Lecture 2b - Annex B

Metabolic disease: mitochondrial remedies

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Astaxanthin

- In patients with T2D, 8mg/day for 8 weeks reduced visceral fat mass and triglycerides (Mashadi NS, Asia Pac J Clin Nutr, 2018)
- Astaxanthin can prevent and treat obesity in rodents, lowering blood glucose, insulin and triglycerides (Ojulari OV, Int J Mol Sci, 2020; Yang Y, Br J Nutr, 2014; Wang J, Mar Drugs, 2019; Arunkumar E, Food Funct, 2012).
- It also improves insulin signalling and sensitivity and glucose tolerance in insulin resistant mice (Bhuvaneswari S, Can J Physiol Pharmacol, 2012; Gao Y, Int J Mol Sci, 2020; Nishida Y, J Cachexia Sarcopenia Muscle, 2020).
- In diabetic rats, astaxanthin protected pancreatic mitochondrial function and antioxidant capacity, resulting in β-cell rejuvenation and restoration of insulin secretion and glycaemic control (Penislusshiyan S, Life Sci, 2020).
- Astaxanthin protects β-cells against glucotoxicity and prevents diabetic nephropathy in diabetic mice (Uchiyama K, Redox Rep, 2002; Naito Y, Biofactors, 2004).

B vitamins

- In paediatric patients with T1D, vitamin B complex decreased fasting blood glucose, HbA1c and triglycerides (Elbarbary NS, Clin Nutr, 2020).
- A meta-analysis found that folate supplementation decreased fasting insulin and insulin resistance (Lind MV, Am J Clin Nutr, 2019).
- In patients with metabolic syndrome, folate and vitamin B12 treatment lowered insulin levels and insulin resistance (Setola E, Eur J Endocrinol, 2004).
- In patients with T2D, folic acid lowered fasting blood glucose, insulin and HbA1c and vitamin B1 prevented diabetic neuropathy, while vitamin B12, particularly as methylcolbalamin, relieved pain (Gargari BP, Diabetes Res Clin Pract, 2011; Thornalley PJ, Curr Diabetes Rev, 2005; Sun Y, Acta Neurol Taiwan, 2005).
- In patients with diabetic neuropathy, 1mg/day folic acid for 16 weeks enhanced nerve conduction velocity (Mottaghi T, Neurol Res, 2019).
- In rodents fed a high fat diet, vitamin B6 lowered fasting blood glucose, normalised glucose tolerance and prevented development of insulin resistance (Abdullah KM, Toxicol Res, 2019; Liu Z, J Diabetes, Res, 2016).
- In diabetic rats, vitamin B3 lowered fasting blood glucose and triglycerides (Abdullah KM, Biomed Pharmacother, 2018; Zeb Shah T, Pak J Med Sci, 2013).

Note: patients on metformin may have a B12 deficiency.

β-lapachone (Pau d'Arco)

- A relatively newly discovered substance, derived from bark of the South American lapacho tree.
- No human studies yet but a 2019 obese mouse study found that β-lapachone prevented weight gain by inducing thermogenesis in brown adipocytes and also by inducing the browning of white adipocytes by upregulating UCP1 and AMPK and increasing mitochondrial number in BAT and mesenchymal stem cells (Kwak HJ, Am J Chin Med, 2019).
- A similar study found a reduction in diet-induced obesity and increased energy expenditure through the browning of WAT and increase in expression of UCP1 (Choi WH, Diabetes, 2016).
- In obese mice, β-lapachone reduced alcoholic fatty liver disease by stimulating fatty acid oxidation through activation of AMPK by increasing the NAD^+/NADH ratio (Shin S, Cell Signal, 2014).

Berberine

- A 2019 meta-analysis of 28 studies in >2300 subjects with T2D showed that berberine significantly lowered blood glucose and HbA1c, but was not effective if continued beyond 90 days, dosage exceeded 2g/day or the subjects were aged >60. There was an additive effect with oral glucose lowering agents. (Liang Y, Endocr J, 2019)
- A 2015 meta-analysis of T2D treatment showed that possibly due to few and low quality trials, berberine was no more effective than lifestyle interventions or medication (Lan J, J Ethnopharmacol, 2015). *However, by implication, this suggests that berberine is as effective as lifestyle intervention and medication.*
- Other RCTs have shown that 1500mg/day berberine for 12 weeks lowered waist circumference, obesity, blood glucose and insulin, insulin resistance and serum triglycerides (Hu Y, Phytomedicine, 2012; Pérez-Rubio KG, Metab Syndr Relat Disord; Yn J, Metabolism, 2008). A lesser dose of 1000mg/day failed to show a difference from the placebo, although glucose disposal was improved (Zhang Y, J Clin Endocrinol Metab, 2008).
- In animal or *in vitro* studies, berberine reduced body weight, improved glucose tolerance and lowered triglycerides (Lee YS, Diabetes, 2006; Turner N, Diabetes, 2008; Sun Y, Nutr Diabetes, 2018; Yerra VG, Neuropharmacology, 2018).

Butyrate (a short chain fatty acid)

- In males given 4 g/day sodium butyrate for 4 weeks, peripheral and hepatic insulin sensitivity was improved in lean subjects but not those with metabolic syndrome (Bouter K, Clin Transl Gastroenterol, 2018). *Could the dosage have been too low in metabolic syndrome patients?*
- In obese rodents, butyrate can reduce weight, obesity, triglycerides and insulin resistance, restore healthy glucose, insulin and leptin concentrations and prevent β-cell hyperplasia (Hong J, Oncotarget, 2016; Henagan TM, Br J Pharmacol, 2015; Jia Y, Exp Physiol, 2017; Mollica MP, Diabetes, 2017; Fang W, J Nutr, 2019; Li HP, Int J Clin Exp Pathol, 2013).
- In diabetic rats, sodium butyrate reduced plasma glucose, HbA1c, insulin resistance and gluconeogenesis to the same extent as metformin treatment (Khan S, Chem Biol Interact, 2016).
- In juvenile rats with T1D, sodium butyrate decreased plasma glucose, insulin, HbA1c and β-cell apoptosis and improved β-cell proliferation, function and glucose homeostasis (Khan S, Chem Biol Interact, 2014; Elgamal DA, Mol Cell Endocrinol, 2020).
- Sodium butyrate alleviated diabetic nephropathy in rats (Dong W, J Endocrinol, 2017).

Capsaicin (chili peppers)

- A 2018 meta-analysis found that capsaicin increased fat oxidation and energy expenditure in overweight or obese subjects (Zsiborás C, Crit Rev Food Sci Nutr, 2018).
- In healthy humans, capsaicin lowered blood glucose while maintaining insulin levels (Chaiyasit K, J Med Assoc Thai, 2009).
- In animal and *in vitro* studies, capsaicin lowered weight and body fat, improved insulin sensitivity and increased fat oxidation through browning of adipocytes and activation AMPK and UCP1 (Panchal SK, Nutrients, 2018).
- In type 1 diabetic rats, capsaicin and capsiate increased body weight, increased glycogen content, inhibited intestinal glucose absorption and raised insulin levels (Zhang S, J Agric Food Chem, 2017).

L-carnitine and Acetyl L-carnitine

- A 2016 meta-analysis of 9 RCTs of overweight adults showed that L-carnitine supplementation lowered weight and BMI, while a 2017 meta-analysis found that L-carnitine taken for at least 9 months was effective in treating insulin resistance.
- In subjects with impaired glucose tolerance or early T2D, 2g/day L-carnitine for 36 days restored metabolic flexibility to near control values, while 4g/day L-carnitine for 10 days decreased plasma insulin and insulin resistance and improved glucose tolerance.
- In patients with T2D, 2g/day L-carnitine for 6 months improved the efficacy of glimepiride in lowering fasting and post-prandial glucose, HbA1c, fasting insulin and insulin resistance but had no additional effect on BMI.
- Both L-carnitine and acetyl L-carnitine can improve insulin-mediated glucose disposal in healthy subjects and in type 2 diabetics. However, contradictory data exist concerning the outcomes of L-carnitine treatment in T2D.
- In patients with diabetic peripheral neuropathy, 1500mg/day acetyl L-carnitine induced reductions in symptoms and disability.
- Acetyl L-carnitine is better absorbed than L-carnitine and crosses the BBB more readily.

