Astaxanthin

- No human treatment RCTs.
- A systematic review found that astaxanthin can induce apoptosis through downregulation of mitochondrial antiapoptotic proteins and upregulation of proapoptotic proteins, it is antiproliferative and enhances the effectiveness of conventional chemotherapic drugs on tumour cells (Faraone I, Pharmacol Res, 2020).
- In vitro studies showed that astaxanthin is effective against breast, prostate, colon, oral, ovarian, gastric, liver, skin, lung and non-small cell lung cancer (Kim MS, Mar Drugs, 2020; Kim HY, Sci Rep, 2019; Kowshik J, IUBMB Life, 2019; Su XZ, Anticancer Agents Med Chem, 2019; Liao KS, Regul Toxicol Pharmacol, 2016; Ko JC, Biochem Pharmacol, 2016; Kim JH, Gut Liver, 2016; Li J, Mar Drugs, 2015; Rao AR, J Agric Food Chem, 2013; Anderson ML, J Herb Pharmacother, 2005).
- Animal studies showed that astaxanthin can reduce oesophageal, prostate, colon, mammary and oral tumours (Cui L, Onco Targets Ther, 2019; Ni X, Mar Drugs, 2017; Yuri T, In Vivo, 2016; Kowshik J, PLoS One, 2014; Yasui Y, Chem Biol Interact, 2011)
- Astaxanthin could also reduce cisplatin-induced hearing loss in chemotherapy patients (Nan B, Drug Des Devel Ther, 2019).
- Astaxanthin enhances the cytotoxicity of erlotinib in human lung tumours and of carbendazim in breast cancer (Chen JC, Toxicol Res, 2018; Atalay PB, In Vitro Cell Dev Biol Anim, 2019).

B vitamins

- No human trials but observational studies show cancer risk for excess and deficient B vitamins.
- Supplementation with folic acid (400 µg) and vitamin B12 (500 µg) for 2-3 years was associated with higher overall cancer risk and specifically higher colorectal cancer risk (Oliai Araghi S, Cancer Epidemiol Biomarkers Prev, 2019).
- A meta-analysis showed an inverse correlation between the consumption of vitamin B6 and folate and the risk of oesophageal cancer in the US, Europe and Australia but not in Asia, although there may be an increased risk for vitamin B12 consumption in the US and Europe (Qiang Y, Nutrients, 2018).
- A 2018 meta-analysis showed that decreased blood levels of folate, vitamin B6 and vitamin B12 levels were associated with increased risks of colorectal cancer but increased vitamin B12 intake was also a risk factor (Shiao SPK, Oncotarget, 2018).
- Similarly, there was a significantly lower risk of lung cancer among men who had higher serum vitamin B6 levels and postmenopausal women taking ≥50 mg/day, with no effect from folate or vitamin B12 (Clarke R, Arch Intern Med, 2010; Brasky TM, Int J Cancer, 2020).
- Among Chinese adults, intake of folate, vitamin B2, vitamin B6 and vitamin B12 was inversely associated with colorectal cancer risk; low vitamin B12 intake was only a risk factor in women (Huang CY, Br J Nutr, 2020).
- Among women, high dietary intake of folate was inversely associated with endometrial and ovarian cancer risk and vitamin B6 with ovarian cancer risk, with no effect from other B vitamins of for breast or colorectal cancer (Arthur RS, Nutr Cancer, 2019; Lu J, Int J Epidemiol, 2019).
- In one study, higher vitamin B12 levels were associated with increased risk of breast cancer and higher folate levels were positively associated with risk of invasive breast cancer with no effect for vitamin B6 but another showed no effect for any B vitamin (Houghton SC, Breast Cancer Res Treat, 2019; Houghton SC, Int J Cancer, 2019).
- There was a positive association between intake of vitamin B3 (niacin) and gastric cancer risk (Dugué PA, Nutr Cancer, 2019), although niacin deficiency has been linked to genomic instability and is common in cancer patients (Bouma G, Ann Oncol, 2014; Kirkland JB, Mutat Res, 2012). Deficiency delays DNA repair and promotes strand breaks, genomic instability and cancer; the RDA is insufficient to make a difference (Spronck JC, Nutr Cancer, 2007). In mouse glioblastoma, niacin increased monocyte and macrophage infiltration into tumours, stimulated antitumour immune responses and extended survival (Sarkar S, Sci Transl Med, 2020).

β-lapachone

- Several clinical trials under way but none reported yet.
- In vitro studies show that β-lapachone dose dependently suppressed cellular proliferation, migration and invasion in human nasopharyngeal carcinoma cells, oral squamous cell carcinoma, non-small cell lung cancer, pancreatic tumour cells and colon cancer cells by increasing ROS and autophagosome production, inducing cell cycle arrest, DNA fragmentation, mitochondrial membrane depolarisation, single-strand DNA breaks, PARP1 hyperactivation and NAD+ and ATP depletion, ROS production and apoptosis. It also downregulated breast cancer and leukaemia stem cells, decreasing cell viability and telomerase activity. (Han Y, Med Sci Monit, 2019; Kim DW, Int J Mol Sci, 2018; Moon DO, J Med Food, 2010; Dias RB, Free Radic Biol Med, 2018; Jeon YJ, Biol Pharm Bull, 2015; Park EJ, Cell Death Dis, 2014; Li LS, Clin Cancer Res, 2011; Liu H, PLoS One, 2015)
- β-lapachone also prevented lung metastasis of melanoma and colorectal cancer (Kee JY, PLoS One, 2017; Kee JY, Integr Cancer Ther, 2017)
- In animals, β-Lapachone protects against doxorubicin-induced nephrotoxicity (Sanajou D, Naunyn Schmiedebergs Arch Pharmacol, 2019).

Baicalin/baicalein

- No human studies.
- Rodent studies showed that baicalein alleviated the effects of carcinogens on lung mitochondria, reducing ROS production and swelling, normalising enzyme activity and reducing carcinogenesis but triggering apoptosis. It also upregulated antioxidant enzymes; the effect on antioxidants was much more effective is baicalein was given pre-exposure (Naveenkumar C, Basic Clin Pharmacol Toxicol, 2013).
- A review article found that, *in vitro*, baicalein induces cancer cell apoptosis and causes cell cycle arrest, showing inhibitory effects on angiogenesis, metastasis and inflammation (all necessary for the promotion and progression of cancer) and may be helpful as chemotherapeutic adjuvants. Others found that baicalin exerted a stronger anti-tumour effect in bladder cancer cells, although both were effective in inducing apoptosis in human breast cancer cells with maximum effect from a combination of the two. It could also decrease cell viability in hepatoma cell lines and disrupt mitochondrial membrane potential, and decrease cellular proliferation in colorectal cancer cells. (Gao Y, Med Chem Res, 2016; De Oliveira MR, Pharmacol Res, 2015)

Berberine

- A Chinese RCT showed that 600 mg/day berberine was more effective than placebo in preventing recurrence of colorectal adenoma and development of colorectal cancer (Chen YX, Lancet Gastroenterol Hepatol, 2020).
- A meta-analysis of animal studies found that berberine exerted anti-tumour effects in many cancers, especially breast and lung cancer (Xu J, BMC Cancer, 2019).
- *In vitro* studies show that berberine can induce apoptosis and reduce proliferation in alveolar epithelial tumour cells, pancreatic cancer cells, endometrial cancer cells, leukaemia cells, oesophageal and gastic cancer cells, melanoma, gliobalstoma and hepatoma cells and breast and colon cancer cells (Kumar R, Life Sci, 2020; Sun Y, Med Sci Monit, 2019; Palmieri A, Int J Immunopathol Pharmacol, 2019; Abrams SL, Adv Biol Regul, 2019; Liu JF, Molecules, 2018; Wang Y, Biomed Pharmacother, 2018; Okubo S, Am J Chin Med, 2017; Jiang SX, World J Gastroenterol, 2017; Wang J, Oncotarget, 2016; Wang HY, Mol Med Rep, 2016; Wang J, Oncotarget, 2016).
- In patients undergoing radiation therapy, berberine reduced abdominal radiation-induced intestinal symptoms and radiation-induced lung injury (Li GH, Med Oncol, 2010; Liu Y, Eur J Cancer, 2008).

Butyrate

- No human treatment RCTs.
- *In vitro* studies found that sodium butyrate inhibited cell growth and proliferation, induced apoptosis, inhibited colony formation and migration and decreased thioredoxin 1 protein expression in colorectal cancer cells but had no effect on normal colon epithelial cells. It also dose-dependently inhibited breast cancer cell proliferation and induced ROS-mediated apoptosis in bladder and prostate cancer and chronic myeloid leukaemia cells and inhibits angiogenesis in oral cancer. (Wang W, Onco Targets Ther, 2020; Zeng H, Mol Nutr Food Res, 2020; Semaan J, Breast Cancer, 2020; Wang F, FASEB J, 2020; Jia X, Mol Genet Genomic Med, 2019; Salimi V, Lipids Health Dis, 2017; Weaver EM, Eur J Pharmacol, 2015; Yamamura T, Anticancer Res, 2014)
- In animals, sodium butyrate induced apoptosis in hepatomas and decreased colon cancer liver metastasis by altering gut microbiota and immune response (Ma X, Cell Biol Toxicol, 2020; Xu S, Signal Transduct Target Ther, 2017).

