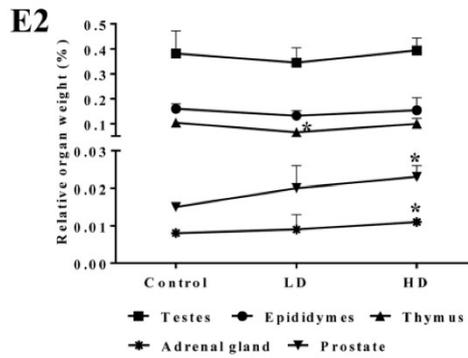
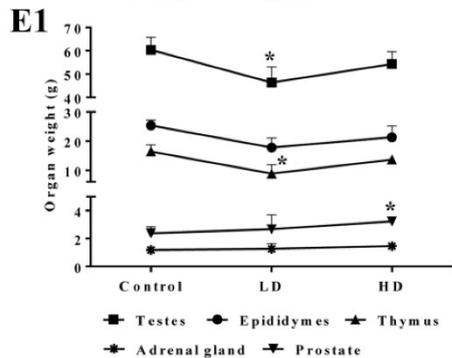
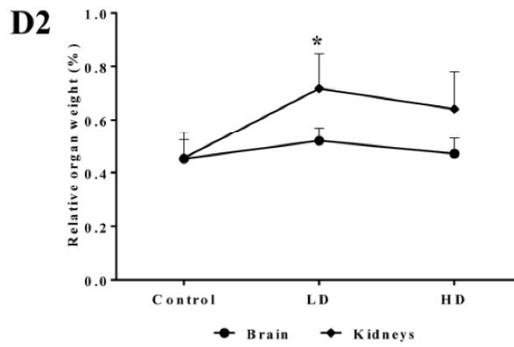
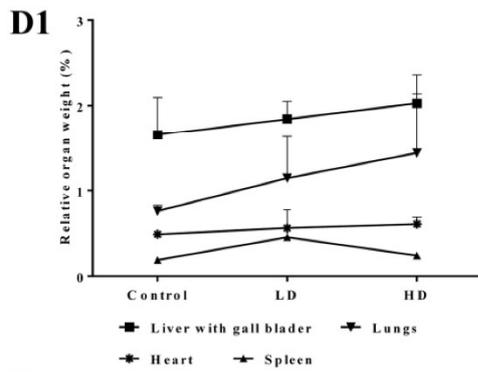
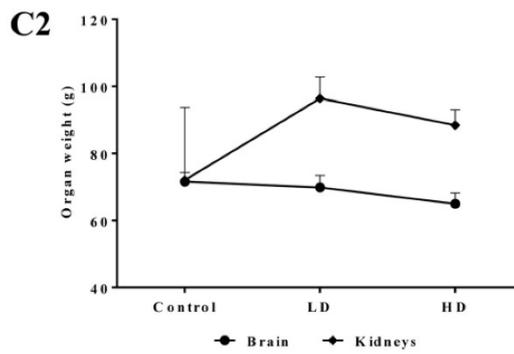
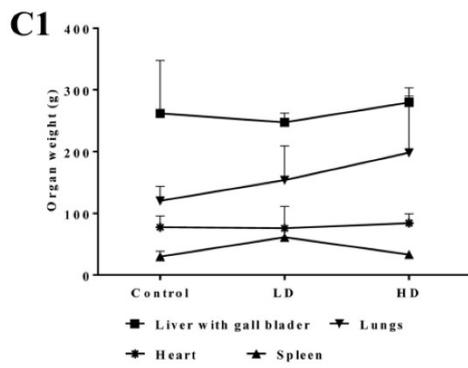
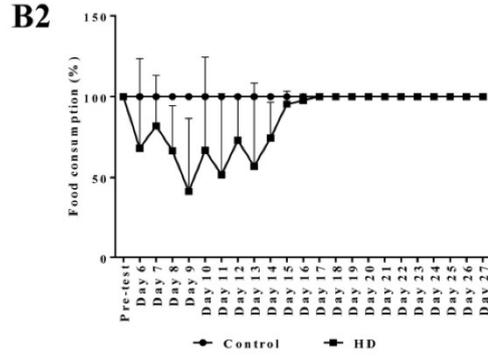
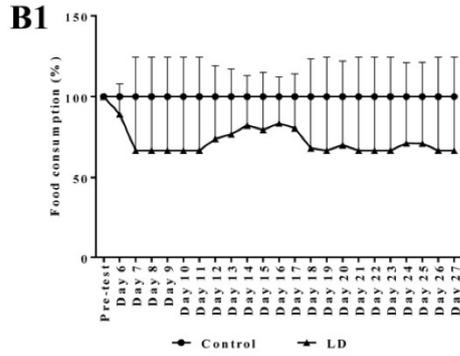
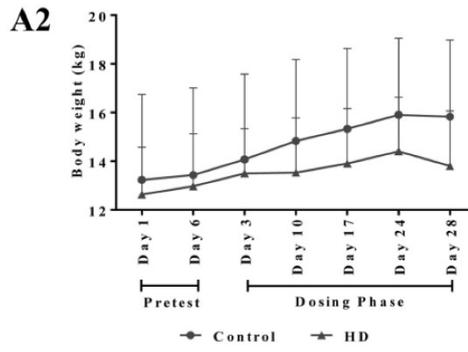
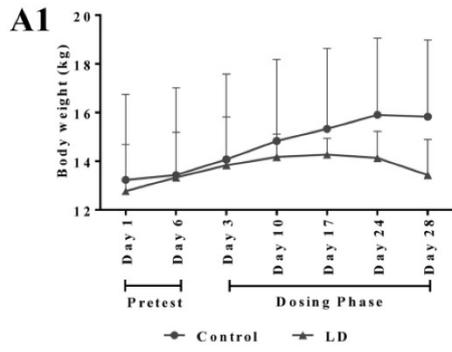
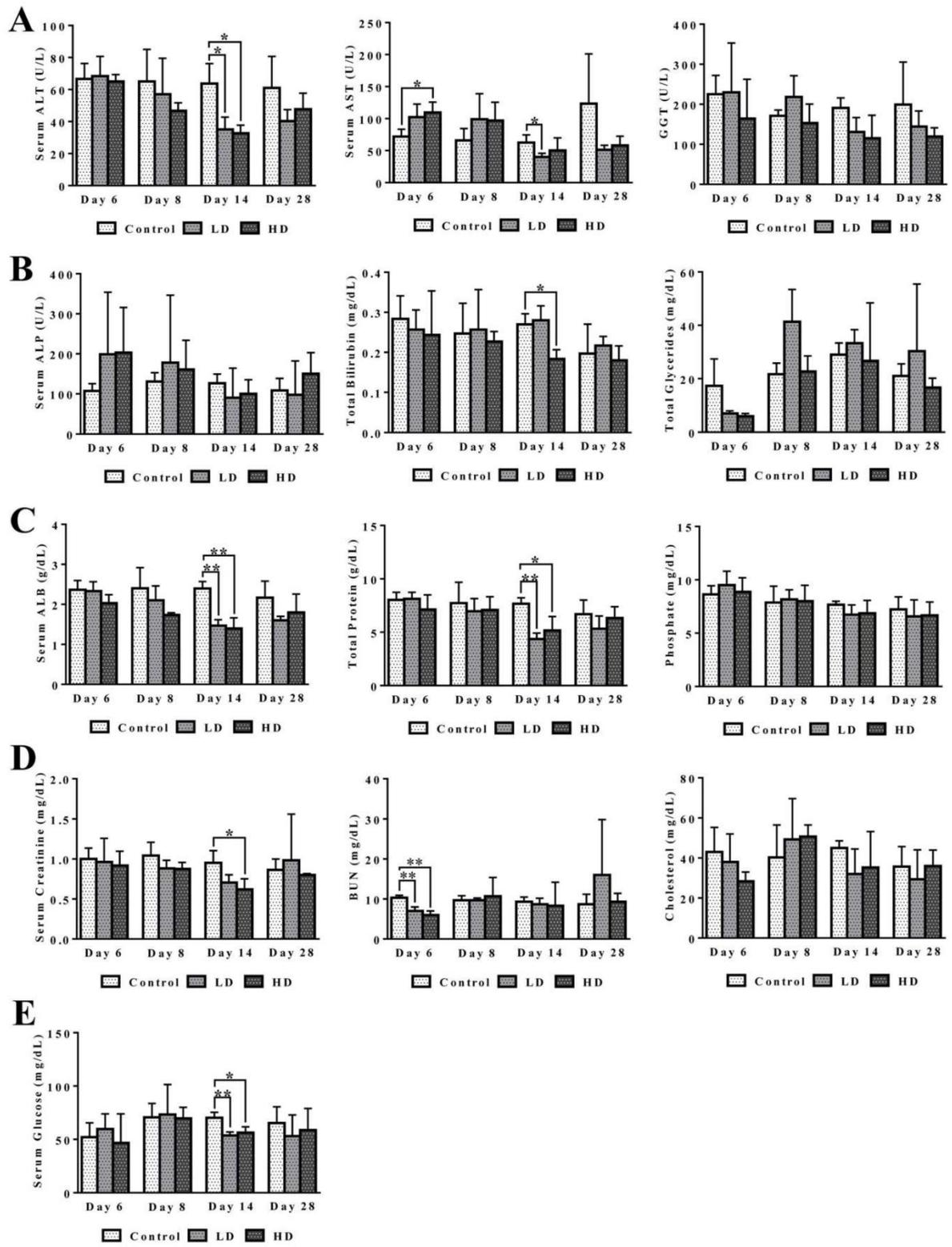


