Table 12.1: Phenolics of Pharmacological interest from the Winteraceae

The following provides details of the most relevant research undertaken in the last decade – albeit comprehensive, this list is not exhaustive. In the last few years there has been an explosion of flavonoid research with a substantial expansion of insight into the therapeutic potential of these compounds, notably chlorogenic acid, rutin and quercetin. Indeed, around 4,300 papers listed on PubMed over the last 10 years specify quercetin in the title – with more than 500 papers published *each year* between 2019 and 2021! In the three decades from 1980–2010 merely 2,000 papers were devoted to quercetin. Consequently many practical advances have been made with regard to the value of phenolics, as well as drug delivery options with enhanced bioavailability. However, it should be noted that experimental studies often use levels of a chemical that are not naturally found in the diet and study designs are restricted in scope. They are therefore an *indication* of pharmacological potential but not a certainty, unless backed by clinical evidence.

Chemical Component: Activity and therapeutic potential	**Resources**
Astilbin (flavonoid)	
Pharmacological properties (summary): potent antioxidant; anti-inflammatory, hepatoprotective, renoprotective, immunomodulatory, anti-allergy, benefit lung function, radioprotective	Williams (2011)
Bioavailability: activity is limited by poor bioavailability; studies show combination with a carrier compound or micro-emulsification can improve absorption; some metabolites (notably 3'-O-methylastilbin) demonstrated enhanced activity; also zein nanoparticle encapsulation using chitosan and sodium caseinate enhanced bioactivity.	Guo et al. (2007); Mezghrani et al. (2011); He et al. (2014); Ruan et al. (2021)
Astilbin can inhibit Vitamin C oxidation, thereby supporting/potentiating antioxidant activity	Mezghrani et al. (2011); He et al. (2014)
Wine flavouring: naturally contributes sweetness to dry-style wines; older wines contained higher levels of neoastilbin	Fayed et al. (2020 & 2021)
Antioxidant, anti-inflammatory (and derivatives): significant activity for astilbin (18%; the primary flavonoid in *Smilax glabra*) and natural derivatives i.e. neoastilbin (11%), isoastilbin (5%), neoisoastilbin (4%), plus (2–2.5% each) engeletin and epicatechin	Lu et al. (2014 & 2015); Feng et al. (2020); Gegentana et al. (2020); Zhao et al. (2020a)
Immunomodulatory: antioxidant; anti-inflammatory, immune suppressive; potential use in myasthenia gravis and lupus erythematosus	Zou et al. (2010); Tang et al. (2013); Guo et al. (2015b); Meng et al. (2016b); Han et al. (2020a); Xu et al. (2020a)
Antiarthritic: benefits for osteoarthritis; potential use in combination with drug treatment (methotrexate); active	Cai et al. (2003); Dong et al. (2017); Bao et al. (2018b); Ma et

component that contributes to anti-arthritic herbal treatment (*Smilax glabra* + *Bolbostemma paniculatum*)	al. (2018b); Chen et al. (2020c); Sun et al. (2020b); Yang et al. (2020b)
Bone metabolism: protect against bone loss (anti-osteoporosis potential)	Jin et al. (2019)
Gout: anti-uricaemia for gout, reduce uric acid levels (source: *Smilax glabra*); high levels also in *Dendrobium officinalis* (herbal complex) with anti-uricaemic activity	Xu et al. (2013); Sun et al. (2015); Wang et al. (2016f); Huang et al. (2019a); Liang et al. (2019b); Chen et al. (2020d)
Anti-allergic (weak activity, with engeletin; source: *Smilax glabra*)	Itharat et al. (2015)
Dental care: reduce virulence of *Streptococcus mutans*	Wang et al. (2019b)
Hair loss: astilbin derivative for prevention of hair loss	Nagasawa et al. (2016)
Skin and Cosmetic: anti-psoriasis, anti-inflammatory and immune regulation (source: *Smilax glabra*); 3'-O-methylastilbin shows anti-inflammatory potential for dermatitis	Guo et al. (2007); Di et al. (2016); Zhang et al. (2017b); Yu et al. (2018); Wang et al. (2019a)
Gastrointestinal tract: anti-inflammatory, potential for use in colonic inflammation (colitis); supportive to intestinal function i.e. anti-inflammatory, enhance antioxidant enzyme activities and intestinal barrier function, improve nutrient transport and absorption; protective against mycotoxin (vomitoxin) damage	Ding et al. (2014); Nakahara et al. (2017); Han et al. (2020a); Xu et al. (2020b); Zhao et al. (2021a)
Metabolic function: anti-hyperglycaemic potential (contribute to antidiabetic activity of *Smilax glabra* with 5-O-caffeoylshikimic acid); anti-obesity properties; also decrease the effective anti-obesity dose of caffeine	Wirasathien et al. (2007); Pérez-Nájera et al. (2018); Nguyen et al. (2020); Fang et al. (2021); Yang et al. (2021a)
Kidney function: antioxidant anti-inflammatory renoprotective; protective against kidney injury and reduced uric acid levels (source: *Rhododendron oldhamii*); benefits for diabetic nephropathy, renoprotective in gout and cisplatin toxicity	Li et al. (2009); Chen et al. (2011); Williams (2011); Tung et al. (2015); Wang et al. (2016f); Chen et al. (2018d & 2018e); Wang et al. (2018a)
Hepatoprotective: antioxidant, antifibrotic; anti-lipid accumulation, contribute to protection against fatty liver (*Rhododendron oldhamii*, *Smilax glabra*)	Wang et al. (2004); Williams (2011); Liu et al. (2017a); Sun et al. (2021a); Zhao et al. (2021a)
Respiratory tract: anti-inflammatory and muscle relaxant; protective against lung injury, pulmonary fibrosis, acute respiratory distress and sepsis-induced lung injury	Bezerra et al. (2013); Kong et al. (2016); Zhang et al. (2017a); Zhang et al. (2018a); Lu et al. (2019)
Cardiovascular: cardioprotective, active against ischaemia injury, anti-inflammatory	Diao et al. (2014)
Venoprotective: maintain and enhance vascular integrity thereby preventing bleeding e.g. reduce bruising and haemorrhagic problems, varicose veins, haemorrhoids etc.	Williams (2011)

Neuroprotective: anti-inflammatory, antioxidant; anti-ischaemic with potential benefits for ischaemic stroke; antidepressant; potential use in memory disorders, anti-Alzheimer's activity (also isoastilbin) and Parkinson's disease	Lv et al. (2014); Wang et al. (2016e); Yu et al. (2019); Zhu et al. (2019a); Li et al. (2019d); Li et al. (2020d); Zhang et al. (2021a)
Chemoprotective: active against cadmium toxicity	Xin et al. (2020)
Cancer studies: active against breast carcinoma cells	Sun et al. (2018a)
Chlorogenic acid (polyphenol; phenolic acid: 3-Caffeoquininic acid)	
Pharmacological properties (summary): antimicrobial; antioxidant, anti-inflammatory, wound-healing, analgesic, diuretic, anti-ulcer, radioprotective; liver and kidney protective, antidiabetic; cardioprotective; anti-aging and general health support; neuroprotective, chemoprotective and anticancer	Percival & Baird (2000); Duke (2002); Chauhan et al. (2012); Liang & Kitts (2015); Tajik et al. (2017); Naveed et al. (2018); Geng et al. (2019); Kim & Park (2019); Lu et al. (2020b); Miao & Xiang (2020)
Bioavailability: difficult to extract and purify, poor stability and solubility, low absolute bioavailability of oral administration, there is also the risk of allergic reaction to injection administration – all of which pose difficulties for medicinal research and development.	Miao & Xiang L. (2020)
Bioavailability: low bioavailability; low intestinal absorption; caffeic acid, p-coumaric acid, and ferulic acid are much more bioavailable than chlorogenic acid, albeit they are also excreted (urinary) more rapidly than chlorogenic acid (which had a low excretion rate)	Kishida & Matsumoto (2019); Mortele et al. (2021)
Bioavailability: soybean oil and coconut oil enhance the absorption of chlorogenic acid	Weerakoon et al. (2021)
Bioavailability (iron): excellent iron chelation properties; formation of chlorogenic acid-Fe(III) complexes, which bind with ferritin as ferritin-chlorogenic acid-Fe(III) complexes; chlorogenic acid could promote iron oxidation and iron release induced by ferritin (iron containing protein involved in iron homoeostasis)	Yang et al. (2021b)
Antimicrobial: antibacterial (including MDR bacteria) e.g. *Stenotrophomonas maltophilia, Helicobacter pylori, Escherichia coli, Staphylococcus epidermidis, S. aureus* and *Vibrio cholera*; significant anti-biofilm activity against *Klebsiella pneumoniae* infections; also anti-yeast (anti-*Candida*); anti-*Aspergillus* and anti-mycobacteria	Kong et al. (2017); Yun & Lee (2017); Naveed et al. (2018); Tiwari et al. (2018); Kim & Park (2019); Zeng et al. (2021a)
Antimicrobial: a combination of ultrasound and chlorogenic acid against *S. aureus* showed remarkable synergistic antibacterial and antibiofilm effects with significant potential for food processing and preservation	Sun et al. (2021)

Antimicrobial (bioavailability): nanoparticles (chlorogenic acid + cadmium selenide in silica base) show enhanced activity against *B. subtilis* and *E. coli;* good antibacterial activity of gold nanoparticles containing chlorogenic acid	Wang et al. (2020b); Zhu et al. (2020)
Antimicrobial: active against food pathogens e.g. *Salmonella enteritidis, S. typhimurium* and *Pseudomonas aeruginosa*; protective against intestinal damage associated with *Salmonella* infection	Su et al. (2019); Wang et al. (2019e); Sun et al. (2020c); Tan et al. (2020a); Xu et al. (2021)
Antimicrobial: active against mycotoxin (deoxyniyalenol ie. vomitoxin) induced cellular toxicity	Xu et al. (2020c)
Antimicrobial (crop pathogens): active against *Fusarium* cherry tomato rot	Kai et al. (2021)
Food preservation: chlorogenic acid is suitable for meat preservation and contributes to the preservation properties of Burdock (*Arctium lappa*); development of food packaging films designed for sustained release of chlorogenic acid for antioxidant and antimicrobial purposes; fish preservation coatings developed egg. antibacterial gelatine coating or chlorogenic acid–chitosan coating	Lou et al. (2016); Fu et al. (2017); Rajasekharan et al. (2017); Cao et al. (2020a); Cao et al. (2020c); Hu et al. (2020a); Zou et al. (2020)
Food preservation: excellent antibacterial properties of chlorogenic acid sol–gel preparations against *Escherichia coli* and *Enterococcus faecalis*	Catauro et al. (2021)
Antimicrobial (poultry farming): active against *Clostridium perfringens*–induced intestinal damage in chickens; improve growth and antioxidant capacity, anti-inflammatory on intestinal function, benefits for blood biochemistry; also anti-stress in heat stress for poultry	Zhao et al. (2019b); Zhang et al. (2020f)
Antimicrobial (water pathogens; source: *Piper betel*): active against *Vibrio* bacteria, which are also a problem in some fish farming operations; synergistic combination of chlorogenic acid with piperidine and eugenyl acetate	Acosta-Smith et al. (2019)
Antibacterial (drug synergist): synergistic with antibiotic (fosfomycin) treatment of *Listeria* infections (drug-resistant foodborne pathogen); caffeic acid also acts as an antibiotic synergist; active against *Klebsiella pneumoniae*, effective synergistic activity with levofloxacin	Tan et al. (2020b); Zhang et al. (2020d); Li et al. (2021f)
Antiviral: anti-HIV; anti-influenza; analogues active against hepatitis B (sourced from *Artemisia capillaris*); active against *Ebola* virus and infectious bronchitis virus, with immunosupportive properties	Zhao et al. (2014); Liu et al. (2016b); Ding et al. (2017); Naveed et al. (2018); Abaidullah et al. (2021)
Antiviral: potential inhibition of Coronavirus (SARS-CoV-2 infection)	Wang et al. (2021g)
Pharmacy: taste-modification properties, masking bitter flavours with potential for use in drug formulations	Shiraishi et al. (2017a & 2017b)

