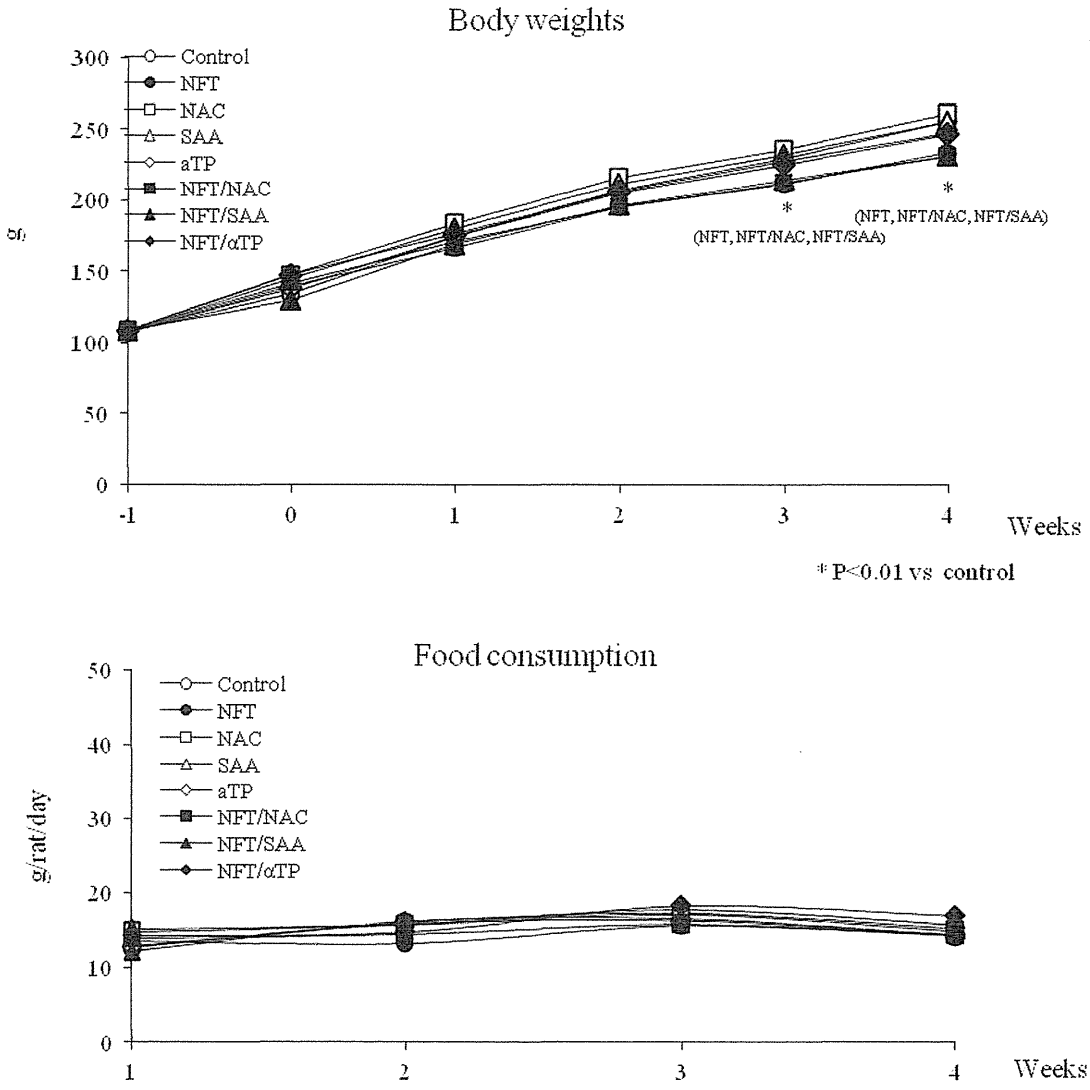


Fig. 25. Body weights and food consumption for F344 *gpt* delta rats treated with NFT and antioxidants.

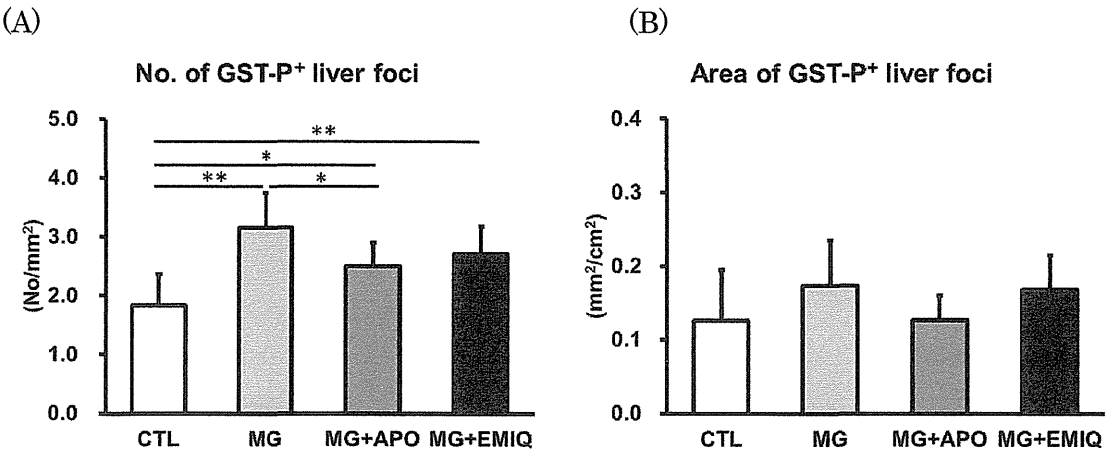


Fig. 26. Quantitative analysis of GST-P$^+$ foci in the liver of rats after DEN initiation or DEN initiation followed by MG treatment with or without co-treatment with APO or EMIQ. (A) The number of GST-P$^+$ foci in each group. (B) The area of GST-P$^+$ foci in each group. Columns represent mean and standard deviation. *, $p<0.05$; **, $p<0.01$ (Tukey's or Steel-Dwass multiple comparison test).

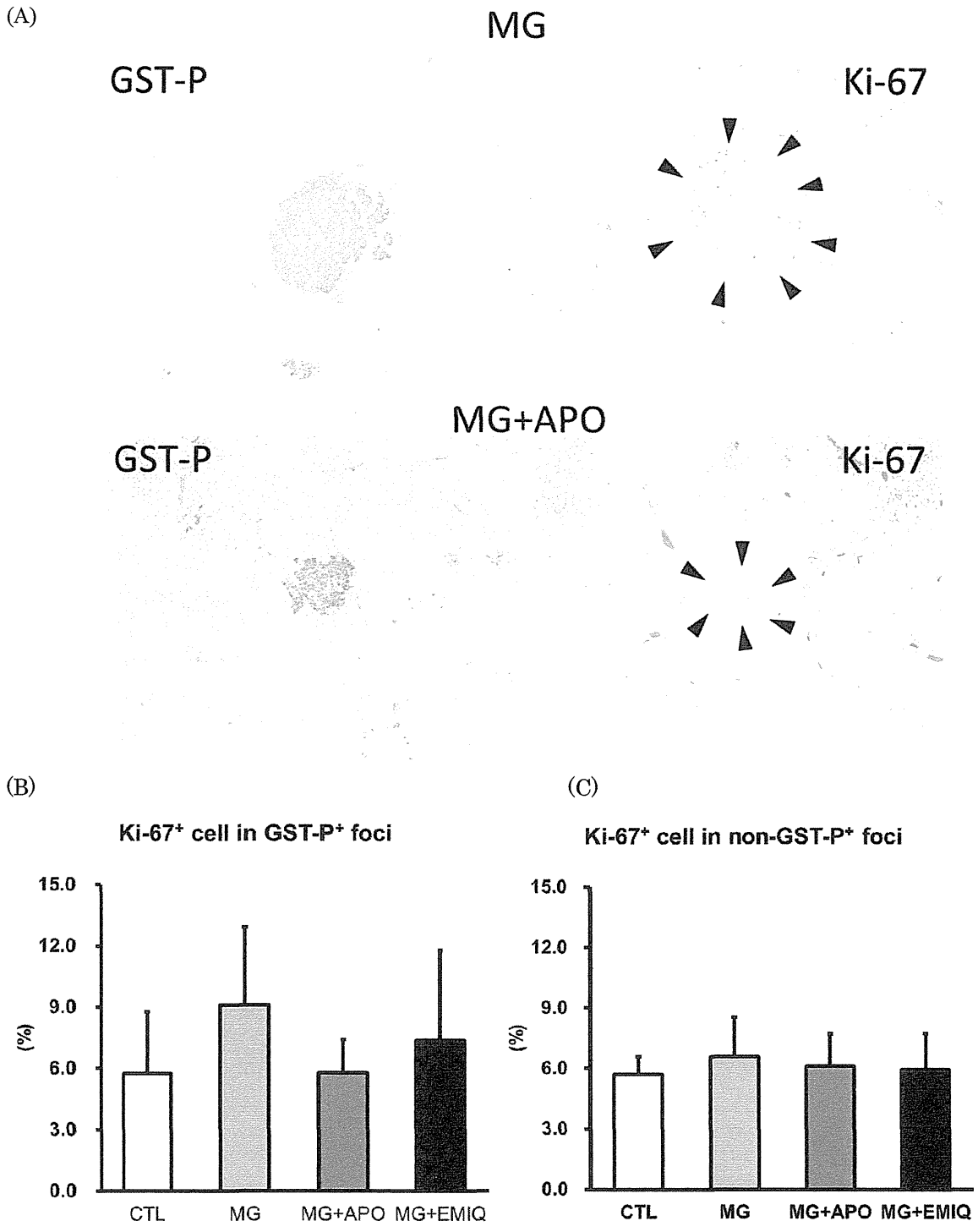
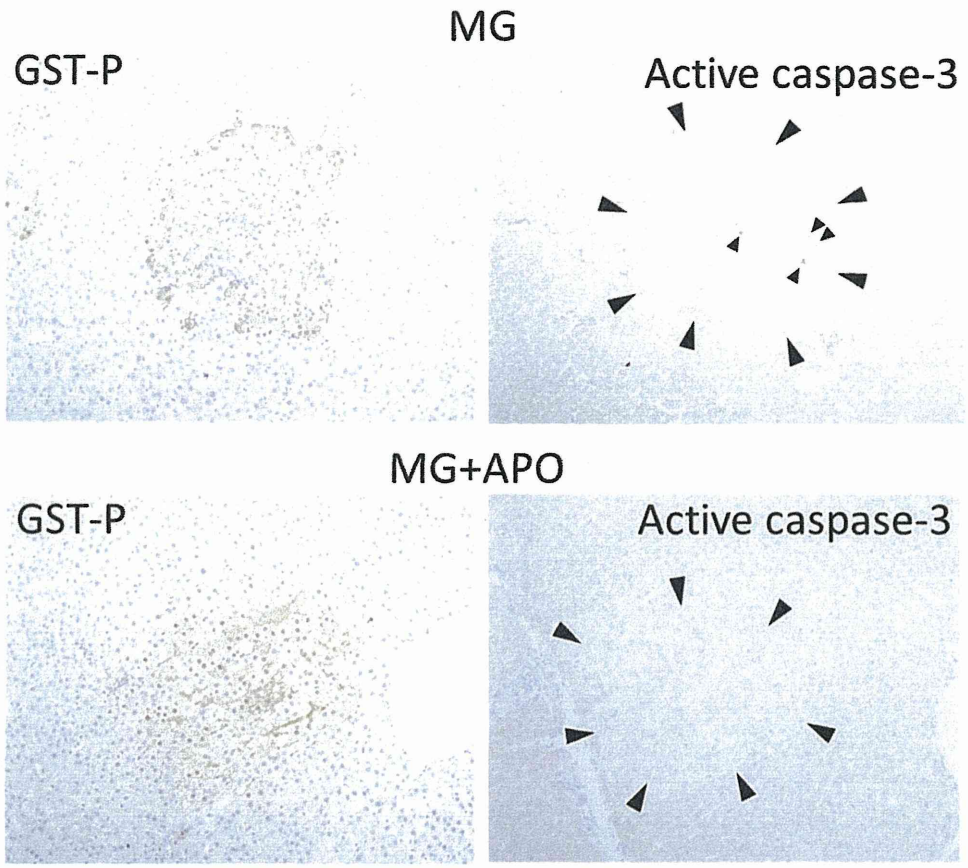
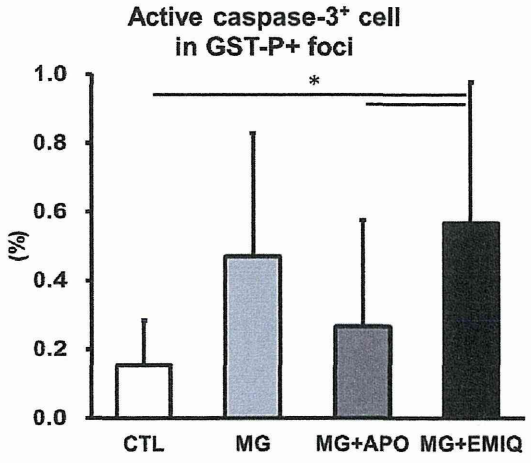