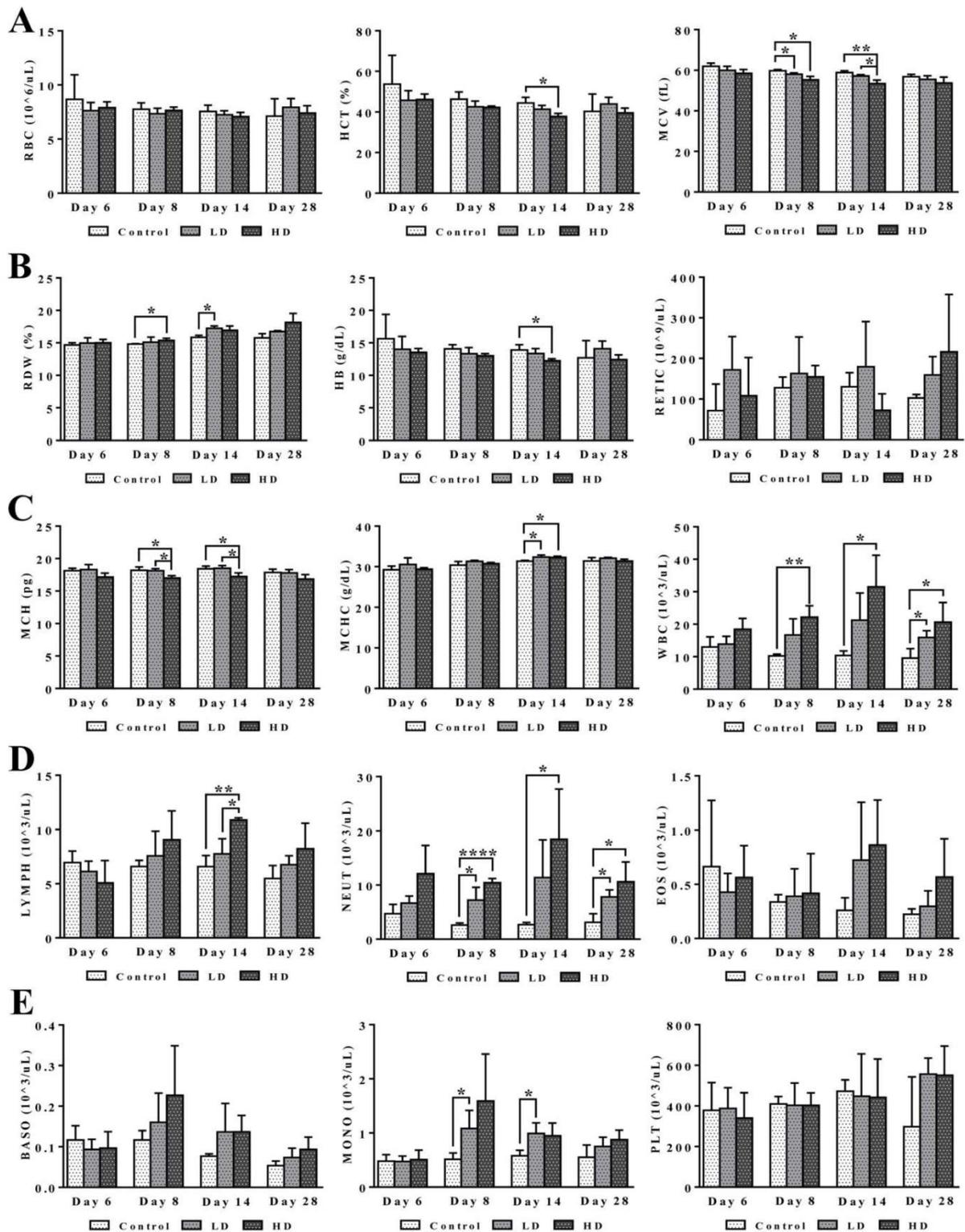
SUPPLEMENTARY MATERIALS



Supplementary Figure S1: Body weight and food consumption after repeated diclofenac treatment for 28 days. Panel A: Body weight at low-dose (A1) and high-dose treatment (A2). **Panel B:** Food consumption at low-dose (B1) and high-dose treatment (B2). **Panel C and D:** Selective organ weights. **Panel E1:** Organ weights. **Panel E2:** Body weight adjusted organ weights. LD = low-dose, HD = high-dose, * $p < 0.05$.

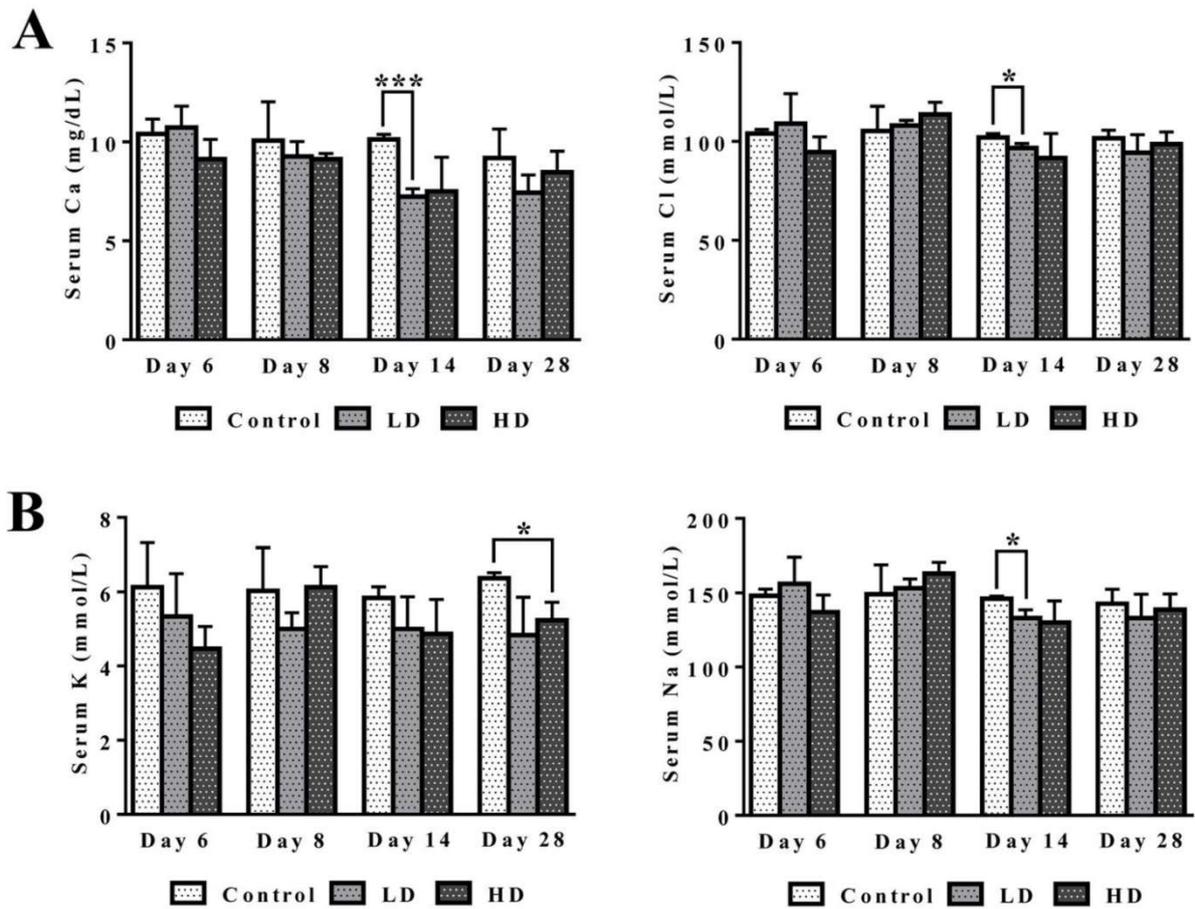


Supplementary Figure S2: Time resolved serum biochemistries after repeated diclofenac treatment for 28 days. Panel A1-A3: ALT, AST and γ GT. Panel B1-B3: ALP, TBIL, TG. Panel C1-C3: ALB, total protein and phosphate. Panel D1-D3: CREA, BUN and cholesterol. Panel E: Serum glucose. LD = low-dose, HD = high-dose, $p < 0.05$, $p < 0.01$, $***p < 0.001$.**

