Electronic Supplementary Material (ESI) for Food & Function.

Supplementary materials

For

Natural polyphenols: a potential prevention and treatment strategy for metabolic syndrome

Shaohui Wang[1], Qinyun Du[2], Xianli Meng[3], Yi Zhang[1*]*

[1]State Key Laboratory of Southwestern Chinese Medicine Resources, School of Ethnic Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, China; [2]State Key Laboratory of Southwestern Chinese Medicine Resources, School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, of Traditional Chinese Medicine, Chengdu, China, [3]State Key Laboratory of Southwestern Chinese Medicine Resources, Innovative Institute of Chinese Medicine and Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, China,

Corresponding authors: Yi Zhang (zhangyi@cdutcm.edu.cn), Xianli Meng (xlm999@cdutcm.edu.cn)

Supplementary Table 1 Plant sources, pharmacological activity and potential mechanism of silibinin.

Compounds	Models	Sources	Molecular mechanisms	Pharmacological effects	References
Silibinin	C57BL/6 male mice fed with HFD	Milk thistle (*Silybum marianum* (L.) Gaertn.)	↓Adipose tissue inflammation and adipocyte hypertrophy; ↓weight gain and obesity development; ↑glucose homeostasis	Anti-inflammatory	(1)
	Male SD rats fed with HFD		↓Serum fat; ↓HOMA-IR; ↑ITT slope; ↓visceral fat; ↑lipolysis, ↑ATGL; ↓gluconeogenesis; ↓FoxO1, PEPCK, and glucose-6-phosphatase	Regulate insulin resistance in the liver with non-alcoholic fatty liver	(2)
	Human hepatoblastoma HepG2 cells		↓PCSK9 promoter; ↓phosphorylation of the p38 MAPK signaling pathway	Treat hypercholesterolemia	(3)
	HFD/STZ-induced T2DM rats; Rat pancreatic β-cell line INS-1		↓Fasting blood glucose; ↑serum insulin; ↑ERα, Nrf2, HO-1 (pancreatic β-cells in pancreatic islets); ↓ROS; ↑Nrf2-antioxidative pathways	Antidiabetic	(4)
	HFD/STZ-induced diabetic SD rats		↓Fasting blood glucose; ↑GLP1R(duodenum); ↑activation of neurons in NTS; ↓glucose production (hepatic); ↑Gut-Brain-Liver Axis	Improve diabetes-impaired glycemic control	(5)

Supplementary Table 2 Plant sources, pharmacological activity and potential mechanism of genistein.

Compounds	Models	Sources	Molecular mechanisms	Pharmacological effects	References
Genistein	Female ovariectomized SD rats fed with an HFHF diet	Soybean, Soy	↓Hepatic lipid accumulation, oxidative stress, and hepatocyte apoptosis; ↓PPARγ; ↑adiponectin	Treat NASH	(6)
	3T3-L1 preadipocyte obese mice		↑Lipid decomposition; ↓miR-222 (adipose tissue); ↓BTG2 and adipor1	Against obesity	(7)
	3T3-L1 preadipocytes		↓Lipid accumulation; ↓PPARγ, C/EBPα, aP2/FABP4; ↓ACL, ACC1, FAS; ↑AMPKα; ↓SREBP-1c	Anti-adipogenic and anti-lipogenic	(8)
	HFD-induced obesity mice		↓MGO (plasma and liver); ↓AGEs(kidney); ↑MGO detoxification pathways; ↓AGE/RAGE pathway	Anti-obesity and anti-glycation	(9)
	MIN6 cells		↑cAMP; ↓phosphodiesterase; ↑calcium	↑Insulin release	(10)

Supplementary Table 3 Plant sources, pharmacological activity and potential mechanism of C3G.

Compounds	Models	Sources	Molecular mechanisms	Pharmacological effects	References
	THP-1 cell		↓TNF-α, ↓IL-6; ↓p-IκBα, ↓NF-κB		(11)
	high-glucose (HG)-stimulated HK-2 cells		↑TC efflux; ↑ABCA1; ↑PPARα; ↑LXRα; ↓ICAM1; ↓MCP1; ↓TGFβ1; ↓NFκB; ↓LXRα pathway	Anti-inflammatory effect	(12)
	3T3-L1 hypertrophic adipocytes exposed to PA; SGBS human adipocytes		↓Lipid accumulation, PPARγ pathway and NF-κB pathway; ↑insulin sensitivity; ↑IRS-1/PI3K/Akt pathway; ↑adiponectin mRNA		(13)
	KK-A^y mice		↓Blood glucose; ↑insulin sensitivity; ↑Glut4; ↓RBP4; ↓MCP-1, TNFα	Ameliorates hyperglycemia and insulin sensitivity	(14)
	MIN6N pancreatic β-cells		↓Intracellular ROS; ↓DNA fragmentation; ↓rate of apoptosis; ↓pancreatic β-cell apoptosis; ↑insulin secretion	Prevention of diabetes	(15)
Cyanidin-3-glucoside (C3G)	Male C57BL/6J obese mice fed a HFD; genetic diabetic db/db mice	Mulberry fruits; black soybean; blueberry; grape; purple corn color	↓Fasting glucose; ↑insulin sensitivity; ↓WAT; ↓TNF-α, IL-6, MCP-1; ↓macrophage infiltration (adipose tissue); ↓hepatic TG content and steatosis; ↓JNK activation; ↑phosphorylation and nuclear exclusion of FoxO1	Antidiabetic effects	(16)
	Patients with T2DM; db/db mice; 3T3 adipocytes		↑Endothelium-dependent relaxation of the aorta; ↑adiponectin expression and secretion; ↑FoxO1; ↑FMD; ↑adiponectin (serum); ↑cAMP-PKA-eNOS signaling pathways; ↑endothelial NO bioavailability	Protects against diabetes-related endothelial dysfunction	(17)
	3T3-L1 adipocytes		↑Increased multilocular LDs and mitochondrial content; ↑TFAM, SOD2, UCP-1, and UCP-2; ↑UCP-1; ↑CITED1 and TBX1; ↑preadipocyte differentiation; ↑C/EBPβ; ↑cAMP	Anti-obesity effects	(18)
	Female KK-A^y mice		↓obesity, accumulation of fat (visceral adipose and liver tissues),	Improves obesity and	(19)