(Marcovina SM, Transl Res, 2013; Dambrova M, Exp Clin Endocrinol Diabetes, 2015; Li S, J Diabetes Investig, 2016; Mingrone G, Ann NY Acad Sci, 2004; Pooyandjoo M, Obes Rev, 2016; Cassano P, Biochim Biophys Acta, 2006; Bruls YM, EBioMedicine, 2019; Molfino A, JPEN J Parenter Enteral Nutr, 2010; El-Sheikh HM, Diabetes Metab Syndr, 2019)

Carnosine

- A meta-analysis of carnosine trials showed that HbA1c was reduced but there was no change in any other variable. Despite this, other studies have also shown a beneficial effect on fat mass, fasting plasma glucose, insulin and triglycerides. Carnosine can also reduce diabetic nephropathy in humans. In children with T2D, 1g/day for 12 weeks lowered HbA1c.
- An RCT of α-lipoic acid, carnosine and thiamine (vit B1) supplementation for 8 weeks lowered blood glucose and HbA1c in obese patients with T2D but appeared to increase insulin and insulin resistance, suggesting that the supplement upregulated insulin production to increase cellular glucose uptake.
- A supplement containing 1.2g/day cinnamon, chromium and carnosine given to moderately obese or overweight pre-diabetic subjects for 4 months decreased fasting plasma glucose and increased lean mass.
- Animal studies show that carnosine reduced weight gain and triglycerides, increased UCP-1 and prevented impairment of β-cell signalling and performance; it also prevented, reduced or delayed development of diabetes-induced osteoarthritis, nephropathy, atherosclerosis and retinopathy and enhanced diabetic wound healing.
- In animals, carnosinol, a carnosine analogue, lowered insulin resistance through scavenging of reactive carbonyl species (sugar- and lipid-derived aldehydes), i.e. diabetic glucolipotoxicity.

(Peng W, Complement Ther Med, 2020; Houjeghani S, Nutr Res, 2018; de Courten B, Obesity, 2016; Elbarbary NS, Pediatr Diabetes, 2018; Peters V, Curr Med Chem, 2020; Schaalan MF, J Cell Physiol, 2018; Aydın AF, Int J Exp Pathol, 2017; Vahdatpour T, J Diabetes Investig, 2019; Yang Y, Front Pharmacol, 2018; Albrecht T, Sci Rep, 2017; Menini S, Diabetologia, 2015; Guo Y, Exp Ther Med, 2019; Ansurudeen I, Amino Acids, 2012; Anderson EJ, J Clin Invest, 2018; Karkabounas S, J Med Food, 2018; Liu T, PLoS One, 2015)

Coenzyme Q10 (CoQ10)

- Meta-analyses found that CoQ10 supplementation reduced blood glucose in subjects with and without T2D (Stojanovic M, Nutr Res, 2017; Moradi M, Arch Iran Med, 2016).
- In South Koreans with prediabetes, CoQ10 for 8 weeks lowered insulin resistance and free radicals (Yoo JY, Biomed Res Int, 2018).
- In patients with T2D, 200mg/day CoQ10 for 12 weeks decreased weight, waist circumference and HbA1c but there was no difference in insulin or insulin resistance (Mehrdadi P, Exp Clin Endocrinol Diabetes, 2017).
- In patients with metabolic syndrome, 100mg/day CoQ10 for 8 weeks lowered serum insulin and insulin resistance, with no difference in plasma glucose (Raygan F, Eur J Nutr, 2016).
- In patients with diabetic nephropathy, a 2019 meta-analysis found that CoQ10 lowered fasting plasma glucose, HbA1c and triglycerides but was not significantly different to the control group (Zhang X, Medicine, 2019).
- In a mouse model of diabetic cardiomyopathy, CoQ10 improved all disease biomarkers (De Blasio MJ, Free Radic Biol Med, 2015).

Creatine

- Creatine is used by body-builders to gain weight (Kutz MR, J Strength Cond Res, 2003; Eckerson JM, J Strength Cond Res, 2008).
- Nevertheless, an RCT of 5g/day creatine for 12 weeks in subjects with T2D found that glucose and HbA1c were significantly reduced compared to placebo and there was increased skeletal muscle glucose uptake and GLUT-4 translocation, possibly due to higher AMPK levels. (Gualano B, Med Sci Sports Exerc, 2011)
- In subjects with T2D, 6g/day creatine reduced blood glucose to a similar extent to metformin, but had no effect on insulin, C-peptide or HbA1c (Rocic B, Clin Invest Med, 2009), while 10g/day over 3 months significantly improved glucose tolerance (Alves CR, Amino Acids, 2012).
- In vitro studies show that creatine reduces adipogenesis by downregulating insulin-induced activation of the phosphatidylinositol 3-kinase signaling pathway (Lee N, Stem Cells Dev, 2015).

Ginkgo biloba

- Diabetic subjects, already taking metformin, given 120mg/day ginkgo for 3 months showed decreased BMI and waist circumference and lowered glucose, insulin and HbA1c, although an earlier study found reduced HbA1c but no effect on BMI or glucose.
- In subjects with metabolic syndrome, ginkgo for 2 months significantly lowered insulin resistance.
- In patients with diabetic retinopathy, ginkgo increased retinal blood flow.
- In obese rodents, gingko reduced energy intake, prevented weight gain, reduced adipocyte volume, restored insulin sensitivity and protected against hyperglycaemia.
- In mice with T1D, ginkgo lowered weight, reduced triglyceride and glucose levels and increased insulin levels.
- In diabetic rats, ginkgo lowered body weight, blood glucose and triglycerides.
- Ginkgo improved glucose tolerance in insulin resistant hepatocytes and protected against diabetic nephropathy, diabetic cardiomyopathy and development of diabetic cataract.

(Aziz TA, Drug Des Devel Ther, 2018; Kudolo GB, Clin Nutr, 2006; Siegel G, Atherosclerosis, 2014; Huang SY, Clin Nutr, 2004; Banin RM, Front Pharmacol, 2017; Hosoda S, Nutrients, 2020; Hirata BKS, Front Endocrinol, 2019; Hirata BK, Mediators Inflamm, 2015; Banin RM, Braz J Med Biol Res, 2014; Zhou L, J Nat Med, 2011; Rhee KJ, Int J Med Sci, 2015; Cheng D, Biomed Res Int, 2013; Zhu R, Pak J Pharm Sci, 2018; Lu Q, Phytother Res, 2014; Qiu JY, Biomed Chromatogr, 2015; Lu Q, Acta Pharmacol Sin, 2007; Saini AS, Pharmacogn Mag, 2014.

Ginseng

- A 2016 meta-analysis showed that in patients with T2D, ginseng improved fasting plasma glucose, postprandial insulin, insulin resistance and triglycerides, but not fasting insulin or HbA1c (Gui QF, Medicine, 2016).
- Since then a study of patients with T2D showed that 3g per day Korean red (Panax) ginseng for 8 weeks lowered fasting blood glucose and HbA1c (Vuksan V, Eur J Nutr, 2019)
- In overweight or obese, non-diabetic adults, 6g/day Panax ginseng for 12 weeks did not improve insulin sensitivity (Cho YH, Asia Pak J Clin Nutr, 2013).
- A meta-analysis of human and animal studies found that withania somnifera (Indian ginseng) lowered blood glucose, insulin and HbA1c (Durg S, Phytother Res, 2020).
- In obese rodents, ginseng lowered weight, fat mass, adipocyte size, blood glucose and triglycerides and improved insulin sensitivity and signalling (Lee H, J Ethnopharmacol, 2016; Lee H, J Ethnopharmacol, 2014; Lee SH, Phytother Res, 2012).
- In diabetic rodents, Panax ginseng decreased blood glucose and increased serum insulin levels (Abdelazim A, Saudi J Biol Sci, 2019; Park SJ, J Ethnopharmacol, 2019). It could also help alleviate diabetic retinopathy (Yang H, J Ginseng Res, 2016).
- In mice with T1D ginseng increased weight, fasting plasma insulin and C-peptide but reduced weight, insulin an C-peptide in mice with T2D; blood glucose and HbA1c were reduced in both groups. This suggests that ginseng is adaptogenic and may cause regeneration of β-cells. (Sen S, J Med Food, 2013)
- In rodents, ginseng also improved diabetic hearing impairment (Hong BN, Evid Based Complement Alternat Med, 2013) and nephropathy (Kang, KS, Biol Pharm Bull, 2010) and prevented diabetic retinopathy and cardiomyopathy (Sen S, Phytother Res, 2013).