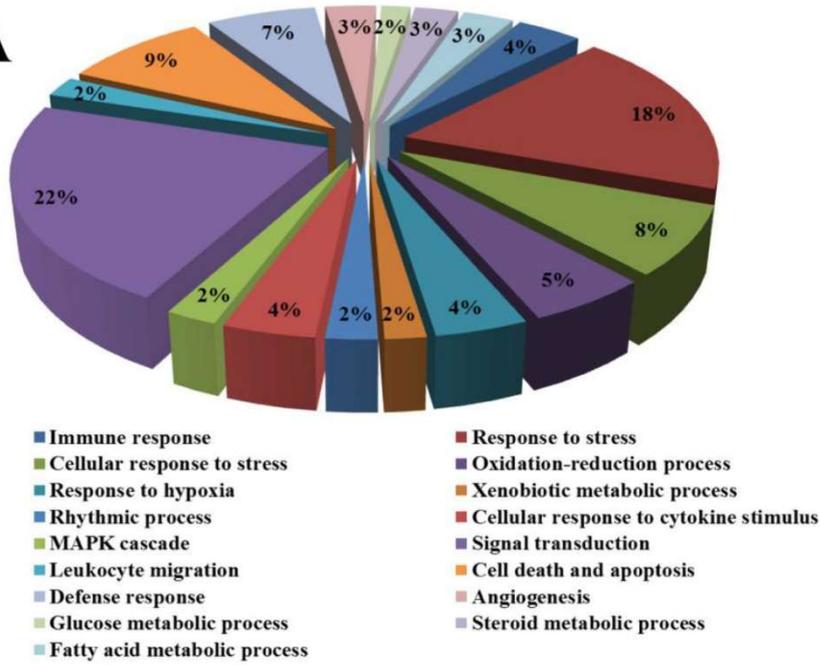
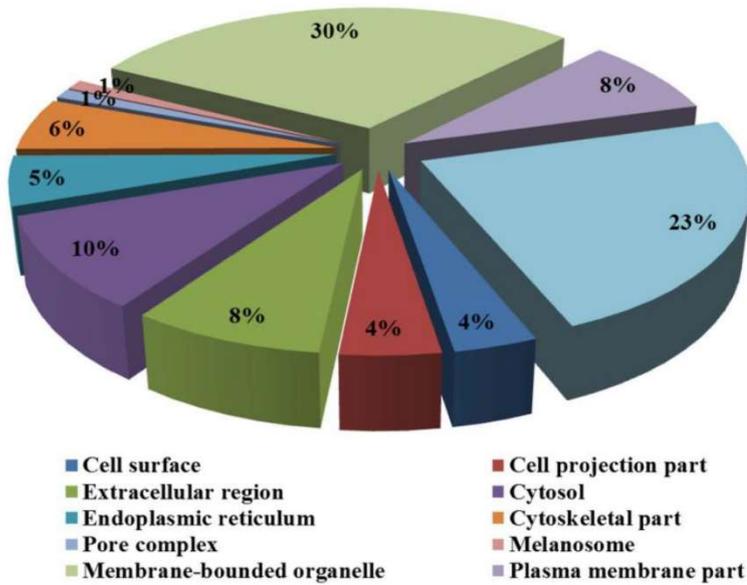
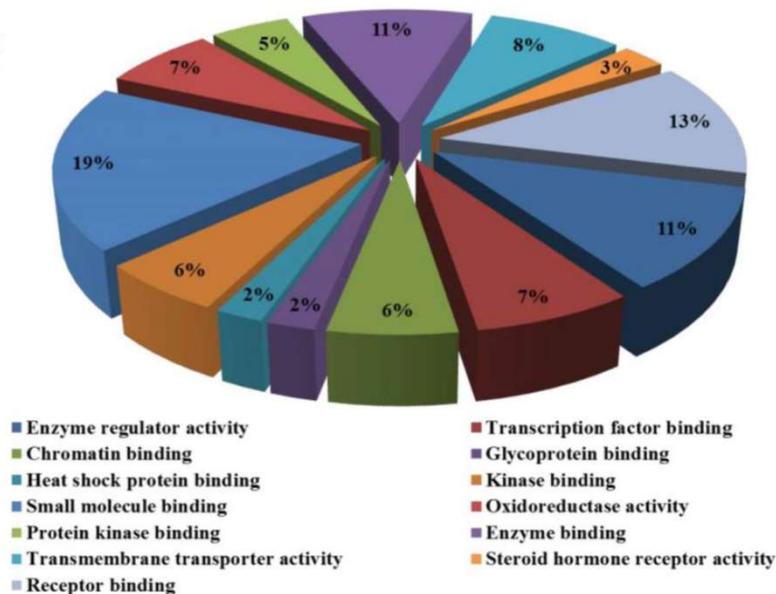


Supplementary Figure S3: Time resolved blood smears after repeated diclofenac treatment for 28 days. Panel A1-A3: RBC, HCT and MCV. Panel B1-B3: RDW, HB and RET. Panel C1-C3: MCH, MCHC and WBC. Panel D1-D3: Lymphocytes, neutrophils and

eosinophils **Panel E1-E3**: Basophils, monocytes and platelets. LD = low-dose, HD = high-dose, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

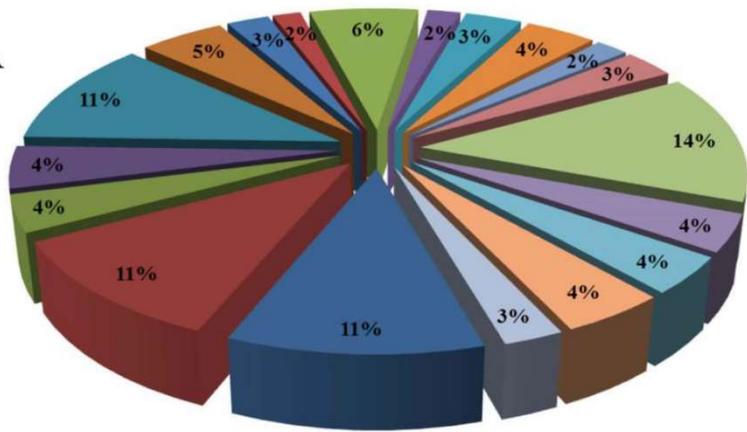


Supplementary Figure S4: Time resolved serum electrolytes after repeated diclofenac treatment for 28 days. Panel A: Serum calcium and chloride. Panel B: Serum potassium and sodium. LD = low-dose, HD = high-dose, * $p < 0.05$, * $p < 0.001$.**

A**B****C**

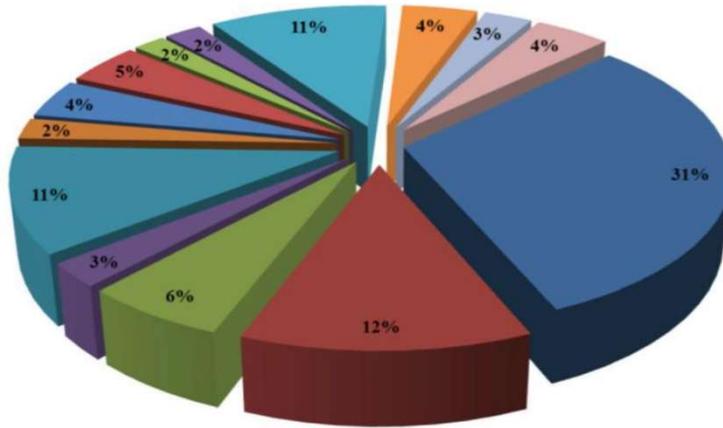
Supplementary Figure S5: GO terms regulated in liver after low-dose diclofenac treatment. The gene ontology properties of DEGs were analyzed using the GeneXplain platform and a *p*-value threshold that was set to <0.05 . The pie charts depict the distribution of A) key biological processes, B) cellular components and C) molecular functions of low-dose diclofenac treatment.

A



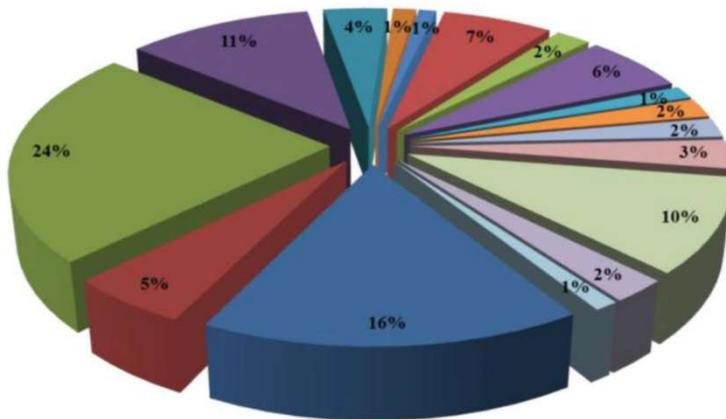
- Immune response
- Response to oxidative stress
- Oxidation-reduction process
- Xenobiotic metabolic process
- Cell cycle
- Rhythmic process
- INF-gamma-mediated signaling pathway
- Response to glucocorticoid stimulus
- Glucose metabolic process
- Cellular response to stress
- Response to hypoxia
- Cytokine-mediated signaling pathway
- Glutathione metabolic process
- Cell cycle arrest
- MAPK cascade
- Leukocyte migration
- Angiogenesis
- Fatty acid metabolic process

B



- Cytosol
- Extracellular matrix
- Golgi apparatus
- Lysosome
- Melanosome
- ER membrane
- Mitochondrial outer membrane
- Extracellular space
- Tight junction
- Peroxisome
- Vacuole
- Microbody
- Cell-cell junction
- Vacuolar part

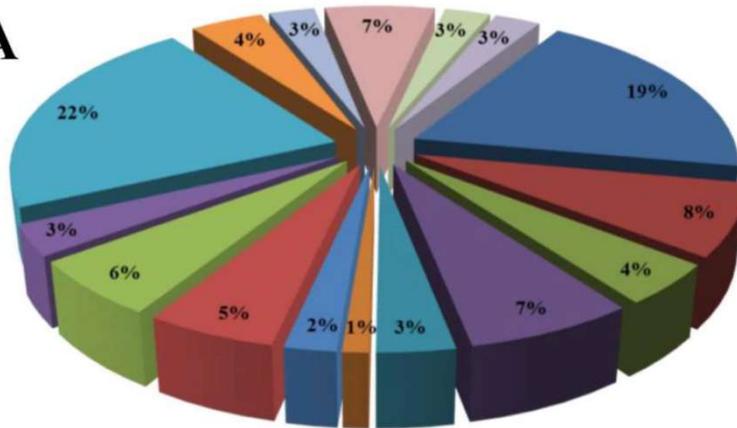
C



- Enzyme regulator activity
- Oxidoreductase activity
- Glutathione peroxidase activity
- Protein complex binding
- Antioxidant activity
- Drug binding
- Coenzyme binding
- Lyase activity
- Kinase binding
- Chemokine receptor binding
- Isomerase activity
- MAP kinase kinase activity
- Transferase activity
- Glutathione transferase activity
- Integrin binding
- Growth factor binding
- Lipid binding

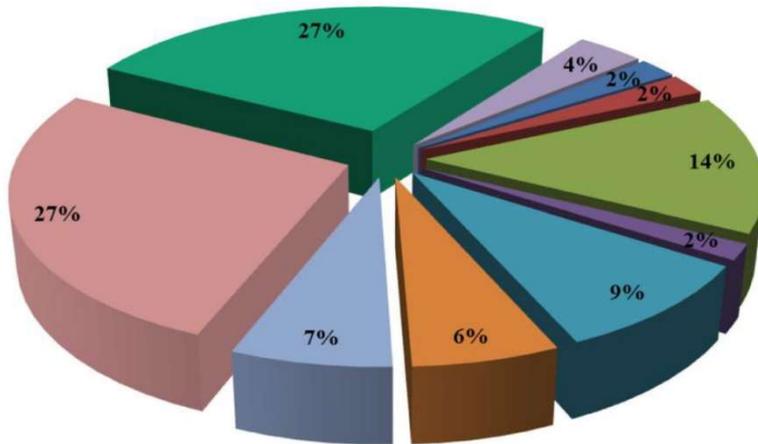
Supplementary Figure S6: GO terms regulated in liver after high-dose diclofenac treatment. The gene ontology properties of DEGs were analyzed using GeneXplain platform and the *p*-value threshold was set as <0.05. The pie charts depict the distribution of A) key biological processes, B) cellular components and C) molecular functions of high-dose diclofenac treatment.