Cannabinoids

- No human treatment RCTs.
- A 2020 systematic review of animal studies with induced colorectal cancer or xenografts found that cannabinoids could reduce aberrant crypt foci and tumour volume through induction of apoptosis, interference with cell survival and growth pathways and inhibition of angiogenesis (Orrego-González E, Evid Based Complement Alternat Med, 2020). Cannabinoids could also reduce melanoma tumour size and increased survival; when compared to cisplatin, cannabinoids were less effective in prolonging survival but gave superior quality of life (Simmerman E, J Surg Res, 2019).
- *In vitro* studies also showed that cannabinoids could reduce tumour weight and volume in human pancreatic cancer cells and reduce prostate cancer cell proliferation, migration, invasion and apoptosis (Aizikovich A, J Pancreat Cancer, 2020; Roberto D, Prostate, 2019).
- In patients with non-small cell lung cancer, those with high expression levels of cannabinoid receptors showed increased survival, while cannabinoids inhibited the proliferation and migration of lung tumour cells (Milian L, PLoS One, 2020).
- However, studies have also shown that cannabinoids can can promote progression of human papillomavirus-related head and neck squamous cell carcinoma and cause DNA damage and chromosomal aberrations in human-derived cells (Liu C, Clin Cancer Res, 2020; Russo C, Arch Toxicol, 2019).
- Various recent meta-analyses found that oral cannabinoid could reduce chemotherapy-induced nausea and vomiting and can increase appetite in cancer patients but it has no effect on pain, sleep problems and opioid consumption for cancer pain. Cannabinoids may also degrade quality of life. (Chow R, Support Care Cancer, 2020; Wang J, Biomed Res Int, 2019; Hauser, W, Schmerz, 2019).

Capsaicin

- No human treatment RCTs.
- A meta-analysis found that among Koreans and Mexicans, low intake of capsaicin elicited gastric cancer protection, while high intake was a risk factor (Pabalan N, J Gastrointest Cancer, 2014).
- *In vitro* studies showed that capsaicin exerted an inhibitory effect on prostate cancer cells and could downregulate prostate cancer stem cells and inhibit their growth and could also induce mitochondrial dysfunction, ROS production, depolarisation of the mitochondrial membrane potential and opening of mPTP, resulting in apoptosis in thyroid carcinoma cells via mitochondrial calcium overload. In nasopharyngeal carcinoma, bladder cancer, melanoma, chondrosarcoma and oral squamous cancer, capsaicin inhibited cell proliferation and migration, through downregulation of SIRT1 deacetylase, and promoted apoptosis. (Zhu M, Phytother Res, 2020; Xu S, Cell Signal, 2020; Chiang C, Theranostics, 2020; Islam A, Am J Cancer Res, 2019; Kamaruddin MF, Medicina, 2019; Chu H, Oncol Lett, 2019; Helvaci N, Turk J Biol, 2018)
- Capsaicin can also of enhance the cytotoxic effect of chemotherapy in human lung cancer, osteosarcoma and prostate cancer cells (Chen JC, Toxicol Res, 2019; Sánchez BG, Cancer Cell Int, 2019; Wang Y, J Exp Clin Cancer Res, 2018).
- However, in animal studies a combination of H. pylori infection and capsaicin consumption leads to gastric carcinogenesis (Aziz F, Cancers, 2020).
- A systematic review found that a capsaicin patch provided significant pain relief in chemotherapy-induced peripheral neuropathy and may lead to regeneration and restoration of sensory nerve fibres (Cabezón-Gutiérrez L, J Pain Symptom Manage, 2020).

L-carnitine and acetyl L-carnitine (ALCAR)

- No human treatment RCTs.
- Serum L-carnitine levels in male smokers was not predictive of colorectal cancer development (Guertin KA, Cancer Epidemiol Biomarkers Prev, 2017), however in women with endometrial cancer, serum L-carnitine levels were significantly lower than those of healthy women and decreased progressively with advancing cancer stage (Arioz DT, Arch Gynecol Obstet, 2015).
- In prostate and colon cancer cells, ALCAR and L-carnitine, respectively, reduced angiogenesis, inflammation and proliferation, induced apoptosis and impaired their adhesion, migration and invasion capabilities; L-carnitine also inhibited cancer cell growth in hepatocytes (Baci D, J Exp Clin Cancer Res, 2019; Huang H, PLoS One, 2012; Roy MJ, Nutrition, 2009; Engel DB, Gynecol Oncol, 2009).
- Rodent models showed that L-carnitine inhibited development of precancerous lesions and macroscopic colonic tumours (Dionne S, Nutr Cancer, 2012).
- Studies have demonstrated that some chemotherapy drugs interfere with the absorption, synthesis and excretion of carnitine in non-tumour tissues, resulting in a secondary carnitine deficiency. This can be reversed by carnitine treatment without affecting chemotherapy efficacy. (Sayed-Ahmed MM, Saudi Pharm J, 2010)
- Chemotherapy patients given 1000mg/day oral liquid l-carnitine for 8 weeks was found to improve quality of life, while 4g/day for 12 weeks helped combat cachexia and improved nutritional status, although a meta-analysis found that carnitine supplementation did not improve cancer-related fatigue. However, 3g acetyl L-carnitine for 24 weeks worsened chemotherapy-induced peripheral neuropathy (Marx W, Nutrients, 2017; Kraft M, Nutr J, 2012; Endo K, Auris Nasus Larynx, 2019; Hershman DL, J Natl Cancer Inst, 2018).

L-Carnosine

- No human treatment RCTs.
- In vitro studies showed that L-carnosine inhibited migration, metastatic cell adhesion and extravasation in human colorectal cancer cells and ovarian cancer cells (Wu CC, Anticancer Res, 2019; Hsieh SL, Am J Chin Med, 2019; Mikuła-Pietrasik J, Anticancer Res, 2016), downregulated mitochondrial proteins which inhibited growth and proliferation of gastric cancer and cervical carcinoma cells (Cheng JY, Acta Pharmacol Sin, 2019; Bao Y, Integr Cancer Ther, 2018), inhibited the growth of liver cancer cells by inducing mitochondrial fragmentation (Ding M, 2018) and induced apoptosis in renal cancer cells (Pandurangan M, Int J Biol Macromol, 2016). L-carnosine also inhibited ATP production in malignant gliomas (Renner C, Neurol Res, 2010).
- In rodents with bladder cancer, carnosine exhibited antitumour activity equivalent to cisplatin, but without the cachexia, and inhibited migration, invasion and angiogenesis (Hwang B, J Nutr Biochem, 2019). It also delayed aggressive tumour growth in skin cancer (Renner C, Mol Cancer, 2010).
- In a phase III RCT, zinc-L-carnosine prevented swallowing difficulties in breast cancer patients undergoing radiotherapy and improved oesophagitis, taste distortion and mucositis in chemotherapy patients (Saldi S, Breast J, 2020; Fujii H, Anticancer Res, 2018; Hayashi H, Med Oncol, 2016; Yanase K, Int J Clin Exp Med, 2015). L-carnosine also protected against chemotherapy-induced peripheral neuropathy (Yehia R, Toxicol Appl Pharmacol, 2019). Zinc L-carnosine has anti-inflammatory properties and promotes genomic stability (Ooi TC, Nutr Cancer, 2017).

Coenzyme Q10 (CoQ10)

- A 2017 systematic review showed 'sparse but promising findings…as an adjunct in prevention and treatment of breast cancer and its comorbidities' (Tafazoli A, Future Oncol, 2017).
- Post-surgical patients with melanoma given 400mg/day CoQ10 and recombinant interferon alpha-2b for 3 years decreased rates of recurrence after 5 years (Rusciani L, Melanoma Res, 2007).
- Breast cancer patients treated with tamoxifen who also received 100 mg/day CoQ10, 10 mg/day vitamin B2 and 50 mg/day vitamin B3 showed significantly reduced tumour markers (Premkumar VG, Biol Pharm Bull, 2007).
- In breast cancer cells, CoQ10 reduced activity of matrix metalloproteinase 2, a key molecule in cellular invasion and metastasis (Bahar M, Nutr J, 2010).
- Higher levels of plasma CoQ10 in postmenopausal women was associated with increased breast cancer risk (Chai W, Cancer Epidemiol Biomarkers Prev, 2010), however there was no association with prostate cancer risk (Chai W, Cancer Epidemiol Biomarkers Prev, 2011). Plasma CoQ10 was significantly lower in women with cervical intraepithelial neoplasia and cervical cancer, with an inverse association with histological grades of epithelial lesions (Palan PR, Eur J Cancer Prev, 2003). In melanoma patients without metastasis, plasma CoQ10 levels were significantly lower than in healthy controls and could predict metastasis; the odds ratio for metastatic disease with CoQ10 levels >0.6 mg/L was 7.9 (Rusciani L, J Am Acad Dermatol, 2006).
- In chemotherapy patients, 300mg/day CoQ10 for 24 weeks improved fatigue (Lesser GJ, J Support Onco, 2013).

Creatine

- No human treatment RCTs.
- In breast cancer cell lines treated with methylgloxal, creatine enhanced apoptosis and cytotoxicity compared to methylgloxal alone (Pal A, Amino Acids, 2016).
- In rodents, creatine uptake deficiency severely impaired anti-tumour T cell immunity and supplementation suppressed tumour growth in multiple cancer models (Di Biase S, J Exp Med, 2019). Creatine supplementation reduced tumour growth by 30%, although survival rate was not altered (Campos-Ferraz PL, Amino Acids, 2016).
- In patients with cancer cachexia, 20 g/day creatine for 5 days followed by 2 g/day had no effect on weight (Jatoi A, Ann Oncol, 2017). Similarly, in colorectal cancer patients creatine had no effect on muscle function, body cell mass or quality of life (Norman K, Clin Nutr, 2006).
- There is concern that creatine supplementation could create carcinogenic heterocyclic amines. A 2015 study found that neither low nor high doses of creatine, given either acutely or chronically, caused increases heterocyclic amines in healthy subjects. (Pereira RT, J Physiol, 2015)

Ginkgo biloba (often as EGB 761)

