

Table S1 Primers used for real-time PCR analysis

Symbol	Gene Name	Forward Primer (5'-3')	Reverse Primer (5'-3')	References	
pdk4	Pyruvate dehydrogenase kinase 4	GACCCAGTCACCAATCAAAATCT	GGTTCATCAGCATCCGAGTAGA	Yue et al., 2019	
pdk3	Pyruvate dehydrogenase kinase 3	TGGCGCCATTACAAGACCAC	CAGAGAGGACCACAGCATTCA		
pdk2	Pyruvate dehydrogenase kinase 2	ATGAAAGAGATCAACCTGCTTCC	GGCTCTGGACATACCAGCTC		
pdk1	Pyruvate dehydrogenase kinase 1	GGATTGCCCATATCACGTCTTT	TCCCGTAACCCTCTAGGGAATA		
kgdh	Ketoglutarate dehydrogenase	GGCTTCCCAGACTGTTAAGAC	GCAGAAATAGCACCGAATCTGTTG		
idh3b	Isocitrate dehydrogenase (NAD(+)) 3 non-catalytic subunit beta	TAGTGCAGAATACGCAGTCTTTG	CAGCATGTTGGAAGCCGAC		
idh3a	Isocitrate dehydrogenase (NAD(+)) 3 catalytic subunit alpha	AGCCGGTCACCCATCTATGAA	TAGAGACACATGGTCGGACAT		
idh2	Isocitrate dehydrogenase (NADP(+)) 2	CGCCACTATGCCGACAAAAG	ACTGCCAGATAATACGGGTCA		
idh1	Isocitrate dehydrogenase (NADP(+)) 1	AGAAGCATAATGTTGGCGTCA	CGTATGGTGCCATTTGGTGATT		
cpt1	Carnitine palmitoyltransferase 1	CAGCATATGTATCGCCTCGC	CTGGACACGTAATCTGGGTT		Gong et al., 2021
cpt2	Carnitine palmitoyltransferase 2	TACGAGTCCTGTAGCACTGC	AACAAGTGTCCGGTCAAAGCC		
acs11	Acyl-CoA synthetase long chain family member 1	GCCTCTCGCCCATATGTTTG	CATCCGGTTCAGCAGTCTTG		
acox1	Acyl-CoA oxidase 1	GTGACATCGGCCCAAATTT	AACACCATGGTCCCCTAAGT	Guo et al., 2021	
glut1	Glucose transporter 1	CGG GCC AAG AGT GTG CTA AA	TGA CGA TAC CGG AGC CAA TG		
acc	Acetyl-CoA carboxylase	GCTGCTCGGATCACTAGTGAA	TTCTGCTATCAGTCTGTCCAG	Shen et al., 2021	
fas	Fatty acid synthase	GAAACTGCAGGAGCTGTC	CACGGAGTTGAGGCGGAT		
cox6a1	Cytochrome c oxidase subunit 6A1	CCACTTCCAACCTGGCTACGA	AAGCAAAGGGATGGGAGACC	Derambure et al., 2017	
ndufs1	NADH ubiquinone oxidoreductase core subunit S1	ACCGAGCCAATGGTCAGAAA	CTGCAACATTCCAGCTACGC	Dziegala et al., 2018	
uqcrfs1	Ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1	AACCCCTGTTTGTGCGTCAT	TTGAGAGGAGCAGGACCCAA		
cox4i1	Cytochrome c oxidase subunit 4I1	ACGAGTGAAGACGGTTGTG	AGGGGGCCGTACACATAGT		
atp5b	ATP synthase, H ⁺ transporting, mitochondrial F1 complex beta polypeptide	AGACTGGTTTTGGAGGTGCGC	GGCCAAAGTCTCAGGACCAA		

Derambure C, Dzangue-Tchoupou G, Berard C, Vergne N, Hiron M, D'Agostino MA, et al. Pre-silencing of genes involved in the electron transport chain (ETC) pathway is associated with responsiveness to abatacept in rheumatoid arthritis. *Arthritis. Res. Ther.* 2017, 19: 109.