A



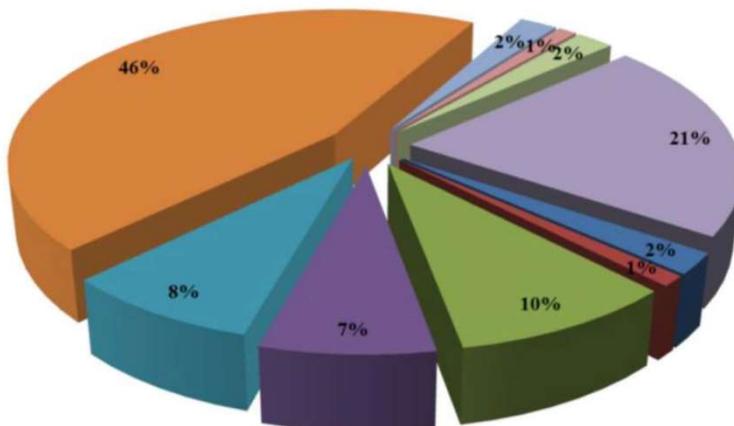
- Response to stress
- Response to oxidative stress
- Response to reactive oxygen species
- Xenobiotic metabolic process
- Response to cytokine stimulus
- Signal transduction
- Mitotic cell cycle
- Angiogenesis
- Cellular response to stress
- Response to hypoxia
- Acute phase response
- Cellular response to cytokine stimulus
- T cell activation involved in immune response
- Rhythmic process
- Cell death and apoptosis
- Lipid metabolic process

B



- Spindle
- Melanosome
- Nucleoplasm
- Endoplasmic reticulum
- Nuclear envelope
- Nucleolus
- Cytoplasm
- Cytoplasmic vesicle
- Nucleus
- Cytosol

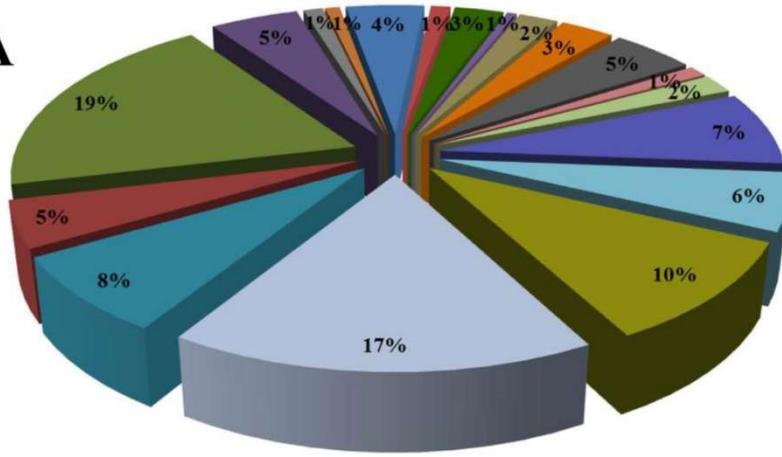
C



- Integrin binding
- Receptor binding
- Enzyme binding
- Microtubule binding
- Drug binding
- Glutathione transferase activity
- Enzyme regulator activity
- Protein binding
- Glutathione binding
- Metal ion binding

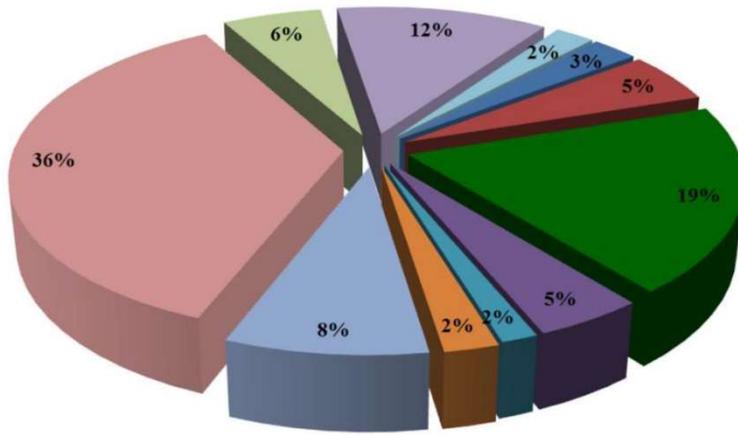
Supplementary Figure S7: GO terms regulated in kidney after low-dose diclofenac treatment. The gene ontology properties of DEGs were analyzed using the GeneXplain platform and a *p*-value threshold that was set to <0.05 . The pie charts depict the distribution of significant A) biological processes, B) cellular components and C) molecular functions of low-dose diclofenac treatment.

A



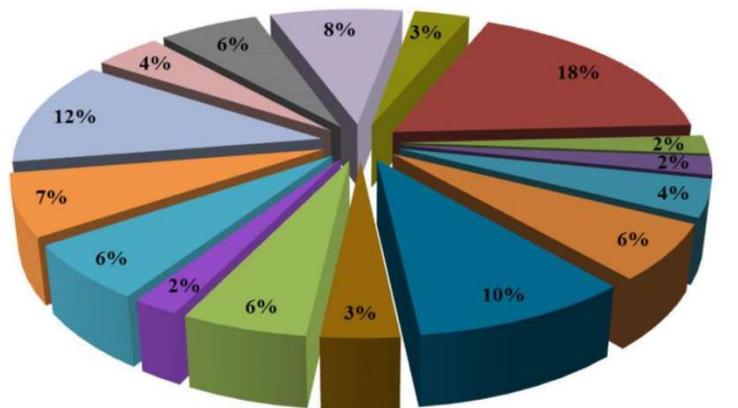
- Immune response
- Response to stress
- Acute phase response
- Response to cytokine stimulus
- Response to LPS
- Complement activation
- Signaling
- Leukocyte migration
- Response to wounding
- Innate immune response
- Inflammatory response
- Glutathione metabolic process
- Response to ROS
- Response to TNF
- Rhythmic process
- Integrin-mediated signaling pathway
- Regulation of cell death and apoptosis
- Defense response

B



- Microtubule cytoskeleton
- Cytosol
- Kinetochores
- Endoplasmic reticulum
- Ribonucleoprotein complex
- Nuclear matrix
- Cell body
- Extracellular matrix
- Spindle
- Nucleus
- Nucleolus

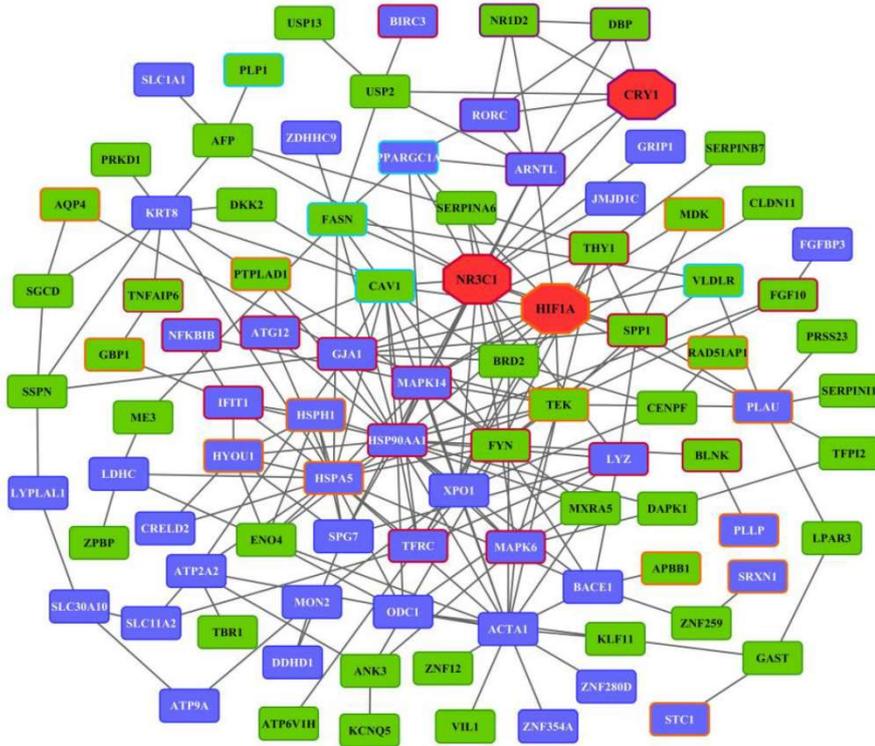
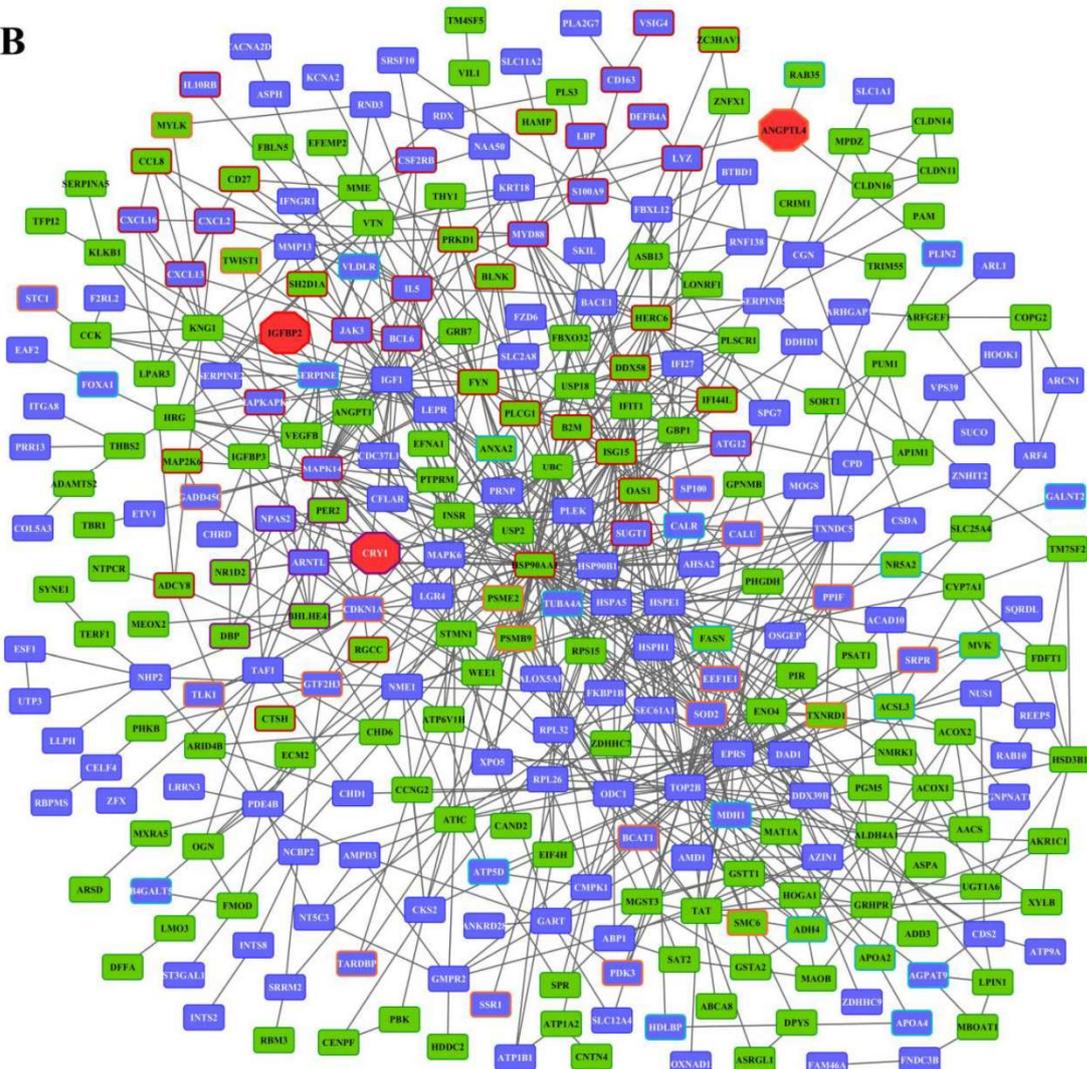
C