Anti-inflammatory and analgesic: anti-arthritic with benefits for osteoarthritis (chondrocyte/cartilage protective), rheumatoid arthritis and gout (active against high uric acid levels; hyperuricaemia)	Chen & Wu (2014); Hara et al. (2014); Meng et al. (2014); Lou et al. (2015); Liu et al. (2016a); Ding et al. (2017); Liu et al. (2017b); Tajik et al. (2017); Fu et al. (2019); Bagdas et al. (2020); Zada et al. (2021); Zhou et al. (2021c)
Anti-inflammatory (synergist): significant enhancement of the anti-inflammatory activity of curcumin	Bisht et al. (2020)
Anti-allergy: antipruritic (anti-itch, anti-histamine) for skin disorders; benefits for hayfever	Inami et al. (2013); Illing et al. (2015); Dong et al. (2020)
Food processing: improve the functional properties of whey protein isolate and reduce its allergic potential; also potential or reduce allergic properties of peanuts	Xu et al. (2019b); He et al. (2020)
Immunomodulatory: contribute to the immunoregulatory properties of *Lonicera japonica* (with luteolin)	Cheng & Yeh (2019)
Functional foods: chlorogenic acid (and quercetin) can intensify the colour of Mulberry anthocyanins (natural red food colourant) with good stability in food products; chlorogenic acid with tryptophan also yielded a red pigment with food dye potential	Khalifa et al. (2021); Moccia et al. (2021)
Skin and cosmetic: anti-aging for skin, antioxidant, anti-inflammatory, antimicrobial, anti-acne; collagen supportive, can repair skin tissue and reinforce barrier; influence melanogenesis; radioprotective (UVA and UVB); contribute to UV protective skin anti-aging properties of *Cecropia obtusifolia*; also Black Chokeberry (*Aronia melanocarpa*) extract (rich in chlorogenic acid and rutin) photoprotective and prevent collagen disruption; as well as extracts of Tart cherry (*Prunus cerasus*; also containing quercetin and kaempferol) against pollution related skin damage	Bhattacharyya et al. (2014); Cha et al. (2014); Li et al. (2014b); Alves et al. (2019); Her et al. (2020); Luo et al. (2020b); Girsang et al. (2021); Kim et al. (2021); Lee et al. (2021)
Eye and vision: antioxidant protective properties potentially useful against degenerative disorders e.g. cataract, diabetic retinopathy and glaucoma	Song et al. (2018b); Gong et al. (2019); Kim & Park (2019)
Hearing: protective potential for diabetic-induced hearing problems	Hong et al. (2017)
Wound healing: anti-inflammatory and promote healing in diabetes; nanofiber wound dressing made from biosynthesized poly(γ-glutamic acid) + polyvinyl alcohol loaded with chlorogenic acid (antibacterial, hypoglycaemic agent) for treatment of diabetic foot disorders	Bagdas et al. (2014a & 2015); Chen et al. (2013); Naveed et al. (2018); Sandova- Herrera et al. (2021)
Dental and oral care: stimulate bone repair in periodontal disease; chlorogenic acid (antimicrobial) loaded calcium phosphate-chitosan nanogel with biofilm degradative properties shows potential use in restorative dentistry	Palaniraj et al. (2019); Hu et al. (2021)

(filling material)	
Musculoskeletal: Cartilage repair, enhance tissue regeneration (tissue-engineering strategies); prevention of intervertebral disc (cartilage endplate) degeneration of the spine	Cheng et al. (2018); Ge et al. (2021)
Bone function: anti-osteoporosis potential to protect against bone loss	Kwak et al. (2013); Zhang & Hu (2016); Zhou et al. (2016d); Min et al. (2018)
Gastrointestinal function: anti-ulcer for gastric ulceration; protective anti-inflammatory effect for intestinal disorders including colitis; benefits for high-fat dietary damage, also gut microbial function, potential benefits for colonic inflammation and depression; combines well with *Lactobacillus* for intestinal inflammation; alleviate mucosal injury in reflux oesophagitis and anti-ulcer activity; protect from *Bacteroides* infection and indomethacin-induced inflammation	Shimoyama et al. (2013); Kang & Lee (2014); Ruan et al. (2014); Shin et al. (2015); Zatorski et al. (2015); Palocz et al. (2016); Zhou et al. (2016c); Tajik et al. (2017); Zhang et al. (2017c); Vukelic et al. (2018); Guo et al. (2019); Kim & Park (2019); Krajewska et al. (2019); Song et al. (2019); Wang et al. (2019c); Zhang et al. (2019c); Lee et al. (2020b); Zeng et al. (2020); Ahmed et al. (2021); Xie et al. (2021b)
Gastrointestinal tract (chemoprotective): chemopreventive; beneficial effects for lead-induced gut dysbiosis and side effects; also cadmium related intestinal injury	Cheng et al. (2019a); Xue et al. (2019); Ding et al. (2021)
Respiratory tract: anti-inflammatory, immunomodulatory; antihistamine, potential use for allergic rhinitis; anti-fibrotic, protect against chemotherapy (bleomycin) induced lung fibrosis	Wang et al. (2017b); Naveed et al. (2018); Shi et al. (2020); Dong et al. (2020)
Liver protective (hepatoprotective): anti-inflammatory, antioxidant, regulate gut microbiotia with benefits for liver function; significant protective properties in acute and chronic liver injury; protect liver function and choleretic (increase bile secretion), protect against cholestatic injury and alcohol liver injury; anticholesterol, antifibrotic, with benefits for fatty liver (can be combined with metformin); antifibrotic on schistosomiasis-induced liver damage	Yun et al. (2012); Ji et al. (2013); Shi et al. (2013); Wan et al. (2013); Ma et al. (2015b); Feng et al. (2016); Tan et al. (2016); Pang et al. (2015); Wu et al. (2015a); Shi et al. (2016); Zhou et al. (2016a); Tajik et al. (2017); Wang et al. (2017c); Kim et al. (2018b); Zhang et al. (2018c); Zhu et al. (2018b); Alqarni et al. (2019); Kim & Park (2019); Shi et al. (2021a); Zamani-Garmsiri et al. (2021)
Hepatoprotective (Clinical trial): no benefit of caffeic or chlorogenic acid in diabetes with fatty liver [comment: this could well be associated with a bioavailability issue];	Mansour et al. (2021)

however higher level of insulin in chlorogenic acid plus caffeine group	
Hepatoprotective (source: *Eucommia ulmoides*)	Hao et al. (2016b)
Liver protective (synergistic): combines well with silymarin and melatonin to protect against liver injury; also geniposide–chlorogenic acid for treating non-alcoholic fatty liver disease (NAFLD)	Al-Rasheed et al. (2014); Peng et al. (2018); Chen et al.(2021g)
Liver protective (chemoprotective): protective against lead and arsenic toxicity; active against liver toxicity due to triptolide (toxic diterpenoid epoxide); acetaminophen (paracetamol) and doxorubicin; also against cadmium toxicity (enhanced by combination with α-lipoic acid)	Wang et al. (2018d); Cheng et al. (2019a); Abbas et al. (2020); Dkhil et al. (2020); Hu et al. (2020b); Ding et al. (2021); Shi et al. (2021b)
Urinary tract: protective effect on bladder function egg. interstitial cystitis (bladder pain)	Luo et al. (2020a)
Kidney function (nephroprotective): antifibrotic, anti-ischaemic, antioxidant, anti-inflammatory; protect against diabetic nephropathy; chemoprotective against cisplatin, sodium arsenite and lead injury; green coffee seeds (rich in chlorogenic acid) could protect kidney function against gentamicin toxicity; also protective against vancomycin nephrotoxicity (does not affect drug antibacterial activity)	Domitrovic et al. (2014); Ye et al. (2016); Bao et al. (2018a); Zhang et al. (2019h); Cheng et al. (2019a); Arfian et al. (2019); Al-Megrin et al. (2020); Bhattacharyya et al. (2020); Qu et al. (2020); Toprak et al. (2020); Yunus et al. (2020); Zhou et al. (2021c)
Cardiovascular: significant cardioprotective properties; prevention and treatment of heart failure; antihypertensive (lower blood pressure); vasodilatory; anticoagulant, anti-thrombotic; anti-cholesterol; anti-ischaemic benefits for cardiovascular and cerebrovascular dysfunction	Ahn et al. (2011); Lee et al. (2012); Zhao et al. (2012); Wan et al. (2013); Fuentes et al. (2014); Hao et al. (2016b); Onakpoya et al. (2015); Akila & Vennila (2016); Choi & Kim (2017); Tajik et al. (2017); Naveed et al. (2018); Agunloye et al. (2019); Bhandarkar et al. (2019); Chen et al. (2019); Kim & Park (2019); Tian et al. (2019); Hada et al. (2020); Liu et al. (2020a); Lukitasari et al. (2020); Wang et al. (2020i)
Cardiovascular (surgery): experimental anti-neuroinflammation activity with potential for prevention of side effects (egg. memory dysfunction) after deep hypothermic circulatory arrest during heart surgery	Chen et al. (2021f)
Cardioprotective: combined in phospholipid complex to help recovery process following heart attack	Li et al. (2018a)
Metabolic function: antidiabetic with good clinical activity;	Meng et al. (2013); Bagdas et al.