- In thyroid patients given ablation, 120 mg/day ginkgo inhibited the ablation-induced increase in micronuclei and other chromosome-damaging factors in lymphocytes (Dardano A, Thyroid, 2012).
- Supplementation of 240mg/day ginkgo for 6 years was associated with an increased risk of breast and colorectal cancer but a reduced risk of prostate cancer (Biggs ML, Pharmacoepidemiol Drug Saf, 2010).
- In patients with gastric cancer, ginkgo reduced tumour area and induced apoptosis in tumour cells (Xu AH, World J Gastroenterol, 2003).
- In gastric and colon cancer, EGB 761 dose-dependently suppressed proliferation and weakened migration and invasion, inducing apoptosis and cell cycle arrest (Fu Z, Med Sci Monit, 2019; Chang L, Med Sci Monit, 2918; Bai Y, Int J Clin Exp Med, 2015), while in hepatic cancer cells, ginkgo dose-dependently induced cell cycle arrest and apoptosis and inhibited proliferation (Li M, Molecules, 2019; Czauderna C, PLoS One, 2018). It also inhibits metastasis in melanoma and colorectal cancer cells (Cao C, Evid Based Complement Alternat Med, 2018; Liu T, Oncotarget, 2017), inhibits aromatase in breast cancer cells (Park YJ, Food Chem Toxicol, 2016) and decreases migration in non-small cell lung cancer cell (Tsai JR, PLoS One, 2014).
- In rodent models, EGB 761 inhibited tumour growth and hepatic metastasis of gastric cancer (Fu Z, Med Sci Monit, 2019) and decreased volume of mammary tumours (Dias MC, BMC Complement Altern Med, 2013).
- However, ginkgo can also induce hepatic carcinoma in mice through increased DNA methylation of certain genes and exacerbated liver metastasis in mouse colon cancer (Kovi RC, Arch Toxicol, 2019; Wang H, BMC Complement Altern Med, 2017). The National Toxicology Program concluded that there was clear evidence of increased mouse hepatocellular carcinoma and hepatoblastoma; ginkgo biloba leaf extract has also been classified as a possible human carcinogen by the International Agency for Research on Cancer (IARC) (Mei N, J Environ Sci Health C Environ Carcinog Ecotoxicol Rev, 2017).
- In patients receiving 120 mg/day of EGB 761 there was no effect on chemotherapy-induced cognitive dysfunction (Barton DL, Support Care Cancer, 2013) but 2 studies showed improvements in chemotherapy-induced hearing impairment, cognitive function and quality of life (Attia A, J Neurooncol, 2012; Dias MA, Int Tinnitus J, 2015).

Lipoic acid

- No human treatment RCTs.
- A team in New Mexico have published case reports of patients with mostly advanced metastatic pancreatic cancer for whom only palliative care was appropriate, who were given a combination of intravenous α-lipoic acid and low-dose naltrexone. In all cases the patients were symptom free and able to return to work with either stable disease or no disease (Berkson BM, Integr Cancer Ther, 2018; Berkson BM, Integr Cancer Ther, 2006; Berkson BM, Integr Cancer Ther, 2009).
- Reviews of animal and *in vitro* studies found that α-lipoic acid induced cell apoptosis, impaired oncogenic signalling and cell growth, increased ROS production and promoted apoptosis in many different type of cancers; it can also reduce the stemness of cancer stem cells (Durand M, Nutr Hosp, 2013; Dörsam B, Cancer Lett, 2016; Moon HS, Ann Nutr Metab. 2016; Farhat D, Biochim Biophys Acta Rev Cancer, 2020; Phiboonchaiyanan PP, Cell Oncol, 2017)
- Since then, *in vitro* studies have shown that α-lipoic acid reduced proliferation, migration and invasion of human gastric cancer, lung cancer, thyroid cancer and metastatic breast cancer cells (Yang Y, Oxid Med Cell Longev, 2019; Tripathy J, Life Sci, 2018; Yang L, Biochem Biophys Res Commun, 2017; Jeon MJ, Mol Cell Endocrinol, 2016).
- In lung cancer cells, α-lipoic acid significantly increased ROS production, decreased cell viability and sensitised the cells to chemotherapeutic agents (Puchsaka P, Int J Oncol, 2016). However, where α-lipoic acid is co-administered with chemotherapy the results are mixed. In neuroblastoma cells it acted against the chemotherapy by rendering the cells more viable and providing an antioxidant effect, although in breast and colorectal cancer cells α-lipoic acid enhanced the apoptotic effect of chemotherapy (Tibullo D, Mol Neurobiol, 2018; Li BJ, Genet Mol Res, 2015; Dörsam B, Arch Toxicol, 2015).
- To prevent chemotherapy-induced peripheral neuropathy, studies found that 1800mg/day α-lipoic acid for 24 weeks had no effect (Guo Y, Support Care Cancer, 2014), while 600mg/day α-lipoic acid, 400mg/day docosahexaenoic acid, 60mg/day vitamin C and 10mg/day vitamin E for 6 months helped prevent development or worsening (Maschio M, Integr Cancer Ther, 2019).

Magnesium

- No human treatment RCTs.
- An in vitro study found that adding magnesium (sulphate or chloride) to ascorbic acid therapy upregulated the sodium-dependent vitamin C transporter and enhanced the anti-cancer effect (Cho S, Transl Oncol, 2020).
- A 2018 meta-analysis found that serum magnesium levels were not different in patients with lung cancer (Song X, World J Surg Oncol, 2018) but studies found they were significantly lower in thyroid and colorectal cancer and oral squamous cell carcinoma (Shen F, Biol Trace Elem Res, 2015; Polter EJ, Cancer Epidemiol Biomarkers Prev, 2019; Aziz NZ, J Oral Maxillofac Pathol, 2018). Magnesium levels were also not predictive for prostate cancer (Fowke JH, Cancer Lett, 2019).
- A 2019 meta-analysis found that higher dietary magnesium intake was protective against colorectal cancer development (Meng Y, Biol Trace Elem Res, 2019); an earlier meta-analysis found that the optimum protection for colorectal cancer occurred with an intake of 200-270 mg/day (Qu X, Eur J Gastroenterol Hepatol, 2013). A 2019 meta-analysis found that magnesium intake was inversely associated with lung cancer incidence, but there was no additional protection conferred by a dose >300mg/day (Dana N, Int J Vitam Nutr Res, 2019).
- In patients using morphine for cancer pain, the addition of 130mg/day oral elemental magnesium had no impact on pain intensity, dose of morphine used, functional performance, quality of life or side effects (Baaklini LG, Am J Hosp Palliat Care, 2017).
- Supplementation of magnesium with chemotherapy was associated with significantly lower nephrotoxicity; 1 successful study used 1500mg/day magnesium carbonate during treatment intervals (Matsui M, J Pediatr Hematol Oncol, 2018; Bodnar L, Eur J Cancer, 2008).

Melatonin

- A 2012 meta-analysis of 21 RCTs found that in patients with solid tumours, melatonin as adjuvant care, significantly reduced mortality and improved complete response, partial response and stable disease and significantly reduced asthenia, leucopenia, nausea and vomiting, hypotension and thrombocytopenia (Seely D, Integr Cancer Ther, 2012). A further trial found that 20mg/day significantly improved complete and partial, as well as 1-year survival rate and decreased radio-chemotherapy-related side effects (Wang YM, Cancer Chemother Pharmacol, 2012). However a 2014 trial found that 10 or 20 mg/day had no impact on survival but was associated with lower DNA damage and improved quality of life (Sookprasert A, Anticancer Res, 2014). Melatonin at 20mg/day could also improve disease stabilisation and survival time in patients with untreatable metastatic solid tumors (Lissoni P, Anticancer Res, 2008).
- A 2019 meta-analysis showed that breast cancer patients had a significantly lower level of serum melatonin (Veiga ECA, Rev Assoc Med Bras, 2019). A 2014 meta-analysis found that urinary melatonin was also inversely associated with breast cancer incidence (Wang XS, Am J Epidemiol, 2014).
- In patients with rectal cancer, 20 mg/day melatonin, 5 days a week for 28 days, melatonin prevented or minimised the radiotherapy-induced adverse effects of radiotherapy on platelets, white blood cells, lymphocytes and neutrophils (Kouhi Habibi N, Clin Transl Oncol, 2019). A 2018 systematic review showed that melatonin protected against chemotherapy-induced nephrotoxicity (Haghi-Aminjan H, Expert Opin Drug Metab Toxicol, 2018). 20mg melatonin before and/or during the first cycle of chemotherapy was found to improve cognitive function, sleep quality and depressive symptoms and reduce severe oral mucositis (Palmer ACS, PLoS One, 2020; Elsabagh HH, Oral Dis, 2020). Melatonin can also delay the onset of oral mucositis (Onseng K, J Altern Complement Med, 2017) and 3 or 5 mg at night can prevent delirium and induce significant improvement in objective sleep quality, sleep fragmentation and quantity, subjective sleep, fatigue severity, global quality of life and social and cognitive functioning in advanced cancer patients, although a dose of 20mg/night had no effect (Bush SH, Trials, 2016; Innominato PF, Support Care Cancer, 2016; Lund Rasmussen C, Cancer, 2015).