Fig. 27. Quantitative analysis of Ki-67$^+$ cells in GST-P$^+$ foci and non-GST-P$^+$ foci in the liver of rats after DEN initiation or DEN initiation followed by MG treatment with or without co-treatment with APO or EMIQ. (A) Representative images of Ki-67$^+$ cells in GST-P$^+$ foci in rats treated with MG and MG+APO (x 40 magnification; margin of the focus is marked with arrowheads). (B) Quantitative data (%) of Ki-67$^+$ cells in GST-P$^+$ foci. (C) Quantitative data (%) of Ki-67$^+$ cells in non-GST-P$^+$ foci. Columns represent mean and standard deviation. No statistical significance is detected in each data by Tukey's or Steel-Dwass multiple comparison test.

(A)



(B)



(C)

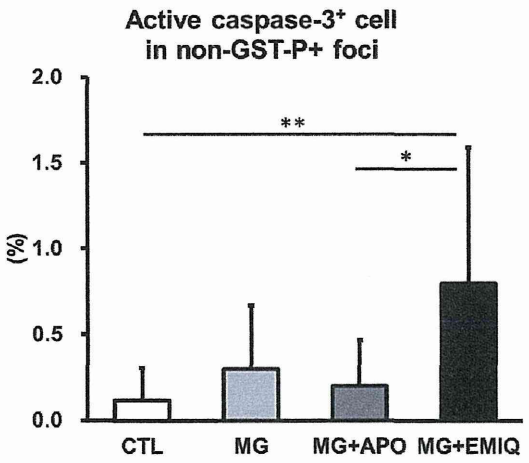
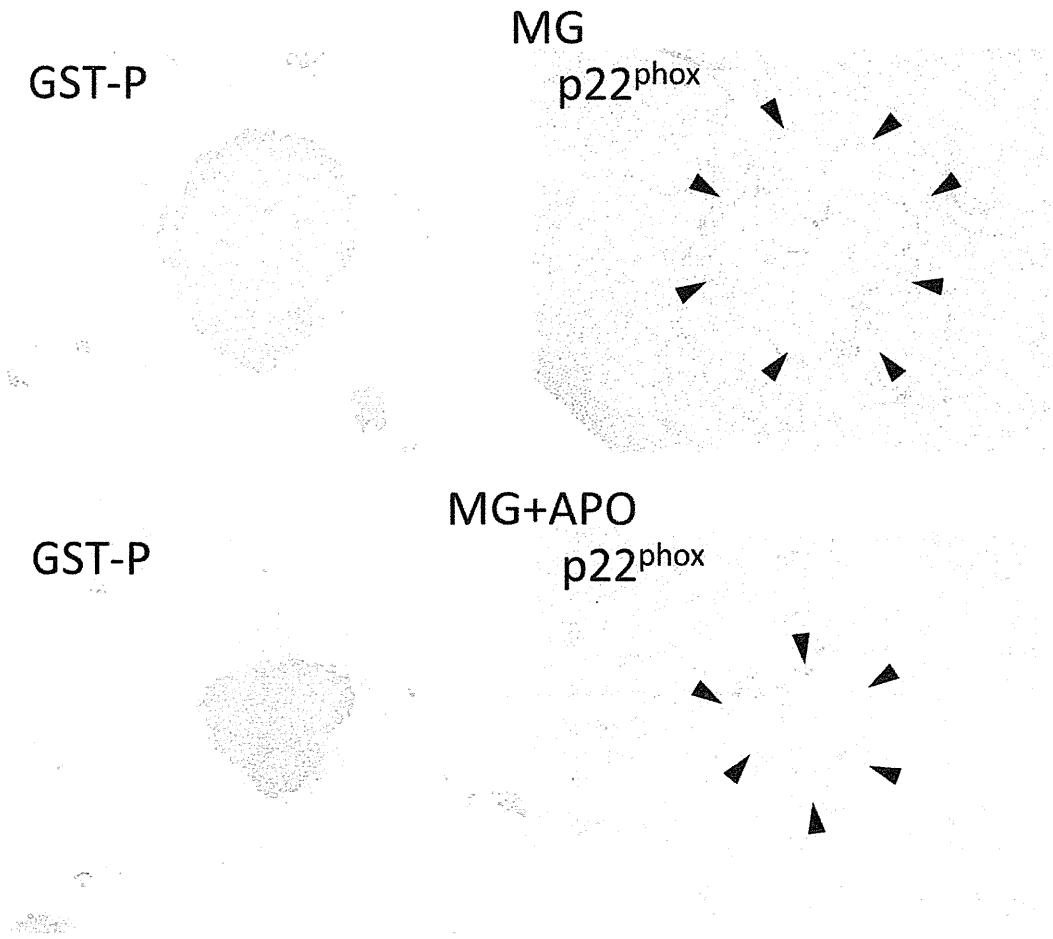


Fig. 28. Quantitative analysis of active caspase-3$^+$ cells in GST-P$^+$ foci and non-GST-P$^+$ foci in the liver of rats after DEN initiation or DEN initiation followed by MG treatment with or without co-treatment with APO or EMIQ. (A) Representative images of active caspase-3$^+$ cells in GST-P$^+$ foci in rats treated with MG and MG+APO (x 40 magnification; margin of the focus is marked with large arrowheads; positive cells are expressed with small arrowheads). (B) Quantitative data (%) of active caspase-3$^+$ cells in GST-P$^+$ foci. (C) Quantitative data (%) of active caspase-3$^+$ cells in non-GST-P$^+$ foci. Columns represent mean and standard deviation. *, $p<0.05$; **, $p<0.01$ (Tukey's or Steel-Dwass multiple comparison test).