protective effect on pancreatic inflammation (pancreatitis); protection against blood sugar dysfunction due to high fat/sugar diet; also protective against high fat diet cardiovascular, liver and metabolic changes; anti-obesity activity (also coffee); metabolic regulation and promote weight loss; promote wound healing in diabetes; antidiabetic component of *Cecropia obtusifolia*, Chicory (*Cichorium intybus,* with chicoric acid), *Sonchus oleraceus* (with caffeic acid) and *Smilax aristolochiifolia* (with astilbin); Highland Barely grain shows anti-hyperglycaemic activity (active principles chlorogenic acid and β-glucan) and pancreatic protective properties	(2015); Ma et al. (2015b); Hao et al. (2016b); Santos & Lima (2016); Ohkawara et al. (2017); Santana-Gálvez et al. (2017); Tajik et al. (2017); Ferrare et al. (2018); Naveed et al. (2018); Perez-Najera et al. (2018); Zuniga et al. (2018); Bhandarkar et al. (2019); Chen et al. (2019); Han et al. (2019); Kim & Park (2019); Wang et al. (2019c); Xu et al. (2019a); Cadena-Zamudio et al. (2020); Kumar et al. (2020b); Pimpley et al. (2020); Saraswat et al. (2020); Yan et al. (2020a); Wang et al. (2020j); Zhong et al. (2020); He et al. (2021); Kong et al. (2021); Liu & Li (2021): Singh et al. (2021); Tarasiuk et al. (2021); Wang et al. (2021f)
Metabolic function: coffee consumption is associated with a protective effect on development of diabetes; chlorogenic acid (high levels found in coffee) probably plays a role	Williamson (2020)
Metabolic function: combines well with geniposide or caffeine; clinical study of use with luteolin in combination formula (Altilix)	Peng et al. (2018); Castellino et al. (2019); Xu et al. (2019a)
Antidiabetic (side effects): protective against diabetes side effects e.g. hearing loss, retinopathy, nephropathy, peripheral neuropathy; cadiomyopathy (egg. anti-fibrosis)	Hong et al. (2017); Saraswat et al. (2020); Yan et al. (2020a); Qin et al. (2021)
Eye and vision: protective effect on eye function and damage due to diabetes; cataract protection with quercetin in Highbush Blueberry leaf (prevent retinal degeneration)	Kim et al. (2011); Shin et al. (2013); Jang et al. (2014 & 2015); Shin & Yu (2014); Ferlemi et al. (2016); Kim et al. (2016)
Haematology: chemoprotective against anaemia and mineral disturbances; protective capacity against red blood cell damage (methemoglobinemia) due to sodium nitrite (nitrite salts are used as a food preservative; also widespread in environment); protective against cadmium-induced erythrocyte damage	Koriem et al. (2018); Cheng et al. (2020); Cheng et al. (2021)
Genitourinary tract (male): prostate function; inhibition of benign hyperplasia; protection against arsenic-induced testicular dysfunction	Huang et al. (2017); El-Khadragy et al. (2021)
Cryopreservation (sperm): antioxidant (antistress) potential for supplementing culture media during semen handling and cryopreservation	Noto et al. (2021)

Genitourinary tract (female): protective effect against zearalenone (a toxin produced by *Fusarium* fungi found in cereals, grain and animal feed) protected against ovarian cellular damage; potential for use in endometritis (animal farming)	Yi et al. (2020); Gao et al. (2021)
Neuroprotective: chemoprotective; antidepressant and anti-anxiety; potential benefits for treating PTSD (post-traumatic stress disorder); anti-epileptic; anti-inflammatory, anti-ischaemic benefits for cerebrovascular dysfunction; protection against cadmium, lead and aluminium toxicity; benefits for diabetic neuropathy and Parkinson's disease	Bagdas et al. (2014b); Hara et al. (2014); Hao et al. (2015); Mikami & Yamazawa (2015); Aseervatham et al. (2016); Fang et al. (2016); Gul et al. (2016); Taram et al. (2016); Wu et al. (2016b); Miao et al. (2017); Wang et al. (2017a); Cheng et al. (2019a & 2019b); Shi et al. (2019a); Yao et al. (2019); Singh et al. (2020); Chen et al. (2021e); Ji et al. (2021); hah et al. (2021)
Neuroprotective: active against corticosterone and rotenone neurotoxicity	Shi et al. (2019a); Youn et al. (2019)
Neuroprotective (brain and memory): antioxidant protection for brain function; anti-ischaemic and anti-amnesic (improve memory); potential protection against alcohol toxicity in developing (neonatal) brain; also lead-induced cognitive impairment	Kwon et al. (2010); Guo & Li (2017); Heitman & Ingram (2017); Nabavi et al. (2017); Tajik et al. (2017); Kato et al. (2018); Cheng et al. (2019a); Hermawati et al. (2020); Kim & Park (2019): Kumar et al. (2019b); Gao et al. (2020b); Lee et al. (2020c); Liu et al. (2020a)
Neuroprotective (nerve injury): potential for combination with analgesics for treatment of nerve pain e.g. trigeminal neuralgia; potential use as anti-inflammatory in spinal cord injury	Kakita et al. (2018); Chen et al. (2018a)
Neuroprotective (drug delivery): intranasal delivery under investigation for treatment of stroke and neurodegenerative disorders	Kumar et al. (2019)
Anticancer: chemoprotective, anti-metastatic, antimutagenic, anti-leukaemia; active in glioma (brain cancer), stomach, oral (tongue), oesophageal, colon, bone (osteosarcoma), breast (synergistic with hesperidin), kidney, lung and liver cancer cell studies	Weng & Yen (2012); Liu et al. (2013b); Gundala & Aneja (2014); Shao et al. (2015); Lewandowska et al. (2016); Hou et al. (2017); Tajik et al. (2017); Xue et al. (2017); Lukitasari et al. (2018); Sadeghi Ekbatan et al. (2018); Zhang et al. (2019g); Huang et al. (2019b); Kim & Park (2019); Liu et al. (2020d); Sapio et al. (2020);

	Wang et al. (2020h); Zhan et al. (2020); Changizi et al. (2020); Hsu et al. (2021); Jiang et al. (2021)
Cancer chemotherapy: used as an IM injection in China for solid tumours; chlorogenic acid sustained-release gel developed for the treatment of glioma and hepatocellular carcinoma.	Yang et al. (2020a); Zhou et al. (2021a)
Cancer (herbal medicine): contribute to anticancer and anti-inflammatory activity of Kudingcha tea (*Ilex kudingcha*)	Zhang et al. (2020e)
Anticancer (herbal medicine): chlorogenic acid-rich extracts of pink flowers of *Nerium oleander* were active in colon cancer cell lines	Ayouaz et al. (2021)
Anticancer (drug enhancement): enhance activity of drug treatment e.g. regorafenib or 5-florouracil in hepatocellular carcinoma (liver cancer cells); enhance activity of doxorubicin in osteosarcoma cells	Yan et al. (2015a); Refolo et al. (2018); Salzillo et al. (2021)
Anticancer (drug delivery): chitosan nanoparticle showed significant concentration-dependent antiproliferation activity in renal carcinoma cells; also enhanced antioxidant properties and cellular accumulation of chlorogenic acid, thereby lowering the required dosage; graphene oxide with protocatechuic acid + chlorogenic acid nanodelivery system for liver cancer treatments	Kavi Rajan et al. (2019); Buskaran et al. (2021)
Anticancer (combination therapy): combination of low-intensity pulsed electric field, thermal-cycling hyperthermia and chlorogenic acid enhanced activity against pancreatic cancer cells	Lu et al. (2020a)
Cancer immunotherapy: anti-metastatic; chlorogenic acid-encapsulated mannosylated liposomes have potential for immunotherapeutic modulation of glioblastoma (good potential in clinical trials); improved anti-tumour immunity in breast cancer; chlorogenic acid liposomes modified with sialic acid plus antibody treatment showed potential as immunotherapy for melanoma	Ye et al. (2020 & 2021); Li et al. (2021e); Zeng et al. (2021b); Zhang et al. (2021e)
Cancer (chemoprotective): protective against tamoxifen induced reproductive dysfunction, liver and kidney damage; combined with silymarin to protect against doxorubicin hepatotoxicity	Abbas et al. (2020); Owumi et al. (2021a & 2021b)

Chemoprotective: protective against lead damage to liver, kidney and brain function; active against aluminium, cadmium and paraquat toxicity; also triptolide-induced liver damage; arsenic and plasticizer BPFL (4,4'-(9-Fluorenylidene)-diphenol) toxicity reproductive (testicular) damage	Wang et al. (2018d); Cheng et al. (2019a); Cheng et al. (2019b); Kong et al. (2019); Dkhil et al. (2020); Ding et al. (2021); El-Khadragy et al. (2021)
Chemoprotective: against thiram (pesticide, fungicide) skeletal toxicity in poultry	Zhang et al. (2019a & 2021f)
Antiparasitic: amoebicidal (source: *Lonicera japonica*)	Mahboob et al. (2016)
Antiparasitic: active against *Leishmania* parasites	Majumder et al. (2020)
Pesticide: insect and herbivore deterrent	Kundu & Vadassery (2019)
Medical materials: sol-gel synthesis of different forms for biological applications egg. tissue binding, antimicrobial and anticancer properties	Catauro et al. (2019 & 2021)
Agrochemical use: chlorogenic acid applied to sweetpotato leaves conferred significant resistance against weevil pests; enhanced levels also developed in response to the weevil attack via. induction of phytohormones (jasmonic acid, salicylic acid, abscisic acid) that stimulated chlorogenic acid formation – suggesting this is a useful trait for development of sweet potato cultivars	Liao et al. (2020)
Agrochemical: arsenic toxicity in plants can be ameliorated by chlorogenic acid (also hesperidin) which have excellent potential to benefit maize crops under arsenic stress by preventing oxidative injury and preserving photosynthesis	Arikan et al. (2021)
Quercetin (flavonoid, flavonol: 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4-Hchromen-4-one)	
Pharmacological properties (overview): antioxidant (one of the most important dietary antioxidants), anti-inflammatory, analgesic, antibacterial, antiviral, gastroprotective, antidiabetic, immunomodulatory, cellular protective (liver, kidney, pancreas, nervous system), protective for sepsis damage, detoxicant, chemoprotective and significant anticancer potential	Kim & Park (2018); Ulusoy & Sanlier (2019); Batiha et al. (2020); Salehi et al. (2020); Yang et al. (2020c)
Bioavailability: enhanced stability of vitamin D2 exposed to high temperatures and different pH values	Chang et al. (2021)
Bioavailability: gut microbiota play a crucial role in absorption; compared to other phenolics has good bioavailability from diet (capers, coriander, red lettuce, green and yellow hot peppers, onions, apples, wine, tea, cocoa powder, buckwheat); found in good quantities in a number of herbal medicines (egg. *Abelmoschus esculentus, Hypericum perforatum, Psidium guajava, Rosa laevigata*); has the ability to cross blood-brain barrier; however, not so	Kim & Park (2018); Ulusoy & Sanlier (2019); Khursheed et al. (2020); Javadinia et al. (2021); Roshanravan et al. (2021)