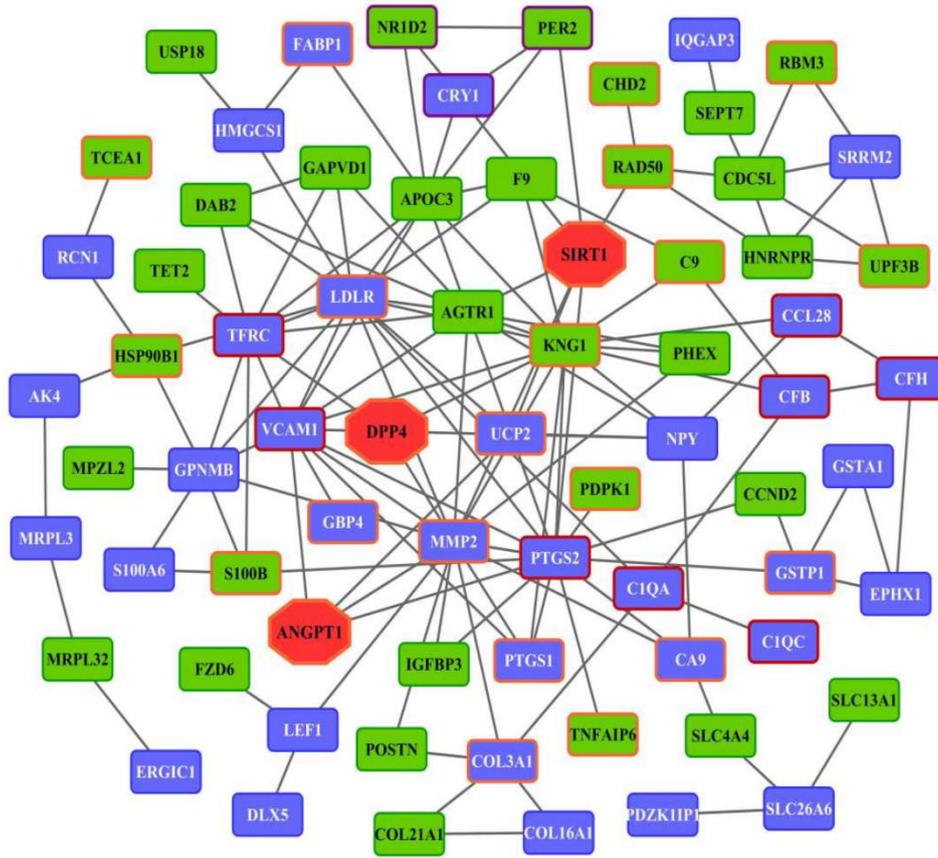
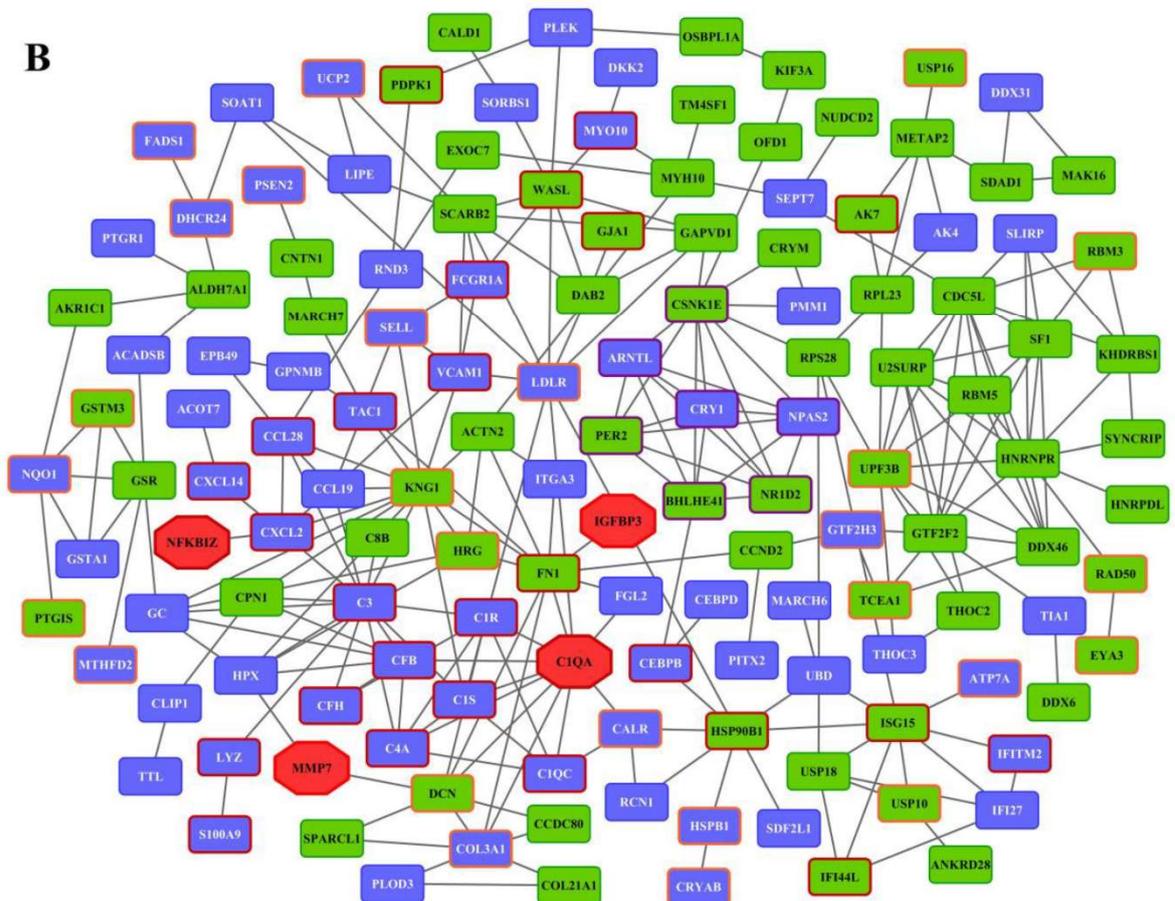
- Chemokine activity
- Complement binding
- Peptidase activity
- Fibronectin binding
- Oxidoreductase activity
- Protein complex binding
- RNA binding
- Integrin binding
- Glycoprotein binding
- Cofactor binding
- Helicase activity
- Glutathione binding
- Peptide binding
- Coenzyme binding
- ATPase activity
- GPCR binding

Supplementary Figure S8: GO terms regulated in kidney after high-dose diclofenac treatment. The gene ontology properties of DEGs were analyzed using the GeneXplain platform and the *p*-value threshold was set to <0.05. The pie charts depict the distribution of significant A) biological processes, B) cellular components and C) molecular functions of high-dose diclofenac treatment.