			TG (plasma); ↑pAMPK (skeletal muscle and visceral adipose); ↑LPL (plasma and skeletal muscle); ↓LPL (visceral adipose)	triglyceride metabolism	
	Obese db/db mice		↑Energy expenditure; ↓weight gain; ↓hepatic steatosis; ↑cold tolerance; ↑BAT activity; ↑transcription of UCP1; ↑mitochondrial number and function	Prevent and control obesity	(20)
	HepG2 cells		↑AMPK; induce ACC phosphorylation and inactivation; ↓malonyl CoA; ↑CPT-1; ↑fatty acid oxidation; AMPK-dependent signaling pathway	Prevent and treat NFLD	(21)

Supplementary Table 4 Plant sources, pharmacological activity and potential mechanism of Phenolic acids.

Compounds	**Models**	**Sources**	**Molecular mechanisms**	**Pharmacological effects**	**References**
Caffeic acid	C57BL/6 mice fed with HFD	Coffee	↓Visceral fat mass, plasma GOT and GPT levels, FAS activity, and FFA; ↓TG and TC (plasma and liver); ↓cholesterol biosynthesis; ↓lipogenesis; ↑p -AMPK; ↓acetyl carboxylase; ↓lipogenic enzymes and hepatic lipid accumulation	Prevent Hyperlipidemia and Obesity	(22)
	HUVEC; THP-1 Monocytes		↓VCAM-1, ICAM-1, and E-selectin and monocyte expression of β1, β2, and α4 integrins; ↓THP-1 cell adhesion on activated endothelium; ↓IL-8 production and TLR4 induction; ↓NF-κB signaling	Preventing obesity-associated atherosclerosis.	(23)
	endothelial dysfunction induced by HG in HUVECs		↑Nrf2/EpRE pathway; ↓nuclear translocation of NF-κB, endothelial adhesion molecule 1	Treat inflammation and oxidative stress	(24)
	high fat diet-induced obese mice; AML12 cells		↓Lipid accumulation and lipogenesis markers; ↓ER stress markers; ↑autophagy markers; ↓Lipid accumulation (liver); ↑Glucose intolerance and insulin 2 sensitivity	Ameliorates hepatic steatosis and decreased ER stress	(25)
	YPEN-1 cells		↓COX-2; ↓NF-κB targeting gene; c-Src/ERK and NIK/IKK pathways	Anti-inflammatory	(26)
	STZ-induced diabetic rats		↓Renal damage; ↓fasting blood glucose, TC and TG; ↓miR-	Treat DN	(27)

			636(kidney)		
	Endothelial cells		↓Glucose uptake; ↓actin rearrangement and FITC-dextran passage; ↓caspase 8 and 9; ↓caspase 7 and 3; ↑p-Bcl-2; ↓p65 subunit nuclear levels; ↓NF-κB signaling pathway	Treat T2DM	(28)
	C57BL/KsJ-db/db Mice		↓Blood glucose and glycosylated hemoglobin; ↑plasma insulin, C-peptide, and leptin; ↓plasma glucagon; ↑glucokinase and glycogen; ↓G6Pase and PEPCK; ↓GLUT2 expression (liver); ↑GLUT4 (adipocyte); ↑SOD, CAT, and GSH-Px; ↓hydrogen peroxide and TBARS (erythrocyte and liver)	Antihyperglycemic and Antioxidant Properties	(29)
	Carrageenan-induced acute inflammation in adult male albino rats		↓MDA; ↓NO; ↓IL-1β; ↓TNF-α; ↓NF-κB; ↑IL-10	Anti-inflammation	(30)
	THP-1 cells; CCD-18Co		↓Colon fibroblast migration; ↓monocyte adhesion to fibroblasts; ↓PGE2, PAI-1, and IL-8	Improve the inflammatory response of colon fibroblasts	(31)
	HFD/STZ-induced T2DM Wistar albino rats; rat NRK 52E proximaltubular epithelial cells		↓Renal dysfunction and oxidative stress; ↓NF-κB; ↓TGF-β; ↓fibronectin; ↓IL-1β, IL-6 and TNF-α; ↓NF-κB pathway	Treat diabetic nephropathy	(32)
Ellagic acid	3T3-L1 murineadipocytes and RAW 264.7 macrophages	Pomegranate	↓TNFα and CCL-2 macrophage secretion, ↓CCL-2 adipocyte secretion; ↓IL-6	Anti-inflammatory	(33)
	Colon cancer induced by 1,2-dimethylhydrazine in Male Wistar albino rats		↓NF-κB, COX-2, iNOS, TNF-a and IL-6	Anti-cancer	(34)
	Nicotine-induced toxicity in rat peripheral blood lymphocytes		↑SOD, CAT and GPx; ↑GSH, Vitamins A, E and C; ↑lipid peroxidative index, severity in DNA damage and micronuclei number	Antioxidant	(35)
	HaCaT		↑HaCaT cell viability; ↓ROS; ↓MDA; ↓DNA damage; ↓apoptosis of HaCaT cells; ↓DNA fragmentation; ↓mitochondria function; ↑ER	Antioxidant	(36)