readily available from supplements; numerous studies undertaken for improving bioavailability and enhanced-targeted drug delivery systems	
Functional foods: excellent potential for food product development and targeted biological activity; quercetin and chlorogenic acid can intensify the colour of Mulberry anthocyanins (natural red food colouring qualities) with good stability in food products	Bhat & Bhat (2021); Khalifa et al. (2021); Lai & Wong (2021)
Bioavailability (synergist): complementary with diverse drugs and natural products in various conditions egg. fish oil and vitamin C in neurodegenerative disorders; enhanced activity of curcumin and resveratrol combinations, as well as cancer chemotherapy; enhance activity of antifungal agents and antibiotics (however, appears to be contraindicated with fluoroquinolone antibiotics)	Batiha et al. (2020)
Bioavailability (iron): chemoprotective; excellent iron chelation properties; regulates iron absorption from intestine; protect against excessive iron uptake from alcohol; significant protection against iron overload in various systems e.g. liver, kidney, brain and cardiovascular system; iron-chelation anticancer activity	Horniblow et al. (2017); Guo et al. (2018a); Lesjak et al. (2019) Sajadi Hezaveh et al. (2019a & 2019b); Chen et al. (2020b); Ding et al. (2021a); Dora et al. (2021); Yin et al. (2021b)
Bioavailability: enhancement of bioavailability and stability is essential for future therapies e.g. nanoformulations show significant benefits for bioavailability	Khursheed et.al. (2020); Negahdari et al. (2021); Zang et al. (2021)
Tonic and adaptogenic: anti-fatigue; anti-aging antioxidant with a protective effect on body/cellular function; adrenal supportive; help with exercise fatigue and performance; also prevent muscle atrophy	Kelly (2011); Wu et al. (2012); Daneshvar et al. (2013); Mahoney et al. (2014); Miles et al. (2014); Correa et al. (2018); Otsuka et al. (2019); El-Far et al. (2020); Chen et al. (2021b)
Thyroid function: protects against cadmium toxicity	Capriglione et al. (2021)
Antifungal: strongest antifungal activities against *Candida albicans, Cryptococcus neoformans;* active against mycotoxins e.g. *Aspergillus flavus, Aspergillus niger*	Li et al. (2019b); Batiha et al. (2020)
Antibacterial: more effective against Gram-positive than Gram-negative bacteria; good activity against *Mycobacterium*; active against *Salmonella, Enterococcus, Pseudomonas, Helicobacter pylori, Staphylococcus, Yersinia enterocolitica, Micrococcus luteus, Acinetobacter baumannii, Campylobacter jejuni, and Escherichia coli,* also *Shigella flexeneri* and *Listeria monocytogenes*	Kelly (2011); Anand David et al. (2016); Sasikumar et al. (2018); Batiha et al. (2020); Yang et al. (2020c)
Antibacterial: protective against *Streptococcus pneumonia* infection (inhibit haemolysin activity)	Lv et al. (2019)
Antimicrobial (anti-biofilm activity): inhibition of biofilm development by diverse bacterial pathogens e.g.	Memariani et al. (2019); Rocha et al. (2019); Yang et al. (2020c)

Enterococcus faecalis, Staphylococcus aureus, Streptococcus mutans, Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa; also antifungal biofilms against *Candida*	
Antiviral: active against a wide range of viruses e.g. influenza, dengue virus, Herpes virus, Epstein-Barr and Japanese encephalitis virus, pseudorabies virus; active against Hepatitis C with potential as adjunct therapy; block Ebola virus infection	Kelly (2011); Zandi et al. (2011); Senthilvel et al. (2013); Lee et al. (2015a); Wu et al. (2015b); Chiow et al. (2016); Lu et al. (2016); Rojas et al. (2016); Liu et al. (2016b); Gansukh et al. (2016); Vaidya et al. (2016); Sharma et al. (2018b); Batiha et al. (2020); Fanuza et al. (2020); Kim et al. (2020); Di Petrillo et al. (2021); Sun et al. (2021c)
Antiviral (chemoprotective): mitigate side effects of anti-HIV drug (Rilpivirine) on metabolic function and lipid metabolism	Behl et al. (2020)
Antiviral (farming): active against porcine epidemic diarrhoea virus with potential for antiviral use in pig farming operations	Li et al. (2020h)
Antiviral: significant potential to interfere with SARS-CoV-2 replication; also shows antithrombotic, renoprotective and anti-inflammatory activity with good clinical potential, particularly in early stages of infection; mitigation of symptoms of infection, facilitated recovery and resolution of infection (returning negative Covid tests more quickly in hospital); enhanced potential for phospholipid delivery form of quercetin (Quercetin Phytosome®) and selenium-quercetin derivatives; quercetin has potential for use in concurrent COVID-19 and Dengue infection.	Diniz et al. (2020); Bastaminejad & Bakhtiyari (2021); Derosa et al. (2021); Di Pierro et al. (2021a, 2021b & 2021c); Gu et al.(2021); Saeedi-Boroujeni & Mahmoudian-Sani (2021) ; Mangiavacchi et al. (2021); Saakre et al. (2021); Zheng et al. (2021b)
Antimicrobial (drug enhancement): antibiotic potentiation with enhanced antibacterial activity e.g. tetracyclines; improve antifungal efficacy of amphotericin and synergistic with amoxicillin; improve antimalarial activity of artemisinin	Abreu et al. (2015); Amin et al. (2015); Oliveira et al. (2016); Siriwong et al. (2016); Puttappa et al. (2017); Qu et al. (2019a)
Antifungal (synergist): inactive against *Clostridium neospora* but when combined with amphotericin B, the antifungal activity was greatly enhanced; antifungal for the clinical management of *Candida* vaginitis (*C. albicans* biofilms) with a synergistic activity with fluconazole	Yang et al. (2020c)
Food packaging: quercetin and gallic acid in PVA poly(vinyl alcohol) packaging films; also poly(butylene succinate)-based (PBS) films enriched with quercetin, and quercetin-starch films	Luzi et al. (2019); Yadav et al. (2020); Lopusiewicz et al. (2021); Tongdeesoontorn et al. (2021)
Anti-inflammatory and immunomodulatory: long-lasting	Kelly (2011); Sakulnarmrat &

anti-inflammatory agent combined with substantial immune activity; potential for inflammatory auto-immune disorders e.g. colitis, lupus erythematosis; also sepsis, asthma and allergic reactions with significant clinical potential	Konczak (2012); Miles et al. (2014); Li et al. (2016c); Mlcek et al. (2016); Escribano-Ferrer et al. (2019); Ulusoy & Sanlier (2019); Batiha et al. (2020); Jafarinia et al. (2020); Sato & Mukai (2020); Yang et al. (2020c); Karimi et al. (2021); Shen et al. (2021b)
Anti-arthritic and cartilage support: analgesic, anti-inflammatory with potential for osteoarthritis and rheumatoid arthritis; prevention of neurological degeneration and intestinal inflammation in rheumatoid arthritis; the sustained-release of quercetin in cartilage degenerative conditions shows substantial protective and treatment benefits e.g. knee arthritis; quercetin can be used to enhance cartilage regeneration combined with PHBV scaffold	Kelly (2011); Javadi et al. (2016); Gokhale et al. (2019); Ma et al. (2019a); Piovezana Bossolani et al. (2019); Permatasari et al. (2019); Mok et al. (2020); Zhang et al. (2019d); Yuan et al. (2020b); Chen et al. (2021c); Goyal & Agrawal (2021); Sadeghi-Ghadi et al. (2021); Shen et al. (2021b)
Anti-gout: lowers uric acid levels in blood and inhibition of xanthine oxidase; quercitrin (quercetin-3-O-ramnoside) also lowered uric acid levels; potential for prevention of oxalate urinary tract stones	Shi & Williamson (2016); Zhang et al. (2018b); Mohos et al. (2019); Adachi et al. (2021); Guzel et al. (2021)
Anti-inflammatory (synergist): combination therapy of atorvastatin and quercetin had an additive anti-inflammatory, antioxidant and hepatoprotective effect in rheumatoid arthritis studies; alternative to methotrexate treatment	Ibrahim et al. (2021)
Anti-inflammatory (drug interaction): antagonistic; appears to reduce efficacy of the anti-inflammatory drug diclofenac (Voltaren), hence this is not a recommended combination	Ventura-Martínez et al. (2021)
Musculoskeletal: analgesic, reduce nerve pain; reduce exercise-induced muscle damage, recovery of neuromuscular function, reduce muscular weakness, fatigue and enhance exercise performance (also Zynamite®, quercetin + mango leaf extract rich in mangiferin); diabetes muscle wasting and fatigue (beneficial combination with CoQ10); anti-ischaemic protection against loss of blood supply to an area; protection against muscle atrophy (sarcopenia) and inflammation associated with obesity; prevention of tendon adhesion (limitation of tendon movement) e.g. fibrosis due to traumatic injury; also brachial plexus neurological injury (shoulder and arm region) with hydrogel sustained-release formulation	Le et al. (2014); Muto et al. (2018); Patrizio et al. (2018); Bazzucchi et al. (2019 & 2020); Huang et al. (2020b); Liang et al. (2020); Martin-Rincon et al. (2020); Mohammadrezaei Khorramabadi et al. (2020); Chen et al. (2021b); Youssef et al. (2021)
Bone and spinal disorders: anti-inflammatory, bone protective, enhance repair and anti-osteoporosis (also	Gomez-Florit et al. (2015); Babosova et al. (2016); Khan et al.

vitamin E); anticancer; prevention of intervertebral disc degeneration; facilitate repair after spinal injury; complex interactions on bone cells with overall benefits for bone health; potential prevention of ferroptosis-induced bone damage	(2016); Guo et al. (2017); Li et al. (2020f); Song et al. (2020a); Wang et al. (2020e); Wang et al. (2020f); Wong et al. (2020); Gui et al. (2020); Goyal & Agrawal (2021); Novais et al. (2021); Shao et al. (2021); Vakili et al. (2021); Wang et al. (2021d); Zhang et al. (2021b)
Bone regeneration (combination therapy): collagen (extracted from duck's feet) + quercetin and hydroxyapatite has substantial potential for bone regeneration strategies; combination of hyaluronic acid + quercetin (noisome preparation) showed significant enhancement of anti-inflammatory activity	Forte et al. (2016); Song et al. (2020a); Sadeghi-Ghadi et al. (2021)
Bone repair: quercetin-coupled magnesium-doped calcium silicate enhanced bone tissue repair (osteogenic activity) potential, but also reduced bacterial contamination particularly against Gram-positive bacteria (e.g. S. aureus); quercetin has metal-chelating ability which resulted in levels of (Ca+Mg)/Si increasing with the quercetin concentration	Preethi & Bellare (2021)
Dental care: effective antimicrobial and anti-inflammatory agent for periodontitis and other oral inflammatory disorders; anti-inflammatory effects on *Porphyromonas gingivalis*; inhibition of inflammatory bone loss for dental care (treatment of periodontitis); positive effects of quercetin on soft and hard tissue regeneration, supporting the healing and restoration of bony defects, as well as the use of quercetin composites as tissue scaffolds and dental implants; anti-biofilm activity and collagen-stabilizing effect that support its use as an endodontic irrigant (to prevent root canal infection)	Napimoga et al. (2013); Xiong et al. (2019); Angellotti et al. (2020); Taskan & Gevrek (2020); Liu et al. (2021d)
Dental implant: anti-bacterial, bone-regenerating, anti-inflammation activity enhanced with bergapten and quercetin to prevent dental implant failure (endosseous implants are surgically placed inside the jawbone and left to heal before placing the artificial tooth/crown on the implant)	Wei et al. (2021a)
Skin and Cosmetic: antipruritic (anti-itching); benefits for skin inflammation and toxin damage; clinical use (phytosome formulation); UV protection, enhance wound healing, anti-inflammatory for atopic dermatitis and psoriasis; limited use due to poor skin penetration, enhanced activity with oleogel (olive oil/pleuronic hydrogel)	Karuppagounder et al. (2016); Maramaldi et al. (2016); Chen et al. (2017a); Lee et al. (2018); Sharma et al. (2018b); Shin et al. (2019); Beken et al. (2020); Nasr & Al-Karaki (2020); Elmowafy et