Omega 3 fatty acids

- An RCT of 1g/day omega-3 fats for 51 days given to advanced breast cancer patients undergoing chemotherapy found that survival and disease-free survival were significantly increased (Darwito D, Asian Pac J Cancer Prev, 2019). Similarly, a higher intake of omega-3 fats in patients with stage III colon cancer undergoing chemotherapy was associated with improved 3-year disease-free survival in KRAS wild-type tumours or DNA mismatch repair deficiency (Song M, Int J Cancer, 2019).
- A 2017 systematic review found that in prostate cancer patients, omega-3 fats showed no impact on prostate-specific antigen levels but did decrease inflammatory or other cancer markers (Aucoin M, Integr Cancer Ther, 2017). In premenopausal women with positive cancer risk biomarkers, 1860 mg/day EPA + 1500 mg/day DHA lowered the cancer biomarkers (Fabian CJ, Cancer Prev Res, 2015).
- An RCT of 2.4 g/day of omega-3 fats (EPA 1.6 g; DHA 0.8 g) in women with advanced breast cancer undergoing chemotherapy showed no effect on toxicity, side effects, body composition, cardiometabolic profile and quality of life but did improve dry mouth (de la Rosa Oliva F, Nutr Hosp, 2019), although omega-3 fats in obese postmenopausal women significantly reduced aromatase inhibitor-related arthralgia (Shen S, Breast Cancer Res Treat, 2018). A 2015 systematic review found that omega-3 supplements were beneficial in patients undergoing chemotherapy (de Aguiar Pastore Silva J, Clin Nutr, 2015).
- In patients with gastrointestinal malignancy, omega-3 fats promoted weight gain and improved nutritional status and inflammation (Feijó PM, Nutrition, 2019; Yu J, BMC Cancer, 2017). They also lowered chemotherapy-induced mucositis (Hashemipour MA, Wounds, 2017) and protected against chemotherapy-induced peripheral neuropathy (Ghoreishi Z, BMC Cancer, 2012).
- A 2020 meta-analysis found that risk of digestive system cancers reduced by 17% in those who consumed omega-3 fats (Wang J, Medicine, 2020), while a 2019 meta-analysis also found a protective effect against breast cancer in Asian women (Nindrea RD, Asian Pac J Cancer Prev, 2019). Nevertheless, a 2014 meta-analysis showed that omega-3 fatty acid supplementation had no effect on cancer incidence (Zhang YF, BMC Public Health, 2014).

Selenium

- No human treatment RCTs.
- A 2020 meta-analysis found an inverse relationship between selenium intake and overall cancer risk, with the protective effect occurring at intake of ≥55 µg/day (Kuria A, Crit Rev Food Sci Nutr, 2020), although a 2018 Cochrane Review found no beneficial effect of selenium supplements in reducing cancer risk (Vinceti M, Cochrane Database Syst Rev, 2018).
- Meta-analyses and reviews found that lower selenium levels were associated with increased risk of lung, bladder, breast, prostate and cervical cancer, hepatocellular carcinoma and colorectal adenoma (Amaral AF, Cancer Epidemiol Biomarkers Prev, 2010; Babaknejad N, Biol Trace Elem Res, 2014; Sayehmiri K, Asian Pac J Cancer Prev, 2018; He D, Biol Trace Elem Res, 2017; Zhang Z, Oncotarget, 2016; Jacobs ET, J Natl Cancer Inst, 2004; Zhuo H, Cancer Epidemiol Biomarkers Prev, 2004). Although 2 studies had found low selenium in thyroid cancer, a 2019 systematic review found the overall evidence to be inconclusive (de Oliveira Maia M, Nutr Cancer, 2019).
- A 2011 meta-analysis found that selenium supplementation may reduce risk of lung cancer in populations with lower baseline selenium status (serum<106 ng/mL) but increase risk of lung cancer in those with higher selenium (≥ 121.6 ng/mL) (Fritz H, PLoS One, 2011).
- 300µg/day selenium was effective in reducing iodine-131 radiation damage in thyroid cancer patients (Son H, Hell J Nucl Med, 2017).

Taurine

- No human treatment RCTs.
- In animal and *in vitro* studies, taurine suppressed Ehrlich ascites carcinoma and colon and breast cancer tumour formation, inhibited its progression, reduced proliferation and increased apoptosis and upregulated immune surveillance against tumour cells (Wang G, Oxid Med Cell Longev, 2020; Vanitha MK, J Biochem Mol Toxicol, 2018; Ibrahim HM, Biomed Pharmacother, 2018, He YU, Anticancer Res, 2018). In nasopharyngeal and cervical carcinoma, colorectal and lung cancer, gliomas and myeloid leukaemia, taurine decreased proliferation and increased mitochondrial apoptosis by activating caspases (He F, Adv Exp Med Biol, 2019; Li H, Chin Med J, 2019; Liu Z, Libyan J Med, 2018; Tu S, Oncol Lett, 2018; El-Houseini ME, Leuk Lymphoma, 2013; Opstad KS, Br J Cancer, 2009).
- Taurine enhanced the effect of chemotherapy in cervical cancer and other tumour cells (Kim T, Adv Exp Med Biol, 2013; Sadzuka Y, Biol Pharm Bull, 2009).
- In animals, taurine prevented chemotherapy-induced brain injury and dysfunction (Owoeye O, Biomed Pharmacother, 2018). It could also reduce chemotherapy-induced intestinal mucositis, hepatic, renal and reproductive organ damage and mammary oxidative damage (Al-Asmari AK, Hum Exp Toxicol, 2016; Parvez S, Basic Clin Pharmacol Toxicol, 2008; Tabassum H, Hum Exp Toxicol, 2007).
- Blood taurine levels were significantly lower in breast cancer patients compared to controls (El Agouza IM, Angiogenesis, 2011) but were higher in patients with oesophageal cancer (Lamônica-Garcia VC, Arq Gastroenterol, 2008).

Vitamin A

- In patients with head, neck or lung cancer, most with a history of smoking, a combination of vitamin A and N-acetylcysteine resulted in no survival benefit (van Zandwijk N, J Natl Cancer Inst, 2000).
- Treatment with 13-Cis retinoic acid, a synthetic vitamin A derivative, for 2 years had no impact on development of second primaries in head and neck cancer (Bhatia AK, Cancer, 2017) and in combination with chemotherapy did not improve the response rate in treatment of locally advanced and metastatic pancreatic cancer (Michael A, Clin Oncol, 2007).
- Studies found no association of serum retinol and liver cancer incidence but for prostate cancer incidence 2 studies showed no association and another showed a positive association, while a 3rd found no association overall but the highest versus lowest concentrations of serum retinol were associated with a 42% reduction in aggressive prostate cancer risk (Leelakanok N, Nutr Health, 2018; Gilbert R, Cancer Causes Control, 2012; Mondul AM, Am J Epidemiol, 2011; Beilby J, Eur J Clin Nutr, 2010; Schenk JM, Cancer Epidemiol Biomarkers Prev, 2009). Blood levels of vitamin A were inversely associated with bladder, cervical and colorectal cancer (Yalçin O, BJU Int, 2004; Zhang X, Gynecol Oncol, 2012; Musil F, Nutrition, 2005).
- Dietary intake of β-carotene was inversely associated with breast cancer survival but other vitamin A derivatives had no effect (He J, Clin Breast Cancer, 2018), while a 2008 Cochrane Review found that β-carotene in combination with vitamin A may increase gastrointestinal cancer mortality (Bjelakovic G, Cochrane Database Syst Rev, 2008).
- A 2020 Cochrane systematic review found that Vitamin A supplements increased lung cancer incidence and mortality in smokers or persons exposed to asbestos (Cortés-Jofré M, Cochrane Database Syst Rev, 2020). Several meta-analyses found that dietary vitamin A intake, including β-carotene, was inversely associated with risk of oesophageal adenocarcinoma, pancreatic, gastric, bladder, cervical, breast and lung cancer (Kubo A, Am J Gastroenterol, 2007; Zhang T, Biosci Rep, 2016; Kong P, PLoS One, 2014; Yu N, Nutrients, 2015; Tang JE, World J Surg Oncol, 2014; Zhang X, Gynecol Oncol, 2012; Fulan H, Cancer Causes Control, 2011), although others found that vitamin A supplements had no effect on incidence of haematological malignancy and colorectal or ovarian cancer (Psaltopoulou T, Nutr Cancer, 2018; Liu Y, Med Oncol, 2015; Crane TE, Cancer Epidemiol Biomarkers Prev, 2014).

Vitamin D

- Two 2019 meta-analyses showed that vitamin D significantly reduced cancer mortality (Zhang Y, BMJ, 2019; Keum N, Ann Oncol, 2019; Liu SL, Chin Med J, 2014), although a 2018 meta-analysis found no evidence of an effect of vitamin D supplementation on cancer-related deaths (Goulão B, Am J Clin Nutr, 2018), indicating no clear result.
- A trial of 40,000 IU/day vitamin D3 for 2-6 weeks in newly diagnosed breast cancer patients found no significant effects on tumour proliferation or apoptosis (Arnaout A, Breast Cancer Res Treat, 2019). A systematic review of supplementation in prostate cancer patients was inconclusive (Petrou S, Int J Vitam Nutr Res, 2018).
- A trial of 1,000 IU/day vitamin D had no effect on markers of proliferation, differentiation and apoptosis in mucosa of colorectal adenoma patients (Gao Y, PLoS One, 2018).
- Meta-analyses showed that serum vitamin D levels were not associated with incidence of lung or pancreatic cancer, although other recent meta-analyses found an inverse association between vitamin D serum level and incidence of breast, bladder, lung and thyroid cancer (Hossain S, Clin Nutr ESPEN, 2019; Zhao J, Nutrition, 2019; Zhao Y, Nutrition, 2016; Liao Y, Tumour Biol, 2015;). There was also a significant inverse dose-response relationship between circulating vitamin D levels and survival in breast cancer patients (Hu K, Integr Cancer Ther, 2018). Meta-analyses found that higher blood vitamin D was associated with an increased risk of non-melanoma skin cancer, adenocarcinoma or oesophageal squamous cell carcinoma (Zgaga L, Cancer Epidemiol Biomarkers Prev, 2016; Caini S, Eur J Cancer, 2014) although a 2015 meta-analysis found an inverse association between serum vitamin D levels and incidence of colorectal adenoma (Choi YJ, World J Gastroenterol, 2015). Both low and high vitamin D concentrations were associated with increased risk of prostate cancer (Kristal AR, Cancer Epidemiol Biomarkers Prev, 2014).
- A 2019 meta-analysis and 2014 Cochrane Review found no firm evidence that vitamin D supplementation affects overall cancer occurrence (Keum N, Ann Oncol, 2019; Bjelakovic G, Cochrane Database Syst Rev, 2014), while a 2019 meta-analysis found an inverse association between vitamin D intake and breast cancer incidence (Hossain S, Clin Nutr ESPEN, 2019). Furthermore, a 2018 meta-analysis showed that a high vitamin D intake was inversely correlated with lung cancer risk; every 100 IU/day increase in vitamin D intake decreased the risk of lung cancer by 2.4% (Wei H, Medicine, 2018).