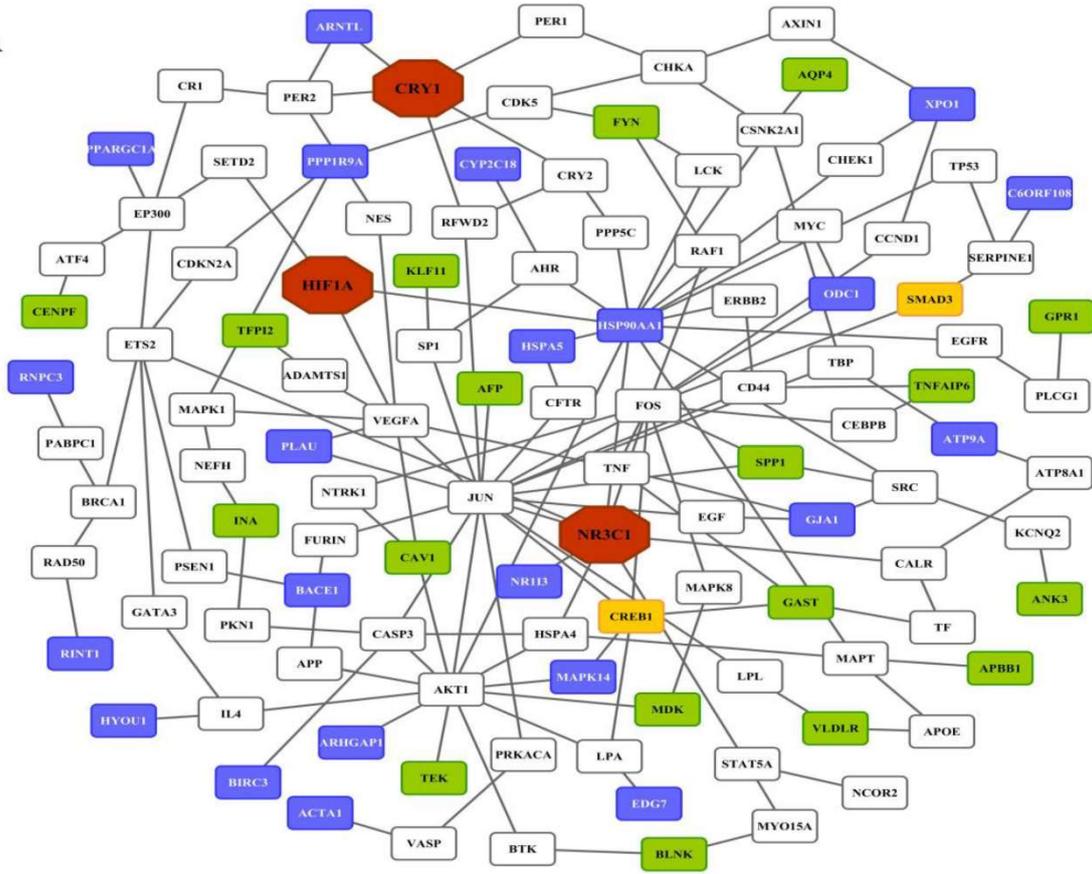
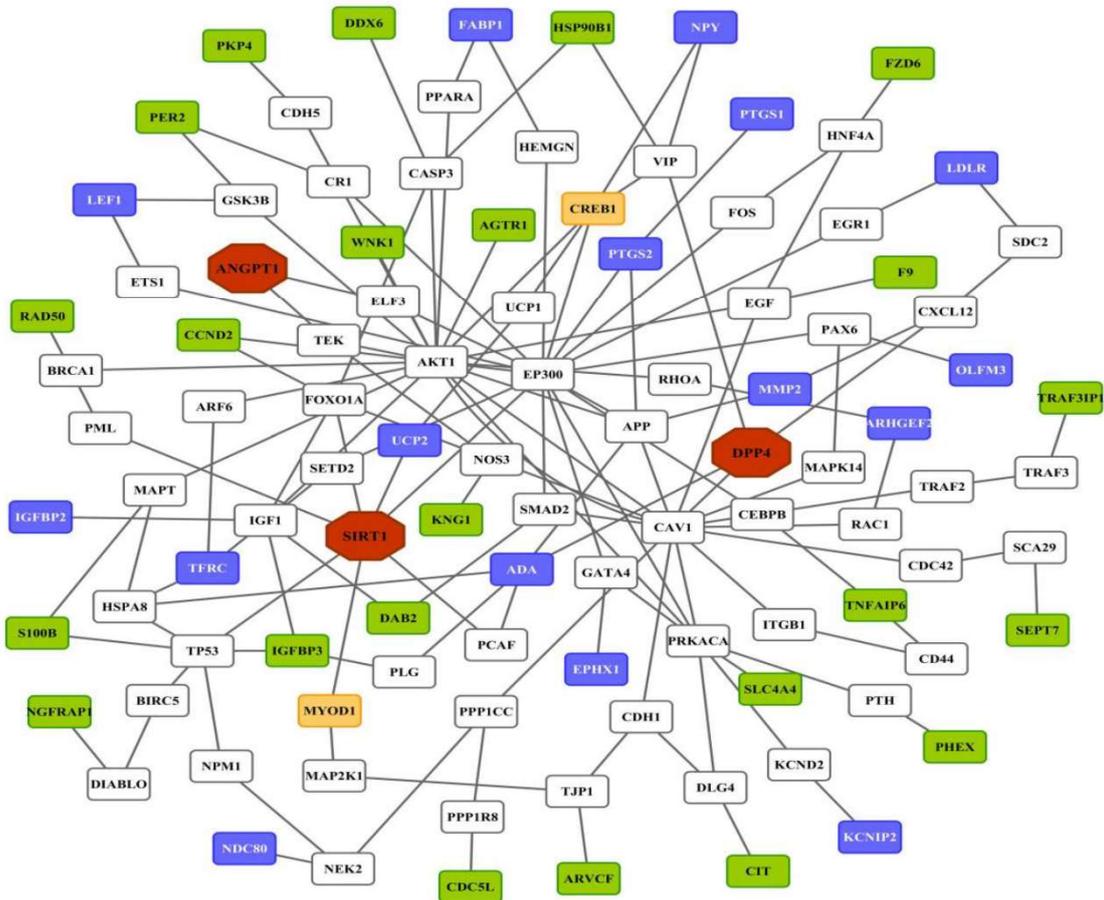
Supplementary Figure S9: Gene ontology and pathway mapping network of DEGs in kidney in response to low-dose diclofenac treatment. A visualization of kidney enriched pathway terms and biological processes computed with the ClueGO and the GeneXplain software of low-dose treated animals. **Panel A:** Network constructed by the plug-in ClueGO of the Cytoscape software. **Panel B:** The enriched biological processes and pathways were annotated by the GeneXplain platform and visualized using the Cytoscape software version 3.4. The red and green colored nodes illustrate up- and down regulated genes, respectively.

A**B**

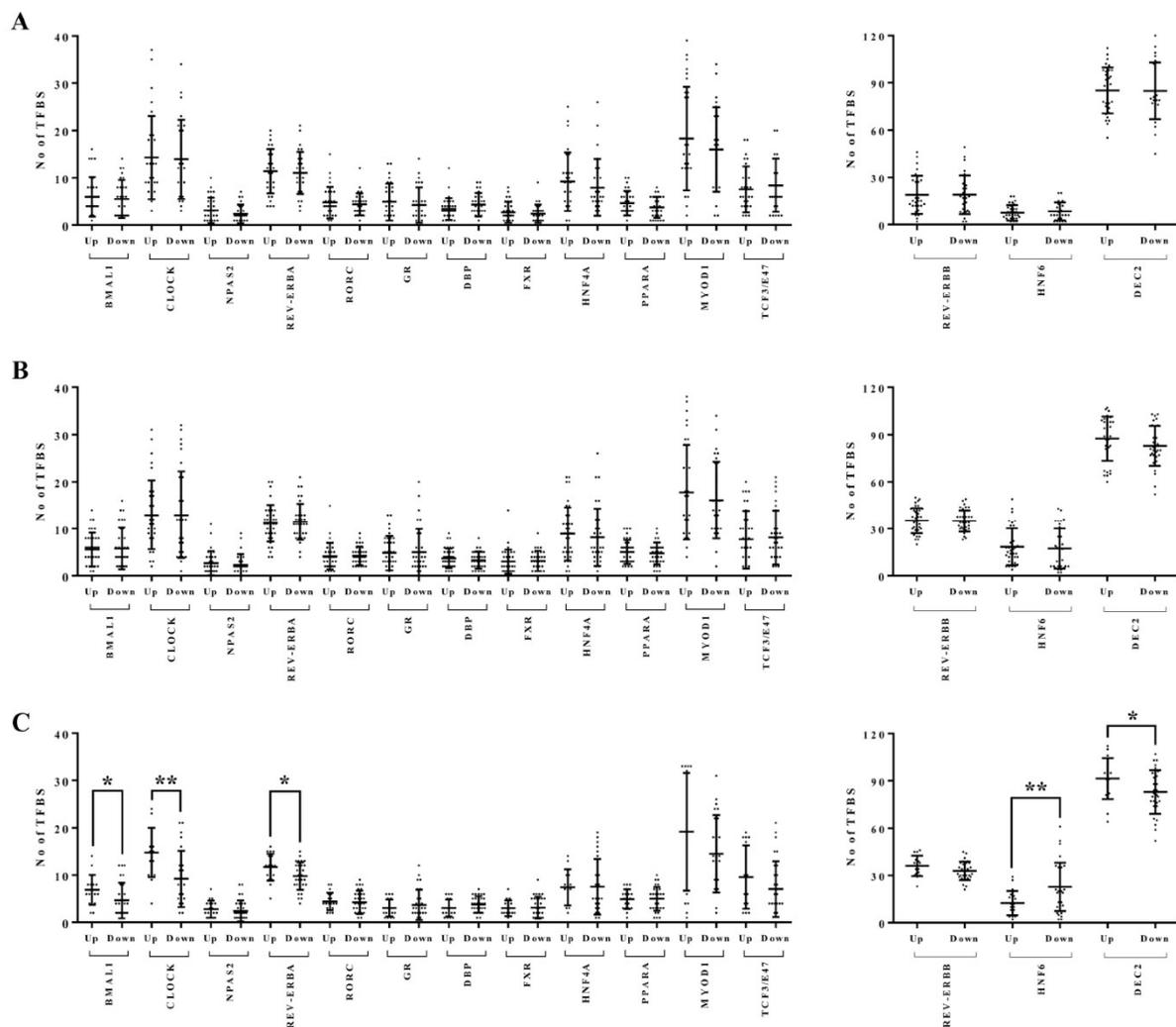
Supplementary Figure S10: Gene/protein interaction networks in the liver of diclofenac treated animals. Panel A: Low-dose treatment. A total of 153 DEGs were used to construct a PPI network of which 92 interacted among 217 PPIs. **Panel B:** High-dose treatment. A total of 488 DEGs were used to construct a PPI network of which 325 engaged in 885 PPIs. The purple and green color highlights up- and down- regulated DEGs. The red hexagon denotes master regulator molecules of the network. Immune and inflammation response genes are marked by red colored boxes, whereas circadian rhythm, stress response genes and lipid metabolic genes are highlighted in maroon, orange and blue colored boxes, respectively. The protein interaction networks were constructed using STRING version 10.5. Zoom in for better readability of individual genes.