(A)



(B)

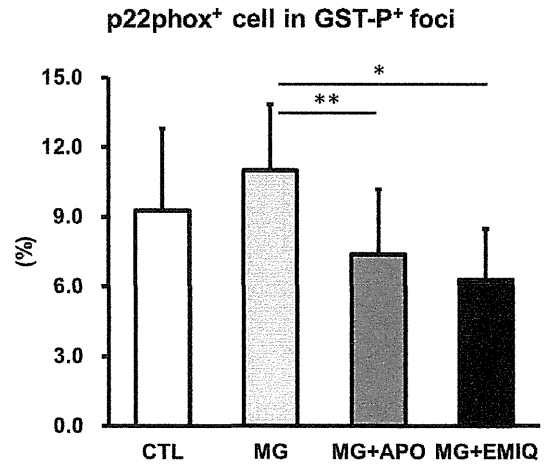
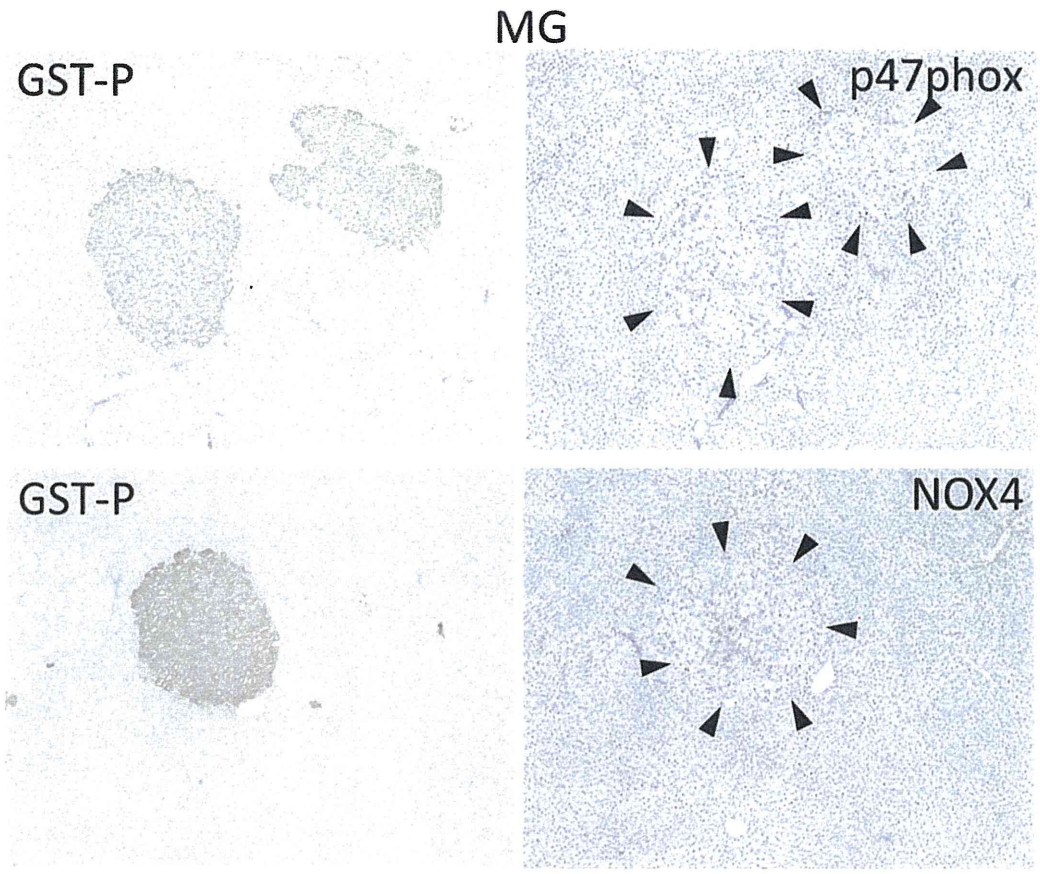
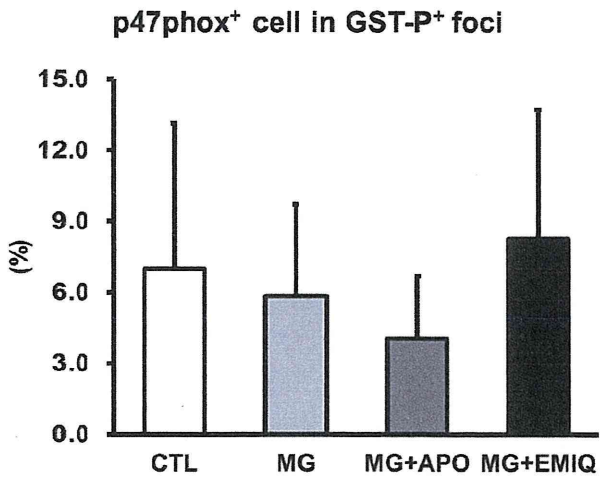


Fig. 29. Quantitative analysis of p22phox$^+$ cells in GST-P$^+$ foci in the liver of rats after DEN initiation or DEN initiation followed by MG treatment with or without co-treatment with APO or EMIQ. (A) Representative images of p22phox$^+$ cells in GST-P$^+$ foci in rats treated with MG and MG+APO (x 40 magnification; margin of the focus is marked with large arrowheads). (B) Quantitative data (%) of p22phox$^+$ cells in GST-P$^+$ foci. Columns represent mean and standard deviation. *, $p<0.05$; **, $p<0.01$ (Tukey's or Steel-Dwass multiple comparison test).

(A)



(B)



(C)

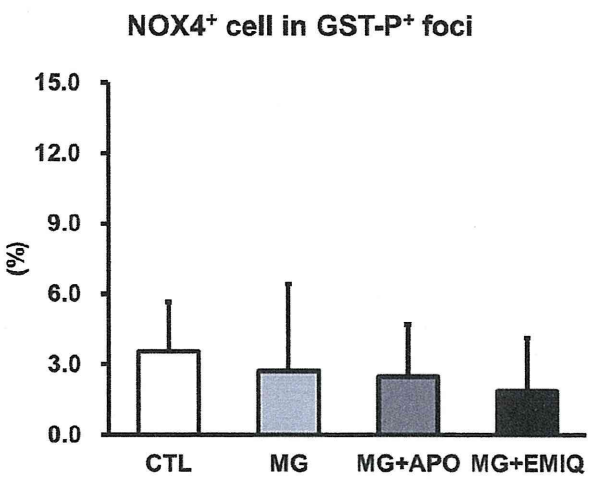


Fig. 30. Quantitative analysis of p47phox$^+$ cells and NOX4$^+$ cells in GST-P$^+$ foci in the liver of rats after DEN initiation or DEN initiation followed by MG treatment with or without co-treatment with APO or EMIQ. (A) Representative images of p47phox$^+$ cells and NOX4$^+$ cells in GST-P$^+$ foci in rats treated with MG (x 40 magnification; margin of the focus is marked with large arrowheads). (B) Quantitative data (%) of p47phox$^+$ cells in GST-P$^+$ foci. (C) Quantitative data (%) of NOX4$^+$ cells in GST-P$^+$ foci. Columns represent mean and standard deviation. No statistical significance is detected in each data by Tukey's or Steel-Dwass multiple comparison test.

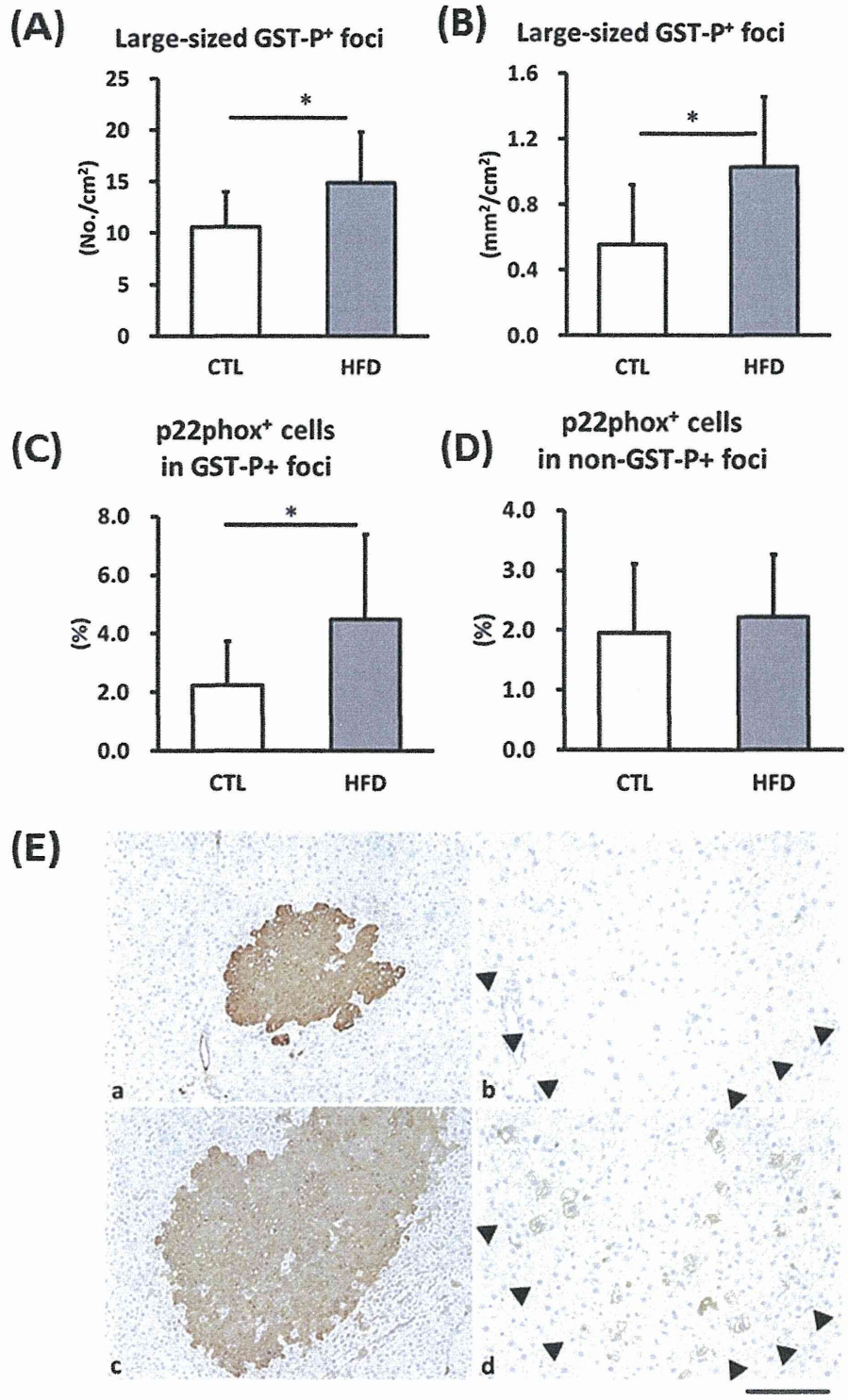


Fig. 31. Quantitative analysis of large-sized GST-P$^+$ foci and expression of p22phox+ cells in the GST-P$^+$ foci and non-GST-P$^+$ foci in the liver of rats fed with basal diet and high fat diet after DEN initiation. (A, B) The number (A) and area (B) of large-sized GST-P$^+$ foci in each group. (C, D) Quantitative data (%) of p22phox$^+$ cells in large-sized GST-P$^+$ foci (C) and non-GST-P$^+$ foci (D). (E) Representative images of large-sized GST-P$^+$ foci (a,c) and p22phox$^+$ cells (b,d) in CTL (a,b) and HFD (c,d) groups. Bar=200 μm (a, b), 100 μm (b, d). Columns represent mean and standard deviation. CTL, control group; HFD, high fat diet group. *: $p<0.05$ (Student's t test or Aspin-Welch test).