			stress; ↑caspase-3; ↓Bcl-2/Bax; ↑HO-1 and SOD; ↓Keap1; ↑nuclear translocation and transcriptional activation of Nrf2		
	3T3-L1 adipocytes; RAW 264.7 macrophages; Diet-induced obese mice		↑Adipocyte differentiation; ↓MCP-1; ↑adiponectin, upstream mediator PPARγ; ↓inflammatory mediator expression; ↓TC (serum); ↓adipocyte size; ↑insulin sensitivity; ↓IL-6, iNOS, COX-2, F4/80, and SREBP-1(adipose tissue)	Treat insulin resistance and dyslipidemia	(37)
	Diabetic rats		↓TC, TG, VLDL-c, TNF-α, blood glucose, HDL-c, MDA, TAC and IL-6; ↑miR-126, miR -24	Improve inflammation, oxidative stress and hypotension	(38)
	Type 2 diabetic rats		↓TNF-α; ↑PPARγ and adiponectin	Antidiabetic action	(39)
	REF cells and pancreatic islet cells		↓β-galactosidase activity; ↓ROS; ↑FARP, thiol; ↓TNF-α, IL-1β and NF-Kb; ↓G0/G1 phase; ↑function of the β cells; ↓caspase-9 activity	Anti-aging and antidiabetic effects	(40)
Gallic acid	3T3-L1 preadipocytes; db/db mice; fructose administered rats	Gallnuts; grapes; tea leaves; oak bark; blackberry and pomegranates; Pomegranate Flower; Berries; fruits; grapes; *Emblica officinalis;* Teas; pequi (*Caryocar brasiliense* Camb.); wine; *Terminalia bellirica*	↑C/EBPs, PPAR-γ, Glut4 translocation; ↑PPAR-γ and Akt signaling	Antidiabetic potential	(40)
	Mouse model of HFD-and STZ-induced NAFLD and diabetes		↓blood glucose; ↓progression of NAFLD; ↑β-oxidation and ketogenesis	Treat MS	(41)
	Swiss male mice fed with HFD		↑SIRT1 (brown adipose tissue)	Improve body metabolism, glucose homeostasis and increase thermogenesis	(42)
	Swiss male mice fed with HFD		↓liver steatosis, body weight and plasma insulin; ↓ACC and FAS	Prevent liver diseases	(43)
	STZ induced DN model		↓creatinine and blood urea nitrogen(plasma); ↑protein and albumin; ↑creatinine clearance ↓oxidative stress (kidney tissues); ↓circulating and tissue levels of TGF-β1	Treat DN	(44)
	Mouse 3T3-L1 cells		↑adiponectin; ↑adipocyte differentiation	Treat MS	(45)

Supplementary Table 5 Plant sources, pharmacological activity and potential mechanism of Tannin.

Compounds	Models	Sources	Molecular mechanisms	Pharmacological effects	References
1,2,3,4,6-penta-O-galloyl-β-D-glucose	3T3-L1 cells	Radix *Paeoniae* Alba; *Rhus chinensis* Mill.; *Schinus terebinthifolius*; *Paeonia lactiflora*; *Spirogyra varians*; *Mangifera indica*; *Lagerstroemia speciosa* (banaba); *Mangifera indica*	↓Adipogenesis, inflammation; ↓lipids accumulation; ↓PPARγ, C/EBPα, SREBP-1; ↓MAPKs; ↓ACC, FAS, and SCD-1; ↓IL-6 and MCP-1; ↓MAPKs and NF-κB activation	Treat chronic inflammation	(46)
	HFD-induced mouse model of NAFLD		↓Liver steatosis, andleukocyte infiltration; ↓TG and glucose (serum); ↓mRNA expression of Hmgcr, Acc1, Abca1, Mttp, and Cd36 (livers); ↓CD36 pro; ↓hepatic steatosis	Treat NAFLD	(47)
	3T3-L1 adipocytes Genetically diabetic db/db mice obese ob/ob mice		↓p-IR, p-Akt; ↑PI 3-kinase; ↑membrane translocation of GLUT 4; ↓blood glucose; ↑insulin-mediated glucosetransport signaling pathway	Anti-diabetic and anti-MS	(48)
	HFD-induced diabetes in C57BL/6 mice		↓11β-HSD-1 (liver and adipose tissue)	Antidiabetic	(49)
Punicalagin	HFD-fed mice 3T3-L1 cells RAW264.7 cells	Pomegranate (*Punica granatum*)	↓Lipid accumulation, inflammatory responses; ↓NF-κB; ↑Nrf2/Keap1 signaling pathway	Control obesity-mediated diseases	(50)
	hyperlipidemic mice HepG2 cells		↓Lipids and liver damage markers (serum); ↓lipid accumulation(liver); ↓hepatic oxidative stress; ↑Nrf2-mediated antioxidant pathway; ↑mitochondrial complex activities(hepatic); ↑mitochondrial DNA copy number; ↑PGC-1α-mediated mitochondrial biogenesis pathway; ↑mitochondrial fusion-related proteins; ↓TG and TC; ↑Nrf2 and mitochondrial biogenesis pathways	Improves hepatic lipid metabolism	(51)
	HepG2 cells		↑Keap1-Nrf2 cytoprotective signaling pathway;	Treat NAFLD	(52)

		↓mitochondrial membrane potential lost, ATP depletion, and ROS; ↑hepatocyte viability; ↓mitochondria-mediated caspase-dependent apoptosis; ↑phosphorylation of extracellular signal regulated kinase; ↑Nrf2 nuclear translocation and target genes induction		
	mice model for diabetes induced by HFD/STZ	↓TXNIP/NLRP3 Pathway; ↓BUN, CREA, UACR; ↓pyroptosis ↓IL-1β, caspase-1, GSDMD, NLRP3; ↓NOX4; ↓mitochondria damage; ↓dissociation of Trx and TXNIP; ↓suppression of NLRP3 inflammasome activation	Protects DN	(53)
	HFD-induced obesity rats cardiomyocytes	↓TG and TC (hearts); ↓myocardial damage; ↑AMPK pathway; ↑mitochondrial biogenesis, prevent mitochondrial loss; ↑phase II enzymes (hearts); ↓oxidative stress; ↓cellular ATP/ADP ratio (cardiomyocytes)	Prevent cardiac metabolic disorders	(54)
	WD-fed mice	↓Fat content; ↓alanine transaminase; ↓inflammation (liver); ↓adiponectin signaling and lipid metabolism (visceral adipose tissue); ↑gut barrier function	Treat NAFLD	(55)
	STZ/HFD induced diabetic mice; glucosamine-induced HepG2 cells HG-induced HK-2 cells	↓gluconeogenesis; ↑glycogenesis; ↓PI3K/AKT signaling pathway; ↑HMGB-1/TLR4/NF-κB signaling pathway	Hypoglycemic effects	(56)
	HepG2 cells	↓LDs and perilipin 2	Treat hepatic steatosis	(57)

Supplementary Table 6 Plant sources, pharmacological activity and potential mechanism of another non-flavonoid.