Zinc

- An RCT of 150mg/day zinc sulphate in patients with head and neck cancers undergoing radiotherapy showed no increase in circulating T lymphocytes, T lymphocyte subpopulations or survival (Sangthawan D, Nutr Cancer, 2015).
- Meta-analyses found that lower blood zinc concentrations were associated with increased breast, cervical, prostate, bladder, head and neck, liver, digestive tract and lung cancer risk (Jouybari L, J Trace Elem Med Biol, 2019; Wang Y, World J Surg Oncol, 2019; Xie Y, J Int Med Res, 2018; Mahmoud AM, PLoS One, 2016; Gumulec J, PLoS One, 2014; Li P, Clin Nutr, 2014; Mao S, Biol Trace Elem Res, 2013).
- A 2018 meta-analysis showed that each 5 mg/day increase in zinc intake was associated with a 15% reduction in oesophageal cancer (Ma J, Nutr Res, 2018), while other meta-analyses showed that higher zinc intake was also protective against pancreatic and colorectal cancer (Li L, Biosci Rep, 2017; Qiao L, Cancer Causes Control, 2013).
- A 2019 meta-analysis showed that zinc supplementation reduced the severity of oral mucositis during chemo/radiotherapy (Chaitanya NC, J Nutr Sci Vitaminol, 2019). RCTs also showed that 70mg/day zinc for 16 weeks prevented fatigue and maintained quality of life of patients with colorectal cancer (Ribeiro SMF, Einstein, 2017), although 100mg/day induced no improvement in chemotherapy-induced alteration in taste or smell (Lyckholm L, J Pain Palliat Care Pharmacother, 2012).

Apigenin

- No human treatment RCTs.
- In hepatocellular carcinoma cells, apigenin with chemotherapy has an additive effect on migration, invasion, apoptosis and gene expression than chemotherapy alone (Şirin N, Gene, 2020).
- In colorectal and hepatocellular carcinoma cells, apigenin reduced cell growth and senescence by induction of apoptosis and inhibited metastasis (Zohreh B, Anticancer Agents Med Chem, 2019; Tong J, Biosci Rep, 2019; Yang J, Biomed Pharmacother, 2018). In triple negative breast, cervical, lung and bladder cancer, malignant melanoma and nasopharyngeal and renal carcinoma cells, apigenin has an anti-invasive, anti-migration and anti-proliferative effect (Lee HH, 2019; Xia Y, J Agric Food Chem, 2018; Zhang Y, Biosci Rep, 2018; Meng S, Oncotarget, 2017; Zhao G, Oncol Rep, 2017; Souza RP, Oxid Med Cell Longev, 2017; Zhou Z, Anticancer Drugs, 2017).
- Apigenin also inhibited hypoxia-induced stem cell marker expression in head and neck squamous cell carcinoma cells, reduced the invasiveness of stem-like cells in glioblastoma, reduced prostate cancer stem cell survival and migration and inhibited the self-renewal capacity of ovarian cancer stem-like cells (Ketkaew Y, Arch Oral Biol, 2017; Kim B, Phytother Res, 2016; Erdogan S, Life Sci, 2016; Tang AQ, Mol Med Rep, 2015).
- In rodents, apigenin inhibited growth of chemotherapy-resistant colon cancer and UVB-induced skin cancer (Chen X, J BUON, 2019; Mirzoeva S, Neoplasia, 2018). *In vitro*, it also overcame chemotherapy resistance in breast and ovarian cancer cells (Seo HS, Oncol Rep, 2017; Suh YA, Int J Oncol, 2015) and enhanced interferon gamma treatment in cervical squamous cell carcinoma and adenocarcinoma (Yang PM, Oncotarget, 2017).

Baicalin/Baicalein

- In cancer patients with cachexia, baicalin supplements for 3 months increased lean body mass (Emanuele E, Neuro Endocrinol Lett, 2016).
- Baicalin and baicalein decreased viability, arrested cell cycle, inhibited proliferation, migration and invasion and stimulated apoptosis in prostate, thyroid, lung, pancreatic, cervical, breast and colorectal cancer, oral squamous cell carcinoma, acute lymphoblastic leukaemia and malignant melanoma cells (Ma SC, J Biol Regul Homeost Agents, 2020; Zeng Q, Mol Med Rep, 2020; Yi S, J BUON, 2020; Deng X, Int J Biol Sci, 2020; Cui J, Biofactors, 2020; Lian H, J Cancer Res Ther, 2019; Liu ZH, Onco Targets Ther, 2019, Yang X, Braz J Med Biol Res, 2019; Gao Z, Int J Oncol, 2020; Du HW, Anal Methods, 2020; Liu DK, Oncotarget, 2020; Yu Z, Mol Cell Biochem, 2020; Orzechowska BU, Int Immunopharmacol, 2020).
- Baicalin and baicalein suppressed stem cell-like characteristics ('stemness') in liver, pancreatic, ovarian, colorectal and triple negative breast cancer cells (Koh SY, Nutrients, 2019; Wu R, Hepatology, 2019; Song L, Acta Biochim Biophys Sin, 2018; Li Y, Onco Targets Ther, 2020; Yang B, J Cancer, 2020).
- *In vitro* studies showed that baicalin and baicalein enhanced the effect of chemotherapy in inhibiting tumour growth, angiogenesis and cell proliferation and invasion and induced apoptosis in gastric, breast, ovarian and non-small cell lung cancer cells (Li P, Biochem Biophys Res Commun, 2020; Lu L, Phytother Res, 2020; Zeng A, Front Pharmacol, 2020; Choi BY, BMC Complement Altern Med, 2017).
- In rodents, baicalein reduced intestinal and rectal cancer progression and tumour number and increased survival by nearly 100% (Wang CZ, Clin Transl Oncol, 2020).

Curcumin

- In patients with metastatic colorectal cancer, the addition of curcumin to chemotherapy increased progression-free survival and overall survival by 70% and 251% respectively (Howells LM, J Nutr, 2019). Similarly, in patients with prostate cancer undergoing intermittent androgen deprivation, 1440 mg/day curcumin for 6 months, a significantly lower proportion of patients had PSA progression (10% vs 30%) but there was no change to other parameters (Choi YH, Prostate, 2019). In pancreatic cancer patients, the addition of curcumin complexed with phospholipids improved chemotherapy response rate (Pastorelli D, Pharmacol Res, 2018).
- A 2019 systematic review of patients undergoing chemo- or radiotherapy found that curcumin gel or mouthwash reduced the symptoms of oral mucositis (Normando AGC, Phytother Res, 2019). In early stage breast cancer patients receiving adjuvant hormonal therapy, a combination of hydroxytyrosol, omega-3 fatty acids and curcumin improved pain and inflammation (Martínez N, Clin Transl Oncol, 2019). Similarly, curcumin improved the oxidative status of patients undergoing radiotherapy and reduce radiation-induced dermatitis (Hejazi J, Nutr Cancer, 2016; Ryan JL, Radiat Res, 2013). When complexed with phospholipids could alleviate many of the chemo- and radiotherapy side effects (Belcaro G, Phytother Res, 2014).
- Two 2020 systematic reviews of *in vitro* studies showed that curcumin could enhance the anti-tumour activity of chemotherapy in acute lymphoblastic leukaemia and gastric cancer cells by inducing apoptosis and increasing expression of the tumour suppressor protein p53 levels (Haghighian HK, Nutr Cancer, 2020; Najafi M, Life Sci, 2020). Similarly, curcumin induced apoptosis by increasing endoplasmic reticulum stress and upregulating the unfolded protein response and increased p53 levels in papillary thyroid carcinoma and colorectal cancer cells (Zhang L, Medicine, 2018; He ZY, Cancer Invest, 2011).
- Curcumin could also enhance the anti-proliferative and pro-apoptotic effects of chemotherapy in colorectal liver metastatic cells, while reducing expression of cancer stem cell-associated markers (James MI, Cancer Lett, 2015).

Epigallocatechin-3-gallate (EGCG)

- In men with prostate cancer, 800 mg/day EGCG plus other catechins reduced serum prostate-specific antigen (PSA) and other prostate cancer markers (McLarty J, Cancer Prev Res, 2009).
- In postmenopausal women at risk of breast cancer taking 1,315 mg/day total catechins, including 843 mg/day EGCG, for 12 months, absolute mammographic density was no different but the percentage had significantly reduced in women aged 50-55 but not in older women, showing an age-dependent effect similar to that of tamoxifen (Samavat H, Cancer Prev Res, 2017). Subjects consuming 800mg/day EGCG showed significantly reduced biomarkers related to colorectal cancer pathogenesis (Hu Y, Br J Nutr, 2016). In men at risk of prostate cancer consuming 400mg/day EGCG for 1 year there was no difference in the incidence of prostate cancer, although with 600mg/day for 1 year there were fewer tumours compared to placebo (3% vs 30%) but no difference in PSA score and among Chinese men prostate cancer risk was inversely associated with EGCG intake (Kumar NB, Cancer Prev Res, 2015; Bettuzzi S, Cancer Res, 2006; Lee PMY, Prostate Cancer Prostatic Dis, 2017).
- *In vitro* studies showed that EGCG induced cytotoxicity and apoptosis and reduced growth, migration and invasion of colorectal, breast, gastric, head and neck and pancreatic cancer, chronic myeloid leukaemia, hepatocellular carcinoma and nasopharyngeal carcinoma cells (Md Nesran ZN, Biomed Res Int, 2019; Wei R, Nutrients, 2019, Sheng J, Molecules, 2019; Ho HC, J Cell Physiol, 2019; Xiao X, Clin Exp Pharmacol Physiol, 2019; Zhao J, Nat Commun, 2021). EGCG can also inhibit DNA repair and enhance the effects of chemotherapy in cancer cells (Heyza JR, Nutrients, 2018; Liu L, Pathol Res Pract, 2017; Shin YS, Phytomedicine, 2016; Li S, Sci Rep, 2016, Yang C, Int J Food Sci Nutr, 2016).
- EGCG also inhibited cancer stem cell-like properties in lung, breast and colorectal cancer cells (Jiang P, J Cell Biochem, 2018; Toden S, Oncotarget, 2016; Pan X, J Pharmacol Sci, 2016).
- In patients undergoing radiotherapy, EGCG alleviated acute radiation esophagitis and could alleviate skin damage when applied topically (Zhao H, Radiother Oncol, 2019; Zhu W, Oncotarget, 2016; Zhao H, Br J Radiol, 2016).