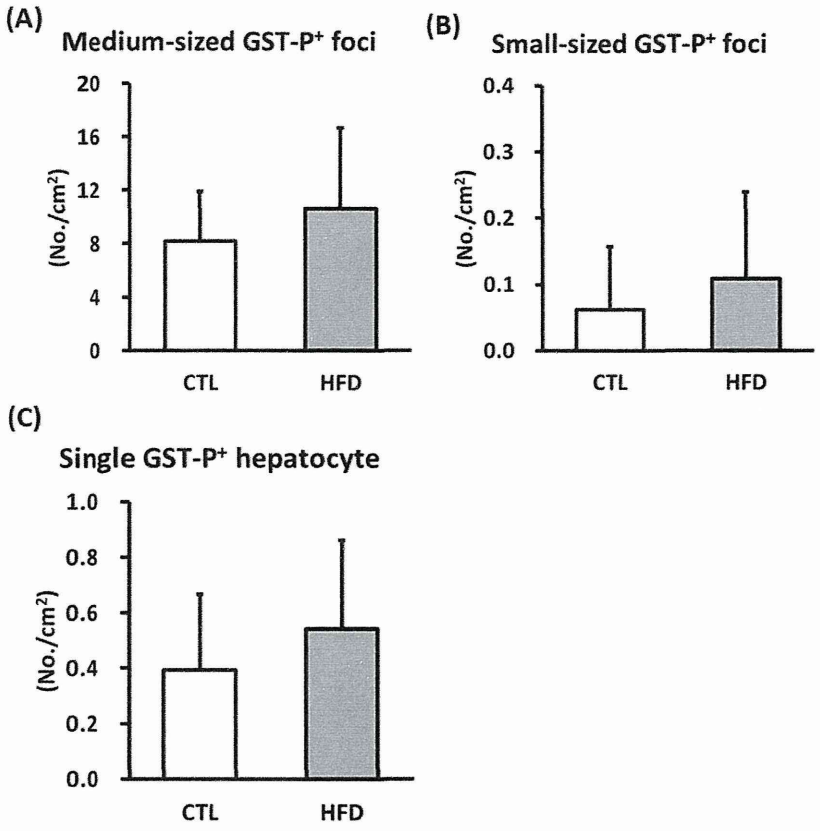


Fig. 32. Quantitative analysis of variable-sized GST-P$^+$ foci and single GST-P+ hepatocyte in the liver of rats fed with basal diet and high fat diet after DEN initiation. The number of medium- (A) or small-sized GST-P$^+$ foci (B) and single GST-P$^+$ hepatocyte (C) in each group are shown. Columns represent mean and standard deviation. CTL, control group; HFD, high fat diet group. *: $p<0.05$ (Student's t test or Aspin-Welch test).

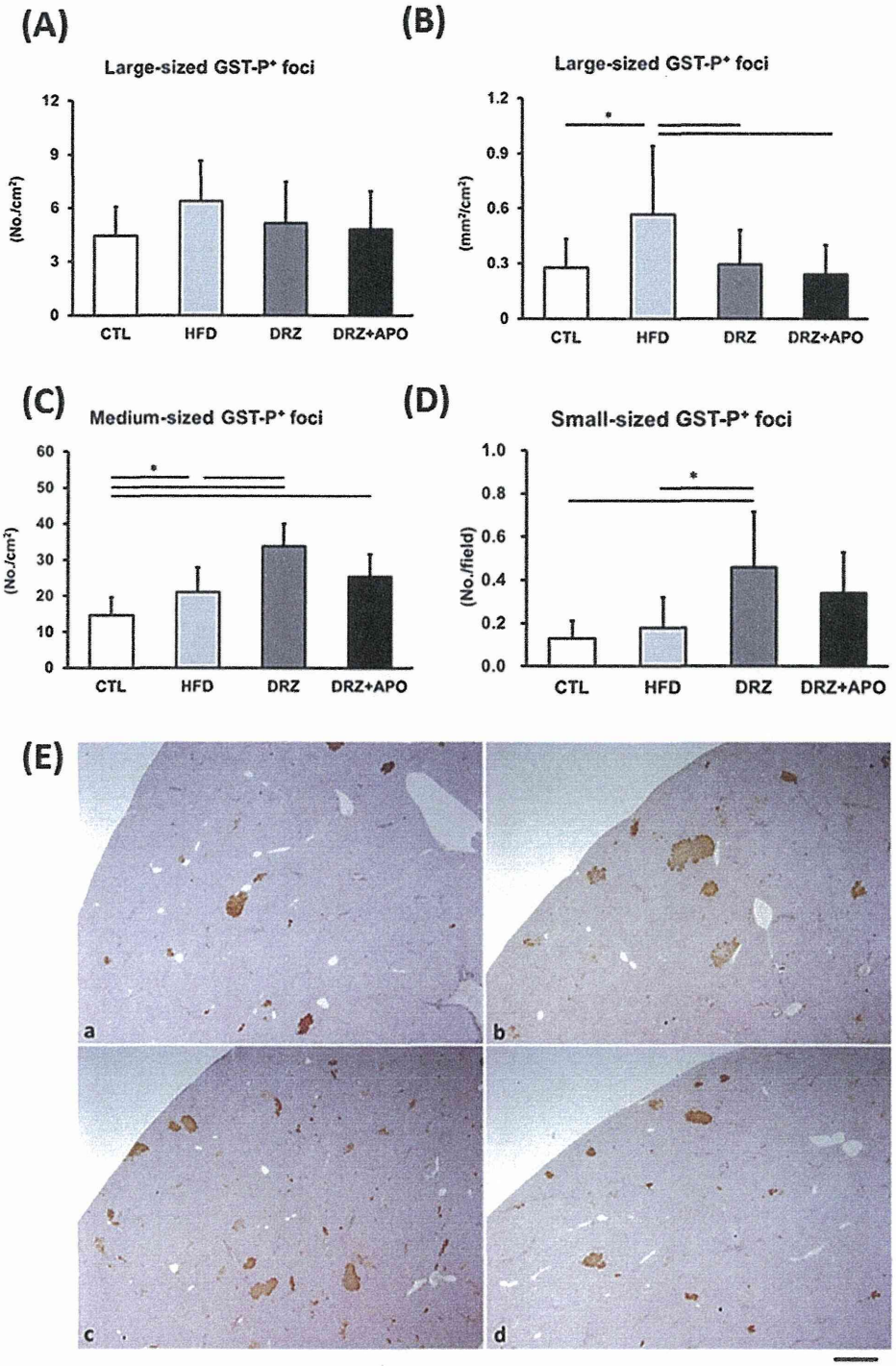


Fig. 33. Quantitative analysis of variable-sized GST-P$^+$ foci in the liver of rats fed basal diet after DEN initiation or fed high fat diet after DEN initiation followed by DRZ treatment with or without co-treatment with APO. (A-D) The number (A) and area (B) of large-sized GST-P$^+$ foci, more than 200 um in diameter, number of medium-sized GST-P$^+$ foci, 50 to 200 um in diameter (C), and small-sized GST-P$^+$ foci, less than 50 um in diameter (D). (E) Representative images of GST-P$^+$ foci in CTL (a) and HFD (b), HFD+DRZ (c), and HFD+DRZ+APO (d) groups. Bar=200 um. Columns represent mean and standard deviation. Abbreviations: CTL, control; HFD, high fat diet; DRZ, dimetridazole; APO, apocynin. *, $p<0.05$ (Tukey's or Steel-Dwass multiple comparison test).