Compounds	Models	Sources	Molecular mechanisms	Pharmacological effects	References
Curcumin	Mice fed with HFD; 3T3-L1 adipocyte	*Curcuma longa* (turmeric)	↑Apoptosis (3T3-L1); ↓adipokine-induced angiogenesis of HUVECs; ↓body weight gain, adiposity, and microvessel density in adipose tissue; ↓VEGF, VEGFR-2; ↑p-AMPK; ↓GPAT-1; ↑CPT-1; ↑oxidation; ↓fatty acid esterification; ↓TC (serum); ↓PPARγ and C/EBP-α	prevent obesity	(58)
	Mice fed with MCD diet		↓Activation of NF-κB; ↓ICAM-1, COX-2 and MCP-1	Treat hepatic inflammation	(59)
	Mice models of STZ-induced by MCD		↓TNF-α, IL-6; ↑PPAR-γ; ↓NF-κB	anti-inflammatory	(60)
	HFD-induced obese and leptin-deficient ob/ob male C57BL/6J mice		↓Macrophage infiltration (white adipose tissue); ↑adiponectin (adipose tissue); ↓hepatic NF-κB activity, hepatomegaly, and markers of hepatic inflammation	Treat inflammatory and metabolic derangements	(61)
	MCD diet mice		↓Fat accumulation and hepatic injury; ↓hepatic inflammation; ↓dependence of O-GlcNAcylation on NF-κB; ↑SOD1, SIRT1; ↓O-GlcNAcylation pathway	Treat NAFLD	(62)
	STZ-induced diabetic mice model		↓Hyperglycemia/glucose intolerance, hypoinsulinemia, and damage of pancreatic islets; ↑islet regeneration/insulin secretion; ↓pancreatic lipid-peroxidation; ↑antioxidant enzymes; ↓TNF-α and IL-1β	antioxidant and anti-inflammatory effects	(63)
	Fructose-fed rats		↓insulin and leptin; ↑p-IR and p-IRS1; ↑Akt, ERK1/2; ↑p-JAK 2; ↓SOC3; ↑PPARα; ↓VLDL, TG; ↓PTP1B	Treat hepatic steatosis	(64)
	Human hepatoma HepG2 cells		↓Lipid accumulation, TG and TC; ↓SREBP-1, and FAS; ↑PPARα; ↑p-AMPK (hepatocytes)	Prevent fatty liver	(65)
	MCD-induced-nonalcoholic steatohepatitis mice model human HSCs		↓ALT (serum); ↓necro-inflammation; ↓oxidative stress(hepatic); ↓Fibrosis; ↓MCP-1, CD11b, procollagen type I and TIMP-1; ↓α-smooth muscle-actin; ↓ROS	antifibrotic	(66)
Hydroxytyrosol	HFD-induced diabetic mouse model; db/db diabetic mouse model	Olive oil	↓SREBP-1c/FAS pathway; ↓lipid deposits; ↑antioxidant enzyme activities; ↓apoptosis activation; ↓mitochondrial carbonyl protein, ↑mitochondrial	Prevent MS	(67)

		complex activities; Db/db; ↓fasting glucose; ↓serum lipid; ↓oxidation levels of lipids and proteins; ↓muscle mitochondrial carbonyl protein; ↑mitochondrial complex activities		
	The aorta of male Lewis rats	Protect the aorta against relaxation impairment; ↓OH•	antioxidant	(68)
	Mouse peritoneal macrophages	↓iNOS; ↓nitric oxide; ↑TNF-α	Anti-inflammation	(69)

References

1. Alsaggar M, Bdour S, Ababneh Q, El-Elimat T, Qinna N, Alzoubi KH. Silibinin Attenuates Adipose Tissue Inflammation and Reverses Obesity and Its Complications in Diet-Induced Obesity Model in Mice. *BMC pharmacology & toxicology* (2020) 21(1):8. Epub 2020/01/25. doi: 10.1186/s40360-020-0385-8.
2. Yao J, Zhi M, Gao X, Hu P, Li C, Yang X. Effect and the Probable Mechanisms of Silibinin in Regulating Insulin Resistance in the Liver of Rats with Non-Alcoholic Fatty Liver. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas* (2013) 46(3):270-7. Epub 2013/03/28. doi: 10.1590/1414-431x20122551.
3. Dong Z, Zhang W, Chen S, Liu C. Silibinin a Decreases Statin-Induced Pcsk9 Expression in Human Hepatoblastoma Hepg2 Cells. *Molecular medicine reports* (2019) 20(2):1383-92. Epub 2019/06/08. doi: 10.3892/mmr.2019.10344.
4. Chu C, Gao X, Li X, Zhang X, Ma R, Jia Y, et al. Involvement of Estrogen Receptor-A in the Activation of Nrf2-Antioxidative Signaling Pathways by Silibinin in Pancreatic B-Cells. *Biomolecules & therapeutics* (2020) 28(2):163-71. Epub 2019/10/28. doi: 10.4062/biomolther.2019.071.
5. Xu F, Yang J, Negishi H, Sun Y, Li D, Zhang X, et al. Silibinin Decreases Hepatic Glucose Production through the Activation of Gut-Brain-Liver Axis in Diabetic Rats. *Food & function* (2018) 9(9):4926-35. Epub 2018/09/05. doi: 10.1039/c8fo00565f.
6. Pummoung S, Werawatganon D, Chayanupatkul M, Klaikeaw N, Siriviriyakul P. Genistein Modulated Lipid Metabolism, Hepatic Pparγ, and Adiponectin Expression in Bilateral Ovariectomized Rats with Nonalcoholic Steatohepatitis (Nash). *Antioxidants (Basel, Switzerland)* (2020) 10(1). Epub 2021/01/02. doi: 10.3390/antiox10010024.
7. Gan M, Shen L, Wang S, Guo Z, Zheng T, Tan Y, et al. Genistein Inhibits High Fat Diet-Induced Obesity through Mir-222 by Targeting Btg2 and Adipor1. *Food & function* (2020) 11(3):2418-26. Epub 2020/03/05. doi: 10.1039/c9fo00861f.
8. Choi YR, Shim J, Kim MJ. Genistin: A Novel Potent Anti-Adipogenic and Anti-Lipogenic Agent. *Molecules (Basel, Switzerland)* (2020) 25(9). Epub 2020/05/01. doi:

10.3390/molecules25092042.