A**B**

Supplementary Figure S11: Gene/protein interaction networks in the kidney of diclofenac treated animals. Panel A: Low-dose treatment. Out of 144 DEGs a network that consists of 76 DEGs was constructed and interacted among 105 PPIs. **Panel B:** High-dose treatment. Out of 286 DEGs a network that consists of 180 DEGs was constructed and interacted among 412 PPIs. The purple and green color highlights up- and down- regulated DEGs. The red hexagon denotes master regulator molecules of the network. Immune and inflammation response genes were marked by red colored boxes, whereas circadian rhythm, stress response genes and lipid metabolic genes are highlighted in maroon, orange and blue colored boxes, respectively. The protein interaction networks were constructed using STRING version 10.5. Zoom in for better readability of individual genes.

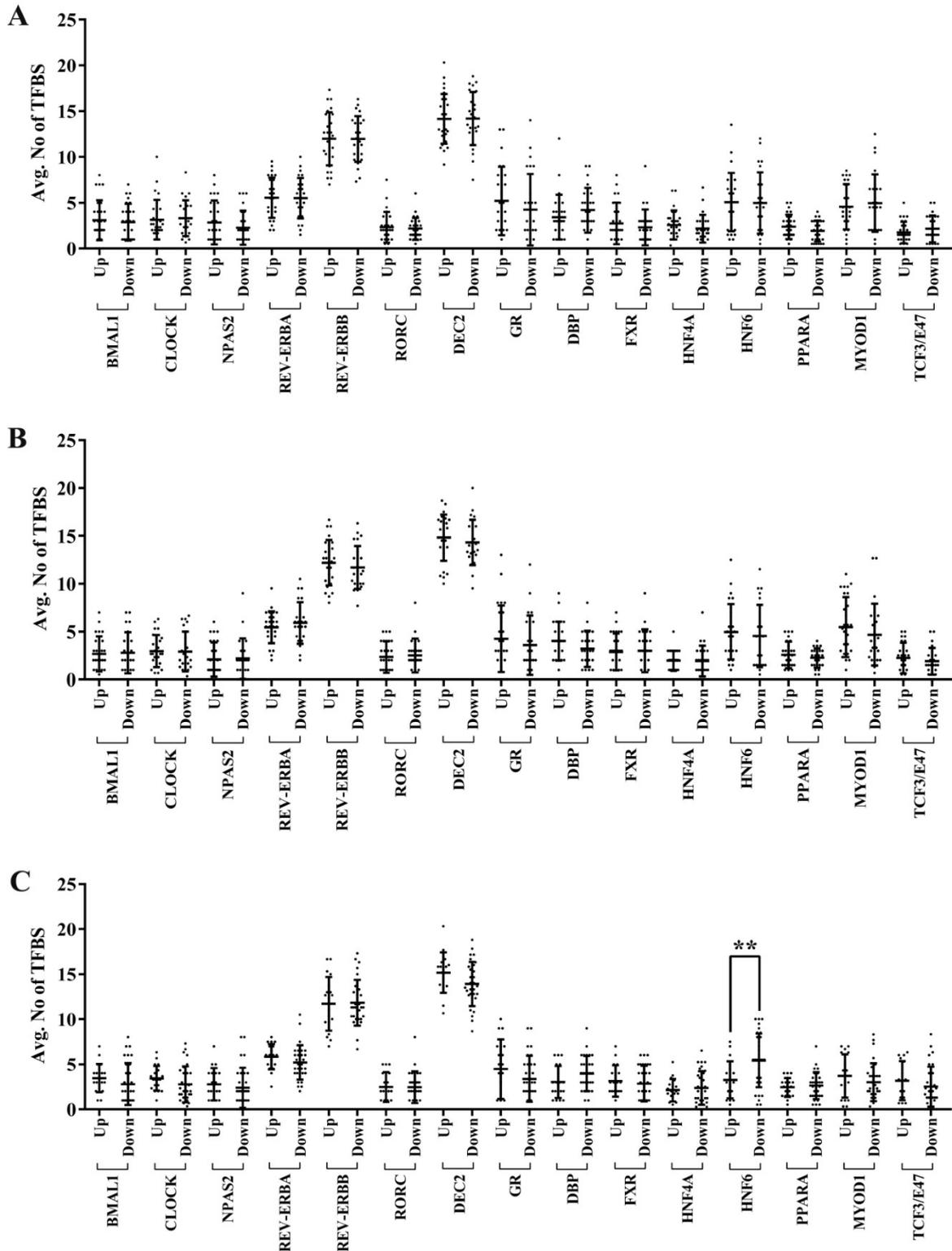
A**B**

Supplementary Figure S12: Master regulatory gene networks in liver and kidney of low-dose diclofenac treated animals. Based on interaction information available in the GeneWays database the master regulatory gene networks were constructed and fused using the GeneXplain platform. The red, violet, green, white and yellow colored nodes represent the genes coding for master regulators, up-, down regulated DEGs, connecting genes and enriched transcription factors, respectively. **Panel A:** Master regulatory network in liver of low-dose diclofenac treatment: The network comprised 114 genes of which 43 were significantly regulated. **Panel B:** Master regulatory network in kidney of low-dose diclofenac treatment: The network comprised 103 genes of which 43 genes were significantly regulated.



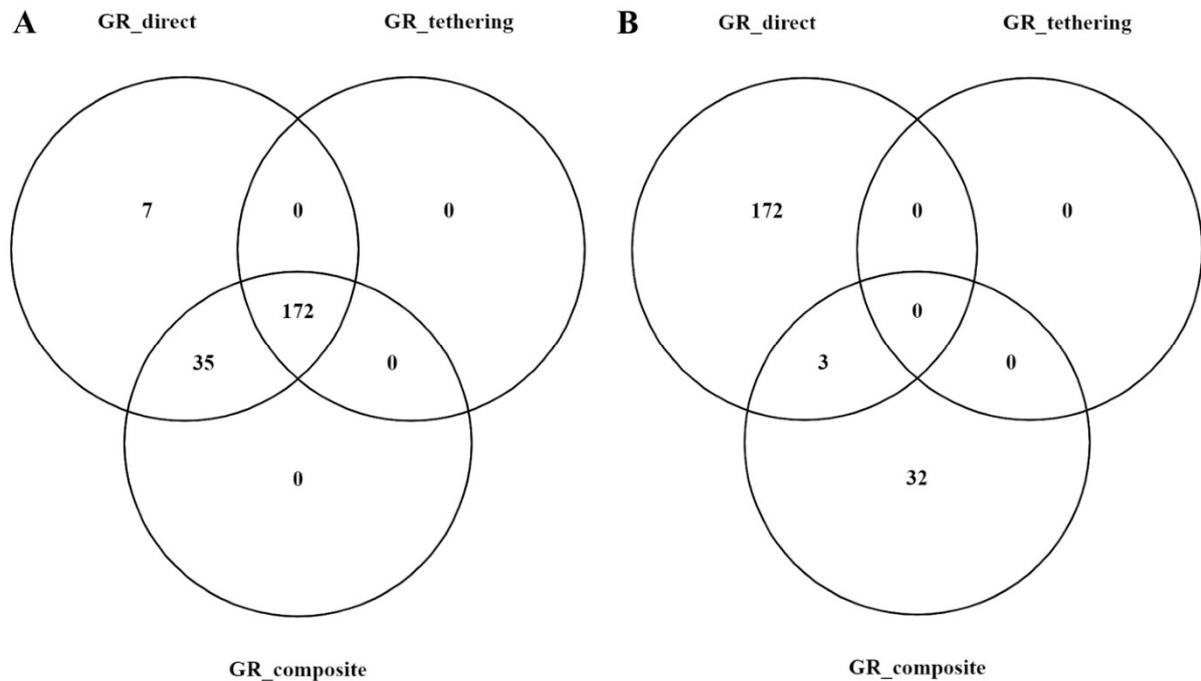
Supplementary Figure S13: Enriched transcription factor binding sites for liver clock regulated genes. Shown are TFBS in promoters of significantly regulated genes of the core

circadian transcription factors BMAL1, CLOCK, NPAS2, REV-ERBA, REV-ERB β , RORC in addition to GR, DBP, FXR, HNF4A, HNF6, PPARA and DEC2 which participate in liver clock oscillations. **Panel A:** TFBS in promoters of DEGs coding for immune and inflammation. **Panel B:** TFBS in promoters of DEGs coding for stress response genes. **Panel C:** TFBS in promoters of DEGs coding for metabolic processes. * $p < 0.05$, ** $p < 0.01$.