Dziegala M, Kobak KA, Kasztura M, Bania J, Josiak K, Banasiak W, et al. Iron depletion affects genes encoding mitochondrial electron transport chain and genes of non-oxidative metabolism, pyruvate kinase and lactate dehydrogenase, in primary human cardiac myocytes cultured upon mechanical stretch. *Cells.* 2018, 7.

Gong Y, Geng N, Zhang H, Luo Y, Giesy JP, Sun S, et al. Exposure to short-chain chlorinated paraffins inhibited PPARalpha-mediated fatty acid oxidation and stimulated aerobic glycolysis in vitro in human cells. *Sci. Total Environ.* 2021, 772: 144957.

Guo HJ, Li HY, Chen ZH, Zhou WJ, Li JJ, Zhang JY, et al. NAMPT promotes hepatitis B virus replication and liver cancer cell proliferation through the regulation of aerobic glycolysis. *Oncol. Lett.* 2021, 21: 390.

Shen M, Xu M, Zhong F, Crist MC, Prior AB, Yang K, et al. A multi-omics study revealing the metabolic effects of estrogen in liver cancer cells HepG2. *Cells.* 2021, 10.

Yue S, Yu J, Kong Y, Chen H, Mao M, Ji C, et al. Metabolomic modulations of HepG2 cells exposed to bisphenol analogues. *Environ. Int.* 2019, 129: 59-67.

Table S2 Quantitative results of the copper hydroxide nanopesticide and copper ions in metabolomics analyses. Table indicated the influence of the nanopesticide and ions on the energy metabolites of cells. The numbers were the ratio of the treated mean divided by the control mean or the nanopesticide treated mean divided by the ions treated mean, and the statistical significance *p* value. Symbol (*) represented the *p* < 0.05 as compared with the control. Symbol (#) represented the *p* < 0.05 as compared with the copper ions. NA indicated not available.

Metabolites	Energy pathway	Nano-Cu(OH) ₂	Ion-CuSO ₄	Ion-Nano
Citrate/Citric acid	TCA	2.91/<0.0001*	4.22/<0.0001*	1.45/0.0008#
Aconitate	TCA	1.89/<0.0001*	2.86/<0.0001*	1.51/0.0014#
Isocitrate	TCA	0.81/0.0005	0.89/0.0405	1.11/0.0821
Alpha-Ketoglutaric Acid	TCA	1.35/0.0437*	2.30/<0.0001*	1.70/0.0003#
Succinyl-CoA	TCA	NA	NA	NA
Succinate/Succinic acid	TCA	1.58/0.0006*	1.77/<0.0001*	1.12/0.1961
Fumarate/Fumaric acid	TCA	3.38/0.0004*	4.82/<0.0001*	1.42/0.0272#
Malate	TCA	2.63/<0.0001*	3.60/<0.0001*	1.37/0.0038#
Oxaloacetate	TCA	1.47/0.0218*	1.52/0.0957	1.04/0.8577
Pyruvate/Pyruvic acid	TCA	NA	NA	NA
Acetyl-CoA	TCA	1.24/0.0021*	1.32/0.0003*	1.07/0.1847
Glutaryl-CoA	TCA	NA	NA	NA
Thiamine pyrophosphate (TPP)	TCA	1.38/0.0071*	1.35/0.0023*	0.98/0.8306
Guanosine diphosphate (GDP)	TCA	1.69/0.0014*	1.78/0.0004*	1.05/0.6385
Guanosine triphosphate (GTP)	TCA	1.60/0.0176*	2.51/0.0003*	1.57/0.0168#
AMP	TCA/glycolysis	0.79/0.0334*	0.59/<0.0001*	0.76/0.0544
ADP	TCA/glycolysis/oxidative phosphorylation	1.16/0.0676	1.18/0.0337	1.02/0.8311
ATP	TCA/glycolysis/oxidative phosphorylation	1.97/<0.0001*	2.52/<0.0001*	1.28/0.0102#
cyclic-AMP	AMP derivative	0.70/0.0004*	0.62/<0.0001*	0.88/0.1046
D-Glucose-6-phosphate (G6P)	glycolysis	0.99/0.9227	1.22/0.1499	1.23/0.1491
Beta-D-Fructose 6 phosphate (β-D-F6P)	glycolysis	1.36/0.0019*	1.68/0.0004*	1.23/0.0268#
Fructose-1,6-biphosphate	glycolysis	1.05/<0.0001	1.08/0.0006	1.03/0.0831
3-Phosphoglycerate (3PG)	glycolysis	1.84/0.0014*	1.85/<0.0001*	1.01/0.9473
Dihydroxyacetone phosphate (DHAP)	glycolysis	1.46/0.0016*	1.70/0.0027*	1.17/0.2044
Phosphoenolpyruvate (PEP)	glycolysis	1.05/0.2621	1.13/0.0390	1.08/0.2142
Lactate	glycolysis	2.13/0.0022*	2.14/0.0016*	1.00/0.9807
NADH	oxidative phosphorylation	1.08/0.6166	1.01/0.9147	0.94/0.6663
NAD+	oxidative phosphorylation	1.00/0.9730	1.35/0.0120*	1.35/0.0121#
FMN	oxidative phosphorylation	1.17/0.0022	1.05/0.3583	0.90/0.0376
NADPH	pentose phosphate	1.32/0.0454*	1.50/0.0038*	1.14/0.1481
NADP+	pentose phosphate	1.36/0.0012*	1.48/0.0025*	1.08/0.3568
GMP	pentose phosphate	1.16/0.3645	0.83/0.1034	0.71/0.0843