and nanocarrier-based solutions	al. (2021)
Skin (skin cancer chemoprevention): protective anti-inflammation, active against precancerous and cancerous skin damage; combination with resveratrol (liposome formulation); also with titanium dioxide; nanostructured lipid carrier gel with quercetin and resveratrol enhance their penetration into deeper skin layers with potential for the treatment of skin cancer	Caddeo et al. (2016); Bagde et al. (2019); Imran et al. (2020)
Cosmetic: use limited by poor skin penetration ability with various techniques under investigation to improve bioavailability e.g. combination with menthol to enhance skin penetration; enhanced quercetin delivery for cosmetic and anti-inflammatory applications by sodium alginate + PVA (poly(vinyl) alcohol)) formulation; quercetin-loaded microcapsules were anti-inflammatory and radioprotective	Cai et al. (2013); Hatahet et al. (2016); Lv et al. (2017); Sharma et al. (2018b); Huang et al. (2019c); Esposito et al. (2020); Vale et al. (2021)
Cosmetic: improved healing of scar tissue (keloid)	Moravvej et al. (2019)
Wound healing: improves pressure ulcer lesions; hydrogel formulations for treatment of wounds; promote wound healing in diabetic injuries (with laser therapy); treatment of diabetic foot ulcers with various formulations e.g. combined with skin growth factor complexes, oxygen carriers or oleic acid; promote healing of burns and reduction in scar tissue (quercetin-silicone gel sheet)	Ahmad et al. (2017); Ahmed et al. (2018); Jangde et al. (2018); Yin et al. (2018); Jee et al. (2019); Beken et al. (2020); Gallelli et al. (2020); Jin et al. (2021)
Healing (bioactivity): starch-based hydrogel grafted onto fumaric acid increased quercetin bioavailability and controlled release	Doosti et al. (2019)
Wound dressings: highly effective quercetin-loaded chitosan oligosaccharide/polycaprolactone nanofibers designed for use as an antibacterial dressing	Zhou et al. (2021b)
Gastrointestinal function: anti-inflammatory gastroprotective and antiulcer; immunomodulatory and anti-inflammatory for gastrointestinal tract with potential for treating colonic inflammation (colitis); also the treatment of intestinal damage in neonates (necrotizing enterocolitis); silk fibroin nanoparticles enhance quercetin's immunomodulatory properties for colitis	Kelly (2011); Dodda et al. (2014); Hu et al. (2015); da Silva Junior et al. (2016); Curgali et al. (2017); Yazici et al. (2017); Zhang et al. (2017d) ; Diez-Echave et al. (2021)
Gastrointestinal function (chemoprotective): quercetin metabolite in onion peels (ie. BZF: 2-(3,4-dihydroxybenzoyl)-2,4,6-trihydroxy-3(2H)-benzofuranone), potent antioxidant with excellent protection against indomethacin (NSAID) related loss of intestinal epithelial barrier function	Fuentes et al. (2021)
Gastrointestinal metabolism: polyphenols such as quercetin are metabolized through intestinal microbiota forming more	Shi et al. (2020a); Roshanravan et al. (2021); Sankaranarayanan et

bioactive metabolites, meanwhile they also beneficially modulate the composition of the gastrointestinal tract, improving gut functions; prebiotic activity against gut dysbiosis due to antibiotic therapy; gut bacterial species influence metabolite production with anticancer (antiproliferative) potential	al. (2021); Shabbir et al. (2021); Tan et al. (2021)
Gastrointestinal function (anticancer): microencapsulated quercetin plus *Bifidobacterium bifidum* and *Lactobacillus gasseri* inhibit colorectal cancer development; melanin-quercetin nanoparticles showed strong anti-tumour activity in small intestine cancer studies	Benito et al. (2021); Wang et al. (2021e)
Gastrointestinal: muscle relaxant with potential for gastric hypermotility problems and dyspepsia; activity significantly enhanced by tamoxifen	Modzelewska et al. (2021)
Gastrointestinal tract: active against drug-induced (loperamide) constipation	Liu & Zhi (2021)
Gastrointestinal tract (surgery): prevention of development of abdominal adhesions post-surgery by a film (polycaprolactone/phospholipid) containing quercetin plus silver (antibacterial properties) nanoparticles	Hosseinpour-Moghadam et al. (2021)
Gastrointestinal (bioavailability): delivery systems developed to enhance stability, bioavailability, and sustained release in intestinal tract e.g. prodrug micelles containing quercetin-glycol chitosan; phytosome formulations or mucoadhesive chitosan-gum arabic nanoparticles enhance absorption and antioxidant activity	Kim et al. (2019); Di Pede et al. (2020); Shen et al. (2021a)
Anti-dysentery: an important component of *Psidium guajava* that contributes to its efficacy against *Shigella flexneri*	Hirudkar et al. (2020)
Probiotic support: quercetin plus resveratrol showed good enhancement of *Lactobacillus* probiotic activity (dosage and strain selection are important)	Dos Santos et al. (2019)
Liver function: inflammatory metal-chelating hepatoprotective; antifibrotic and anti-cirrhosis; protect against injury and chemical toxins; chemoprotective against liver damage e.g. alcohol, cadmium, aluminium, lead, nicotine, BPA (bisphenol A) and pesticide (e.g. rotenone) toxicity; combines well with resveratrol to prevent paracetamol-induced liver damage	Lee et al. (2013); Liu et al. (2013a); El-Shafey et al. (2015); Liu et al. (2015); Wang et al. (2015b); Miltonprabu et al. (2016); Verma et al. (2016); Zhang et al. (2016); Casas-Grajales et al. (2017); Mohammed et al. (2017); Yarahmadi et al. (2017); Afifi et al. (2018); Akinmoladun et al. (2018); Li et al. (2018b); Al Humayed et al. (2019); Lee et al. (2019); Liu et al.

	(2019); Mahdavinia et al. (2019); Salehi et al. (2020)
Hepatoprotective: extensive range or protection against hepatotoxic agents e.g. 2-butoxyethanol, acrylamide, acrylonitrile, aflatoxin B1, aroclor-1254, arsenic, sodium arsenite, azathioprine, cadmium chloride, carbon tetrachloride, chlorpyrifos, cyclosporine A, diazinon, dimethylnitrosamine, doxorubicin, epirubicin, ethanol, fenvalerate, isoniazide, rifampicin, lead acetate, lindane, D-galactosamine, methotrexate, methylmercury, nickel sulfate, paracetamol, perfluorooctanoic acid, polychlorinated biphenyls, pyrrolizidine alkaloid (clivorine), sodium fluoride, streptazotocin, tert-butyl hydroperoxide, thioacetamide, titanium dioxide, tumor necrosis factor-α, tripterygium glycoside, triptolide, concavalin A	Pingili et al. (2020)
Hepatoprotective: protective effect against maternal alcohol-induced oxidative and inflammatory damage in the liver and lymphoid tissues in animal studies	Ince (2020)
Liver function: hepatoprotective in beta-thalassemia patients receiving desferrioxamine therapy; assist in reduction of iron overload	Sajadi Hezaveh et al. (2019a & 2019b)
Kidney function: renoprotective, antifibrotic; potential for use in cystic renal disease and for prevention of renal failure; chemoprotective against chemotherapy (doxorubicin) and drug-induced (paracetamol) kidney damage; as well as renal damage due to iodinated contrast in radiological examinations and surgery; combines well with resveratrol	El-Shafey et al. (2015); Chang et al. (2017); Khalil et al. (2018); Lu et al. (2018a); Zhu et al. (2018a); Liu et al. (2019); Vicente-Vicente et al. (2019); Dallak et al. (2020)
Kidney function: protective against lead toxicity; renoprotective against iron-mediated damage (ferroptosis)	Mohammed et al. (2017); Wang et al. (2020d)
Anti-toxin (Venom): protective against snake venom hepatic and renal toxicity	Al-Asmari et al. (2018)
Respiratory tract: substantial anti-inflammatory protective effect on pulmonary function; anti-asthmatic muscle relaxant; anti-allergy for acute rhinosinusitis (sinus and nose inflammation, hayfever); potential for use in chronic lung disease e.g. bronchopulmonary dysplasia in infants; chemoprotective and anti-fibrosis; active against cancer chemotherapy (bleomycin) fibrosis (also gallic acid); potential for use in treating fibrosis of the throat (laryngotracheal stenosis) following trauma; radioprotective (radiation pneumonitis); benefits for hypoxic lung tissue damage with fluid retention	Townsend & Emala (2013); Wang et al. (2014); Khan et al. (2016); Meng et al. (2016a); Somerville et al. (2016); Qin et al. (2017); Kim & Park (2018); Maturu et al. (2018); Ulusoy & Sanlier (2019); Tripathi et al. (2019 & 2020); Boots et al. (2020); Tiboc-Schnell et al. (2020); Xiao et al. (2020); Mehrzadi et al. (2021)
Respiratory tract: active against *Pseudomonas aeruginosa*, the main bacterial pathogen in bronchiectasis of the lungs;	Tran et al. (2021)

enhanced solubility and efficacy by nanoparticle complex of quercetin and chitosan	
Respiratory Tract (clinical use): quercetin restored corticosteroid sensitivity in steroid resistant patients; potential for use in combination with steroids for chronic obstructive pulmonary disease (COPD); clinical use in combined chemotherapy of pulmonary tuberculosis with good results; potential for clinical use in asthma, rhinitis (anti-allergy activity) and viral-induced lower respiratory tract infections; inhalation treatment reduced radiation-induced lung inflammation; potential use in pleural inflammation; doses up to 2,000mg/day useful for the treatment of COPD (chronic obstructive pulmonary disease) were well tolerated without side effects	Butov et al. (2016); Mitani et al. (2017); Kim & Park (2018); Cesarone (2019); Bidian et al. (2020); Han et al. (2020b): Jafarinia et al. (2020); Brito et al. (2021)
Vascular function: vasoprotective; reduce capillary fragility; useful for disorders such as varicose veins, various bleeding problems and haemorrhoids (combine with rutin to enhance results)	Williams (2011)
Cardioprotective: extensive repertoire or cardioprotective activity; hypotensive, anti-arrhythmia; anti-atherosclerosis; vasodilatory with good potential for treating hypertension; cholesterol-lowering cardioprotective against effects of high-cholesterol diet; substantial benefits for cholesterol status and reduce LDL-cholesterol levels; anti-thrombotic, vasoprotective; anti-ischaemic with potential benefits for recovery following heart attack or other trauma; cardioprotective and vascular protective against excessive iron uptake e.g. alcoholism	Larson et al. (2010); Kelly (2011); Li et al. (2013); Miles et al. (2014); Monori-Kiss et al. (2014); Gormaz et al. (2015); Basu et al. (2016); Elumalai & Lakshmi (2016); Jing et al. (2016); Khan et al. (2016); Kumar et al. (2017b); Serban et al. (2016); Xiao et al. (2017); Ferenczyova et al. (2020); Guo et al. (2019); Nie et al. (2019); Peng et al. (2019); Ulusoy & Sanlier (2019); Wu et al. (2019); Ashrafizadeh et al. (2020); Chen et al. (2020b); Deng et al. (2020); Huang et al. (2020a); Mirsafaei et al. (2020); Najmanova et al. (2020); Sato & Mukai (2020); Salehi et al. (2020); Siti et al. (2020); Tabrizi et al. (2020); Yang et al. (2020c); Zhang et al. (2020c); Javadinia et al. (2021)
Anti-thrombotic (anti-platelet activity): quercetin metabolites enhance activity of aspirin	Stainer et al. (2019); Yang et al. (2019b)
Cardioprotective: clinical cardioprotective properties in coronary heart disease, gout, essential hypertension and renal function	Chekalina et al. (2017); Kim & Park (2018); Kondratiuk & Synytsia et al. (2018); Ulusoy & Sanlier (2019)