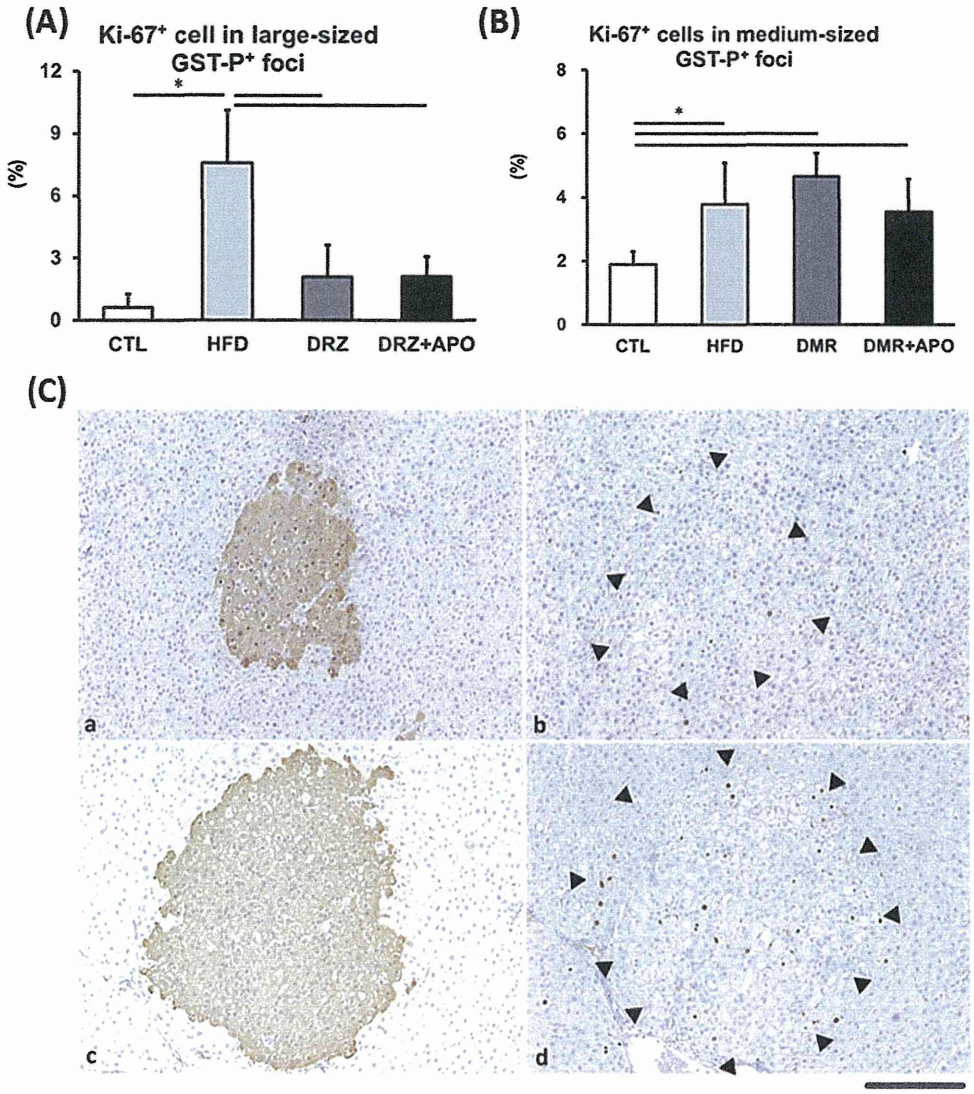


Fig. 34. Quantitative analysis of Ki-67$^+$ cells in GST-P$^+$ foci in the liver of rats after DEN initiation or DEN initiation followed by DMR treatment with or without co-treatment with APO. (A, B) Quantitative data (%) of Ki-67$^+$ cells in large-sized (A) or medium-sized (B) GST-P$^+$ foci. (C) Representative images of large-sized GST-P$^+$ foci (a, c) and Ki-67$^+$ cells (b, d) in CTL (a, b) and HFD (b, d) groups. Bar=200 um. Columns represent mean and standard deviation. Abbreviations: CTL, control; HFD, high fat diet; DRZ, dimetridazole; APO, apocynin. *, $p<0.05$ (Tukey's or Steel-Dwass multiple comparison test).

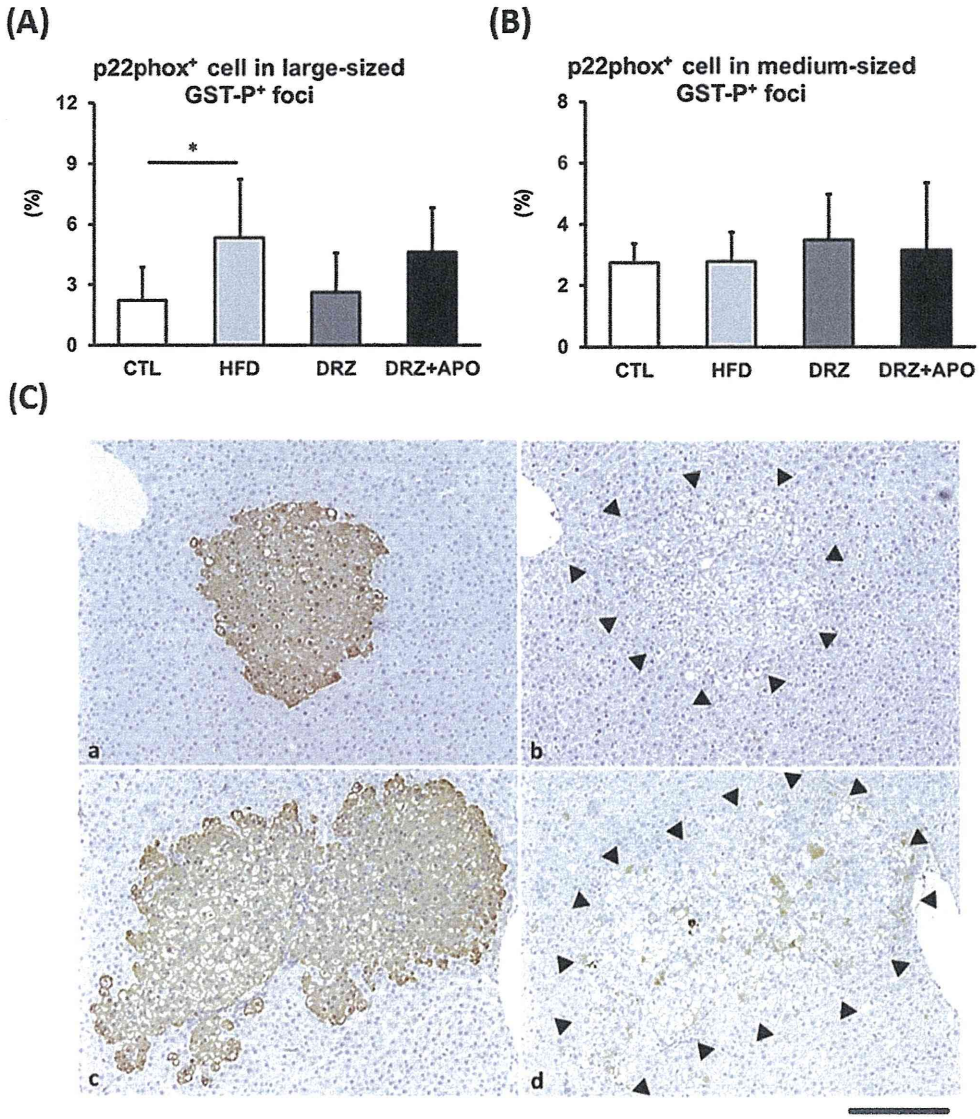


Fig. 35. Quantitative analysis of p22phox$^+$ cells in GST-P$^+$ foci in the liver of rats after DEN initiation or DEN initiation followed by DMR treatment with or without co-treatment with APO. (A, B) Quantitative data (%) of p22phox$^+$ cells in large-sized (A) or medium-sized (B) GST-P$^+$ foci. (C) Representative images of large-sized GST-P$^+$ foci (a, c) and p22phox$^+$ cells (b, d) in CTL (a, b) and HFD (b, d) groups. Bar=200 um. Columns represent mean and standard deviation. Abbreviations: CTL, control; HFD, high fat diet; DRZ, dimetridazole; APO, apocynin. *, $p<0.05$ (Tukey's or Steel-Dwass multiple comparison test).

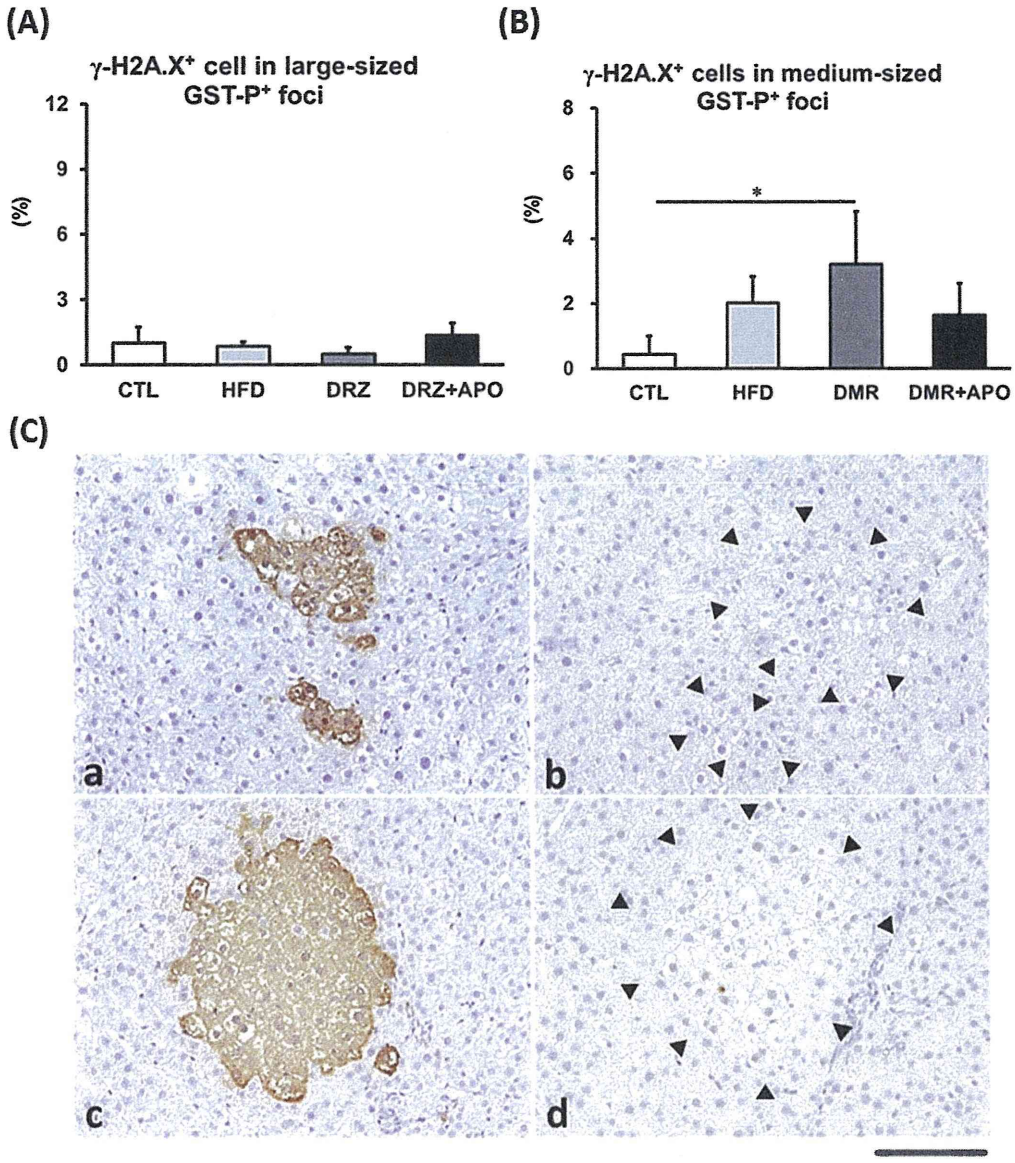


Fig. 36. Quantitative analysis of γ-H2A.X$^+$ cells in GST-P$^+$ foci in the liver of rats after DEN initiation or DEN initiation followed by DMR treatment with or without co-treatment with APO. (A, B) Quantitative data (%) of p22phox$^+$ cells in large-sized (A) or medium-sized (B) GST-P$^+$ foci. (C) Representative images of medium-sized GST-P$^+$ foci (a, c) andγ-H2A.X$^+$ cells (b, d) in CTL (a, b) and HFD (b, d) groups. A small-sized focus is also observed (a, b). Bar=100 um. Columns represent mean and standard deviation. Abbreviations: CTL, control; HFD, high fat diet; DRZ, dimetridazole; APO, apocynin. *, $p<0.05$ (Tukey's or Steel-Dwass multiple comparison test).