Supplementary ketones and medium chain triglycerides (MCTs)

- A 2015 meta-analysis of RCTs of MCTs showed decreased weight, waist circumference, hip circumference and subcutaneous and visceral fat (Mumme K, J Acad Nutr Diet, 2015).
- In a study of obese or overweight subjects, MCT oil for 6 weeks showed no significant change in fasting glucose, insulin, insulin resistance or fasting total ketones (Thomas DD, PLoS One, 2019).
- 18g/day MCT oil for 90 days in Chinese subjects with T2D showed a reduction in weight, waist circumference and insulin resistance, together with a reduction in energy intake (Han JR, Metabolism, 2007).
- A 2014 systematic review of MCTs in rodent studies found that some showed a decrease in food consumption and weight, while others found no difference (Ferreira L, J Anim Physiol Anim Nutr, 2014).
- Later studies: In obese rodents, MCTs prevented increase in weight, adiposity, blood glucose and insulin and glucose intolerance and stimulated BAT thermogenesis (Geng S, Eur J Nutr, 2016; Rial SA, Biochim Biophys Acta Mol Cell Biol Lipids, 2020; Sung MH, Nutrients, 2018).
- No studies of ketone supplements in humans.
- Studies of raspberry ketones in obese rodents show reduced weight, fat mass, adipocyte volume and triglycerides and enhanced insulin sensitivity but one team found increased mortality (Mir TM, J Diet Suppl, 2019; Morimoto C, Life Sci, 2005; Mehanna ET, Eur J Pharmacol, 2018; Liu SY, J Agric Food Chem, 2017). Other ketone supplements, including MCTs, reduced fasting blood glucose with no change in triglycerides (Kesl SL, Nutr Metab, 2016; Ari C, Nutrients, 2019).

Lipoic acid

- A 2020 meta-analysis showed that α-lipoic acid reduced weight and BMI, with no effect on waist circumference except in females; study duration was also a factor in success (Vajdi M, Int J Clin Pract, 2020). It was also effective in obese children and adolescents (Vajdi M, Cytokine, 2020).
- A 2018 meta-analysis showed that in patients with metabolic disease, α-lipoic acid reduced glucose, HbA1c, insulin, insulin resistance and triglycerides (Akbari M, Metabolism, 2018).
- In patients with T2D, 600mg/day α-lipoic acid for 6 weeks had no significant effect on weight loss (Usta Atmaca H, Acta Endocrinol, 2017), although the same dosage for 20 weeks in patients on metformin significantly lowered weight and triglycerides, with no effect on blood glucose (Okanović A, Med Glas, 2015).
- A 2012 meta-analysis showed that in patients with diabetic peripheral neuropathy, 300-600mg/day α-lipoic acid for 2-4 weeks improved nerve conduction velocity and neuropathic symptoms, although the authors warned about study quality (Han T, Eur J Endocrinol, 2012).
- Subcutaneous white adipocytes from overweight or obese subjects given α-lipoic acid exhibited some characteristics of BAT, with up-regulation of some brown/beige adipocyte markers (Fernández-Galilea M, Biochim Biophys Acta, 2015).

Magnesium (Mg)

- Supplementation beneficial in subjects with low magnesium: In obese subjects given 382mg/day elemental Mg for 4 months, fasting glucose, triglycerides and insulin resistance were significantly reduced. In obese or prediabetic subjects with renal disease, 365mg/day Mg for 3 months lowered waist circumference, fasting glucose and insulin, insulin resistance, triglycerides and HbA1c. In subjects with T2D, Mg supplementation for 16 weeks had lower fasting glucose, HbA1c and insulin resistance. In non-diabetics, 3 months of Mg supplementation improved β-cell health and function.
- Mixed results in subjects with normal magnesium levels: 360mg/day Mg for 3 months induced no change in fasting glucose, HbA1c, insulin or insulin resistance. In overweight, insulin resistant, non-diabetic subjects, Mg improved fasting glucose and some measures of insulin sensitivity
- Most studies do not bother to test Mg levels before supplementing, which probably accounts for the mixed results.
- A 2017 meta-analysis found that in subjects with T2D, Mg lowered fasting glucose and triglycerides, with a greater effect in those with low Mg levels. In subjects with T2D, 250mg/day elemental magnesium for 3 months also improved HbA1c, insulin levels and insulin resistance.
- In T1D, chronically low magnesium levels are linked to neuropathy; determining factors are T1D duration and extent of Mg depletion. In adults, 300mg/day Mg for 5 years significantly improved diabetic neuropathy. In children with T1D, oral magnesium reduced HbA1c and improved their lipid profile.

(Rodríguez-Moran M, Arch Med Res, 2014; Toprak O, Kidney Blood Press Res, 2017; Rodríguez-Morán M, Diabetes Care, 2003; Guerrero-Romero F, Eur J Clin Invest, 2011; Navarrete-Cortes A, Magnes Res, 2014; Mooren FC, Diabetes Obes Metab, 2011; Verma H, J Hum Nutr Diet, 2017; (ElDerawi WA, Nutrients, 2018; De Leeuw I, Magnes Res, 2004; Shahbah D, Medicine, 2017.

Melatonin

- A 2017 systematic review of 7 clinical trials showed no significant effect of melatonin supplementation on body weight (Mostafavi SA, Curr Pharm Des, 2017), although one study found a reduction in fat mass (Amstrup AK, Clin Endocrinol, 2017).
- Since then, 10mg/day melatonin for 30 days in obese subjects induced body weight reduction and improved antioxidant defences (Szewczyk-Golec K, Oxid Med Cell Longev, 2017).
- A 2018 meta-analysis of 12 RCTs found that melatonin reduced fasting glucose and increased one (but not another) measure of insulin resistance but not HbA1c (Doosti-Irani A, Horm Metab Res, 2018).
- In elderly diabetics, 5mg/day melatonin for 30 days decreased markers of lipid oxidation and increased SOD (Kedziora-Kornatowska K, J Pineal Res, 2009).
- In animal or *in vitro* studies, melatonin reduced obesity, oxidative stress and mitochondrial proton leak and inhibited the mtPTP opening in WAT and restored OXPHOS, reduced UCP2 expression and improved antioxidant status in obese diabetic hepatocytes. Melatonin also prevented reduced mitochondrial respiration, downregulated mitochondrial biogenesis and low levels of TCA cycle intermediates in insulin-resistant skeletal muscle. (Jimenéz-Aranda A, J Pineal Res, 2014; Agil A, J Pineal Res, 2015; Zavodnik IB, J Physiol Pharmacol, 2011; Teodoro BG, J Pineal Res, 2014)

Molecular hydrogen (H_2)

- Molecular hydrogen reduces oxidative stress and improves redox homeostasis partly mediated via the Nrf2 pathway, which regulates levels of glutathione, SOD and catalase. It also has anti-inflammatory and anti-apoptotic effects.
- An RCT showed that in middle-aged overweight females given hydrogen-generating minerals to give 6 ppm/day H_2 for 4 weeks, there was no difference in weight, BMI or body circumference but body fat percentage and serum insulin and triglycerides were significantly reduced (Korovljev D, Ir J Med Sci 2018).
- In diabetic mice, molecular hydrogen reduced hepatic oxidative stress and alleviated fatty liver. Long term hydrogen water consumption controlled fat and body weights and decreased levels of plasma glucose, insulin and triglycerides through enhanced expression of hepatic fibroblast growth factor 21 (FGF21), which functions to enhance fatty acid and glucose expenditure. Hydrogen also stimulated energy metabolism as measured by oxygen consumption. (Kamimura M, Obesity, 2011)