Metabolic disorders and diabetes: good antidiabetic properties, antihyperglycaemic (regulate blood sugar, substantial benefits); combines well with resveratrol and insulin as antidiabetic treatments; regulate gut microbiota; anti-obesity potential; protection against pancreatic cellular damage and inflammation (pancreatitis), including iron damage (ferruptosis inhibition); protective against diabetes complications e.g. nephropathy, liver function, neurological dysfunction	Kelly (2011); Miles et al. (2014); Weber et al. (2014); Nabavi et al. (2015); Amiot et al. (2016); Carrasco-Pozo et al. (2016); Haddad & Eid (2016); Zheng et al. (2016a); Ahmad et al. (2017); Kim & Park (2018); Seo et al. (2018); Srinivasan et al. (2018); Yang & Kang (2018); Zhuang et al. (2018); Bule et al. (2019); Ostadmohammadi et al. (2019); Peng et al. (2019); Ulusoy & Sanlier (2019); Li et al. (2020e); Salehi et al. (2020); Sato & Mukai (2020); Roshanravan et al. (2021); Tan et al. (2021); Zhao et al. (2021d)
Neuroprotective (diabetes): protective against diabetic nerve damage e.g. sciatica; peripheral neuropathy	Chis et al. (2017); Zhang et al. (2021d)
Eye and vision: significant clinical potential; anti-inflammatory, anti-cataract and anti-glaucoma; latest developments in therapeutic quercetin for the treatment of keratoconus, Graves' orbitopathy, ocular surface, retinoblastoma, and other retinal diseases; cataract protection with chlorogenic acid from Highbush Blueberry leaf; potential use with resveratrol for anti-inflammatory ocular disorders and glaucoma; anti-ischaemia and protect retinal function with potential for diabetic retinopathy; protective against macular degeneration, allergic conjunctivitis, cigarette smoke and UV damage of eye vascular system	Kumar et al. (2014a); Miles et al. (2014); Abengozar-Vela et al. (2015); Arikan et al. (2015); Chen et al. (2015); Ferlemi et al. (2016); Gao et al. (2017); Natesan et al. (2017); Lu et al. (2018b); Cheng et al. (2019c); Koyama et. al. (2019); Patil et al. (2019); Shao et al. (2019); Zhu et al. (2019b); Ding et al. (2020); Wang et al. (2020a); Zhao et al. (2021c)
Eye (antimicrobial): active against *Aspergillus* (*A. fumigatus*) keratitis (corneal inflammation ie. 'pink eye')	Yin et al. (2021a)
Hearing: anti-inflammatory protection against hearing loss due to otitis media; also protection against cisplatin side effects on hearing	Ma et al. (2018a); Gundogdu et al. (2019)
Hormonal influence (female): oestrogenic, potential for hormone replacement therapy with improved bioavailability formulations; potential stimulation of breast milk production (galactagogue); clinical potential for use in alleviating hormonal and metabolic disturbances associated with polycystic ovarian syndrome (PCOS: combines well with resveratrol), endometriosis and adenomyosis; combination natural therapy for reducing inflammation and pain associated with endometriosis (quercetin, turmeric, N-	Abd El-Fattah et al. (2017); Jahan et al. (2018b); Lin et al. (2018); Rezvan et al. (2018); Park et al. (2019); Shafabakhsh & Asemi (2019);.Yang et al. (2019a); Fadin et al. (2020); Jafari Khorchani et al. (2020); Pourteymour Fard Tabrizi (2020); Samare-Najaf et al. (2020a & 2020b); Xu et al.

acetylcysteine); also benefits for ovarian cancer (potential for combination drug therapy) and protect against doxorubicin reproductive system toxicity;	(2020d); Jamali et al. (2021); Rashidi et al. (2021); Zheng et al. (2021a)
Hormonal influence (female): phytoestrogen, mimic activity of oestrogen; administration of quercetin plus Vitamin E affected hormonal function similar oestradiol and have been suggested as an alternative for oestrogen replacement therapy	Jafari Khorchani et al. (2020 & 2021)
Obstetrics: benefits for prevention of pregnancy complications in diabetics (oestrogenic, antihyperglycaemic); potential use in combination with aspirin for management of pre-eclampsia (hypertension); prevention of premature birth (preterm birth)	Yang et al. (2019b); Bolouki et al. (2020); Li et al. (2020g); Sun et al. (2020d); Zhang et al. (2021c)
Genitourinary tract (male): protect against chronic prostatitis (prostate inflammation); chemoprotective against cadmium, lead and pyrethroid insecticide toxicity (combines well with curcumin); also BPA (bisphenol A) toxicity; may improve sperm function and is a candidate for treating male infertility (leukocytospermia); prevent pesticide (rotenone) and chemotherapy (cisplatin) testicular damage; may have benefits for erectile dysfunction	Meng et al. (2018); Sharma et al. (2018a); Ujah et al. (2018); Diao et al. (2019); Mahdavinia et al. (2019); Akinmoladun et al. (2020); Bostancıeri et al. (2021); Khodabandeh et al. (2021); Olabiyi et al. (2021)
Neuroprotective: influence brain biochemistry, bioavailable across blood-brain barrier and may improve drug availability in brain tissue; analgesic; antidepressant, anti-anxiety e.g. following traumatic brain injury; quercetin-metal complexes enhance activity; antioxidant stress-protective (can be combined with resveratrol); protective against diabetic neuropathy and encephalopathy; protective against encephalitis damage; restoration of blood serum elemental imbalance in depression and stress	Dajas et al. (2015); Dong et al. (2014); Barreca et al. (2016); Costa et al. (2016); Demir et al. (2016); Elumalai & Lakshmi (2016); Galho et al. (2016); Khan et al. (2016); Lee et al. (2016a); Maciel et al. (2016); Pei et al. (2016); Ravikumar Reddy et al. (2016); Dureshahwar et al. (2017); Ji et al. (2017); Mehta et al. (2017); Dhiman et al. (2019); Kosari-Nasab et al. (2019); Hu et al. (2020c); Ke et al. (2020); Park et al. (2020); Sahin et al. (2019); Ulusoy & Sanlier (2019); da Silva et al. (2020b); Wang et al. (2020d); Chen et al. (2021d); Guan et al. (2021)
Neuroprotective (bioavailability): strategies to enhance bioavailability to brain tissue for enhanced treatment options e.g. quercetin-hydroxypropyl-β-cyclodextrin nasal powders	Papakyriakopoulou et al. (2021)
Neuroprotective (autoimmune disease): potential use in	Hen et al. (2021)

myasthenia gravis, multiple sclerosis etc.	
Neuroprotective (analgesic): analgesic for nerve (neuropathic) pain; diabetic peripheral neuropathy	Muto et al. (2018); Espinosa-Juárez et al. (2021); Zhang et al. (2021d)
Neuroprotective (anti-trauma): anti-ischaemia, anti-spasmodic for cerebral vascular spasm with potential benefits in stroke; protection against various forms of ischaemic and traumatic brain injury, as well as neuronal injury (e.g. sciatic nerve damage, spinal cord injury); anti-ischaemic activity involves modulation of essential elements, transition metals, Cu/Zn ratio, and antioxidant activity	Lee et al. (2016a); Ahmad et al. (2018); Du et al. (2018); Turedi et al. (2018);Wang et al. (2018b); Ashrafizadeh et al. (2020); Gul et al. (2020); Javadinia et al. (2021); Lin et al. (2021)
Neuroprotective (degenerative disorders): applications for many neurodegenerative disorders including paediatric neurological conditions; chemoprotective; protective against neuroinflammation due to zidovudine (AZT) anti-HIV treatment; neuroprotective against radiation injury and anticancer drug therapies; prevention of neurological degeneration and intestinal inflammation in rheumatoid arthritis	Azevedo et al. (2013); Gupta et al. (2017); Halder et al. (2016); Beghoul et al. (2017); Kale et al. (2018); Kim & Park (2018); Yang et al. (2018b); Amanzadeh et al. (2019); Halder et al. (2019); Jakaria et al. (2019); Piovezana Bossolani et al. (2019); Alvarez-Arellano et al (2020)
Neuroprotective (clinical trial): dietary trial (24 weeks quercetin-enriched onion) prevented age-related cognitive decline, improved depression and elevated motivation.	Nishihira et al. (2021)
Neuroprotective (chemoprotective): including protection against experimental rotenone and iron toxicity in combination with piperine (Parkinson's disease); protection against aluminium, lead, manganese, iron, cadmium, PCBs (polychlorinated biphenyls) and insecticide neurotoxicity; chemoprotective against glyphosate-induced depression and anxiety; protection against the peripheral nerve damage caused by chemotherapy (e.g. vincristine)	Sharma et al. (2016a); Bahar et al. (2017); Mohammed et al. (2017); Selvakumar et al. (2018); Amanzadeh et al. (2019); Donmez et al. (2019); Liu et al. (2019); Chen et al. (2020b); Sharma et al. (2020b); Ibrahim et al. (2020); Yardim et al. (2020); Bicca et al. (2021)
Neuroprotective (anti-epileptic): anti-inflammatory, antioxidant, anti-seizure activity, no adverse interaction with epileptic drugs; potential benefits for fever-induced childhood convulsions due to infection-inflammation	Moghbelinejad et al. (2016); Nieoczym et al. (2014); Mkhize et al. (2017); Carmona-Aparicio et al. (2019); Wu et al. (2020a); Akyuz et al. (2021)
Neuroprotective (behaviour): protective against amphetamine-induced manic behaviour; neuroprotective in an animal model of autism	De Mattos et al. (2020); Ren et al. (2021b)
Neuroprotective (memory): significant AChE inhibition; anti-stress activity to support memory; dietary benefits for early Alzheimer's disease; restorative potential to improve cognition (also silymarin and naringenin); potential to	Palle & Neerati (2017); Pattanashetti et al. (2017); Lu et al. (2018c); Sarubbo et al. (2018); Amanzadeh et al. (2019); Jakaria