Grape seed extract (GSE)

- No human treatment RCTs.
- GSE can inhibit cell viability, growth, proliferation and invasion and induce DNA damage and apoptosis in breast, liver, prostate, colorectal, bladder, skin, non-small cell lung and head and neck cancer cells and oral squamous cell carcinoma (Abroodi Z, Asian Pac J Cancer Prev, 2019; Leone A, Int J Mol Sci, 2019; Kumar A, Nutrients, 2018; Hamza AA, Sci Rep, 2018; Shrotriya S, Mol Carcinog, 2015; Kumar S, Oncotarget, 2014; Aghbali A, Bosn J Basic Med Sci, 2013; Raina K, Food Chem Toxicol, 2013; Tyagi A, Nutr Cancer, 2013; Derry M, Cancer Lett, 2013; Perde-Schrepler M, J Photochem Photobiol B, 2013; Shrotriya S, Carcinogenesis, 2012).
- GSE could inhibit the self-renewal of prostate cancer stem cells (Tyagi A, Mol Carcinog, 2019).
- GSE can also enhance chemotherapy-induced growth inhibition, cell cycle arrest, double-strand breaks and p53 accumulation in colorectal cancer cells (Ravindranathan P, Carcinogenesis, 2019) and can enhance the growth inhibition of chemotherapy in rodent models of colon cancer and reduced incidence of mucositis (Cheah KY, PLoS One, 2014).
- In rodent models, GSE reduced prostate tumour growth and decreased the metastasis of colon cancer to the lungs (Derry MM, Exp Toxicol Pathol, 2014; Kaur M, Pharm Res, 2009).

Icariin

- No human treatment RCTs.
- In oestrogen receptor-negative breast cancer cells, icariin was found to stimulate proliferation (Ma HR, Int J Mol Med, 2014).
- Icariin inhibited growth, proliferation, migration and invasion and promoted apoptosis in breast, ovarian, cervical, pancreatic, colon, oesophageal, gastric, thyroid, osteosarcoma, epidermoid carcinoma, melanoma, glioblastoma and lung cancer cells (Wang S, J Ethnopharmacol, 2020; Alhakamy NA, Pharmaceutics, 2020; Wu X, Life Sci, 2019; Huang S, J BUON, 2019; Zheng X, Biomed Pharmacother, 2019; Fang L, Biomed Pharmacother, 2011; Tian M, Braz J Med Biol Res, 2018; Ren Y, Oncol Lett, 2018; Jiang S, Cell Mol Biol, 2018; Wang D, Oncotarget, 2017; Gu ZF, Environ Toxicol Pharmacol, 2017; Xu B, Clin Exp Pharmacol Physiol, 2015; Wu J, Mol Med Rep, 2013; Wang Y, Eur J Pharmacol, 2010).
- Icariin enhances the apoptotic effect and tumour growth reduction of chemo/radiotherapy in colorectal, gallbladder, ovarian, osteosarcoma, glioblastoma and breast cancer cells and hepatocellular carcinoma (Kim B, Int J Oncol, 2020; Cheng X, Breast Cancer, 2019; Jiang S, Int J Oncol, 2019; Wang ZD, Chin J Nat Med, 2018; Yang L, Cell Biochem Biophys, 2015; Zhang Y, Cell Biochem Biophys, 2014; Li W, Cell Biochem Biophys, 2014; Zhang DC, Acta Pharmacol Sin, 2013).
- It also reduced chemotherapy-induced neuropathic pain, renal injury, bone marrow microvascular damage and bone loss in rodents (Gui Y, Mol Pain, 2018; Hassanshahi M, J Cell Physiol, 2019; Ma P, Am J Transl Res, 2015).

Kaempferol

- No human treatment RCTs.
- In vitro studies showed that kaempferol can induce cell cycle arrest and DNA damage, inhibit cell growth, proliferation, migration and invasion and promote apoptosis in prostate, breast, ovarian, cervical, renal, liver, pancreatic, bladder, lung, oral, colorectal, gastric and endometrial cancer, leukaemia, osteosarcoma and malignant melanoma cells (Da J, Anal Cell Pathol, 2019; Lei X, J BUON, 2019; Yang S, J BUON, 2019; Zhu G, Int J Immunopathol Pharmacol, 2018; Wu P, Molecules, 2018; Han X, Biomed Pharmacother, 2018; Choi JB, J Agric Food Chem, 2018; Kim TW, Cell Death Dis, 2018; Zhu L, Oncol Res, 2019; Yang J, J BUON, 2018; Hung TW, Int J Med Sci, 2017; Kashafi E, Biomed Pharmacother, 2017; Lee J, PLoS One, 2016; Wu LY, Am J Chin Med, 2015; Lin CW, PLoS One, 2013; Chen HJ, Oncol Rep, 2013).
- Kaempferol also suppresses UV radiation-induced skin cancer (Yao K, Cancer Prev Res, 2014).
- Kaempferol can enhance the apoptotic effect of chemo- and radiotherapy, as well as reduction of cell viability, angiogenesis and proliferation in colorectal, non-small cell lung and ovarian cancer, glioma and leukaemia cells (Hassanzadeh A, Anticancer Agents Med Chem, 2019; Li Q, Mol Med Rep, 2019; Riahi-Chebbi I, Sci Rep, 2019; Zhao Y, Med Sci Monit, 2017; Kuo WT, Oncol Rep, 2015; Siegelin MD, Mol Cancer Ther, 2008).

Luteolin

- No human treatment RCTs.
- In vitro studies show that luteolin upregulates apoptosis, damages DNA and inhibits angiogenesis, proliferation, migration and invasion in liver, colorectal, non-small cell lung, gastric, pancreatic, prostate, ovarian, cervical and breast cancer, melanoma, myeloid leukaemia and glioblastoma cells (Lee Y, Biochem Biophys Res Commun, 2019; Gao G, Artif Cells Nanomed Biotechnol, 2019; Yao Y, Oncol Rep, 2019; Yu Q, Cell Death Dis, 2019; Yao X, Food Funct, 2019; El Gueder D, Environ Sci Pollut Res Int, 2018; Li Z, Food Funct, 2018; Chen PY, Int J Mol Sci, 2018; Liu H, Cancer Biol Ther, 2017; Zang M, Biochem Biophys Res Commun, 2017; Seo Y, PLoS One, 2017; Lin TH, Food Funct, 2017; Tjioe KC, Nutr Cancer, 2016).
- Luteolin enhances the effect of chemo- and radiotherapy to inhibit growth, reduce cell viability, proliferation, migration and invasion and induce cell cycle arrest and apoptosis in pancreatic, breast, ovarian, prostate, liver, non-small cell lung and colorectal cancer cells (Moeng S, Anticancer Res, 2020; Jang CH, Nutrients, 2019; Yin H, Pharmazie, 2019; Wang H, J Ovarian Res, 2018; Nazim UM, Int J Oncol, 2019; Cho HJ, Int J Oncol, 2015; Sakurai MA, PLoS One, 2014).
- Luteolin suppresses ‘stemness’, self-renewal and proliferation in prostate and oral cancer stem cells and enhanced the effect of radiotherapy (Han K, Sci Rep, 2018; Tsai PH, Anticancer Res, 2016; Tu DG, J Formos Med Assoc, 2016).
- In rodents, luteolin inhibits tumour growth and induced apoptosis in bladder, gastric and ovarian cancer and head and neck squamous cell carcinoma (Iida K, Cancer C, 2020; Wang H, J Ovarian Res, 2018; Selvi RB, Oncotarget, 2015; Lu J, J Transl Med, 2015).

Milk thistle (silybin, silibinin, silymarin)

- In subjects with prostate cancer, 13g/day silybinin for 2-4 weeks had no effect on IGF-1 or IGF-1 binding protein (Flaig TW, Prostate, 2010). A similar study administered 13g/day silybin for 4 weeks but there was no effect on PSA (Flaig TW, Invest New Drugs, 2007). Similarly, patients with early breast cancer randomised to 2.8g/day of a silybin-phosphatidylcholine complex for 4 weeks showed no effect on IGF-1 or nitric oxide levels (Lazzeroni M, Cancer Prev Res, 2016). *Note short study durations.*
- In patients with brain metastases from non-small cell lung cancer, silibinin induced significant clinical and radiological improvement in the brain but had no effect on the lung tumours (Bosch-Barrera J, Oncotarget, 2016).
- *In vitro* studies showed that silymarin, silibinin and silybin decreased tumour growth, cell viability, proliferation and migration, damaged DNA and increased apoptosis in gastric, oral, bladder, renal, breast, ovarian, skin, liver and colorectal cancer cells (Kim SH, Oncol Rep, 2019; Zappavigna S, Int J Mol Sci, 2019; Won DH, Tumour Biol, 2018; De Oliveira DT, J Biosci, 2017; Zheng N, Acta Pharmacol Sin, 2017; Li F, Int J Mol Sci, 2015; Tilley C, Mol Carcinog, 2016; Eo HJ, Int Immunopharmacol, 2015; Fan L, Eur J Pharmacol, 2014). In hepatocellular carcinoma cells, silymarin had no effect on proliferation but significantly decreased telomerase activity (Yurtcu E, J BUON, 2015).
- Silibinin can enhance chemotherapy-induced inhibition of proliferation, as well as cell cycle arrest and apoptosis in gastric, breast and bladder cancer, myeloid leukaemia, glioma, colon adenocarcinoma and hepatocellular carcinoma cells. Silibinin also enhanced chemotherapy-induced downregulation of cancer stem cell formation and self-renewal. (Zhang Y, Mol Med Rep, 2018; Mao J, Eur J Pharmacol, 2018) (Zhang Y, Mol Med Rep, 2018; Mao J, Eur J Pharmacol, 2018; Sun Y, Int J Oncol, 2017; Elhag R, Anticancer Res, 2015; Rastegar H, Acta Med Iran, 2013; Kauntz H, Apoptosis, 2012)
- In patients undergoing radiotherapy, 420mg/day silymarin for 6 weeks delayed development and progression of mucositis, while silymarin also protected against chemotherapy-induced renal damage (Elyasi S, Phytother Res, 2016; Ninsontia C, Pharm Biol, 2011).