9. Zhao Y, Zhu Y, Wang P, Sang S. Dietary Genistein Reduces Methylglyoxal and Advanced Glycation End Product Accumulation in Obese Mice Treated with High-Fat Diet. *Journal of agricultural and food chemistry* (2020) 68(28):7416-24. Epub 2020/06/24. doi: 10.1021/acs.jafc.0c03286.
10. Ohno T, Kato N, Ishii C, Shimizu M, Ito Y, Tomono S, et al. Genistein Augments Cyclic Adenosine 3'5'-Monophosphate(Camp) Accumulation and Insulin Release in Min6 Cells. *Endocrine research* (1993) 19(4):273-85. Epub 1993/12/01. doi: 10.1080/07435809309026682.
11. Zhang Y, Lian F, Zhu Y, Xia M, Wang Q, Ling W, et al. Cyanidin-3-O-Beta-Glucoside Inhibits Lps-Induced Expression of Inflammatory Mediators through Decreasing Ikappabalpha Phosphorylation in Thp-1 Cells. *Inflammation research : official journal of the European Histamine Research Society [et al]* (2010) 59(9):723-30. Epub 2010/03/24. doi: 10.1007/s00011-010-0183-7.
12. Du C, Shi Y, Ren Y, Wu H, Yao F, Wei J, et al. Anthocyanins Inhibit High-Glucose-Induced Cholesterol Accumulation and Inflammation by Activating Lxrα Pathway in Hk-2 Cells. *Drug design, development and therapy* (2015) 9:5099-113. Epub 2015/09/18. doi: 10.2147/dddt.s90201.
13. Molonia MS, Occhiuto C, Muscarà C, Speciale A, Bashllari R, Villarroya F, et al. Cyanidin-3-O-Glucoside Restores Insulin Signaling and Reduces Inflammation in Hypertrophic Adipocytes. *Archives of biochemistry and biophysics* (2020) 691:108488. Epub 2020/07/22. doi: 10.1016/j.abb.2020.108488.
14. Sasaki R, Nishimura N, Hoshino H, Isa Y, Kadowaki M, Ichi T, et al. Cyanidin 3-Glucoside Ameliorates Hyperglycemia and Insulin Sensitivity Due to Downregulation of Retinol Binding Protein 4 Expression in Diabetic Mice. *Biochemical pharmacology* (2007) 74(11):1619-27. Epub 2007/09/18. doi: 10.1016/j.bcp.2007.08.008.
15. Lee JS, Kim YR, Park JM, Kim YE, Baek NI, Hong EK. Cyanidin-3-Glucoside Isolated from Mulberry Fruits Protects Pancreatic Β-Cells against Glucotoxicity-Induced Apoptosis. *Molecular medicine reports* (2015) 11(4):2723-8. Epub 2014/12/17. doi: 10.3892/mmr.2014.3078.
16. Guo H, Xia M, Zou T, Ling W, Zhong R, Zhang W. Cyanidin 3-Glucoside Attenuates Obesity-Associated Insulin Resistance and Hepatic Steatosis in High-Fat Diet-Fed and Db/Db Mice Via the Transcription Factor Foxo1. *The Journal of nutritional biochemistry* (2012) 23(4):349-60. Epub 2011/05/06. doi: 10.1016/j.jnutbio.2010.12.013.
17. Liu Y, Li D, Zhang Y, Sun R, Xia M. Anthocyanin Increases Adiponectin Secretion and Protects against Diabetes-Related Endothelial Dysfunction. *American journal of physiology Endocrinology and metabolism* (2014) 306(8):E975-88. Epub 2014/03/07. doi: 10.1152/ajpendo.00699.2013.
18. Matsukawa T, Villareal MO, Motojima H, Isoda H. Increasing Camp Levels of Preadipocytes by Cyanidin-3-Glucoside Treatment Induces the Formation of Beige Phenotypes in 3t3-L1 Adipocytes. *The Journal of nutritional biochemistry* (2017) 40:77-85. Epub 2016/11/20. doi: 10.1016/j.jnutbio.2016.09.018.
19. Wei X, Wang D, Yang Y, Xia M, Li D, Li G, et al. Cyanidin-3-O-Β-Glucoside Improves Obesity and Triglyceride Metabolism in Kk-Ay Mice by Regulating Lipoprotein

Lipase Activity. *Journal of the science of food and agriculture* (2011) 91(6):1006-13. Epub 2011/03/02. doi: 10.1002/jsfa.4275.