enhance anti-Alzheimer's drug treatments (e.g. donepezil and rivastigmine); quercetin-metal complexes show enhanced activity	et al. (2019); Khan et al. (2019); Nakagawa & Ohta (2019); Zhang et al. (2020b); Ulusoy & Sanlier (2019); Batiha et al. (2020); da Silva et al. (2020b)
Neuroprotective: protect against motor neurone degeneration; Parkinson's disease, Huntington's disease, multiple sclerosis, and amyotrophic lateral sclerosis; anti-inflammatory, antidepressant benefits; improve movement disorder in Huntington's disease; potential benefits for Parkinson's disease	Karuppagounder et al. (2013); Chakraborty et al. (2014); Lazo-Gomez & Tapia (2017); Amanzadeh et al. (2019); Jakaria et al. (2019); Tamtaji et al. (2019); Islam et al. (2021b)
Anticancer: chemopreventive agent in diet; potential prevention of colorectal cancer; antitumour, inhibit tumour promotion, anti-melanogenesis; combines well with other polyphenols and has significant anticancer supportive potential; shows anticancer activity in numerous cell lines e.g. gastrointestinal, liver, nasopharyngeal, pancreatic, prostate, ovarian and breast cancer; chemopreventive benefits for colon cancer	Kelly (2011); Miles et al. (2014); Brito et al. (2015 & 2016); Yang et al. (2015); Balakrishnan et al. (2016); Gavrilas et al. (2016); Kashyap et al. (2016); Khan et al. (2016); Niedzwiecki et al. (2016); Quagliariello et al. (2017); Darband et al. (2018); Jana et al. (2018); Ulusoy & Sanlier (2019); Batiha et al. (2020); Salehi et al. (2020); Tang et al. (2020)
Anticancer (enhance drug treatments and radiotherapy): enhance effect of adriamycin in leukaemia cells and protect against cardiac damage; brain cancer (glioblastoma; sensitize cells to radiation); oral cancer with increased drug sensitivity (vincristine); potential combination therapy with vincristine for lymphoma chemotherapy; improve chemotherapy-induced fatigue; bladder cancer (improve response to treatment); enhance chemotherapy ie. doxorubicin in breast and prostate cancer cells, also sorafenib in thyroid cancer cells and adriamycin in leukaemia	Maciejczyk & Surowiak (2013); Mahoney et al. (2014); Schwingel et al. (2014); Han et al. (2015b); Yuan et al. (2015); Di Lorenzo et al. (2016); Jana et al. (2018); Lagerweij et al. (2016); Wang et al. (2016g); Zhu et al. (2017); Kim & Park (2018); Li et al. (2018c); Li et al. (2019a); Shi et al. (2019b); Celano et al. (2020); Li et al. (2020b); Rather & Bhagat et al. (2020); Tavana et al. (2020); Zhang et al. (2020a)
Anticancer: iron-chelation anticancer activity	Yin et al. (2021b)
Anticancer (clinical: under investigation): potential for use in treatment of leukaemia and lymphoma (small pilot study), potential for oral mucositis	Kooshyar et al. (2017); Baron et al. (2018); Lotfi et al. (2021)
Anticancer (bioavailability): new formulations under investigation for better bioavailability e.g. quercetin-curcumin liposome; nanoparticle encapsulation for breast cancer	Men et al. (2014); Miles et al. (2014); Sharma et al. (2015); Nam et al. (2016); Saha et al. (2016); Ravichandiran et al. (2017); Jana et al. (2018); Sharma et al. (2018b); Vinayak & Maurya (2019;

	Zang et al. (2021)
Chemoprotective: active against arsenic toxicity e.g. testicular and sperm damage, as well as blood cell damage due to arsenic exposure; also attenuates nicotine, cadmium and lead toxicity; protection against pesticide toxicity e.g. atrazine, glyphosate and synthetic pyrethroids; mitigate bisphenol A (BPA) and insecticide (chlorpyrifos and deltamethrin) toxicity, also active against dichloromethane (a chlorinated industrial solvent)	Ghosh et al. (2011); Hernandez et al. (2015); Sangai et al. (2014); Baltaci et al. (2016); Cao et al. (2016); Jahan et al. (2016a); Mohammed et al. (2017); Abdel Aziz et al. (2018); Kim & Park (2018); Sangai et al. (2018); Sharma et al. (2018b); Fereidouni et al. (2019); Owumi et al. (2019); Soudani et al. (2019); Jia et al. (2020a); Kumar et al. (2020a)
Chemoprotective: against chemotherapy side effects e.g. cyclophosphamide lung and urotoxicity (affecting the bladder); protect against oxaliplatin neurotoxicity and testicular damage due to doxorubicin; can enhance anticancer activity of cisplatin and reduce side effects (e.g. toxicity on hearing and kidney function) without compromising efficacy of the drug	Azevedo et al. (2013); Senqul et al. (2017); Sherif (2018); Ahmed et al. (2019); Najafi et al. (2020)
Chemoprotective (honeybees): quercetin, which is one of the most abundant plant phenolics, is an integral part of the honeybee diet; it can be supportive to the detoxification system in the bees and is active against fungicide (boscalid) and selected pesticide (imidacloprid) toxicity	Liao et al. (2019); Ardalani et al. (2021); Liu et al. (2021c)
MRI (magnetic resonance imaging): iron (III)–quercetin complex could be used as an imaging probe for tracking stem cells with MRI	Papan et al. (2020)
Photodynamic therapy: co-administration of a flavonoid can enhance the photodynamic anticancer activity of a photosensitiser e.g. zinc phthalocyanine, which was encapsulated with quercetin in lipid polymer nanoparticles to enhance activity against breast cancer cells	Thakur et al. (2021)
Radioprotective: neuroprotective against radiation-induced brain tissue injury; also lung injury (radiation pneumonitis)	Patil et al. (2017); Qin et al. (2017); Kale et al. (2018);
Antiparasitic: varying degrees of activity against *Babesia, Plasmodium, Theileria, Toxoplasma, Trypanosoma,* and *Leishmania*; well-known growth inhibitory efficacy against *Trypanosoma* and *Leishmania*	Sousa-Batista et al. (2017); Cataneo et al. (2019); da Silva et al. (2019); Batiha et al. (2020); Yang et al. (2020c)
Anti-protozoal: antimalarial potential	Ali et al. (2021)
Antiparasitic: good potential activity against *Entamoeba histolytica* and *Trichomonas vaginalis*	Elizondo-Luévano et al. (2021)
Chemoprotective (antiprotozoal drug side effects): active against metronidazole (Flagyl) neurotoxicity, an antibiotic and antiprotozoal medication	Chaturvedi et al. (2020)

Agrochemical potential (biopesticide): utilised as a defence chemical by plants; long-term exposure to quercetin had an inhibitory effect on silkworm immune function, influencing insect growth, development and susceptibility to pathogens, which increased silkworm deaths	Shi et al. (2020b & 2021)
Rutin (flavonoid; Quercetin-3-rutinoside)	
Pharmacological properties (summary): potent antioxidant, anti-inflammatory, antiviral, immunomodulatory, cardioprotective; protective for kidney, liver and lung function; chemoprotective, anticancer and radioprotective	Williams (2011); Ganeshpurkar & Saluja (2017)
Bioavailability: inhibition of Vitamin C oxidation that supports/potentiates antioxidant activity	Chua (2013)
Bioavailability: improved bioavailability with encapsulation using quinoa and maize starch nanoparticles; biodegradable polymer (PLGA) foams developed for sustained release of rutin for medical applications; also microencapsulation strategies improve rutin availability in digestive and renal (dialysis) processes	Mel et al. (2020); Remanan & Zhu (2021); Valor et al. (2021)
Bioavailability (functional food): Tartary Buckwheat breeding selection for high rutin-yielding varieties; Buckwheat is high in rutin (low in rutinosidase) with functional food potential e.g. cellular protective activity on liver, kidney and brain function, general antioxidant and anti-inflammatory activity; antimicrobial properties; rutin degradation (via. enzymatic processes ie. rutinosidase activity) also yields quercetin with benefits for blood sugar regulation	Luthar et al. (2020); Rakshit et al. (2021); Suzuki et al. (2021)
Adaptogenic potential: support for general cellular function and metabolism; pro-longevity in experiments with flies (*Drosophila melanogas*ter) and mice; benefits for liver function	Chattopadhyay & Thirumurugan (2020); Li et al. (2021a)
Anti-fatigue: influence thyroid function	Panda & Kar et al. (2014); Al-Dhabi et al. (2015)
Anti-inflammatory (anti-allergy): potential for treating hayfever	Kim et al. (2015a)
Anti-inflammatory and analgesic: antiarthritic protection of joint integrity; benefits for osteoarthritis; anti-oedema, potential for rheumatoid arthritis with gold-nanoparticle delivery; rutin-phospholipid complex for inflammatory disorders; synergistic with paracetamol and NSAIDs e.g. naproxen, ketorolac, diclofenac	Chua (2013); Sharma et al. (2013); Gul et al. (2018); Kalita & Das (2017); Carvalho et al. (2019); Liu et al. (2020c); Saccol et al. (2020); Chen et al. (2021a); Zapara-Morales et al. (2021)
Anti-inflammatory: rutin-rich *Hypericum capitated* shows significant activity	Farcas et al. (2019)
Anti-inflammatory and antioxidant: nanoformulations significantly improved bioavailability	AbouAitah et al. (2021)