Table 1. Antibodies used for immunohistochemistry

Antigen	Abbreviated name	Host species	Clone name	Dilution	Antigen retrieval [a]	Manufacturer (City, State, Country)
Cleaved caspase 3 (Asp175)	—	Rabbit	Polyclonal	1:500	Autoclaving in target retrieval solution	Cell Signaling Technology, Inc. (Danvers, MA, USA)
Glutathione *S*-transferase placental form	GST-P	Rabbit	Polyclonal	1:1000	None	Medical & Biological Laboratries (Nagoya, Japan)
Histone H2AX (phospho Ser139)	γH2AX	Rabbit	Monoclonal (EP854(2)Y)	1:1000	Autoclaving in citrate buffer	Abcam
Ki-67 antigen	Ki-67	Mouse	Monoclonal (MIB-5)	1:200	Autoclaving in citrate buffer	Dako (Glostrup, Denmark)
Mitotic arrest deficient-2	MAD2	Mouse	Monoclonal (48/MAD2)	1:400	Microwaving in citrate buffer	BD Transduction Laboratories (Lexington, KY, USA)
Phosphorylated histone H3 (Ser10)	Phospho-Histone H3	Rabbit	Polyclonal	1:400	Autoclaving in citrate buffer	Santa Cruz Biotechnology, Inc. (Santa Cruz, CA, USA)
Phosphorylated MDM2 (Ser166)	p-MDM2	Rabbit	Polyclonal	1:400	Autoclaving in target retrieval solution	Cell Signaling Technology, Inc. (Danvers, MA, USA)
$p21^{Cip1}$	—	Mouse	Monoclonal (CP74)	1:1000	Microwaving in citrate buffer	Abcam (Cambridge, UK)
Topoisomerase II alpha	TOP2A	Rabbit	Monoclonal (EP1102Y)	1:400	Autoclaving in citrate buffer	Epitomics, Inc. (Burlingame, CA, USA)
Ubiquitin D	UBD	Rabbit	Polyclonal	1:400	Autoclaving in citrate buffer	Proteintech Group, Inc. (Chicago, IL, USA)

Antigen retrieval was applied for immunohistochemistry. Retrieval conditions were either autoclaving at 121°C for 10 min in 10 mM citrate buffer (pH 6.0) or in target retrieval solution (3-in-1; pH 9.0, Dako), or microwaving at 90°C for 10 min in 10 mM citrate buffer (pH 6.0).

Table 2. Sequence of primers used for real-time RT-PCR

Gene	Accession no.	Forward primer (5'→3')	Reverse primer (5'→3')
G_1/S checkpoint-related genes			
Cdkn1a	NM_080782	ACCAGCCACA GGCACCAT	CGGCATACTT TGCTCCTGTG T
Cdkn2a	NM_031550	CAAACGCCCC GAACACTT	CACTTTGACG TTGCCCATCA
Rb1	NM_017045	CACCAGGCCT CCTACCTTGT C	AGGAATCCGC AAGGGTGAAC
Rbl2	NM_031094	AAGTGAATCG CCTGCAAAAA G	CTCGGTCATT AGCTACATCT TGGA
Mdm2	NM_001108099	GAAGGAGGAC ACACAAGACA AAGA	ATGGCTCGAT GGCGTTCA
Tp53	NM_030989	CATGAGCGTT GCTCTGATGG T	GATTTCCTTC CACCCGGATA A
Spindle checkpoint and M phase-related genes			
Aurka	NM_153296	AAGAGAGTCA TCCACAGAGA CATCAA	CGATCTTCAA CTCCCCATTT G
Aurkb	NM_053749	CGGATGCATA ATGAGATGGT AGAT	TCCCCACCAT CAGTTCATAG C
Bub1	NM_001106507	CCCTAGCTCC CAGTCCTAAA AGT	TTGTGGAATG GTGTAGATGA AAGC
Mad1l1	NM_001109387	TCCAGGAGTT CCGCAAGGT	GAGGCGGTAT TGGCTCTCAG T
Mad2l1	NM_001106594	ACAGCCACTG TGACATTTCT ACCA	CCCGATTCTT CCCACTTTTC A
Plk1	NM_017100	TCCCACCAAG GTTTTCAATA GC	TGTGAGAGGC TTCCTGTTGC T
DNA damage-related genes			
Atm	NM_001106821	AGGCTGTCGG CAGGTGTTT	TGGTGTACGG CGTATCTTTG C
Brca1	AF036760	TGATGTGGGA CTGGGTGTTG	CTGTACCAGG TAGGCATCCA GAT
Brca2	NM_031542	AGGCTTTCGG TTGGCAGAT	AGAGACCCAG ACGCTAGAAA TCA
Brcc3	NM_001127300	CCACATCCAC TCGGTCATCA T	AAATCTCCAC GCGGTCCTT
Chek1	NM_080400	TGGCAGCTGG CAAAGGA	AATCCCAGTC TTCCACAAAA GG
Chek2	NM_053677	TTGCTTCGAT GGACCACTGT T	GATGCGAAAG TGCTTCTTGC T
Esco1	NM_001126299	CCAAATCCCA CTGCCGTTA	GCTGCCTCTT TTGCTCTTTC C
Gadd45a	NM_024127	CACCATAACT GTCGGCGTGT A	GGCACAGGAC CACGTTGTC
Rad17	NM_001024778	GACTGGGTAG ATCCGGCATT T	AAACGGTGAT GGTGGTGACA
Rad50	NM_022246	TGGCCCCTGG CAGTGA	AACTTCGCAC GCCCAGAGT
Housekeeping gene			
Hprt1	NM_012583	GCCGACCGGT TCTGTCAT	TCATAACCTG GTTCATCATC ACTAATC
Actb	NM_031144	CCCTGGCTCCTAGCACCAT	AGAGCCACCAATCCACACAGA
Gapdh	NM_017008	GGCCGAGGGC CCACTA	TGTTGAAGTC ACAGGAGACA ACCT

Abbreviations: *Actb*, actin, beta; *Atm*, ATM serine/threonine kinase; *Aurka*, aurora kinase A; *Aurkb*, aurora kinase B; *Brca1*, breast cancer 1, early onset; *Brca2*, breast cancer 2, early onset; *Brcc3*, BRCA1/BRCA2-containing complex, subunit 3; *Bub1*, BUB1 mitotic checkpoint serine/threonine kinase; *Cdkn1a*, cyclin-dependent kinase inhibitor 1A; *Cdkn2a*, cyclin-dependent kinase inhibitor 2A; *Chek1*, checkpoint kinase 1; *Chek2*, checkpoint kinase 2; *Esco1*, establishment of sister chromatid cohesion N-acetyltransferase 1; *Gadd45a*, growth arrest and DNA-damage-inducible, alpha; *Gapdh*, glyceraldehyde 3-phosphate dehydrogenase; *Hprt1*, hypoxanthine phosphoribosyltransferase 1; *Mad1l1*, MAD1 mitotic arrest deficient-like 1 (yeast); *Mad2l1*, MAD2 mitotic arrest deficient-like 1 (yeast); *Mdm2*, MDM2 proto-oncogene, E3 ubiquitin protein ligase; *Plk1*, polo-like kinase 1; *Rad17*, RAD17 homolog (S. pombe); *Rad50*, RAD50 homolog (S. cerevisiae); *Rb1*, retinoblastoma 1; *Rbl2*, retinoblastoma-like 2; RT-PCR, reverse transcription polymerase chain reaction; *Tp53*, tumor protein p53.

Table 3. Antibodies for immunohistochemistry

Antigen	Host species	Clonality (Clone)	Dilution	Antigen retrieval	Manufacture
GST-P	Rabbit	Polyclonal	1:1000	none	Medical & Biological Laboratories (Nagoya, Japan)
Ki-67	Mouse	Monoclonal (MIB-5)	1:50	Autoclaving at 121°C for 10 min in citrate buffer, pH6.0	Dako (Glostrup, Denmark)
p22phox	Rabbit	Polyclonal	1:200	Autoclaving at 121°C for 10 min in antigen retrieval solution (Dako), pH9.0	Bioss Inc. (Woburn, MA, USA)
p47phox	Rabbit	Polyclonal	1:1000	none	Bioworld Technology, Inc.(MN, USA)
p67phox	Rabbit	Polyclonal	1:200	Autoclaving at 121°C for 10 min in antigen retrieval solution (Dako), pH9.0	Merck KGaA.(darmstadt, Germany)
NOX4	Rabbit	Polyclonal	1:1000	none	Bioworld Technology, Inc.
Histone H2AX (phospho S139)	Rabbit	Monoclonal (EP854(2)Y)	1:3000	Autoclaving at 121°C for 10 min in citrate buffer, pH6.0	Abcam (Cambridge, UK)

