</i>	1.03	1.03	0.94	1.45	1.20	1.03	chromobox homolog 3-like
<i>Hmgb2 (Includes Others)</i>	1.16	1.16	1.12	1.46	1.27	1.06	high mobility group box 2
<i>Hpgd</i>	0.66	0.71	0.67	0.69	0.71	0.94	15-hydroxyprostaglandin dehydrogenase
<i>Dctd</i>	1.13	1.16	0.96	1.29	1.35	1.00	dCMP deaminase
<i>Cenpu</i>	1.13	1.17	1.13	1.43	1.31	1.02	centromere protein U
<i>Hist1h2bb</i>	1.20	1.07	1.07	1.26	1.28	1.13	histone cluster 1 H2B family member b
<i>Mastl</i>	1.43	1.63	1.14	2.57	1.99	1.20	microtubule associated serine/threonine kinase like
<i>Znf367</i>	1.21	1.26	1.15	1.57	1.42	0.97	zinc finger protein 367
<i>Cd14b</i>	1.08	1.07	1.10	1.13	1.16	1.22	cell division cycle 14B
<i>Hist1h2ab</i>	1.12	1.10	1.10	1.28	1.28	1.05	histone cluster 1 H2A family member b
<i>Rbbp8</i>	1.07	1.12	1.06	1.41	1.16	1.02	RB binding protein 8, endonuclease
<i>Csf1r</i>	0.61	0.62	0.46	0.61	0.65	0.92	colony stimulating factor 1 receptor
<i>Tubb6</i>	1.07	1.12	1.06	1.21	1.27	1.03	tubulin beta 6 class V
<i>Slc39a6</i>	1.27	1.27	1.09	1.19	1.27	1.06	solute carrier family 39 member 6
<i>Nr3c1</i>	0.76	0.82	0.80	0.67	0.76	0.99	nuclear receptor subfamily 3 group C member 1

fold change



<i>Mcm5</i>	1.29	1.33	1.10	1.72	1.50	1.07	Minichromosome maintenance complex component 5
<i>Cdh13</i>	1.03	1.38	1.09	1.17	1.01	0.96	cadherin 13
<i>Itgb1</i>	1.03	1.07	0.95	1.15	1.13	0.99	integrin subunit beta 1
<i>Coq9</i>	1.02	0.95	1.01	0.93	0.92	0.99	coenzyme Q9
<i>H2-T22</i>	1.14	1.07	1.01	1.00	1.13	0.96	histocompatibility 2, T region locus 22
<i>Tcf19</i>	1.12	1.20	0.98	1.52	1.40	1.03	transcription factor 19
<i>Tap1</i>	1.08	1.16	0.95	1.21	1.06	0.94	transporter 1, ATP binding cassette subfamily B member
<i>Cdkn1a</i>	2.06	3.13	2.44	2.72	2.28	1.13	cyclin dependent kinase inhibitor 1A
<i>Pln</i>	1.13	1.31	1.02	1.44	1.07	1.04	phospholamban
<i>Fyn</i>	1.14	1.13	1.05	1.10	1.23	1.01	FYN proto-oncogene, Src family tyrosine kinase
<i>Hace1</i>	1.00	1.10	1.05	1.20	1.06	0.97	HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1
<i>Ftcd</i>	0.96	0.95	0.97	0.83	0.90	1.01	formimidoyltransferase cyclodeaminase
<i>Slc25a16</i>	1.05	1.03	0.99	1.11	1.10	1.00	solute carrier family 25 member 16
<i>Clic1</i>	1.11	1.02	1.02	1.11	1.18	0.95	chloride intracellular channel 1
<i>Fcgr2a</i>	0.86	0.86	0.70	0.86	0.87	0.98	Fc fragment of IgG receptor IIa

Table S2: Summary of probe sets that are significantly different expressed by 3.3 mg individual PA per kg bw compared to vehicle control (one-way ANOVA, $q < 0.05$).