N-acetyl cysteine (NAC)

- A 2019 systematic review found that NAC improved insulin sensitivity in obese humans (Dludla PV, Pharmacol Res, 2019).
- In females with polycystic ovarian syndrome, 1.8g/day for 5-6 weeks, or 3g/day in the morbidly obese, fasting glucose and insulin were unchanged but insulin sensitivity improved (Fulghesu AM, Fertil Steril, 2002).
- A 2018 systematic review showed that NAC protected against diabetic heart failure and ischaemia (Dludla PV, Am J Cardiovasc Drugs, 2018).
- In patients with diabetic nephropathy, NAC decreased serum triglycerides (Rouhi H, J Nephropathol, 2013).
- In rodents, NAC delayed development of T1D (Bogdani M, J Endocrinol, 2013), protected from diabetic cardiomyopathy (Liu C, BMC Cardiovasc Disord, 2015) and diabetic nephropathy (Furfaro AL, Biofactors, 2005) and improved diabetic wound healing (Ozkaya H, Wounds, 2019).

NAD+ and precursors nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN)

- In a 12 week RCT of males with obese insulin resistance, given NR at 1000 mg twice daily, there was no change to glucose tolerance, pre-diabetes biomarkers, endogenous glucose production, glucose disposal, gut hormones, resting energy expenditure, lipolysis, oxidation of lipids or body composition. (Dollerup OL, J Clin Endocrinol Metab, 2019; Dollerup OL, Am J Clin Nutr, 2018).
- Nevertheless, NR seems to prevent and reverse diabetic peripheral neuropathy, in part by increasing NAD+ levels and SIRT1 activity (Chandrasekaran K, Int Rev Neurobiol, 2019).
- In obese male mice, NR improved glucose tolerance, reduced weight gain and hepatic steatosis in those with prediabetes, while in those with T2D, NR reduced blood glucose and weight gain. NR protected both groups against hepatic steatosis and diabetic neuropathy (Trammell SA, Sci Rep, 2016).
- NMN improves glucose tolerance by restoring NAD+ levels in mice with T2D, enhances hepatic insulin sensitivity, improves lipid profiles and restores gene expression related to oxidative stress, inflammation and circadian rhythm, partly through SIRT1 activation (Yoshino J, Cell Metab, 2011).

(Long chain) omega 3 fatty acids

- A 2019 meta-analysis found that intake of long chain omega-3 fats and the omega-3/omega-6 ratio were not associated with plasma glucose, insulin, HbA1c, insulin resistance or risk of T2D.
- A 2017 meta-analysis showed that omega-3 fats reduced waist circumference and triglycerides but reduction in weight, BMI and fasting glucose was not significant.
- A 2016 meta-analysis of RCTs which undertook gender-specific analysis, showed that although there was no pooled effect of omega-3 fats on insulin resistance, in trials of >6 weeks duration a significant improvement was seen in females but not males. *This suggests that the meta-analyses above might have shown different results if gender-specific analysis had been carried out.*
- In animal and *in vitro* studies, omega-3 fats have been shown to reduce weight gain, fat mass, blood glucose and insulin and insulin resistance and improve glucose tolerance by increasing β-oxidation, lowering oxidative stress and increasing mitochondrial fusion, mass, content, TCA cycle enzymes, oxygen consumption and respiration in skeletal muscle by upregulating AMPK, PGC-1α, UCP3 and Nrf1. They also suppressed adipocyte differentiation in pre-adipocytes. Note that α-linolenic acid supplementation prevented exercise-induced improvements in WAT mitochondrial bioenergetics and whole-body glucose homeostasis in obese rats.

(Brown TJ, BMJ, 2019; Zhang YY, J Nutr Health Aging, 2017; Abbott KA, Am J Clin Nutr, 2016; Lepretti M, Nutrients, 2018; Sergi D, Front Physiol, 2019; Lanza IR, Physiol Endocrinol Metab, 2013; Lionetti L, PLoS One, 2014; Lionetti L, Food Nutr. Sci, 2013; Casanova E, Biochim Biophys Acta, 2014; Cavaliere G, PLoS One, 2016; Valli V, Oxid Med Cell Longev, 2018; Martins AR, J Nutr Biochem, 2018; Monaco CMF, Diabetologia, 2018)

Pyrroloquinoline quinone (PQQ)

- A relatively newly discovered substance for which there are almost no human trials. It has antioxidant properties, can increase mitochondrial biogenesis and improve ATP production. It is found in some foods but may also be synthesised by gut bacteria.
- However, animal studies show that in induced diabetes, PQQ dose-dependently reduced oxidative stress and improved blood glucose and insulin, insulin signalling and glucose tolerance and increased glucose uptake through translocation of GLUT-4 (Kumar N, Chem Biol Interact, 2015; Takada M, Biochem Biophys Res Commun, 2012).

Selenium

- A 2019 systematic review of 4 RCTs found that selenium supplementation reduced fasting insulin levels and insulin resistance but the effect on fasting glucose was not clear (Stróżyk A, J Hum Nutr Diet, 2019). However, a further study found that 200 200 µg/day was not associated with any change in insulin sensitivity or on β-cell function (Jacobs ET, BMJ Open Diabetes Res Care, 2019).
- Nevertheless, a 2018 meta-analysis showed that supplementation of 200 µg/day was associated with a higher risk of developing T2D (Vinceti M, Eur J Epidemiol, 2018). Similarly, in patients with T2D, selenium increased fasting glucose and HbA1c (Faghihi T, Am J Ther, 2014).
- A 2017 meta-analysis showed that in patients with metabolic syndrome, selenium lowered insulin and a measure of insulin resistance but had no effect on fasting glucose or triglycerides (Tabrizi R, Horm Metab Res, 2017).

Sulphoraphane and Glucoraphanin (Cruciferous vegetables)

- Broccoli sprout extract reduced fasting blood glucose and HbA1c in obese patients with T2D (Axelsson AS, Sci Transl Med, 2017).
- In obese rodents, sulphoraphane lowered weight, triglycerides, visceral adiposity, adipocyte hypertrophy and hepatic fat accumulation via AMPK phosphorylation; it also protected against glucose intolerance and insulin resistance (Choi KM, J Nutr Biochem, 2014; Xu Y, Food Funct, 2018; Shawky NM, Environ Toxicol Pharmacol, 2019).
- Sulphoraphane can suppress adipocyte differentiation, while inducing browning and promotion of glucose and lipid utilisation (Valli V, Oxid Med Cell Longev, 2018; Zhang HQ, Mol Nutr Food Res, 2016).
- In rodents with T2D, sulphoraphane decreased glucose production in hepatocytes and improved glucose tolerance (Tubbs E, Mol Cell Endocrinol, 2018). It also lowered serum triglycerides and improved insulin sensitivity (de Souza CG, Food Funct, 2016).
- In rodents with T2D, sulphoraphane lowered fasting glucose, triglycerides, insulin sensitivity and hepatic glycogen to control group levels (de Souza CG, J Med Food, 2012).
- A review of animal and *in vitro* studies showed that sulphoraphane exerts beneficial effects on diabetic vascular damage and inhibits formation of advanced glycation end products (AGEs) and expression of AGE receptors (Yamagishi S, Pharm Biol, 2016). It also protected against diabetic cardiomyopathy and nephropathy and lowers diabetic retinopathy and neuropathy (Sun Y, Metabolism, 2020; Gu J, Diabetes, 2017; Li S, Exp Anim, 2019; Wu H, Free Radic Biol Med, 2015; Negi G, Curr Neurovasc Res, 2011).