Table 4. Sequence of primers used for real-time RT-PCR

Accession no.	Gene	Forward primer (5' →3')	Reverse primer (5' →3')
NM_012540.2	Cyp1a1	GCCTTCACATCAGCCACAGA	TTGTGACTCTAACCACCCAGAATC
NM_001134844.1	*Cyp2b1/2*	GGGACACTGAAAAAGAGTGAAGCT	AATGCCTTCGCCAAGACAAAT
NM_017000.3	*Nqo1*	GCTCTATCGTGCTCGCATGA	TCTTCTGTCACCCTGTGCTTGA
NM_183403.2	*Gpx2*	GTGTGATGTCAATGGGCAGAAT	AGGGCAGCTTGTCTTTCAGGTA
NM_023965.1	*Cybb*	AAGAAGAAGGGATTCAGGATGGA	ACACTGCGGGACGCTTGA
NM_134366.1	*Rac1*	TCTCCTACCCGCAAACAGAC	CGGGTAGGTAATGGGAGTCA
NM 001100984	*P67phox*	GAAAGCATGAAGGATGCCTGG	ATAGCACCAAGATCACATCTCC
NM 024160	*P22phox*	TGTTGCAGGAGTGCTCATCTGTCT	AGGACAGCCCGGACGTAGTAATTT
NM 001105816	*Poldip2*	GCTGCTGGCTCTGCTAAGGT	AACTACTGCCCCCAGGAGATG
NM 013196	*Ppara*	CCCCACTTGAAGCAGATGACC	CCCTAAGTACTGGTAGTCCGC
NM 001145366	*Pparg*	GACCACTCCCATTCCTTTGA	CATTGGGTCAGCTTGTGA
NM 017340	*Aox1*	GCGCAAGGAGCGGGCCTCC	CTCGACGGCGCCGGGTATTC
NM 001007144	*Plin2*	CCGAGCGTGGTGACGAGGG	GAGGTCACGGTCCTCACTCCC
NM 012589	*Il10*	GAGGATACCACTCCCAACAGACC	AAGTGCATCATCGTTGTTCATAC
NM 001108509	*Pnpla2*	CGGTGGATGAAGGAGCAGACA	TGGCACAGACGGCAGAGACT
NM 001183664	*Dga1*	CACGAATCATTGAGCGTCTCTTA	GCCAATAGAAGAAGATGAGCCATATC
NM 175837	*Cyp4a1*	CGGGCGATCAGATCCAAA	GAGCAAACCATATCCGATCCA
NM 017332	*Fasn*	GCGGGCGTGGTAATGCT	CTGTTCGCAAATACGCTCCAT
NM 139192	*Scd1*	CACACGCCGACCCTCACAACT	TCCGCCCTTCTCTTTGACAGCC
NM 001134637	*Plin5*	GGATGTCCGGTGATCAGAC	GTGCACGTGGCCCTGACCAG
NM 012520	*Catalase*	ATTGCCGTCCGATTCTCC	CCAGTTACCATCTTCAGTGTAG
NM 017051	*Mn-SOD*	GACCTGCCTTACGACTATG	TACTTCTCCTCGGTGACG
NM 030826	*Gpx1*	GCTGCTCATTGAGAATGTCG	GAATCTCTTCATTCTTGCCATT
NM 012675	*Tnf-alpha*	ATACACTGGCCCGAGGCAAC	CCACATCTCGGATCATGCTTTC
NM 012541	*Cyp1a2*	AAGCGCCGGTTGCATTG	TGCAGGAGGATGGCTAAGAAG
NM 031543	*Cyp2e1*	TGACTTTGGCCGACCTGTTC	TGAGGATCAGGAGCCCATATCT
NM_012583	*Hprt*	GTCAAGCAGTACAGCCCCAAA	CAACACTTCGAGAGGTCCTTTTC
NM_031144.3	*Actb*	CCCTGGCTCCTAGCACCAT	AGAGCCACCAATCCACACAGA

Abbreviations:

Cyp1a1, cytochrome P450, family 1, subfamily a, polypeptide 1; Cyp2b1/2, cytochrome P450, family 2, subfamily b, polypeptide 1/2; Nqo1, NAD(P)H dehydrogenase, quinone 1; Gpx2, glutathione peroxidase 2; Cybb, cytochrome b-245, beta polypeptide; Rac1, ras-related C3 botulinum toxin substrate 1; Poldip2, Polymerase (DNA-directed), delta interacting protein 2; Ppara, Peroxisome proliferator activated receptor alpha; Pparg, peroxisome proliferator activated receptor alpha; Aox1, Alternative oxidase1; Plin2, Perilipin2; Il10, Interleukin-10; Pnpla2, Patatin-Like Phospholipase Domain Containing 2; Dga1, diacylglycerol O-acyltransferase; Cyp4a1, Cytochrome P450, family 4, subfamily a, polypeptide 1; Fasn, Fatty acid synthase; Scd1, Stearoyl-Coenzyme A desaturase 1; Plin5, Perilipin 5; Mn-SOD, Manganese superoxide dismutase; Gpx1, Glutathione peroxidase 1 ; Tnf-alpha, tumor necrosis factor alpha; Cyp1a2, Cytochrome P450, family 1, subfamily a, polypeptide 2; Cyp2e1, Cytochrome P450, family 2, subfamily e, polypeptide 1; Hprt, Hypoxanthine phosphoribosyltransferase; Actb, actin, beta.

Table 5. Initial and final body weights and liver weight of rats after partial hepatectomy, or after treatment with hepatocarcinogens or hepatotoxicants

Group	Number of animals	Initial body weight (g)	Final body weight (g)	Liver weight	
				Absolute (g)	Relative (g/100g BW)
Day 3 (Experiment 1)					
CONT	10	123.8±3.8[a]	147.7±5.1	6.40±0.31	4.33±0.13
PH	11	121.3±4.4	124.5±4.9**	3.91±0.38**	3.14±0.22
MEG	11	121.8±4.7	129.0±5.4**	6.92±0.36*	5.37±0.24**
TAA	10	123.0±6.7	134.3±4.9**	6.39±0.36	4.76±0.18**
APAP	10	122.2±2.7	142.1±4.5	6.94±0.54*	4.88±0.25**
ANIT	10	122.4±3.0	125.8±4.0**	6.28±0.43	4.99±0.27**
PMZ	11	121.2±4.4	118.3±9.0**	6.03±0.44	5.11±0.38**
Day 7 (Experiment 1)					
CONT	10	124.2±9.9	167.4±13.9	6.95±0.71	4.15±0.14
PH	10	121.1±10.4	141.8±9.0**	5.19±0.65**	3.66±0.34
MEG	11	122.7±10.0	139.4±5.8**	7.21±0.42	5.17±0.30**
TAA	10	122.7±7.4	141.5±8.0**	7.21±0.38	5.10±0.19**
APAP	10	123.3±8.4	150.4±12.0**	6.82±0.88	4.52±0.29*
ANIT	10	123.1±8.2	121.7±5.4*	5.71±0.36**	4.70±0.23**
PMZ	11	121.0±9.4	136.2±7.1**	7.22±0.42	5.30±0.29**
Day 28 (Experiment 2)					
CONT	10	128.0±7.8	250.8±10.5	10.20±0.48	4.07±0.14
PH	12	128.1±5.3	240.5±10.2	9.40±0.52*	3.91±0.07
MEG	10	128.3±5.8	186.0±16.3**	10.54±1.20	5.65±0.22**
TAA	10	126.9±7.3	152.4±10.4**	7.71±0.79**	5.05±0.30**
APAP	10	127.4±5.9	218.6±8.6**	9.48±0.62	4.33±0.13**
ANIT	11	126.3±7.2	162.8±11.3**	8.79±0.64**	5.40±0.16**
PMZ	11	126.7±6.8	212.4±13.2**	11.39±0.90**	5.36±0.20**

Abbreviations: ANIT, α-naphthyl isothiocyanate; APAP, acetaminophen; CONT, untreated control; MEG, methyleugenol; PH, partial hepatectomy; PMZ, promethazine; TAA, thioacetamide.

[a] Values are expressed as mean ± SD.

* $P < 0.05$, ** $P < 0.01$ vs. untreated controls (Dunnett's or Steel's test).

Table 6. Relative transcript levels in the liver of rats treated with MEG, TAA or PMZ for up to 28 days

Gene	Day 3			Day 7			Day 28		
	MEG[a]	TAA[a]	PMZ[a]	MEG[a]	TAA[a]	PMZ[a]	MEG[a]	TAA[a]	PMZ[a]
G_1/S checkpoint-related genes									
Cdkn1a	2.13±0.59[b,**]	2.61±0.38**	0.41±0.13**	2.14±0.43**	2.21±0.26**	0.30±0.07**	2.67±0.40**	2.99±0.62**	0.28±0.08**
Cdkn2a	0.32±0.18*	0.47±0.31*	0.43±0.29*	0.57±0.46*	0.70±0.28	0.47±0.37*	1.58±0.49	2.52±0.19**	0.73±0.15
Rb1	0.54±0.33*	0.52±0.10**	0.30±0.09**	0.49±0.09**	0.52±0.07**	0.55±0.04**	0.79±0.05	0.40±0.06**	0.57±0.15**
Rbl2	0.55±0.28*	0.33±0.06**	0.65±0.32	0.42±0.07**	0.30±0.04**	0.70±0.15*	0.55±0.06**	0.33±0.04**	0.82±0.14
Mdm2	2.86±1.65	3.36±0.64**	0.86±0.35	4.55±0.76**	3.75±0.67**	0.85±0.14	3.74±1.13**	3.20±0.36**	0.90±0.14
Tp53	0.73±0.34*	1.51±0.19**	0.49±0.10**	0.64±0.11**	1.41±0.18**	0.67±0.12**	0.96±0.08	1.63±0.27**	0.99±0.11
Spindle checkpoint and M phase-related genes									
Aurka	0.22±0.12**	1.27±0.38	0.13±0.04**	0.36±0.07**	0.87±0.18	0.80±0.36	1.34±0.32	1.96±0.26**	1.03±0.31
Aurkb	0.34±0.31*	0.42±0.34*	0.02±0.01**	0.21±0.07**	0.30±0.07**	0.58±0.45	2.61±0.82**	1.87±0.36*	1.12±0.36
Bub1	0.17±0.10**	0.79±0.31	0.08±0.02**	0.23±0.08**	0.38±0.09**	0.75±0.42	2.16±0.52**	1.50±0.15	1.22±0.36
Madl1l	0.73±0.32	0.56±0.10**	0.72±0.27	0.60±0.06**	0.49±0.07**	0.80±0.14**	0.93±0.29	0.52±0.07**	0.87±0.11
Mad2l1	0.75±0.57	0.69±0.47	0.16±0.05**	0.43±0.07**	0.95±0.17	0.66±0.32	2.18±0.64**	2.68±0.43**	1.25±0.34
Plk1	0.13±0.09**	0.94±0.34	0.02±0.01**	0.21±0.09**	0.36±0.11**	0.85±0.56	2.24±0.83**	1.92±0.37**	1.21±0.35
DNA damage-related genes									
Atm	0.79±0.32	0.92±0.18	0.67±0.22*	0.71±0.07	0.78±0.09	0.94±0.11	0.76±0.10*	0.95±0.08	0.88±0.11
Brca1	0.27±0.15**	0.76±0.25*	0.25±0.12**	0.24±0.03**	0.47±0.08**	0.68±0.26	1.18±0.31	0.97±0.07	0.87±0.14
Brca2	0.48±0.26*	1.19±0.39	0.26±0.09**	0.54±0.12**	1.03±0.25	0.91±0.37	0.73±0.06	0.72±0.06	0.86±0.13
Brcc3	0.78±0.41	0.76±0.10**	0.70±0.25*	0.62±0.09**	0.67±0.09**	0.57±0.12**	1.87±0.37*	3.17±0.86**	1.37±0.40
Chek1	0.73±0.42	0.81±0.41	0.30±0.11**	0.61±0.08**	1.06±0.22	0.93±0.15	1.98±0.48**	1.94±0.27**	1.24±0.28
Chek2	0.45±0.22**	1.28±0.36	0.36±0.16**	0.46±0.03**	1.27±0.26	0.84±0.17	0.84±0.29	1.29±0.11	0.70±0.13
Esco1	0.70±0.35*	1.53±0.25**	0.57±0.15**	0.51±0.05**	1.74±0.21**	0.72±0.18**	0.61±0.12**	1.51±0.15**	0.59±0.09**
Gadd45a	1.88±1.31	3.18±0.61**	1.97±0.11**	1.10±0.25	2.35±0.46**	0.47±0.14**	1.83±0.56	3.07±0.50**	1.18±0.63
Rad17	0.89±0.45	1.94±0.29**	0.79±0.17	0.69±0.12**	2.20±0.23**	0.65±0.17**	0.88±0.07	2.15±0.17**	0.74±0.09**
Rad50	0.94±0.50	1.18±0.26	0.62±0.22	0.71±0.15**	1.00±0.13	0.80±0.22	0.85±0.08	1.27±0.14**	0.95±0.10