PA	gene symbol	entrez gene name
echimidine	<i>Loc102554389</i> <i>Loc102546846</i> <i>Pros1</i>	zinc finger protein 862-like uncharacterized LOC102546846 protein S
heliotrine	<i>Tbcel</i> <i>Pdgfc</i> <i>Fam49a</i> <i>Nhej1</i>	tubulin folding cofactor E like platelet derived growth factor C family with sequence similarity 49 member A non-homologous end joining factor 1
lasiocarpine	<i>Gabrg2</i> <i>Kiss1</i> <i>Ankfy1</i> <i>Rrbp1</i> <i>Cd244</i> <i>Nupr1</i>	gamma-aminobutyric acid type A receptor gamma2 subunit KiSS-1 metastasis-suppressor ankyrin repeat and FYVE domain containing 1 ribosome binding protein 1 CD244 molecule nuclear protein 1, transcriptional regulator
senecionine	<i>C1s</i> <i>Ccnd1</i> <i>Sspl2a</i> <i>Uroc1</i> <i>Hsd17b11</i> <i>Gbp6</i> <i>Klc4</i> <i>E2f1</i> <i>Igsf10</i> <i>Shbg</i> <i>Chdh</i> <i>Abcb1b</i> <i>Sdhb</i> <i>Herc6</i> <i>Cav2</i> <i>Casp12</i>	complement C1s cyclin D1 signal peptide peptidase like 2A urocanate hydratase 1 hydroxysteroid 17-beta dehydrogenase 11 guanylate binding protein family member 6 kinesin light chain 4 E2F transcription factor 1 immunoglobulin superfamily member 10 sex hormone binding globulin choline dehydrogenase ATP binding cassette subfamily B member 1 succinate dehydrogenase complex iron sulfur subunit B HECT and RLD domain containing E3 ubiquitin protein ligase family member 6 caveolin 2 caspase 12
senkirkine	<i>Emp1</i> <i>Bmp3</i> <i>Rgd1310209</i> <i>Nos3</i> <i>Mcam</i> <i>Adgrl4</i> <i>Krt79</i> <i>Clic1</i> <i>Akr1B10</i> <i>Tinagl1</i> <i>Loxl2</i> <i>Tmem88</i> <i>Cd28</i> <i>Adam19</i> <i>Kit</i> <i>Dab2</i> <i>Loc100910701</i> <i>Myo1c</i> <i>Mpv17</i>	epithelial membrane protein 1 bone morphogenetic protein 3 similar to KIAA1324 protein nitric oxide synthase 3 melanoma cell adhesion molecule adhesion G protein-coupled receptor L4 keratin 79 chloride intracellular channel 1 aldo-keto reductase family 1 member B10 tubulointerstitial nephritis antigen like 1 lysyl oxidase like 2 transmembrane protein 88 CD28 molecule ADAM metallopeptidase domain 19 KIT proto-oncogene receptor tyrosine kinase DAB2, clathrin adaptor protein uncharacterized LOC100910701 myosin 1C MPV17, mitochondrial inner membrane protein