20. You Y, Yuan X, Liu X, Liang C, Meng M, Huang Y, et al. Cyanidin-3-Glucoside Increases Whole Body Energy Metabolism by Upregulating Brown Adipose Tissue Mitochondrial Function. *Molecular nutrition & food research* (2017) 61(11). Epub 2017/07/12. doi: 10.1002/mnfr.201700261.
21. Guo H, Liu G, Zhong R, Wang Y, Wang D, Xia M. Cyanidin-3-O-B-Glucoside Regulates Fatty Acid Metabolism Via an Amp-Activated Protein Kinase-Dependent Signaling Pathway in Human Hepg2 Cells. *Lipids in health and disease* (2012) 11:10. Epub 2012/01/17. doi: 10.1186/1476-511x-11-10.
22. Liao CC, Ou TT, Wu CH, Wang CJ. Prevention of Diet-Induced Hyperlipidemia and Obesity by Caffeic Acid in C57bl/6 Mice through Regulation of Hepatic Lipogenesis Gene Expression. *Journal of agricultural and food chemistry* (2013) 61(46):11082-8. Epub 2013/10/26. doi: 10.1021/jf4026647.
23. Lee ES, Park SH, Kim MS, Han SY, Kim HS, Kang YH. Caffeic Acid Disturbs Monocyte Adhesion onto Cultured Endothelial Cells Stimulated by Adipokine Resistin. *Journal of agricultural and food chemistry* (2012) 60(10):2730-9. Epub 2012/02/24. doi: 10.1021/jf203774y.
24. Fratantonio D, Speciale A, Canali R, Natarelli L, Ferrari D, Saija A, et al. Low Nanomolar Caffeic Acid Attenuates High Glucose-Induced Endothelial Dysfunction in Primary Human Umbilical-Vein Endothelial Cells by Affecting Nf-Kb and Nrf2 Pathways. *BioFactors (Oxford, England)* (2017) 43(1):54-62. Epub 2016/07/15. doi: 10.1002/biof.1312.
25. Kim HM, Kim Y, Lee ES, Huh JH, Chung CH. Caffeic Acid Ameliorates Hepatic Steatosis and Reduces Er Stress in High Fat Diet-Induced Obese Mice by Regulating Autophagy. *Nutrition (Burbank, Los Angeles County, Calif)* (2018) 55-56:63-70. Epub 2018/07/01. doi: 10.1016/j.nut.2018.03.010.
26. Kim SR, Jung YR, Kim DH, An HJ, Kim MK, Kim ND, et al. Caffeic Acid Regulates Lps-Induced Nf-Kb Activation through Nik/Ikk and C-Src/Erk Signaling Pathways in Endothelial Cells. *Archives of pharmacal research* (2014) 37(4):539-47. Epub 2013/07/28. doi: 10.1007/s12272-013-0211-6.
27. Salem AM, Ragheb AS, Hegazy MGA, Matboli M, Eissa S. Caffeic Acid Modulates Mir-636 Expression in Diabetic Nephropathy Rats. *Indian journal of clinical biochemistry : IJCB* (2019) 34(3):296-303. Epub 2019/08/09. doi: 10.1007/s12291-018-0743-0.
28. Natarelli L, Ranaldi G, Leoni G, Roselli M, Guantario B, Comitato R, et al. Nanomolar Caffeic Acid Decreases Glucose Uptake and the Effects of High Glucose in Endothelial Cells. *PloS one* (2015) 10(11):e0142421. Epub 2015/11/07. doi: 10.1371/journal.pone.0142421.
29. Jung UJ, Lee MK, Park YB, Jeon SM, Choi MS. Antihyperglycemic and Antioxidant Properties of Caffeic Acid in Db/Db Mice. *The Journal of pharmacology and experimental therapeutics* (2006) 318(2):476-83. Epub 2006/04/29. doi: 10.1124/jpet.106.105163.
30. El-Shitany NA, El-Bastawissy EA, El-desoky K. Ellagic Acid Protects against Carrageenan-Induced Acute Inflammation through Inhibition of Nuclear Factor Kappa B,

Inducible Cyclooxygenase and Proinflammatory Cytokines and Enhancement of Interleukin-10 Via an Antioxidant Mechanism. *International immunopharmacology* (2014) 19(2):290-9. Epub 2014/02/19. doi: 10.1016/j.intimp.2014.02.004.

31. Giménez-Bastida JA, Larrosa M, González-Sarrías A, Tomás-Barberán F, Espín JC, García-Conesa MT. Intestinal Ellagitannin Metabolites Ameliorate Cytokine-Induced Inflammation and Associated Molecular Markers in Human Colon Fibroblasts. *Journal of agricultural and food chemistry* (2012) 60(36):8866-76. Epub 2012/04/03. doi: 10.1021/jf300290f.
32. Ahad A, Ganai AA, Mujeeb M, Siddiqui WA. Ellagic Acid, an Nf-Kb Inhibitor, Ameliorates Renal Function in Experimental Diabetic Nephropathy. *Chemico-biological interactions* (2014) 219:64-75. Epub 2014/06/01. doi: 10.1016/j.cbi.2014.05.011.
33. Winand J, Schneider YJ. The Anti-Inflammatory Effect of a Pomegranate Husk Extract on Inflamed Adipocytes and Macrophages Cultivated Independently, but Not on the Inflammatory Vicious Cycle between Adipocytes and Macrophages. *Food & function* (2014) 5(2):310-8. Epub 2013/12/18. doi: 10.1039/c3fo60443h.
34. Umesalma S, Sudhandiran G. Differential Inhibitory Effects of the Polyphenol Ellagic Acid on Inflammatory Mediators Nf-Kappab, Inos, Cox-2, Tnf-Alpha, and Il-6 in 1,2-Dimethylhydrazine-Induced Rat Colon Carcinogenesis. *Basic & clinical pharmacology & toxicology* (2010) 107(2):650-5. Epub 2010/04/22. doi: 10.1111/j.1742-7843.2010.00565.x.
35. Sudheer AR, Muthukumaran S, Devipriya N, Menon VP. Ellagic Acid, a Natural Polyphenol Protects Rat Peripheral Blood Lymphocytes against Nicotine-Induced Cellular and DNA Damage in Vitro: With the Comparison of N-Acetylcysteine. *Toxicology* (2007) 230(1):11-21. Epub 2006/12/26. doi: 10.1016/j.tox.2006.10.010.
36. Hseu YC, Chou CW, Senthil Kumar KJ, Fu KT, Wang HM, Hsu LS, et al. Ellagic Acid Protects Human Keratinocyte (Hacat) Cells against Uva-Induced Oxidative Stress and Apoptosis through the Upregulation of the Ho-1 and Nrf-2 Antioxidant Genes. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association* (2012) 50(5):1245-55. Epub 2012/03/06. doi: 10.1016/j.fct.2012.02.020.
37. Tanaka M, Sugama A, Sumi K, Shimizu K, Kishimoto Y, Kondo K, et al. Gallic Acid Regulates Adipocyte Hypertrophy and Suppresses Inflammatory Gene Expression Induced by the Paracrine Interaction between Adipocytes and Macrophages in Vitro and in Vivo. *Nutrition research (New York, NY)* (2020) 73:58-66. Epub 2019/12/17. doi: 10.1016/j.nutres.2019.09.007.
38. Ramezani Ali Akbari F, Badavi M, Dianat M, Mard SA, Ahangarpour A. Gallic Acid Improves Oxidative Stress and Inflammation through Regulating Micrornas Expressions in the Blood of Diabetic Rats. *Acta endocrinologica (Bucharest, Romania : 2005)* (2019) 15(2):187-94. Epub 2019/09/12. doi: 10.4183/aeb.2019.187.
39. Abdel-Moneim A, El-Twab SMA, Yousef AI, Reheim ESA, Ashour MB. Modulation of Hyperglycemia and Dyslipidemia in Experimental Type 2 Diabetes by Gallic

Acid and P-Coumaric Acid: The Role of Adipocytokines and Pparγ. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* (2018) 105:1091-7. Epub 2018/07/20. doi: 10.1016/j.biopha.2018.06.096.