Myricetin

- No human treatment RCTs.
- *In vitro* studies showed that myricetin inhibited growth, angiogenesis, proliferation, migration and invasion and induced double strand DNA breaks, cell cycle arrest and apoptosis in lung, liver, skin, breast, ovarian prostate, thyroid, bladder, gastric and colon cancer and cholangiocarcinoma, squamous cell carcinoma, leukaemia and lymphoma cells (Rajendran P, Mol Cell Biochem, 2020; Zhu ML, BMC Complement Med Ther, 2020; Li M, Cells, 2019; Tuponchai P, J Cancer Res Ther, 2019; Ye C, Cell Physiol Biochem, 2018; Knickle A, Food Chem Toxicol, 2018; Ha TK, Biomed Pharmacother, 2017; Jose J, Biomed Pharmacother, 2016; Pan H, Biochem Biophys Res Commun, 2016; Xu Y, Mol Med Rep, 2016; Huang H, J Funct Foods, 2015; Feng J, Mol Cell Biochem, 2015; Maggioni D, Nutr Cancer, 2014; Sun F, Nutr Cancer, 2012; Kang NJ, Ann N Y Acad Sci, 2011).
- Myricetin enhanced the effect of chemo- and radiotherapy in inhibiting cell survival and migration and increasing apoptosis in lung, ovarian and breast cancer and glioma and oesophageal carcinoma cells (Kang HR, Food Sci Nutr, 2020; Maroufi NF, Naunyn Schmiedebergs Arch Pharmacol, 2020; Zheng AW, Oncol Lett, 2017; Wang L, Cancer Cell Int, 2014; Siegelin MD, Cancer Lett, 2009). Myricetin inhibited proliferation, migration and invasion of glioblastoma cells; the addition of chemotherapy did not add to myricetin's effectiveness (Zhao HF, CNS Neurol Disord Drug Targets, 2018). The cytotoxicity of myricetin was greater than that of cisplatin, with no effect on healthy cells (Huang H, Int J Oncol, 2015).
- In rodents, myricetin inhibited colorectal tumorigenesis and reduced the size of colorectal polyps (Zhang MJ, Biomed Pharmacother, 2018). It also reduced chemotherapy-induced nephrotoxicity (Hassan SM, Pharm Biol, 2017).

Naringin/Naringenin

- No human treatment RCTs.
- Naringenin reduced tumour cell growth and viability, angiogenesis, proliferation, migration and invasion and upregulated apoptosis in prostate, breast, gastric, lung, bladder, colorectal and pancreatic cancer, glioblastoma, leukaemia, squamous cell carcinoma and hepatocellular carcinoma cells (Kang Q, J Agric Food Chem, 2019; Han KY, Anticancer Res, 2018; Chen YY, Environ Toxicol, 2019; Park HJ, Food Chem Toxicol, 2017; Zhao Y, Eur J Cancer, 2016; Chandrika BB, Life Sci, 2016; Li Q, Fitoterapia, 2016; Zhang F, Breast Cancer Res, 2016; Bao L, Tumour Biol, 2016; Bodduluru LN, Int Immunopharmacol, 2016; Maggioni D, Nutr Cancer, 2014; Liao AC, Mol Med Rep, 2014; Li H, Cancer Res, 2014; Jin CY, Toxicol In Vitro, 2009).
- Naringin also inhibited tumour growth, metabolism, proliferation, migration and invasion and induced apoptosis in breast, gastric, bladder, cervical and thyroid cancer, glioblastoma, melanoma, hepatocellular carcinoma and osteo- and chondrosarcoma cells (Zhou J, Pathol Res Pract, 2019; Raha S, Am J Chin Med, 2020; Ming H, Aging, 2018; Banjerdpongchai R, Asian Pac J Cancer Prev, 2016; Li J, J Drug Target, 2017; Yoshinaga A, Eur J Pharmacol, 2016; Guo B, Tumour Biol, 2016; Aroui S, Tumour Biol, 2016; Zeng L, Int J Oncol, 2014; Tan TW, Int Immunopharmacol, 2014; Li H, Toxicol Lett, 2013; Kim DI, Carcinogenesis, 2008).
- It also enhanced the effect of chemotherapy in inhibiting tumour cell growth, survival, proliferation and migration and induced apoptosis in breast and lung cancer cells (Xu Z, Toxicology, 2018; Hatkevich T, Exp Cell Res, 2014; Jin CY, Mol Nutr Food Res, 2011; Zhang FY, Pharm Res, 2009). Naringin could enhance the chemotherapy-induced reduction in tumour size in xenograft oesophageal cancer in mice (Tajaldini M, Biomed Pharmacother, 2020).
- Naringenin also inhibited the transition of hepatocellular carcinoma cells to cancer stem cells (Kang Q, J Agric Food Chem, 2019).
- It also inhibited the metastasis of breast tumour cells to lung tumour cells (Qin L, Protein Cell, 2011).

Nobiletin

- No human treatment RCTs.
- In vitro studies show that nobiletin inhibits tumour cell growth, angiogenesis, proliferation, migration and invasion and induced cell cycle arrest, DNA fragmentation and damage and apoptosis in pancreatic, lung, renal, bladder, gastric, colon, prostate, ovarian and breast cancer, acute myeloid leukaemia, glioma, osteosarcoma, fibrosarcoma and oral squamous cell, hepatocellular and nasopharyngeal carcinoma cells (Jiang H, J BUON, 2020; Jiang H, J Environ Pathol Toxicol Oncol, 2020; Lin CX, Food Sci Nutr, 2020; Deveci Ozkan A, Immunopharmacol Immunotoxicol, 2020; Zhang R, J Agric Food Chem, 2020; Goan YG, Molecules, 2019; Zheng CD, Food Sci Nutr, 2019; Chen PY, J Agric Food Chem, 2018; Liu F, J Cell Biochem, 2018; Sp N, Int J Mol Sci, 2017; Zhang X, Oncol Rep, 2017; Wu X, J Nutr Biochem, 2017; Moon JY, Molecules, 2016; Cheng HL, Oncotarget, 2016; Da C, Oncol Rep, 2016; Ma X, Phytother Res, 2014; Miyata Y, Biochem Biophys Res Commun, 2008).
- Nobiletin could also enhance chemotherapy-induced reduction of tumour cell size, viability and proliferation and increase in cell cycle arrest and apoptosis in lung, non-small cell lung, breast, gastric, colorectal and thyroid cancer and chronic myeloid leukaemia cells (Yen JH, Cells, 2020; Feng S, Acta Pharm Sin B, 2020; Feng SL, Phytomedicine, 2020; Sousa DP, Nutr Cancer, 2020; Guney Eskiler G, Nutr Cancer, 2019; Li N, Front Biosci, 2019; Rahideh ST, Biochem Cell Biol, 2017; Ma W, Sci Rep, 2015; Uesato S, Planta Med, 2014; Moon JY, Nutr Cancer, 2013).
- Nobiletin also inhibited breast cancer cell migration and invasion and stem cell formation (Sp N, Nutrients, 2018).
- In rodents with induced lung, non-small cell lung, colon or kidney cancer and hepatocellular carcinoma, nobiletin reduced tumour volume, angiogenesis and metastasis and induced cell cycle arrest and apoptosis (Sun Y, Food Funct, 2019; Wei D, Front Pharmacol, 2019; Moon JY, Nutrients, 2018; Wu X, Carcinogenesis, 2017). It could also reduce chemotherapy-induced renal injury (Malik S, Exp Toxicol Pathol, 2015; Ma X, Phytother Res, 2014).

Quercetin

- A human clinical trial found that in patients with familial adenomatous polyposis (precursor to colorectal cancer) who received 60mg/day quercetin and 1140mg/day curcumin for 6 months there was a decrease in polyp number and size (Cruz-Correa M, Clin Gastroenterol Hepatol, 2006).
- A systematic review for ovarian cancer studies found that although animal and *in vitro* studies suggest that quercetin inhibits tumour growth and angiogenesis and induces cell cycle arrest and apoptosis, human epidemiological studies found no effect on decreasing ovarian cancer risk at quercetin levels commonly consumed in a typical diet (1-32 mg/day) (Parvaresh A, J Res Med Sci, 2016).
- Similarly, a systematic review for hepatocellular carcinoma rodent studies found that quercetin was anti-proliferative and pro-apoptotic (Fernández-Palanca P, Nutrients, 2019), while *in vitro* studies found that quercetin inhibited proliferation and migration and induced cell cycle arrest and apoptosis in gastric and hepatocellular carcinoma (Hisaka T, Anticancer Res, 2020; Yamada N, Arch Biochem Biophys, 2020; Huh S, Molecules, 2019).
- Quercetin enhanced the cytotoxic, anti-proliferative and pro-apoptotic effect of chemotherapy in pancreatic and breast cancer and myeloid leukaemia cells. (Lan CY, J Food Drug Anal, 2019; Pham TND, Int J Mol Sci, 2019; Naimi A, J Cell Physiol, 2019; Li S, Phytother Res, 2018).
- Quercetin also suppressed gastric, breast and prostate cancer stem cell self-renewal, proliferation and invasion (Li S, Phytother Res, 2018; Li X, Life Sci, 2018; Wang R, Med Sci Monit, 2018; Erdogan S, Biomed Pharmacother, 2018; Shen X, Int J Mol Med, 2016).