Abbreviations: *Atm*, ATM serine/threonine kinase; *Aurka*, aurora kinase A; *Aurkb*, aurora kinase B; *Brca1*, breast cancer 1, early onset; *Brca2*, breast cancer 2, early onset; *Brcc3*, BRCA1/BRCA2-containing complex, subunit 3; *Bub1*, BUB1 mitotic checkpoint serine/threonine kinase; *Cdkn1a*, cyclin-dependent kinase inhibitor 1A; *Cdkn2a*, cyclin-dependent kinase inhibitor 2A; *Chek1*, checkpoint kinase 1; *Chek2*, checkpoint kinase 2; *Esco1*, establishment of sister chromatid cohesion N-acetyltransferase 1; *Gadd45a*, growth arrest and DNA-damage-inducible, alpha; *Hprt1*, hypoxanthine phosphoribosyltransferase 1; *Madl1l*, MAD1 mitotic arrest deficient-like 1 (yeast); *Mad2l1*, MAD2 mitotic arrest deficient-like 1 (yeast); *Mdm2*, MDM2 proto-oncogene, E3 ubiquitin protein ligase; MEG, methyleugenol; *Plk1*, polo-like kinase 1; PMZ, promethazine; *Rad17*, RAD17 homolog (S. pombe); *Rad50*, RAD50 homolog (S. cerevisiae); *Rb1*, retinoblastoma 1; *Rbl2*, retinoblastoma-like 2; TAA, thioacetamide; *Tp53*, tumor protein p53.

[a] n = 6.

[b] Values represent relative expression levels expressed as mean ± SD.

* $P < 0.05$, ** $P < 0.01$ vs. untreated controls (Dunnett's or Steel's test).

Table 7. Initial and final body weight and liver weight of rats after treatment with hepatocarcinogens, hepatocarcinogenic promoters or non-carcinogenic hepatotoxicants

Group	Number of animals	Initial body weight (g)	Final body weight (g)	Liver weight	
				Absolute (g)	Relative (g/100g BW)
Day 7					
CONT	10	119.1±4.7	161.9±6.8	7.26±0.35	4.49±0.10
MP	10	118.9±4.1	150.4±5.0**	7.39±0.43	4.91±0.14**
CRB	10	118.9±4.5	152.1±4.9**	7.17±0.34	4.72±0.20*
LMG	10	119.0±4.7	149.7±3.7**	8.76±0.35**	5.85±0.22**
BNF	10	117.4±2.9	154.6±6.9**	8.05±0.41**	5.21±0.28**
OX	10	120.1±4.2	162.8±4.6	8.71±0.40**	5.35±0.23**
PMZ	11	117.1±3.0	134.3±5.2**	6.89±0.41	5.13±0.25**
Day 28					
CONT	10	119.9±9.4	252.6±13.2	10.47±0.82	4.15±0.26
MP	10	119.4±8.6	176.2±9.1**	7.54±0.49**	4.28±0.20
CRB	10	120.4±7.3	230.7±10.6**	10.07±0.63	4.36±0.14**
LMG	10	119.1±7.9	216.4±9.0**	12.00±0.66**	5.55±0.25**
BNF	10	117.4±8.2	230.3±10.0**	11.37±0.76**	4.94±0.19**
OX	10	118.7±6.9	238.8±8.0**	12.41±0.71**	5.20±0.17**
PMZ	11	117.4±6.6	192.5±8.8**	10.16±0.54	5.28±0.18**
Day 90					
CONT	10	134.5±8.5	351.8±30.6	11.04±1.37	3.13±0.13
MP	10	134.3±8.0	236.2±18.2**	7.95±0.85**	3.36±0.14*
TAA	10	133.5±7.5	223.9±8.8**	11.18±0.81	4.99±0.23**
CRB	10	131.7±6.4	302.1±13.7**	11.43±0.50	3.79±0.16**
LMG	10	132.2±6.3	293.1±12.0**	13.04±0.70**	4.45±0.19**
BNF	10	133.6±7.0	324.7±8.9*	13.08±0.72**	4.03±0.14**
OX	10	132.4±6.7	348.9±14.0	14.84±0.96**	4.26±0.26**
APAP	10	131.2±6.4	327.1±12.6*	12.01±0.76*	3.67±0.18**
PMZ	11	131.6±6.9	277.8±8.6**	13.75±0.53**	4.95±0.22**

Abbreviations: APAP, acetaminophen; BNF, β-naphthoflavone; CONT, untreated controls; CRB, carbadox; LMG, leucomalachite green; MP, methapyrilene; OX, oxfendazole; PMZ, promethazine; TAA, thioacetamide.
Values are expressed as mean ± SD.
* $P < 0.05$, ** $P < 0.01$ vs. untreated controls (Dunnett's or Steel's test).

Table 8. Relative transcript levels in the liver of rats treated with MP, CRB, OX or PMZ at day 28 and day 90

Gene	Relative transcript level normalized to *Hprt1*				Relative transcript level normalized to *Actb*			
	MP[a]	CRB[a]	OX[a]	PMZ[a]	MP[a]	CRB[a]	OX[a]	PMZ[a]
Day 28								
Cdkn1a	0.77±0.13	1.88±0.36**	1.02±0.23	0.25±0.09**	1.05±0.13	2.23±0.55**	1.36±0.42	0.29±0.04**
Chek1	1.57±0.36*	0.81±0.28	1.34±0.23	1.51±0.05*	2.17±0.51**	0.95±0.34	1.73±0.20**	2.11±0.38**
Mad2l1	1.93±0.49**	0.82±0.13	0.79±0.16*	1.18±0.11*	2.64±0.63**	0.95±0.10	1.03±0.19	1.70±0.38**
Mdm2	1.80±0.27**	1.89±0.31**	1.39±0.18**	1.03±0.10	2.49±0.36**	2.22±0.44**	1.82±0.33**	1.26±0.31
Rbl2	0.45±0.13**	1.06±0.18	0.97±0.17	0.88±0.32	0.62±0.20**	1.24±0.20*	1.27±0.28	1.01±0.14
Tp53	1.38±0.25*	1.04±0.16	1.17±0.20	1.21±0.27	1.89±0.24**	1.24±0.28	1.53±0.33**	1.52±0.71
Day 90								
Cdkn1a	0.93±0.21	2.58±0.85**	0.76±0.27	0.20±0.05**	1.00±0.43	2.60±1.03**	0.81±0.32	0.23±0.03**
Chek1	2.05±0.25**	0.94±0.24	0.71±0.09*	1.10±0.20	2.13±0.46*	0.94±0.28	0.74±0.08	1.25±0.22
Mad2l1	3.03±0.38**	0.99±0.14	1.03±0.22	0.96±0.26	3.20±0.87**	1.00±0.23	1.07±0.19	1.07±0.14
Mdm2	1.69±0.37**	1.99±0.76*	1.18±0.13	1.03±0.22	1.70±0.18**	2.07±1.00	1.23±0.21	1.19±0.34
Rbl2	0.70±0.16**	0.92±0.07	1.04±0.11	0.82±0.15*	0.71±0.13**	0.92±0.12	1.08±0.12	0.93±0.13
Tp53	1.49±0.23**	0.93±0.25	0.76±0.14*	1.03±0.13	1.55±0.42	0.91±0.12	0.79±0.11	1.19±0. 30

Abbreviations: *Actb*, actin, beta; *Cdkn1a*, cyclin-dependent kinase inhibitor 1A; *Chek1*, checkpoint kinase 1; CRB, carbadox; *Hprt1*, hypoxanthine phosphoribosyltransferase 1; *Mad2l1*, MAD2 mitotic arrest deficient-like 1 (yeast); *Mdm2*, MDM2 proto-oncogene, E3 ubiquitin protein ligase; MP, methapyrilene; OX, oxfendazole; PMZ, promethazine; *Rbl2*, retinoblastoma-like 2; *Tp53*, tumor protein p53.

[a] n = 6.

Values represent relative expression levels expressed as mean ± SD.

* $P < 0.05$, ** $P < 0.01$ vs. untreated controls (Dunnett's or Steel's test).