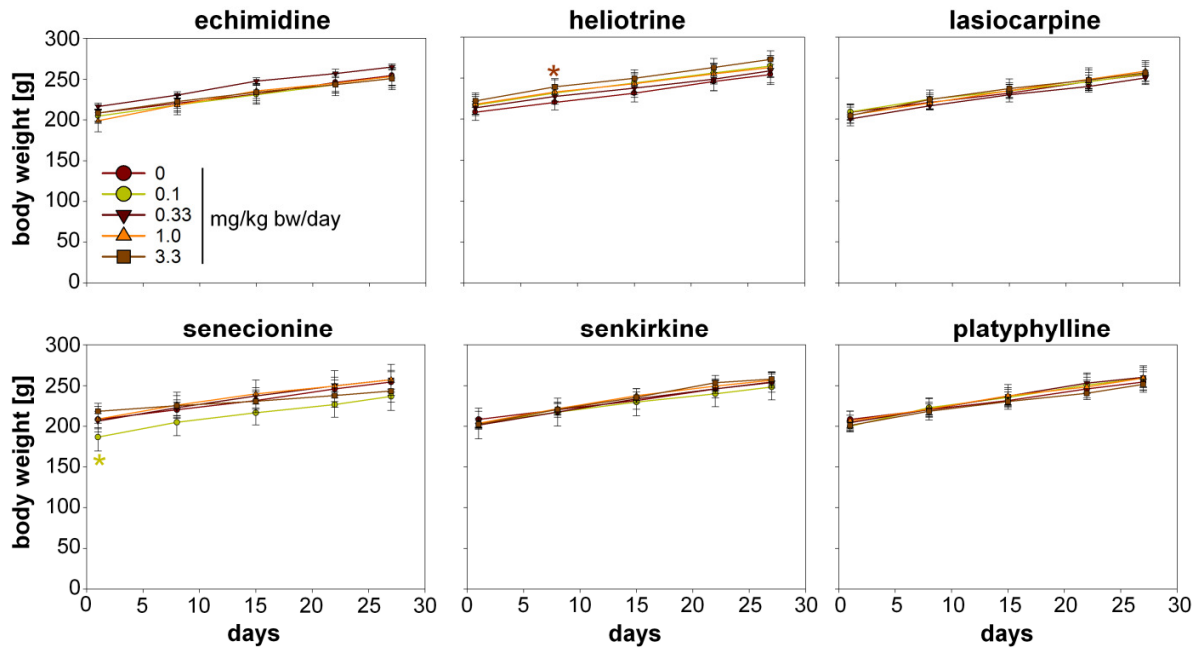


Fig. S1: Development of body weight of all animals throughout the study. Individual body weights were recorded to the nearest 0.1 g once a week on day 1, 8, 15, 22 and 27. Data are shown as mean \pm SD of all 5 animals of the same treatment group (8 animals in vehicle group). Statistical significant differences were calculated by one-way ANOVA followed by Dunnett's post-hoc test ($p < 0.05$).

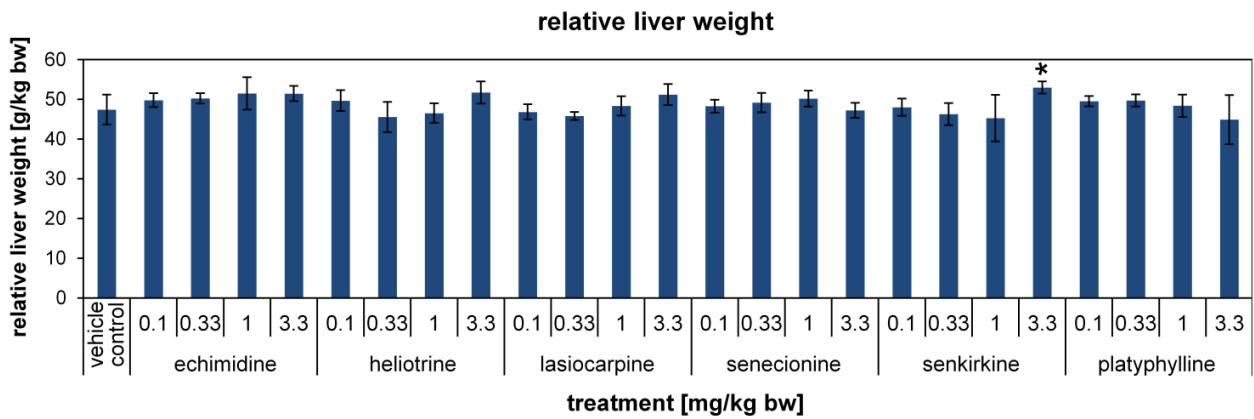


Fig. S2: Relative liver weight for all animals at the end of the study. Wet liver weights were recorded upon necropsy on day 29 (1 day after the last treatment) and related to the body weight upon necropsy. Data are shown as mean \pm SD of all 5 animals of the same treatment group (8 animals in vehicle group). Statistical significant differences vs. vehicle control were calculated by one-way ANOVA followed by Dunnett's post-hoc test ($p < 0.05$).