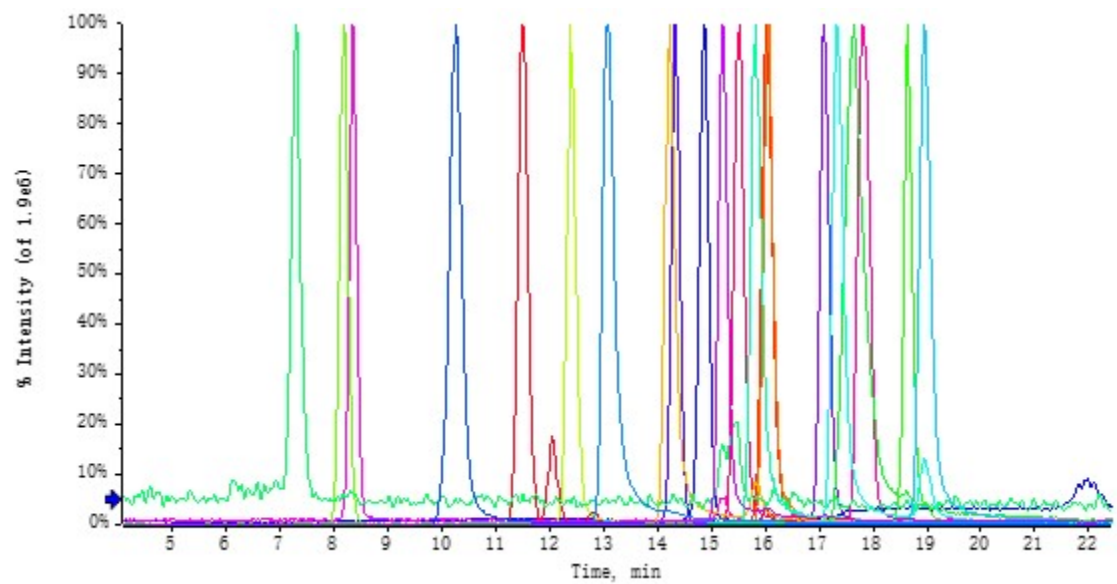


Figure S1. Extracted ion chromatogram (XIC) annotated with each metabolite and retention time for the mixture of standards