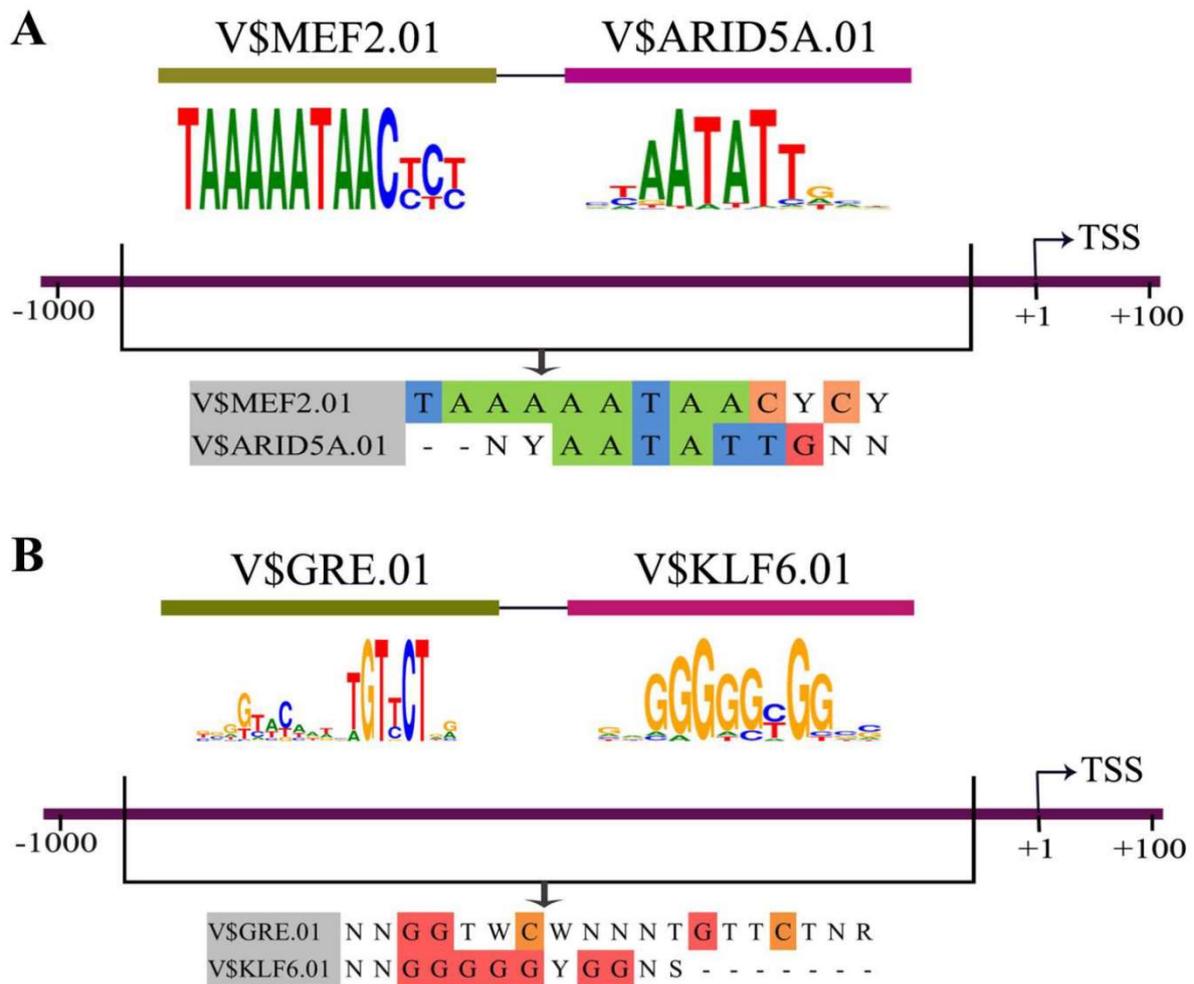


Supplementary Figure S14: Enriched TFBS in association with liver clock genes. The enriched TFBS at gene specific promoters of significantly regulated DEGs coding for immune, stress, inflammation and metabolism with the length of -1000 to +100 base pairs relative to TSS were interrogated using the GeneXplain software version 6.0. Each dot illustrates an average

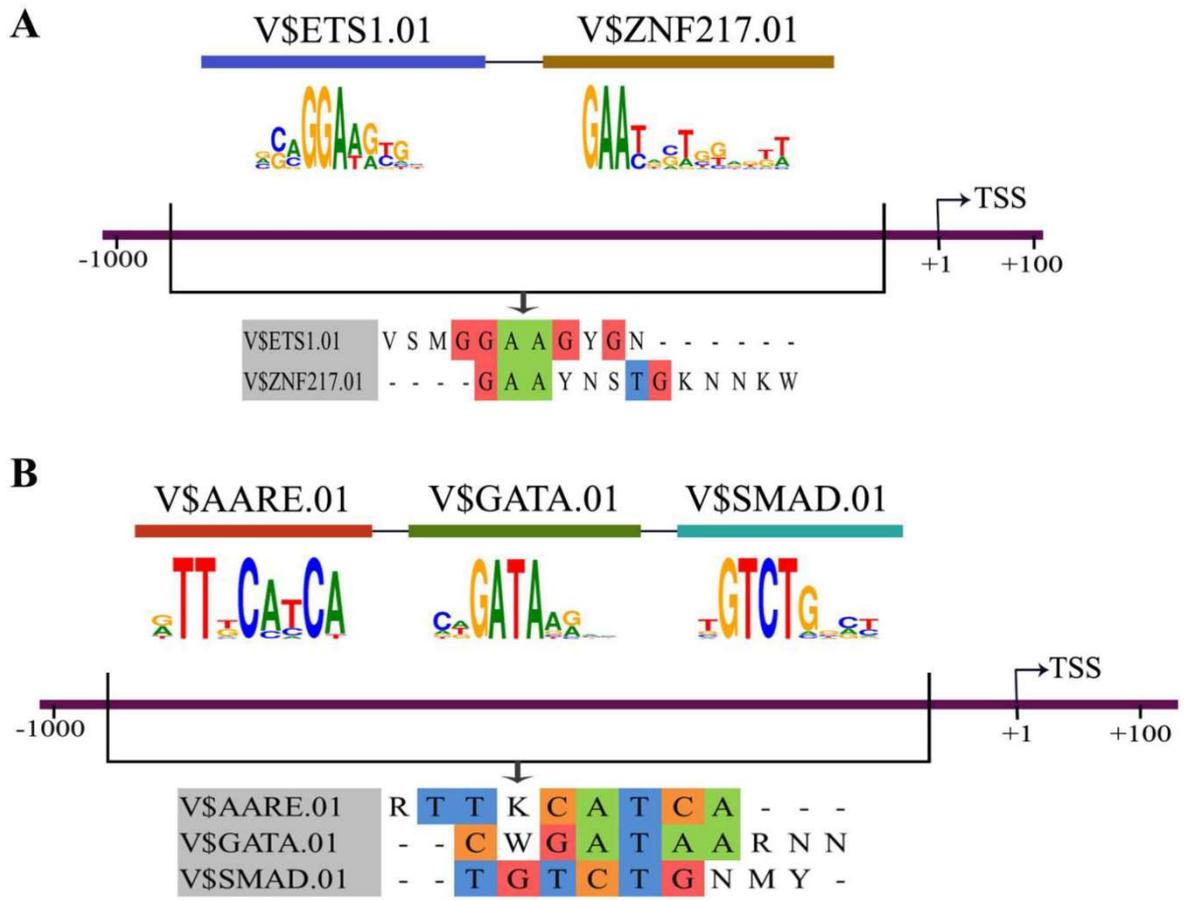
number of TFBS at the promoter region of the genes. **Panel A:** Average number of TFBS for immune and inflammation coding genes. **Panel B:** Average number of TFBS at promoters of stress response genes. **Panel C:** Average number of TFBS at promoters of DEGs coding for metabolic processes. $**p < 0.01$.



Supplementary Figure S15: Comparison of proposed GR signaling models in hepatic DEGs. The direct, tethering or composite models of GR activity was proposed by Oakley and Cidlowski [50] that results in either activated or repressed transcriptional responses. The proposed models were interrogated at gene specific promoters of hepatic DEGs using the GeneXplain software version 6.0. **Panel A:** Venn diagram illustrates the number of up-regulated genes associated with direct, tethering or composite model of glucocorticoid receptor activity. **Panel B:** Venn diagram illustrates the number of down-regulated genes associated with glucocorticoid receptor activity.



Supplementary Figure S16: Composite modules search to predict gene regulation in liver in response to diclofenac treatment. DEGs coding for immune, stress, inflammation, hypoxia, cytokine and acute-phase responses were interrogated using the Genomatix FrameWorker tool. Transcription factor binding sites at gene specific promoters with the length of -1000 to +100 base pairs relative to TSS were analyzed. The sequence alignment defines the overlapping regions of consensus sequences specific for TFBS. **Panel A:** Composite modules of co-bound transcription factors at promoters of low-dose diclofenac induced DEGs. **Panel B:** Composite module of regulated DEGs after high-dose diclofenac treatment in liver.



Supplementary Figure S17: Composite modules search to predict gene regulation in kidney in response to diclofenac treatment. Cis-regulatory modules at gene specific promoters of DEGs with the length of -1000 to +100 base pairs relative to TSS were interrogated using the Genomatix FrameWorker tool. The sequence alignment defines the overlapping regions of consensus sequences specific for TFBS. **Panel A:** Composite module of low-dose regulated DEGs after diclofenac treatment. **Panel B:** Composite module of high-dose regulated DEGs after diclofenac treatment.

Supplementary Table S1: Drug metabolism genes and solute carriers regulated in liver and kidney after diclofenac treatment.

Supplementary Table S2: Enriched biological processes in kidney. The functional properties of DEGs were analyzed using the GeneXplain platform and the p -value <0.05 considered as significant.

Supplementary Table S3: Over-represented transcription factor binding sites in liver and kidney DEGs after low- and high-dose diclofenac treatment.

Supplementary Table S4: Composite modules of enriched liver clock and glucocorticoid receptor (GR) regulated genes in response to diclofenac treatment.

Co-occupancy of circadian transcriptional regulators and glucocorticoid receptor was evaluated at the gene specific promoters of hepatic DEGs with the length of -1000 to +100 base pairs relative to TSS. The default filtering criteria of the GeneXplain platform were applied to determine statistically significant composite modules.

Supplementary Table S5: Glucocorticoid receptor binding in hepatic DEGs.

The direct, tethering or composite models of GR activity was proposed by Oakley and Cidlowski (PMID: 24084075) that results in either activated or repressed transcriptional responses. The proposed models were interrogated at gene specific promoters of hepatic DEGs using the GeneXplain software.

Supplementary Table S6: Primer sequences used in real-time RT-PCR analyses.