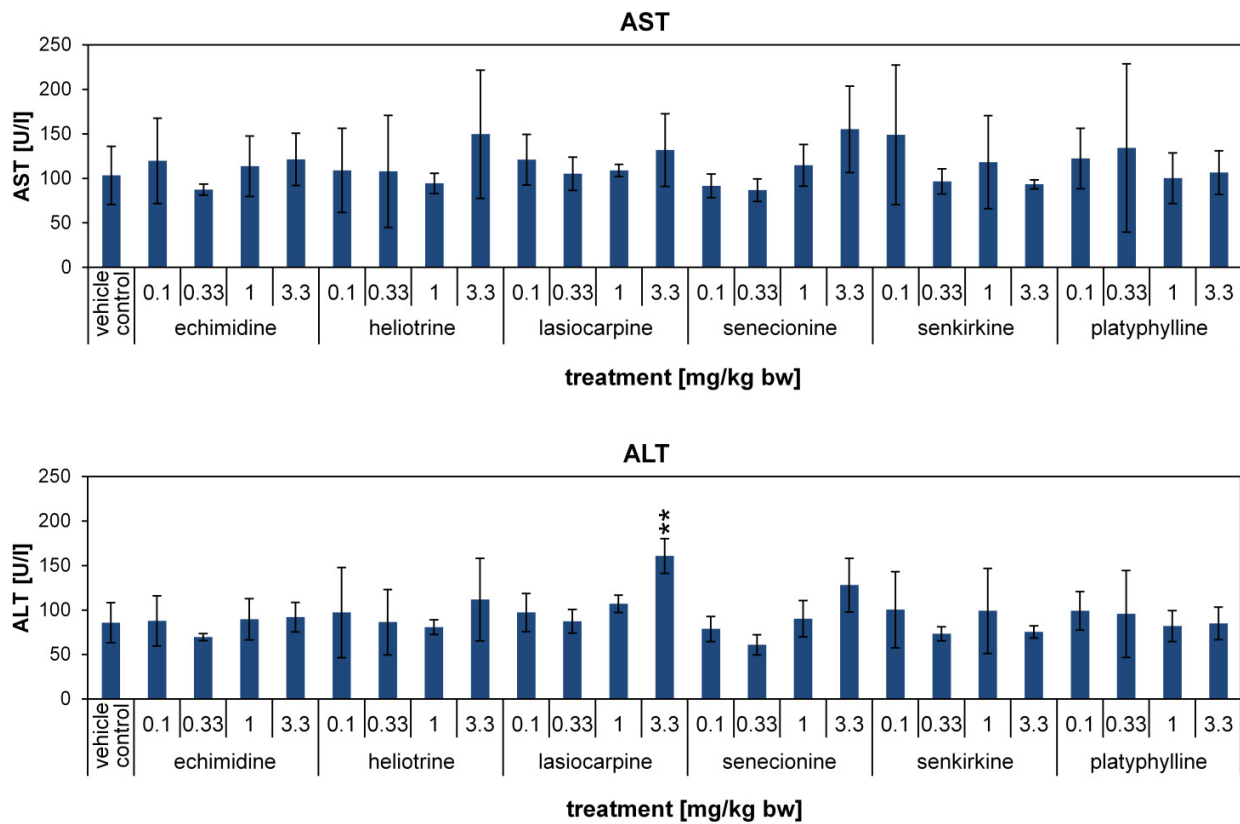


Fig. S3: Levels of the enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the blood plasma of the treated animals. AST and ALT levels were analyzed in the blood plasma sampled on day 29. Mean results \pm SD of all 5 animals of the same treatment group (8 animals in vehicle group) are shown. Statistical significant differences vs. the vehicle control were analyzed by one-way ANOVA followed by Dunnett's post-hoc test (** $p < 0.01$).