Taurine

- In overweight or obese young adults, 3g/day taurine for 7 weeks reduced weight and triglycerides (Zhang M, Amino Acids, 2004).
- In overweight males without T2D but 1st degree relatives of T2D patients, 1.5g/day taurine for 8 weeks had no effect on insulin secretion or sensitivity or triglycerides (Brøns C, Eur J Clin Nutr, 2004). In overweight or obese males, taurine ameliorated functional β-cell decompensation and insulin resistance (Xiao C, Diabetologia, 2008).
- In patients with T2D, 3g/day taurine for 8 weeks lowered fasting blood glucose, insulin and insulin resistance, with no significant improvement in HbA1c and triglycerides (Maleki V, Amino Acids, 2020).
- In obese animal studies, taurine lowered weight through inhibition of adipogenesis in WAT and improved insulin sensitivity, glucose tolerance and triglyceride levels (Kim KS, Amino Acids, 2019; Zhao D, Adv Exp Med Biol, 2019; Borck PC, Amino Acids, 2018). But one study of postmenopausal mice showed that taurine worsened glucose intolerance and insulin resistance (de Souza Santos R, Amino Acids, 2018).
- In rodents with T2D, taurine improved glucose tolerance and increased pancreatic β- and α-cell area (Nakatsuru Y, Diabetol Int, 2019). Where treated with metformin, taurine further lowered fasting glucose and triglycerides and raised insulin levels (Pandya K, Adv Exp Med Biol, 2019).
- In a rodent model of T1D and T2D, taurine lowered blood glucose and reduced diabetic nephropathy and retinopathy (Zhang R, Nephron, 2020; Das J, Amino Acids, 2012; Yu X, Neurochem Res, 2008) and prevented development of cardiomyopathy by downregulating angiotensin II type2 receptor expression (Li C, Cardiovasc Drugs Ther, 2005).

Tauroursodeoxycholic acid (TUDCA)

- In obese adults, 1,750 mg/day TUDCA for 4 weeks increased hepatic and muscle insulin sensitivity and muscle insulin signalling (Kars M, Diabetes, 2010).
- In rodents, TUDCA ameliorated obesity-induced myocardial contractile dysfunction, diabetic retinopathy and diabetic nephropathy (Ceylan-Isik AF, J Mol Cell Cardiol, 2011; Wang CF, J Ethnopharmacol, 2016; Gaspar JM, Neuroscience, 2013; Zhang J, Nutrients, 2016).

Vitamin D

- Conflicting results in a number of RCTs and meta-analysis. The most recent results from meta-analyses are shown below but essentially indicate that if baseline vitamin D levels are very low, there is no beneficial effect of supplementation on metabolic disease. This suggests that if the trials had been longer, then an effect might have been detected, since if baseline levels are very low, triage theory suggests that vitamin D will not immediately prevent metabolic disease but some other vital function such as bone health.
- A 2019 meta-analysis of 19 RCTs found that vitamin D decreased waist circumference and BMI but not weight (Perna S, Medicina, 2019).
- A 2018 meta-analysis of 23 papers found that vitamin D lowered fasting glucose only in those with baseline 25(OH)D levels <75nmol/L (<30ng/ml) and with baseline BMI <25, while insulin resistance was reduced only in those with 25(OH)D levels ≥75nmol/l (≥30ng/ml). Furthermore, vitamin D without concomitant calcium supplementation could prevent T2D development when the dose was >2,000IU/day. (He S, Biomed Rep, 2018) A further 2017 meta-analysis showed that only a minimum dose of 4,000IU/day was effective (Mirhosseini N, J Clin Endocrinol Metab, 2017).
- In subjects with T2D, a 2017 meta-analysis of 29 RCTs showed that vitamin D could reduce HbA1c but there was no effect on fasting glucose, except in those with a baseline deficiency (Lee CJ, J Diabetes Complications, 2017; Wu C, Metabolism, 2017).
- A 2008 meta-analysis of observational studies showed that vitamin D supplementation from early childhood prevented development of T1D (Zipitis CS, Arch Dis Child, 2008).

Zinc

- Zinc is required in pancreatic β-cells in the process of insulin biosynthesis, the maturation of insulin secretory granules and regulation of insulin receptors. Deficiency is involved in the pathogenesis of T2D but high concentrations of zinc can also be toxic because of enhanced oxidative damage (Wijesekara N, Diabetes Obes Metab, 2009; Bjørklund G, Curr Med Chem, 2019).
- Mixed results for obesity. In obese adults, 30mg/day zinc for 4 weeks or 8 weeks had no impact on BMI, waist circumference or leptin concentrations (Marreiro DN, Biol Trace Elem Res, 2006; Kim J, Nutr Res Pract, 2012). However, two further studies found that 30mg/day for 4 weeks and 15 weeks lowered weight, waist and hip circumference and BMI (Payahoo L, Adv Pharm Bull, 2013; Khorsandi H, Diabetol Metab Syndr, 2019).
- Two 2019 meta-analyses and a 2017 systematic review showed that in adults with or without T2D, vitamin D lowered fasting and post-prandial glucose, HbA1c, fasting insulin, insulin resistance and triglycerides; inorganic zinc performed better than organic zinc (Wang X, Am J Clin Nutr, 2019; Jafarnejad S, Prev Nutr Food Sci, 2019; Cruz KJ, Biol Trace Elem Res, 2017).
- In US females aged 9-11, 9mg/day zinc for 4 weeks had no effect on insulin (Lobene AJ, J Nutr, 2017). *Note: this seems a very low zinc dose.* RCTs also showed a significant improvement in β-cell function (Islam MR, Diabetes Res Clin Pract, 2016).
- In patients with diabetic foot ulcers, 50mg/day zinc for 12 weeks significantly reduced the ulcer size, as well as lowering glucose, insulin, HbA1c and insulin resistance (Momen-Heravi M, Wound Repair Regen, 2017).
- In obese rodents, zinc improved glucose homeostasis by enhancing β-cell function (Cooper-Capetini V, Nutrients, 2017) and rescued obesity-induced cardiac hypertrophy (Wang S, J Cell Mol Med, 2017).

Apigenin

- In obese rodents, apigenin significantly reduced body weight and visceral (abdominal) adipose tissue, but not subcutaneous adipose tissues (Su T, Pharmacol Res, 2020). Apigenin also lowered fasting blood glucose, insulin, insulin resistance and triglycerides and improved glucose tolerance without causing weight gain, as with rosiglitazone (Jung UJ, Nutrients, 2016; Feng X, EBioMedicine, 2016).
- In hyperglycaemic rodents, apigenin lowered blood glucose and stimulated glucose-induced insulin secretion (Cazarolli LH, Eur J Med Chem, 2009).
- In diabetic mice, apigenin increased serum insulin and decreased glucose concentrations (Panda S, J Pharm Pharmacol, 2007), while a combination of apigenin and naringenin decreased the levels of blood glucose and the insulin resistance index and improved impaired glucose tolerance (Ren B, Eur J Pharmacol, 2016).
- In rodents, apigenin protected against diabetic nephropathy (Zhang J, Med Sci Monit, 2019; Malik S, Am J Physiol Renal Physiol, 2017) and diabetes-induced myocardial infarction (Mahajan UB, Int J Mol Sci, 2017) and diabetic cardiomyopathy (Liu HJ, Mol Cell Biochem, 2017).