40. Rahimifard M, Baeeri M, Bahadar H, Moini-Nodeh S, Khalid M, Haghi-Aminjan H, et al. Therapeutic Effects of Gallic Acid in Regulating Senescence and Diabetes; an in Vitro Study. *Molecules (Basel, Switzerland)* (2020) 25(24). Epub 2020/12/17. doi: 10.3390/molecules25245875.

41. Chao J, Cheng HY, Chang ML, Huang SS, Liao JW, Cheng YC, et al. Gallic Acid Ameliorated Impaired Lipid Homeostasis in a Mouse Model of High-Fat Diet-and Streptozotocin-Induced Nafld and Diabetes through Improvement of Β-Oxidation and Ketogenesis. *Frontiers in pharmacology* (2020) 11:606759. Epub 2021/03/02. doi: 10.3389/fphar.2020.606759.

42. Paraíso AF, Sousa JN, Andrade JMO, Mangabeira ES, Lelis DF, de Paula AMB, et al. Oral Gallic Acid Improves Metabolic Profile by Modulating Sirt1 Expression in Obese Mice Brown Adipose Tissue: A Molecular and Bioinformatic Approach. *Life sciences* (2019) 237:116914. Epub 2019/10/18. doi: 10.1016/j.lfs.2019.116914.

43. Sousa JN, Paraíso AF, Andrade JMO, Lelis DF, Santos EM, Lima JP, et al. Oral Gallic Acid Improve Liver Steatosis and Metabolism Modulating Hepatic Lipogenic Markers in Obese Mice. *Experimental gerontology* (2020) 134:110881. Epub 2020/02/23. doi: 10.1016/j.exger.2020.110881.

44. Garud MS, Kulkarni YA. Gallic Acid Attenuates Type I Diabetic Nephropathy in Rats. *Chemico-biological interactions* (2018) 282:69-76. Epub 2018/01/15. doi: 10.1016/j.cbi.2018.01.010.

45. Makihara H, Koike Y, Ohta M, Horiguchi-Babamoto E, Tsubata M, Kinoshita K, et al. Gallic Acid, the Active Ingredient of Terminalia Bellirica, Enhances Adipocyte Differentiation and Adiponectin Secretion. *Biological & pharmaceutical bulletin* (2016) 39(7):1137-43. Epub 2016/07/05. doi: 10.1248/bpb.b16-00064.

46. Peng J, Li K, Zhu W, Nie R, Wang R, Li C. Penta-O-Galloyl-Β-D-Glucose, a Hydrolysable Tannin from Radix Paeoniae Alba, Inhibits Adipogenesis and Tnf-Α-Mediated Inflammation in 3t3-L1 Cells. *Chemico-biological interactions* (2019) 302:156-63. Epub 2019/02/06. doi: 10.1016/j.cbi.2019.01.037.

47. Kant R, Lu CK, Nguyen HM, Hsiao HH, Chen CJ, Hsiao HP, et al. 1,2,3,4,6 Penta-O-Galloyl-Β-D-Glucose Ameliorates High-Fat Diet-Induced Nonalcoholic Fatty Liver Disease and Maintains the Expression of Genes Involved in Lipid Homeostasis in Mice. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* (2020) 129:110348. Epub 2020/06/20. doi: 10.1016/j.biopha.2020.110348.

48. Li Y, Kim J, Li J, Liu F, Liu X, Himmeldirk K, et al. Natural Anti-Diabetic Compound 1,2,3,4,6-Penta-O-Galloyl-D-Glucopyranose Binds to Insulin Receptor and Activates Insulin-Mediated Glucose Transport Signaling Pathway. *Biochemical and biophysical research communications* (2005) 336(2):430-7. Epub 2005/09/03. doi: 10.1016/j.bbrc.2005.08.103.

49. Mohan CG, Viswanatha GL, Savinay G, Rajendra CE, Halemani PD. 1,2,3,4,6 Penta-O-Galloyl-Β-D-Glucose, a Bioactivity Guided Isolated Compound from Mangifera Indica Inhibits 11β-Hsd-1 and Ameliorates High Fat Diet-Induced Diabetes in C57bl/6 Mice. *Phytomedicine : international journal of phytotherapy and phytopharmacology* (2013) 20(5):417-26. Epub 2013/01/29. doi: 10.1016/j.phymed.2012.12.020.

50. Kang B, Kim CY, Hwang J, Jo K, Kim S, Suh HJ, et al. Punicalagin, a Pomegranate-Derived Ellagitannin, Suppresses Obesity and Obesity-Induced Inflammatory Responses Via the Nrf2/Keap1 Signaling Pathway. *Molecular nutrition & food research* (2019) 63(22):e1900574. Epub 2019/08/25. doi: 10.1002/mnfr.201900574.

51. Cao K, Wang K, Yang M, Liu X, Lv W, Liu J. Punicalagin Improves Hepatic Lipid Metabolism Via Modulation of Oxidative Stress and Mitochondrial Biogenesis in Hyperlipidemic Mice. *Food & function* (2020) 11(11):9624-33. Epub 2020/09/26. doi: 10.1039/d0fo01545h.

52. Yan C, Sun W, Wang X, Long J, Liu X, Feng Z, et al. Punicalagin Attenuates Palmitate-Induced Lipotoxicity in Hepg2 Cells by Activating the Keap1-Nrf2 Antioxidant Defense System. *Molecular nutrition & food research* (2016) 60(5):1139-49. Epub 2016/03/19. doi: 10.1002/mnfr.201500490.