Resveratrol

- In patients with colorectal cancer and hepatic metastases, 5g/day micronised resveratrol for 14 days, a marker of apoptosis was increased by 39% in malignant hepatic tissue, compared to placebo patients (Howells LM, Cancer Prev Res, 2011).
- In colorectal cancer patients, 0.5g/day and 1.0g/day for 8 days reduced tumour cell proliferation by 5% (Patel KR, Cancer Res, 2010).
- A 2016 meta-analysis of animal and *in vitro* studies of resveratrol in lung cancer found a significant reduction in tumour incidence (relative risk 0.64) (Feng Y, J BUON, 2016). A 2012 systematic review of animal and *in vitro* studies found evidence that resveratrol inhibited proliferation and induced apoptosis, regardless of cancer type (Aluyen JK, J Diet Suppl, 2012).
- Since then, animal and *in vitro* studies have shown that resveratrol inhibited tumour growth, proliferation, migration and invasion and increased cell cycle arrest and apoptosis in breast, prostate, renal, non-small cell lung, colon and pancreatic cancer, leukaemia and nasopharyngeal and oral squamous cell carcinoma cells (Tian X, J Nutr Biochem, 2020; Wang H, Onco Targets Ther, 2020; Qin T, Front Oncol, 2020; Kim JY, Exp Mol Med, 2020; Zhang J, Med Sci Monit, 2020; Siedlecka-Kroplewska K, J Physiol Pharmacol, 2019; Yuan L, Mol Med Rep, 2019; Giménez-Bastida JA, Mol Nutr Food Res, 2019; Jang YG, J Steroid Biochem Mol Biol, 2019).
- Resveratrol also inhibits the stem cell characteristics of pancreatic cancer cells and reduces the epithelial-mesenchymal transition in glioblastoma cells (Qin T, Front Oncol, 2020; Song Y, Biomed Res Int, 2019).
- Furthermore, resveratrol enhances the chemotherapy-induced inhibition of proliferation, reduction of cell viability and induction of cell cycle arrest and apoptosis in leukaemia, glioblastoma, colon, renal, breast and head and neck cancer cells (Bostan M, Nutrients, 2020; Ivanova D, Anticancer Res, 2019; Yan C, Curr Pharm Des, 2019; Zhang W, J Cell Biochem, 2019; Jie KY, Front Biosci, 2019; Öztürk Y, Oxid Med Cell Longev, 2019).

Rutin

- No human treatment RCTs.
- *In vitro* studies show that rutin has anti-cancer effects, including inducing cell cycle arrest and apoptosis in renal, colon, liver and cervical cancer cells (Caparica R, Biomolecules, 2020; Khan F, Endocr Metab Immune Disord Drug Targets, 2020; Guon TE, Oncol Lett, 2016; Alía M, Eur J Nutr, 2006).
- Rodent studies show that rutin can inhibit proliferation of leukaemia cells (Lin JP, Leuk Res, 2009).
- Rutin can enhance the radio- and chemotherapy-induced decrease in tumour volume and cell viability, inhibition of cell proliferation and induction of cell cycle arrest and apoptosis in gastric, colon, pancreatic, lung, breast and prostate cancer cells (Li Q, Biomed Res Int, 2019; Satari A, Adv Pharm Bull, 2019; Saleh A, Naunyn Schmiedebergs Arch Pharmacol, 2019; Iriti M, Phytother Res, 2017; Wu F, Exp Ther Med, 2017; Ben Sghaier M, Biomed Pharmacother, 2016; Vijay M, Bratisl Lek Listy, 2016).
- Rutin can protect against chemotherapy-induced liver, kidney, testicular and cardio- and neurotoxicity and peripheral neuropathy in rodents (Prasad R, Hum Exp Toxicol, 2020; Zaazaa AM, Pak J Biol Sci, 2019; Yaşar H, Adv Clin Exp Med, 2019; Fei J, Biosci Rep, 2019; Almutairi MM, BMC Complement Altern Med, 2017).

Genistein

- In males with prostate cancer, 30mg/day genistein for 3-6 weeks had no effect on proliferation, cell cycle arrest or apoptosis but it significantly reduced the expression of several biomarkers be related to prostate cancer prediction and progression. Serum prostate specific antigen (PSA) decreased by 7.8% in the genistein arm and increased in controls but the difference was not significant. (Lazarevic B, Br J Nutr, 2012; Lazarevic B, Nutr Cancer, 2011)
- In vitro studies show that genistein can suppress leukaemia and laryngeal, pancreatic, colon and kidney cancer, decreasing cell viability, migration and invasion and increasing cell cycle arrest, apoptosis and DNA damage and fragmentation (Imai-Sumida M, Cell Physiol Biochem, 2020; Hsiao YC, Environ Toxicol, 2019; Ma CH, Biomed Pharmacother, 2018; Zhu J, Mol Med Rep, 2018; Bi YL, Phytomedicine, 2018).
- It can also inhibit stem cell formation, reduce 'stemness' and proliferation and induce apoptosis in colon, ovarian and nasopharyngeal cancer cells (Zhang Q, Phytother Res, 2019; Ning Y, J Exp Clin Cancer Res, 2019; Zhou P, BMC Cancer, 2017).
- Genistein can enhance the radio- and chemotherapy-induced cell cycle arrest and apoptosis and reduce tumour growth and volume, cell viability, angiogensis and proliferation in breast, prostate and thyroid cancer and glioblastoma cells (Kaushik S, Life Sci, 2019; Ferrari SM, Nutr Cancer, 2019; Tang Q, Oncol Rep, 2018; Liu X, Radiother Oncol, 2018; Ozturk SA, J Cancer Res Ther, 2018).
- Rodents fed genistein showed decreased BRCA1 methylation and arylhydrocarbon receptor activity in mammary glands and enhanced the antiproliferative effects of chemotherapy. It alsoreduced incidence of hepatocellular carcinoma. (Donovan MG, Nutrients, 2019; Lee SR, BMC Cancer, 2019)
- In vitro studies show that genistein suppressed cell invasion in prostate cancer cells with long term treatment but increased it in the short term (Zhang H, PLoS One, 2019). Furthermore, in ovariectomised mice, low doses of genistein negated the beneficial effects of chemotherapy in breast cancer and enhanced drug resistance, while long term consumption of genistein promoted tumour growth (Du M, Carcinogenesis, 2012; Andrade JE, Mol Nutr Food Res, 2015; Rigalli JP, Cancer Lett, 2016).

Daidzein

- No human treatment trials.
- Among Japanese prostate cancer patients, serum concentrations of daidzein were higher than among healthy controls (Akaza H, Jpn J Clin Oncol, 2002).
- In vitro studies show that daidzein inhibited migration, invasion, proliferation, and colony formation, reduced viability and induced cell cycle arrest, DNA damage and apoptosis in lung, colon, liver, ovarian, thyroid, bladder and pancreatic cancer and neuroblastoma cells (Guo S, Immunol Lett, 2020; Gundogdu G, Drug Chem Toxicol, 2018; Liang YS, Food Nutr Res, 2018; Chan KKL, Cancer Cell Int, 2018; He Y, Neoplasma, 2016; Park HJ, Food Chem Toxicol, 2013; Somjen D, Thyroid, 2012; Lo FH, Biomed Pharmacother, 2007).
- In ovarian cancer stem cells, daidzein could also dose-dependently inhibit cell growth and decrease cell viability through upregulation of apoptosis (Green JM, Cancer Biol Ther, 2009).
- Daidzein can also enhance the radio- and chemotherapy-induced cell cycle arrest and apoptosis and inhibition of tumour growth in breast and prostate cancer and glioma cells (Guo J, Pharmacol Res, 2019; Singh-Gupta V, Pharm Res, 2010; Siegelin MD, Neurosci Lett, 2009).
- In rodents, daidzein suppressed induced mammary tumours and human xenografts to a greater extent that genistein and tamoxifen (Liu X, Life Sci, 2012).
- However, daidzein can stimulate growth of breast cancer cells and potentiate oestrogen-induced cell proliferation in the uterus (Gaete L, J Med Food, 2012; Murata M, Biochemistry, 2004), while in colon cancer cells, low doses of daidzein stimulated growth but higher doses inhibited growth (Guo JM, Food Chem Toxicol, 2004).

Puerarin

- No human studies.
- *In vitro* and animal studies found that puerarin reduced cell cycle progression, cell growth and viability, proliferation, migration and invasion and upregulated apoptosis in cervical, breast, bladder, colorectal and non-small cell lung cancer and hepatocellular and lung carcinoma cells (Huang SR, Neoplasma, 2020; Li L, Cancer Med, 2020; Jia L, Exp Ther Med, 2019; Li J, Eur J Pharmacol, 2019; Ye G, Oncol Lett, 2019; Li Z, Mol Med Rep, 2019; Chen T, Pharm Biol, 2016).
- Puerarin also inhibited cancer stem cell 'stemness', growth, self-renewal and invasion in lung cancer and hepatocellular carcinoma cells *in vitro* and *in vivo* (Li L, Cancer Med, 2020; Tau X, Clin Exp Pharmacol Physiol, 2020).
- These studies also showed that puerarin enhanced chemotherapy-induced decrease in cell viability, volume, weight, survival and proliferation and increase in apoptosis in lung, oesophageal and gastric cancer and hepatocellular carcinoma cells. In rodents, puerarin also enhanced chemotherapy-induced decrease in cell viability and survival and tunour growth. (Huang P, Cancer Manag Res, 2020; Guo XF, Mol Med Rep, 2015; Zeng YP, Oncol Lett, 2014; Wang J, Mol Med Rep, 2014)