Baicalin/Baicalein

- In patients with T2D, baicalin had no effect on fasting glucose or HbA1c but improved renal function and delayed progression of diabetic nephropathy (Yang M, Exp Ther Med, 2019).
- In rodents, baicalein can improve glucose metabolism in insulin resistant hepatocytes (Yang Z, Eur J Pharmacol, 2019), increase glucose tolerance and insulin secretion in pancreatic β-cells (Fu Y, Int J Endocrinol, 2014), decrease triglycerides while protecting against NAFLD but lower glucose uptake in adipocytes (Nakao Y, PLoS One, 2016).
- In rodents with T2D, baicalin dose-dependently decreased fasting glucose, with no effect on insulin, and alleviated pancreatic injury to the same extent as metformin (Li HT, Phytother Res, 2011). Other studies showed it could reduce food intake, weight, levels of fasting glucose, insulin and triglycerides and improve glucose tolerance and insulin resistance (Xi YL, Chin J Nat Med, 2016; Xi Y, Cell Physiol Biochem, 2015; Fang P, Diabetes Res Clin Pract, 2018).
- In rodent skeletal muscle cells, baicalin enhanced glucose uptake (Kuo YT, J Food Drug Anal, 2019; Fang P, Life Sci, 2019).
- In hepatocytes, baicalin enhanced glucose uptake in insulin resistant hepatocytes and inhibited hepatic gluconeogenesis (Xu J, Pharmacol Res, 2018; Wang T, Eur J Med Chem, 2017).
- Both baicalin and baicalein could alleviate diabetic retinopathy (Dai C, Exp Mol Pathol, 2019; Yang LP, Invest Ophthalmol Vis Sci, 2009) and diabetic nephropathy (Ahad A, Biochimie, 2014; Nam JE, Life Sci, 2020), while baicalein also protected against diabetic cardiomyopathy (Ma L, Med Sci Monit, 2018) and diabetic peripheral neuropathy (Stavniichuk R, Exp Neurol, 2011).

Curcumin

- Two meta-analyses of RCTs found that in patients with or without metabolic disease, curcumin reduced weight and BMI. With respect to waist circumference, one meta-analysis showed a reduction and the other showed a reduction only when the dose was ≥1000 mg/day, the intervention lasted >8 weeks and the subjects were overweight at baseline (Akbari M, Front Pharmacol, 2019; Mousavi SM, Crit Rev Food Sci Nutr, 2020). A further meta-analysis of NAFLD patients showed that curcumin lowered BMI and waist circumference but not weight (Baziar N, Phytother Res, 2020).
- Overweight or obese female Iranian adolescents given 500mg/day curcumin for 10 weeks showed no difference from placebo in BMI, waist and hip circumference and triglycerides (Saraf-Bank S, Sao Paulo Med J, 2019).
- In pre-diabetics, curcumin treatment for 9 months prevented progression to T2D, improved β-cell function and lowered insulin resistance (Chuengsamarn S, Diabetes Care, 2012).
- A 2018 meta-analysis of 11 RCTs showed that curcumin lowered fasting glucose and HbA1c but not insulin resistance in hyperglycaemic subjects (de Melo ISV, Pharmacol Res, 2018). In subjects with T2D, 1500mg/day for 10 weeks lowered triglycerides (Adibian M, Phytother Res, 2019).
- 80mg/day nanocurcumin for 8 weeks alleviated diabetic neuropathy, as well as lowering fasting glucose and HbA1c (Asadi S, Complement Ther Med, 2019) and could also improve diabetic microangiopathy (Appendino G, Panminerva Med, 2011).
- A meta-analysis of studies in rodents also showed that curcumin alleviated diabetic nephropathy (Wu W, J Tradit Chin Med, 2014).

Epicatechin

- A 2019 review found that epicatechin improves insulin sensitivity and glucose tolerance in normal weight, overweight, obese and diabetic subjects (Cremonini E, Free Radic Biol Med, 2019).
- Nevertheless, in subjects with metabolic syndrome, 25mg/day (-)-epicatechin for 2 weeks had no significant effect on energy intake, weight, fat mass, fasting glucose, insulin triglycerides or insulin resistance (Kirch N, Am J Clin Nutr, 2018). [Note: this was a very short study duration and low dosage]
- In obese rodents, epicatechin protected against obesity and insulin resistance (Sano T, Nutr Metab Cardiovasc Dis, 2017; Cremonini E, Redox Biol, 2018; Cremonini E, Arch Biochem Biophys, 2016).
- In obese diabetic rodents, epicatechin protected against diabetic vascular damage and mortality but had no effect on food intake, weight or fasting glucose (Si H, J Nutr, 2011).
- In rodents with T1D, epicatechin reduced levels of blood glucose, HbA1C, triglycerides and leptin and increased levels of insulin (Lin CH, PLoS One, 2017).
- Epicatechin could also prevent the onset of T1D (Fu Z, J Agric Food Chem, 2013) and protect against diabetic retinopathy (Al-Gayyar MM, Diabetologia, 2011).

Epigallocatechin gallate (EGCG): Green tea extract

- A 2017 systematic review of 15 human studies found that dosage of 100-460 mg/day may be effective in reducing body fat and weight in intervention periods of at least 12 weeks (Vázquez Cisneros LC, Nutr Hosp, 2017). Nevertheless, the vast majority of RCTs seem to show no effect on weight, BMI or fat mass.
- A 2017 meta-analysis of subjects with T2D or prediabetes found that EGCG had no effect on fasting glucose, insulin, HbA1c or insulin resistance (Yu J, Diabetes Metab J, 2017). A 2014 meta-analysis also showed no effect on these parameters or glucose tolerance (Wang X, J Hum Nutr Diet, 2014).
- A 2020 meta-analysis of patients with T2D found that doses of >800 mg/day for >8 weeks lowered serum triglycerides (Asbaghi O, Diabetes Metab Syndr, 2020).
- In overweight females, EGCG was superior to metformin in reducing fasting glucose and blood lipids, but when combined with metformin the glucose reduction was abolished (Alves Ferreira M, Clin Nutr ESPEN, 2017).
- A Chinese study found that regular green tea consumption increased risk for T2D (Liu X, Int J Epidemiol, 2018).
- 800 mg/day EGCG reduced nephropathy in diabetic patients (Borges CM, Sci Rep, 2016) and regular green tea consumption was protective against diabetic retinopathy (Ma Q, J Diabetes Res, 2015).

Grape seed extract

- A 2020 meta-analysis of 50 RCTs found that grape seed extract significantly decreased fasting glucose and triglycerides, with no effect on weight or HbA1c (Asbaghi O, Phytother Res, 2020).
- Since then an RCT showed that in overweight or obese subjects, 300mg/day grape seed lowered weight, BMI, waist circumference and waist to hip ratio (Parandoosh M, Phytother Res, 2020).
- 100mg/day and 300mg/day grape seed extract with a carbohydrate meal can both lower post-prandial glucose (Sapwarobol S, Pharmacogn Mag, 2012).
- In subjects with T2D, 600mg/day grape seed for 4 weeks did not alter insulin resistance (Kar P, Diabet Med, 2009).
- In subjects with diabetic retinopathy, 150mg/day grape seed for 12 months lessened the retinopathy severity (Moon SW, Medicine, 2019).

Icariin

- No human clinical trials.
- In skeletal muscle cells from obese and diabetic mice, icariin lowered insulin resistance and upregulated AMPK (Li M, Front Pharmacol, 2018; Han Y, Eur J Pharmacol, 2015).
- In rodents with T2D, icariin reduced blood glucose levels and up regulated AMPK (Li X, Exp Ther Med, 2020).
- Icariin could also alleviate diabetic osteoporosis, decreasing bone turnover and increasing bone mineral density and ameliorate diabetic nephropathy, retinopathy and cardiomyopathy via SIRT3 activation (Qi S, Molecules, 2019; Qiao C, Mol Cell Endocrinol, 2018; Ni T, Front Pharmacol, 2020; Qiao C, Pharmacology, 2020; Xin H, Int J Mol Sci, 2012; Qi MY, J Ethnopharmacol, 2011).