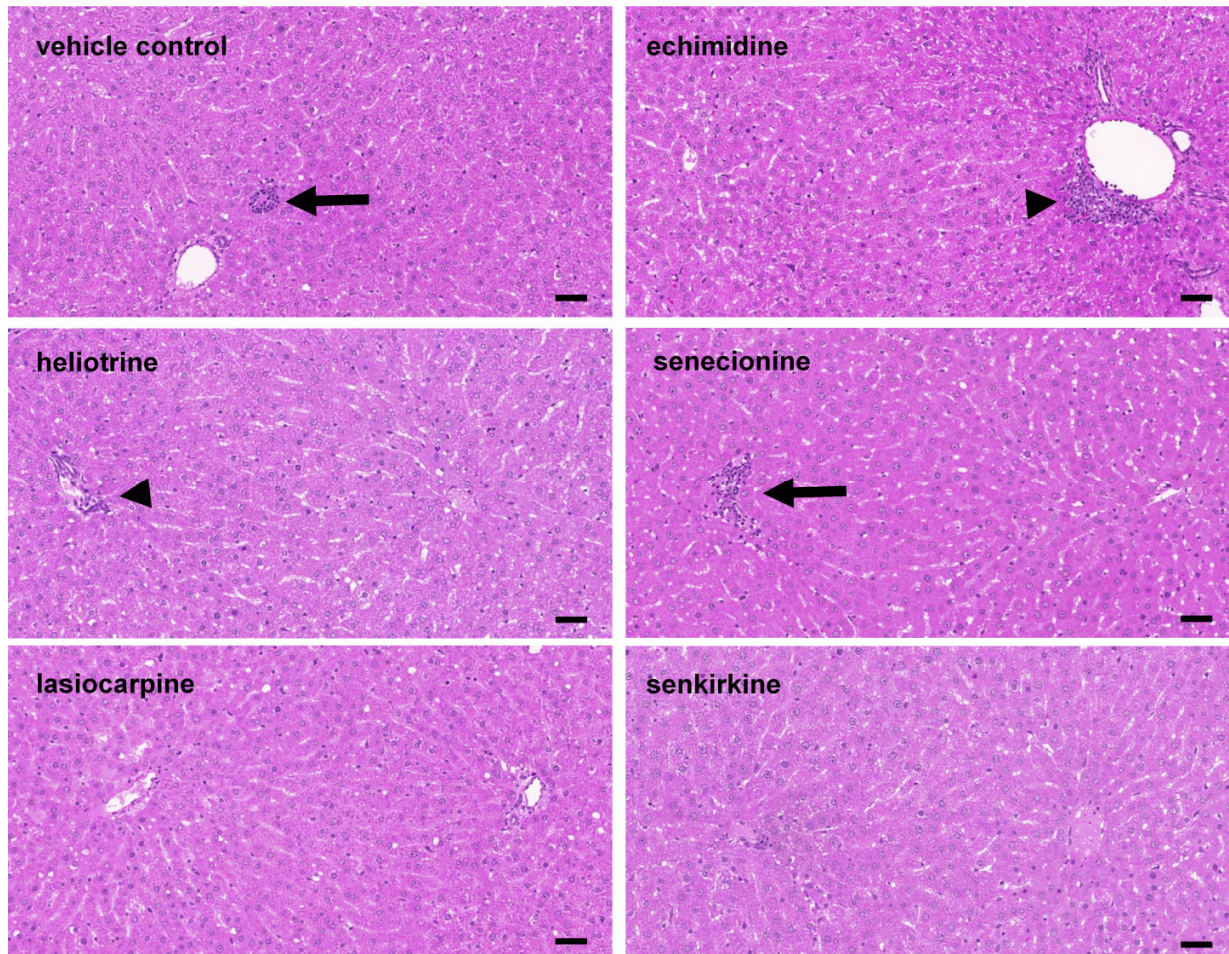


Fig. S4: Histological slides stained with hematoxylin and eosin of the livers of male Fischer rats orally treated daily for 28 days with 3.3 mg/kg body weight of the respective pyrrolizidine alkaloid or vehicle control. A multifocal random mixed inflammatory cell infiltration (arrows) as well as multifocal periportal mononuclear cell infiltration (arrow heads) were seen to a very slight extent in up to two animals per group in most groups. The lesions represent commonly found background lesions in rat livers. Portal or biliary fibrosis, bile duct proliferation, hepatocellular