53. An X, Zhang Y, Cao Y, Chen J, Qin H, Yang L. Punicalagin Protects Diabetic Nephropathy by Inhibiting Pyroptosis Based on Txnip/Nlrp3 Pathway. *Nutrients* (2020) 12(5). Epub 2020/05/28. doi: 10.3390/nu12051516.

54. Cao K, Xu J, Pu W, Dong Z, Sun L, Zang W, et al. Punicalagin, an Active Component in Pomegranate, Ameliorates Cardiac Mitochondrial Impairment in Obese Rats Via Ampk Activation. *Scientific reports* (2015) 5:14014. Epub 2015/09/16. doi: 10.1038/srep14014.

55. Liu H, Zhan Q, Miao X, Xia X, Yang G, Peng X, et al. Punicalagin Prevents Hepatic Steatosis through Improving Lipid Homeostasis and Inflammation in Liver and Adipose Tissue and Modulating Gut Microbiota in Western Diet-Fed Mice. *Molecular nutrition & food research* (2021) 65(4):e2001031. Epub 2020/12/29. doi: 10.1002/mnfr.202001031.

56. Jin D, Zhang B, Li Q, Tu J, Zhou B. Effect of Punicalagin on Multiple Targets in Streptozotocin/High-Fat Diet-Induced Diabetic Mice. *Food & function* (2020) 11(12):10617-34. Epub 2020/11/20. doi: 10.1039/d0fo01275k.

57. Korovila I, Jung T, Deubel S, Grune T, Ott C. Punicalagin Attenuates Palmitate-Induced Lipid Droplet Content by Simultaneously Improving Autophagy in Hepatocytes. *Molecular nutrition & food research* (2020) 64(20):e2000816. Epub 2020/09/13. doi: 10.1002/mnfr.202000816.

58. Ejaz A, Wu D, Kwan P, Meydani M. Curcumin Inhibits Adipogenesis in 3t3-L1 Adipocytes and Angiogenesis and Obesity in C57/Bl Mice. *The Journal of nutrition* (2009) 139(5):919-25. Epub 2009/03/20. doi: 10.3945/jn.108.100966.

59. Leclercq IA, Farrell GC, Sempoux C, dela Peña A, Horsmans Y. Curcumin Inhibits Nf-Kappab Activation and Reduces the Severity of Experimental Steatohepatitis in

Mice. *Journal of hepatology* (2004) 41(6):926-34. Epub 2004/12/08. doi: 10.1016/j.jhep.2004.08.010.

60. Wang Y, Li J, Zhuge L, Su D, Yang M, Tao S, et al. Comparison between the Efficacies of Curcumin and Puerarin in C57bl/6 Mice with Steatohepatitis Induced by a Methionine- and Choline-Deficient Diet. *Experimental and therapeutic medicine* (2014) 7(3):663-8. Epub 2014/02/13. doi: 10.3892/etm.2013.1461.
61. Weisberg SP, Leibel R, Tortoriello DV. Dietary Curcumin Significantly Improves Obesity-Associated Inflammation and Diabetes in Mouse Models of Diabesity. *Endocrinology* (2008) 149(7):3549-58. Epub 2008/04/12. doi: 10.1210/en.2008-0262.
62. Lee DE, Lee SJ, Kim SJ, Lee HS, Kwon OS. Curcumin Ameliorates Nonalcoholic Fatty Liver Disease through Inhibition of O-Glcnacylation. *Nutrients* (2019) 11(11). Epub 2019/11/14. doi: 10.3390/nu11112702.
63. El-Azab MF, Attia FM, El-Mowafy AM. Novel Role of Curcumin Combined with Bone Marrow Transplantation in Reversing Experimental Diabetes: Effects on Pancreatic Islet Regeneration, Oxidative Stress, and Inflammatory Cytokines. *European journal of pharmacology* (2011) 658(1):41-8. Epub 2011/02/26. doi: 10.1016/j.ejphar.2011.02.010.
64. Li JM, Li YC, Kong LD, Hu QH. Curcumin Inhibits Hepatic Protein-Tyrosine Phosphatase 1b and Prevents Hypertriglyceridemia and Hepatic Steatosis in Fructose-Fed Rats. *Hepatology (Baltimore, Md)* (2010) 51(5):1555-66. Epub 2010/03/12. doi: 10.1002/hep.23524.
65. Kang OH, Kim SB, Seo YS, Joung DK, Mun SH, Choi JG, et al. Curcumin Decreases Oleic Acid-Induced Lipid Accumulation Via Ampk Phosphorylation in Hepatocarcinoma Cells. *European review for medical and pharmacological sciences* (2013) 17(19):2578-86. Epub 2013/10/22.
66. Vizzutti F, Provenzano A, Galastri S, Milani S, Delogu W, Novo E, et al. Curcumin Limits the Fibrogenic Evolution of Experimental Steatohepatitis. *Laboratory investigation; a journal of technical methods and pathology* (2010) 90(1):104-15. Epub 2009/11/11. doi: 10.1038/labinvest.2009.112.
67. Cao K, Xu J, Zou X, Li Y, Chen C, Zheng A, et al. Hydroxytyrosol Prevents Diet-Induced Metabolic Syndrome and Attenuates Mitochondrial Abnormalities in Obese Mice. *Free radical biology & medicine* (2014) 67:396-407. Epub 2013/12/10. doi: 10.1016/j.freeradbiomed.2013.11.029.
68. Rietjens SJ, Bast A, de Vente J, Haenen GR. The Olive Oil Antioxidant Hydroxytyrosol Efficiently Protects against the Oxidative Stress-Induced Impairment of the Nobullet Response of Isolated Rat Aorta. *American journal of physiology Heart and circulatory physiology* (2007) 292(4):H1931-6. Epub 2006/12/19. doi: 10.1152/ajpheart.00755.2006.
69. Takeda Y, Bui VN, Iwasaki K, Kobayashi T, Ogawa H, Imai K. Influence of Olive-Derived Hydroxytyrosol on the Toll-Like Receptor 4-Dependent Inflammatory Response of Mouse Peritoneal Macrophages. *Biochemical and biophysical research communications* (2014) 446(4):1225-30. Epub 2014/04/01. doi:

10.1016/j.bbrc.2014.03.094.