Kaempferol

- No human clinical trials.
- Obese rodents given kaempferol showed reduced body and liver weight gain, fat mass, fasting glucose, HbA1c and triglycerides and improved insulin resistance (Wang T, Biomed Res Int, 2020; Zang Y, Food Funct, 2015).
- Similar studies have shown no effect on weight but a reduction in fasting glucose, hepatic glucose production and insulin resistance, and lowered the incidence of T2D development using a dose equivalent to 240mg/day in humans (Alkhalidy H, J Nutr Biochem, 2018; Alkhalidy H, Molecules, 2018).
- Rodents with T2D given kaempferol has lowered fasting glucose and triglycerides; there was no effect on normal healthy rodents (Yin P, Molecules, 2018), indicating that kaempferol is adaptogenic. It also lowered insulin and insulin resistance and improved glucose tolerance and islet β-cell mass (Alkhalidy H, J Diabetes Res, 2015).
- In rats with T1D, kaempferol lowered fasting glucose and insulin (Al-Numair KS, Redox Rep, 2015).
- In cell lines, kaempferol can act as an insulin sensitiser (Jia Y, J Agric Food Chem, 2019) and can inhibit adipocyte development from pre-adipocytes (Torres-Villarreal D, J Physiol Biochem, 2019).
- In diabetic rats, kaempferol reduced pain sensitivity in diabetic neuropathy (Kishore L, Inflammopharmacology, 2018) and lessened diabetic myocardial injury (Suchal K, Int J Mol Sci, 2017). In cell lines kaempferol appeared protective against diabetic retinopathy (Zhao L, Neurosci Lett, 2020) and diabetic nephropathy (Sharma D, Biomed Pharmacother, 2019).

Luteolin

- No human clinical trials.
- In obese rodents, luteolin reduced body weight and epididymal fat weight, lowered adipocyte hypertrophy, increased adipocyte glucose disposal and improved glucose intolerance and insulin resistance by normalising pancreatic islet dysfunction (Gentile D, Front Pharmacol, 2018; Xu N, Mol Nutr Food Res, 2014; Kwon EY, Nutrients, 2018; Xiao N, Planta Med, 2014).
- In ovariectomised (i.e. postmenopausal) obese mice, luteolin had no effect on body weight or fat mass but improved insulin resistance (Baek Y, J Nutr Biochem, 2019).
- In obese hyperglycaemic mice, luteolin improved hepatic insulin sensitivity (Kwon EY, Diabetes, 2015).
- Luteolin reduces diabetic nephropathy in rodents, protects against diabetic cardiomyopathy, delays diabetic cataract development, improves diabetic peripheral neuropathy and encephalopathy and enhances diabetic wound healing (Zhang M, Exp Clin Endocrinol Diabetes, 2020; Yu Q, Life Sci, 2019; Li L, Phytomedicine, 2019; Chen Y, Arch Pharm Res, 2017; Li M, Int J Clin Exp Pathol, 2015; Liu Y, Brain Res Bull, 2013; Lodhi S, Asian Pac J Trop Med, 2013).

Milk thistle (silymarin, silybum, silibinin)

- A 2016 meta-analysis found that silymarin reduced fasting blood glucose and HbA1c in humans, while a 2018 meta-analysis of patients with T2D showed that silymarin can decrease fasting glucose, HbA1c and insulin but had no effect on triglyceride concentrations. A later study showed that silymarin can also reduce insulin resistance and triglycerides. Furthermore, in patients with T2D, 600mg/day silybum for 4 months decreased fasting glucose, HbA1c and triglycerides.
- In patients with T2D who had a poor response to glibenclamide, silymarin improved glycaemic control and in patients with diabetic nephropathy, 420mg/day for 3 months significantly improved the condition.

(Voroneanu L, J Diabetes Res, 2016; Hadi A, Complement Ther Med, 2018; Ebrahimpour-Koujan S, Phytomedicine, 2018; Huseini HF, Phytother Res, 2006; Hussain SA, J Med Food, 2007; Fallahzadeh MK, Am J Kidney Dis, 2012

- In obese rodent studies, silibinin prevented adipocyte hypertrophy, weight gain and obesity with no effect on food intake; it also restored glucose homeostasis, reversed hyperglycaemia, hyperinsulinaemia and hypertriglyceridaemia and improved insulin resistance (Alsaggar M, BMC Pharmacol Toxicol, 2020; Wang F, Front Pharmacol, 2020; Lu CP, Chem Biol Interact, 2018). In rodents with T2D, silibinin improved fasting glucose, hepatic glucose production and glycaemic contro and lowered fasting insulin and triglycerides (Xu F, Food Funct, 2018; Bouderba S, J Diabetes, 2014). In rodents with T1D, silymarin decreased fasting glucose and restored damaged β-cells.

(Amniattalab A, Iran J Pharm Res, 2016). Silymarin and silibinin can also improve diabetic cardiomyopathy, neuropathy, retinopathy and nephropathy (Meng S, Cell Biol Int, 2019; Liu Y, Eur J Pharmacol , 2019; Goli F, Indian J Clin Biochem, 2019; Chu C, Arch Pharm Res, 2018)

Myricetin

- Human epidemiological studies have shown that myricetin intake from food was associated with a lower incidence of T2D (Zamora-Ros R, J Nutr, 2014; Yao Z, Nutr Res, 2019). No human clinical trials.
- In obese rodents, myricetin reduced body weight, fasting glucose and triglycerides, improved glucose tolerance and adipocyte size and increased fatty acid consumption. In insulin resistant rodents, myricetin also lowered fasting insulin and insulin resistance. (Akindehin S, Nutrients, 2018; Chao HC, J Food Sci, 2017; Su HM, J Zhejiang Univ Sci B, 2016; Choi HN, Nutr Res Pract, 2014)
- In diabetic rodents, myricetin lowered weight and BMI and improved insulin resistance through activation of BAT and browning of WAT; it also lowered fasting glucose and normalised triglycerides (Hu T, Eur J Nutr, 2018; Ong KC, Life Sci, 2000).
- *In vitro* studies showed that myricetin protects pancreatic β-cells against glucose-induced apoptosis and inhibits glucose uptake in adipocytes (Karunakaran U, Diabetes Metab J, 2019; Strobel P, Biochem J, 2005).
- In rodents, myricetin alleviated diabetic nephropathy and protected against diabetic cardiomyopathy (Yang ZJ, Front Pharmacol, 2019; Liao HH, Oxid Med Cell Longev, 2017).

Naringin/Naringenin

- In a study of subjects with dyslipidaemia, 450mg/day naringin for 3 months decreased weight and BMI (Barajas-Vega JL, Int J Vitam Nutr Res, 2020).
- In obese rodents, naringin dose-dependently decreased weight, fat mass, fasting glucose, insulin and triglycerides (Sui GG, J Agric Food Chem, 2018; Raffoul-Orozco AK, Life Sci, 2018).
- In adipocytes, naringenin inhibited adipogenesis and reduced insulin resistance and insulin-stimulated glucose uptake (Richard AJ, Evid Based Complement Alternat Med, 2013).
- In rodents with T1D, naringenin decreased fasting glucose, HbA1c and triglycerides, promoted glycolysis, inhibited gluconeogenesis, prevented pancreatic β-cell apoptosis and restored insulin secretion to non-diabetic levels; however one study showed no effect on glucose (Rajappa R, Front Pharmacol, 2019; Lim YJ, Mol Nutr Food Res, 2018; Pari L, Gen Physiol Biophys, 2017; Xulu S, J Cardiovasc Pharmacol, 2012).
- In rodents, naringenin alleviated pain in diabetic neuropathy and reduced diabetic cardiac hypertrophy, diabetic cataract and diabetic retinopathy, while naringin alleciated diabetic nephropathy (Singh P, Food Funct, 2020; Zhang J, Biomed Pharmacother, 2019; Wojnar W, Biomed Pharmocother, 2018; Lui L, Iran J Basic Med Sci, 2017; Zhang J, Eur J Pharmacol, 2017).
- Naringenin can interfere with the glucose-lowering action of pioglitazone (Yoshida H, J Nat Med, 2017).

Nobiletin

- No human clinical trials.
- In obese rodents, nobiletin lowered weight, fat mass, insulin and triglycerides, improved glucose tolerance and insulin resistance and inhibited adipocyte differentiation (Lee YS, J Nutr Biochem, 2013; Kim YJ, Mol Nutr Food Res, 2017; Kanda K, Biochim Biophys Acta, 2012).
- In diabetic rodents, nobiletin improved fasting glucose, glucose tolerance and insulin resistance and increased glucose uptake in adipocytes (Lee YS, Biochem Pharmacol, 2010; Onda K, Phytother Res, 2013).
- Nobiletin reduced diabetic cardiovascular dysfunction (Parkar NA, Food Funct, 2016).