degeneration (necrosis), swelling of hepatocytes, megalocytosis or karyomegaly of liver cells or any other adverse finding were not seen in any group. Bar = 50 μ m.

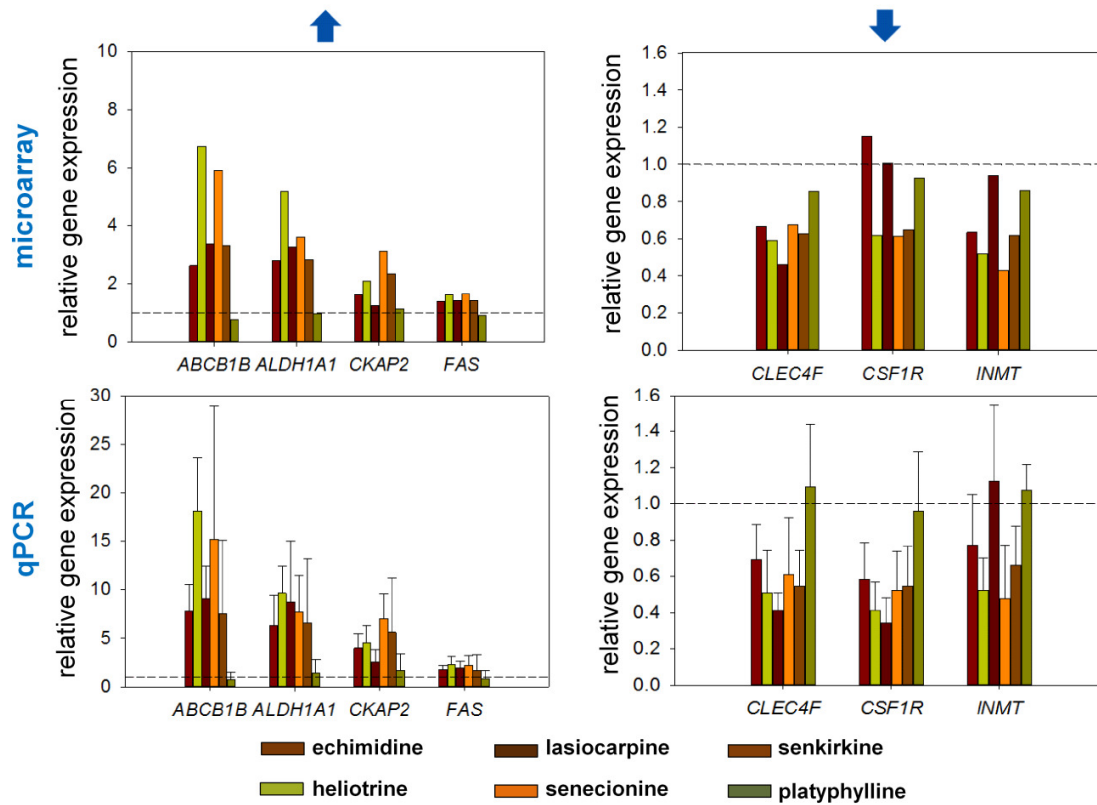


Fig. S5: Validation of PA-induced gene regulation in rat livers by qPCR. Total mRNA of rat liver samples was analyzed by qPCR for the expression of selected genes. A total of in the microarray analysis 4 up- and 3 downregulated genes was analyzed and results from microarray analysis (top) and qPCR (bottom) were compared. Fold changes compared to vehicle control are shown as mean \pm SD of 5 individual animals.