Quercetin

- A meta-analysis of 9 studies involving subjects with metabolic syndrome found that quercetin supplementation reduced fasting plasma glucose provided the study duration was ≥8 weeks and used quercetin in dosages of ≥500 mg/day, but otherwise it did not affect fasting plasma glucose, HbA1c or measures of insulin resistance (Ostadmohammadi V, Phytother Res, 2019).
- In overweight or obese females with polycystic ovary syndrome quercetin induced no significant difference in fasting glucose, insulin or insulin resistance (Khorshidi M, Phytother Res, 2018), although another study found a reduction in insulin resistance with a dose of 1g/day for 12 weeks (Rezvan N, Horm Metab Res, 2017).
- Two meta-analyses looking at quercetin's effect on triglycerides differed in their findings (Guo W, Curr Pharm Des, 2019; Huang H, Nutr Rev, 2020).
- Nevertheless, an observational study showed that quercetin intake was inversely related to the prevalence of T2D in the Chinese population (Yao Z, Eur J Nutr, 2019).
- Numerous animal and *in vitro* studies have shown that quercetin is effective in reducing weight, insulin resistance and diabetes, inducing apoptosis in mature adipocytes and protecting diabetic pancreatic cells from damage (Houghton MJ, Free Radic Biol Med, 2018; Ahn J, Biochem Biophys Res Commun, 2008; Carrasco-Pozo C, Redox Biol, 2016).

Resveratrol

- A 2020 meta-analysis found that resveratrol decreased body weight, BMI, fat mass and waist circumference, while increasing lean mass (Tabrizi R, Crit Rev Food Sci Nutr, 2020). Resveratrol can also decrease adipocyte size in obese men and activate fat browning (Konings E, Int J Obes (Lond), 2014; Kim OY, Pharmacol Res, 2019).
- A Cochrane Review of only 3 RCTs of subjects with T2D found that resveratrol showed no effect on fasting glucose, HbA1c (which could be due to the short trial follow-up) or insulin (Jeyaraman MM, Cochrane Database Syst Rev, 2020).
- Although there have been some negative trials, a 2017 meta-analysis of 9 RCTs in subjects with T2D found that resveratrol lowered fasting glucose, insulin and insulin resistance, with doses of ≥100 mg/day being more successful (Zhu X, Nutr Metab (Lond), 2017). Later studies have shown similar results (Khodabandehloo H, Nutr Res, 2018; Abdollahi S, Phytother Res, 2019; Khodabandehloo H, Nutr Res, 2018; Hoseini A, Food Funct, 2019).
- In subjects with T2D, a 2019 meta-analysis also showed that resveratrol given for ≥6 months also lowered triglycerides (Zhao H, Obesity, 2019).
- As an adjunct to pharmacological management, a 2015 meta-analysis found that resveratrol could improve HbA1c but had no effect on fasting glucose, insulin or insulin resistance (Hausenblas HA, Mol Nutr Food Res, 2015).
- A 2019 systematic review showed that resveratrol can benefit diabetic retinopathy (Toro MD, Int J Mol Sci, 2019).
- Numerous animal and *in vitro* studies showed benefit in obesity, insulin resistance and T2D (Cao MM, Exp Ther Med, 2018; Beaudoin MS, Am J Physiol Regul Integr Comp Physiol, 2013; Haohao Z, J Physiol Biochem, 2015).

Rutin

- No human clinical trials.
- In obese rodents, rutin decreased weight gain, BMI, adipocyte size, fasting glucose and triglycerides and protected against insulin resistance; it also induced browning of subcutaneous WAT (Yang J, Nutrients, 2020; Yuan X, FASEB J, 2017; Gao M, Pharm Res, 2013).
- In insulin resistant rodents, rutin normalised glucose tolerance (Hsu CY, Mol Nutr Food Res, 2014).
- In rodents with T2D, rutin decreased weight and fasting glucose and prevented diabetes progression (Tanko Y, Niger J Physiol Sci, 2017; Aitken JF, Biochem Biophys Res Commun, 2017).
- In rodents with T1D, rutin improved body weight, reduced plasma glucose and HbA1c, increased insulin secretion, improved the structure of β-cell islets and reversed hepatocyte hypertrophy (Niture NT, Indian J Exp Biol, 2014; Stanley Mainzen Prince P, J Biochem Mol Toxicol, 2006).
- Rutin also protected against diabetic nephropathy, cardiomyopathy, neuropathy (Gong B, Pak J Pharm Sci, 2020; Ganesan D, Mol Cell Biochem, 2020; Tian R, Eur J Pharmacol, 2016).

Genistein

- In subjects with NAFLD, 250mg/day genistein for 8 weeks lowered waist-to-hip ratio, fat mass and fasting triglycerides but there was no change in BMI or fasting glucose (Amanat S, Clin Nutr, 2018).
- In obese insulin resistant subjects, 50 mg/day genistein for 2 months reduced insulin resistance (Guevara-Cruz M, BMJ Open Diabetes Res Care, 2020).
- A 2017 meta-analysis of 7 RCTs of postmenopausal females showed that genistein lowered fasting glucose, insulin and insulin resistance and improved glycaemic control and insulin sensitivity (Liu Y, Maturitas, 2017). Since then an RCT showed that in postmenopausal females with T2D, 108mg/day genistein for 12 weeks lowered fasting glucose, HbA1c and triglycerides and improved insulin sensitivity (Braxas H, Can J Diabetes, 2019).
- Among Chinese females aged 30-70, 50mg/day genistein for 24 week had no effect on fasting glucose, 2-h glucose, HbA1c, fasting insulin and 2-h insulin (Ye YB, Mol Nutr Food Res, 2015).
- In obese rodent studies, genistein is effective in lowering weight, fasting glucose and triglycerides and insulin resistance, with no effect on insulin (Rockwood S, Diabetes Metab Syndr Obes, 2019; Incir S, Life Sci, 2016).
- In diabetic rodents, genistein protects against diabetic nephropathy and neuropathy (Kim MJ, Mediators Inflamm, 2013; Valsecchi AE, Eur J Pharmacol, 2011) and aids diabetic wound healing (Tie L, J Nutr Biochem, 2013).

Daidzein

- No human clinical trials.
- In obese rats, most studies show that daidzein induces a reduction in body weight, fat mass and energy intake and improves glucose toleranceand insulin sensitivity (Luo T, Food Funct, 2018; Crespillo A, Br J Pharmacol, 2011; Cao YK, Climacteric, 2013).
- In rodents with T1D, daidzein increased the insulin/glucagon ratio and lowered fasting and post-prandial glucose, HbA1c and triglycerides (Choi MS, Diabetes Metab Res Rev, 2008; Ae Park S1, Life Sci, 2006; Park MH, Eur J Pharmacol, 2013).

Puerarin

- No human clinical trials.
- In obese rodents, puerarin reduced body weight, fasting glucose and insulin levels, glucose tolerance and insulin resistance (Wang L, PLoS One, 2019; Jung HW, Nutrients, 2017).
- In obese diabetic rodents, puerarin improved weight, fasting glucose, insulin resistance, triglycerides and glucose homeostasis, protected islets, increased β-cell mass and proliferation but decreased β-cell apoptosis and promoted neogenesis (Wang C, Phytomedicine, 2020; Yang F, Zhongguo Ying Yong Sheng Li Xue Za Zhi, 2019; Chen X, Am J Chin Med, 2018; Yang L, Mol Endocrinol, 2016).
- In rodents with T1D, puerarin reduced hyperglycaemia and increased insulin production (Wu K, Food Chem Toxicol, 2013).
- Puerarin attenuated diabetic nephropathy and prevented diabetic cataract and reinopathy and diabetic cardiomyopathy (Li X, Front Physiol, 2020; Zhang D, Mol Med Rep, 2019; Yin MS, J Asian Nat Prod Res, 2019; Teng Y, Mol Biol Rep, 2009).