Anti-gout: rutin had excellent activity against hyper-uraemia; derivatives also show xanthine-oxidase inhibition	Malik et al. (2019); Adachi et al. (2021)
Aquaculture (fish farming): chemoprotective anti-inflammatory; ant oxidative and immune benefits against *Aero monas hydrophilic* in Silver catfish; dietary protection against pesticide neurotoxicity (trichflorfon); antioxidant and protective against antibiotic stress (oxytetracycline)	da Rosa et al. (2019); Baldissera et al. (2021a & 2021b); Londero et al. (2021)
Antimicrobial: antibacterial, antifungal, antimycobacterial; active against a wide range of microbial and fungal pathogens, including *Candida*	Sharma et al. (2013); Ganeshpurkar & Saluja (2017)
Antibacterial: significant antioxidant and antibiofilm activity against *Klebsiella pneumonia*e strains isolated from hospitalized patients	Wang et al. (2021b)
Antimicrobial (food packaging): rutin and chitosan antioxidant and antibacterial properties suggest their use as food packaging e.g. polycaprolactone, chitosan plus rutin as packaging film for rainbow trout; also edible rutin-β-cyclodextrin plus chitosan films; and gelatin-films with rutin based chitosan-coated microparticles	Dammak et al. (2017) Jiang et al. (2020); Piri et al. (2021)
Antibiotic potentiation: enhance antibacterial activity; improve antifungal efficacy of amphotericin; also florfenicol (against drug-resistant *Aeromonas hydrophila*)	Oliveira et al. (2016); Amin et al. (2015); Deepika et al. (2019b)
Antiviral: potential for norovirus treatment (gastroenteritis); active against influenza virus etc.; antiviral potential against SARS-CoV-2	Sharma et al. (2013); Cheron et al. (2015); Huynh et al. (2020); Kumari et al. (2020); Ibrahim et al. (2021); Joshi et al. (2021); Rahman et al. (2021a)
Antiviral: significant immunomodulatory and anti-inflammatory activity against highly pathogenic porcine reproductive and respiratory syndrome virus (also good activity of vitamin C and α-tocopherol)	Ruansit & Charerntantanakul (2020); Suebsaard & Charerntantanakul (2021)
Skin and cosmetic: anti-allergy, anti-inflammatory, useful for atopic or allergic dermatitis; anti-aging effect on skin cells; combines well with vitamin C to enhance radioprotective activity; also proniosomal gel enhanced rutin bioactivity for treating skin disorders	Choi & Kim (2013); Choi et al. (2014 & 2016); Pinzaru et al. (2021)
Cosmetic: anti-photoaging; UV protectant effect which could be used in sunscreens; rutin nanocrystal gel effectively prevented UV irradiation tissue damage and skin photoaging	Kamel & Mostafa (2015); Tomazelli et al. (2018); Gegotek et al. (2018 & 2019); Li et al. (2020g); Li et al. (2021b)
Wound healing: promote wound healing; reduce the risk of diabetic wound ulceration and promote wound healing; formulations to allow increase bioavailability (via. enhanced water solubility)	Asfour et al. (2017); Pivec et al. (2019); Chen et al. (2020a); Fu et al. (2020)

Wound dressings: rutin-loaded chitosan oligosaccharide/polycaprolactone nanofibers developed for use as antibacterial dressing	Zhou et al. (2021b)
Hair loss: prevention of hair loss	Ganeshpurkar & Saluja (2017)
Gastrointestinal disorders: gastroprotective, anti-inflammatory, antiulcer; protective effect in inflammatory bowel disorders e.g. colitis; beneficial potential in gastric-oesophageal reflux; potential for use for inflammation and gut dysbiosis (combined with inulin)	Dubey et al. (2013); Hosseinzadeh & Nassiri-Asl (2014); Kumar et al. (2014b); Mascaraque et al. (2014); da Silva Junior et al. (2016); Power et al. (2016); Guo et al. (2018b); Habtemariam & Belai (2018); Sharma et al. (2021)
Liver function: hepatoprotective; antioxidant and anti-inflammatory liver protection; protect against diabetes damage (enhanced activity in combination with sitagliptin); potential use for fatty liver; antioxidant and metal chelation; chemoprotective; protection alcohol damage, mercuric chloride, cadmium and lead toxicity; also insecticide (deltamethrin) toxicity	Williams (2011); Lee et al. (2013); Chuffa et al. (2014); Erdogan et al. (2015); AlSharari et al. (2016); Abarikwu et al. (2017b); Liang et al. (2018); Caglayan et al. (2019); Elsawy et al. (2019); Attia et al. (2020); Manzoni et al. (2020); Kucukler et al. (2021); Liu et al. (2021a)
Liver function (chemoprotective): protective against iron overload with potential benefits for haemochromatosis; decreased iron levels in the liver and serum, with increased serum unsaturated iron binding capacity	Aziza et al. (2014); Hawula et al. (2021)
Liver function: protection from malaria damage	Oludele et al. (2020)
Kidney function: significant chemoprotective and renoprotective properties; prevention of diabetic kidney damage (nephropathy); antifibrotic and protection against obstructive injury; protect against alcohol, chemotherapy (cisplatin, carfilzomib, vancomycin), heavy metal (cadmium, lead) and insecticide (rotenone, deltamethrin) toxicity	Chua (2013); Han et al. (2015a); Kandemir et al. (2015); Abarikwu et al. (2017a & 2017b); Wang et al. (2016c); Wang et al. (2016d); Alhoshani et al. (2017); Ganeshpurkar & Saluja (2017); Ma et al. (2018c); Qu et al. (2018 & 2019b); Al-Harbi et al. (2019); Crown et al. (2019); Ganesan et al. (2020); Manzoni et al. (2020); Kucukler et al. (2021)
Renoprotective (bioavailability): rutin coated gold nanoparticles prevent rhabdomyolysis-induced kidney injury; renoprotective activity enhanced with alpha-lipoic acid against cisplatin toxicity	Zaazaa et al. (2019); Saifulah et al. (2020)
Respiratory tract: antioxidant, anti-asthmatic; anti-inflammatory protection in studies of acute lung injury and inflammation; also protective against cigarette smoke	Chua (2013); Chen et al. (2014); Feng et al. (2014); Huang et al. (2016); Ganeshpurkar & Saluja

damage and desflurane (anaesthetic) lung damage	(2017); Liu et al. (2018c); da Silva Araujo et al. (2020); Paudel et al. (2020); Mehta et al. (2021); Tosun et al. (2021)
Respiratory tract (chemoprotective): protective against pulmonary oedema induced by cytarabine (anti-leukaemia drug) and bleomycin-induced lung fibrosis (antifibrotic)	Bai et al. (2020); Bilgin et al. (2020)
Cardiovascular: anti-inflammatory antifibrotic, antithrombotic cardioprotective; positive effect on cholesterol levels (combined with curcumin); benefits for cardiomyopathy and sepsis infection; preventive action on infective endocarditis; antihypertensive, anti-atherosclerosis; significant reduction in aortic aneurysm growth; chemoprotective, protect against cardiac damage due to heavy metals (cadmium, lead), diabetic cardiomyopathy, alcohol damage, drug-induced cardiotoxicity (e.g. anthracycline, pirarubicin and cisplatin cardiac damage) and environmental pollutants such as plastic-components (phthalates and bisphenol A)	Sharma et al. (2013); Chu et al. (2014); Chuffa et al. (2014); Czepas & Gwozdzinski (2014); Li et al. (2014a); Al-Dhabi et al. (2015); Choi et al. (2015); Guimaraes et al. (2015); Wang et al. (2015a); Saklani et al. (2016); Li et al. (2018d); Lv et al. (2018); Topal et al. (2018); Xianchu et al. (2018); Manzoni et al. (2019); Sundaram et al. (2019); Ganesan et al. (2020); Gutierrez-Venega et al. (2020); Li et al. (2020a); Oyagbemi et al. (2020); Wang et al. (2020g); Oluranti et al. (2021a & 2021b); Qin et al. (2021); Wang et al. (2021a)
Antithrombotic: anti-platelet properties; excellent antithrombotic activity; rutin-loaded silver nanoparticles	Wu et al. (2020b); Rakshit et al. (2021); Zaragoza etal. (2021)
Radioprotective: good activity against radiation-induced haematopoietic (blood cell production, bone marrow) damage	Dutta (2021); Ranjan et al. (2021)
Venoprotective: maintain and enhance vascular integrity, prevent bleeding e.g. reduce bruising and haemorrhagic problems, varicose veins, haemorrhoids etc.	Williams (2011)
Blood disorders (sickle cell disease): anti-sickling activity	Muhammed et al. (2019)
Metabolic disorders: pancreas protective, with supportive activity on pancreatic cellular repair; antidiabetic, glucose-lowering effect; combines well with vitamin C for anti-diabetic effect; benefits for diabetic neuropathy, memory problems, cardiac function and pain; benefits for pancreatic function including pancreatitis; protection from alcohol damage; also potential benefits for obesity, help promote weight loss (with exercise)	Chua (2013); Sharma et al. (2013); Aruna et al. (2014a & 2014b); Hosseinzadeh & Nassiri-Asl (2014); Al-Dhabi et al. (2015); Abreu et al. (2016); Chen et al. (2016b); Han et al. (2016); Lee et al. (2016b); Li et al. (2016a); Mittal et al. (2018); Tanko et al. (2017); Guo et al. (2018b); Hasanein et al. (2018); Ragheb et al. (2020); Sun et al. (2020a)
Antidiabetic (combination formulation): rutin, catechin plus	Mechchate et al. (2021)

epicatechin prevented hyperglycaemia with potential for clinical use	
Antidiabetic: protective (antifibrotic and anti-acidosis) benefits for cardiac function in diabetes ie. prevention of cardiomyopathy and diabetic nephropathy (kidney dysfunction)	Ganesan et al. (2020) Wang et al. (2021a)
Eye and vision: antioxidant; significant protective effect on the eye function; good activity for retinal disorders e.g. diabetic retinopathy and cataract (active component, with procyanidin B2, in *Ginkgo biloba*); chemoprotective against cisplatin toxicity	Sasikala et al. (2013); Ola et al. (2015); Zhou et al. (2016b); Lu et al. (2018b); Tasli et al. (2018); Gupta et al. (2020); Li et al. (2021c)
Eye injury: rutin delivery utilising gelatin hydrogel/contact lens composites to facilitate corneal wound healing	Zhao et al. (2021b)
Hearing: protective potential for diabetic-induced hearing loss (auditory neuropathy)	Doostkam et al. (2021)
Anti-toxin: protective against snake venom haemostatic effects	Sachetto et al. (2018)
Neuroprotective (anticonvulsant): antioxidant, anti-inflammatory, acetylcholinesterase activity; neuroprotective against anti-epileptic drug toxicity; variable reports of anti-seizure activity; reduce schizophrenic-like behaviour in mice; no adverse interaction with epileptic drugs	Chua (2013); Nieoczym et al. (2014); Al-Dhabi et al. (2015); Dubey et al. (2015); Oshodi et al. (2021)
Neuroprotective: anti-ischaemic for traumatic brain injury and spinal cord damage; mild hypothermia combined with rutin show benefits for the treatment of spinal cord injury; protective against diabetic neuropathy	Sharma et al. (2013); Qu et al. (2014); Ahmad et al. (2016); Hao et al. (2016a); Wu et al. (2016a); Zhai et al. (2016); Liu et al. (2018a); Mittal et al. (2018); Song et al. (2018a); Yuceli et al. (2020); Yao et al. (2021a)
Neuroprotective (neurodegenerative disorders): protective effect e.g. Parkinson's disease, synergistic with vitamin E; protect against alcohol and fluoride toxicity; protection for drug-induced peripheral neuropathy	Azevedo et al. (2013); Sharma et al. (2013); Song et al. (2014); Sharma et al. (2016b); Enogieru et al. (2018); Nkpaa & Onyesco (2018); Sharma et al. (2020a); Yao et al (2021)
Neuroprotective (anti-stress, mental disorders): adaptogenic, anti-stress; protect against anxiety-induced stress damage; antidepressant; antipsychotic for schizophrenia and neuropsychiatric conditions	Machawal & Kumar et al. (2014); Ganeshpurkar & Saluja (2017); Pandy & Vijeepallam (2017); Parashar et al. (2017); Anesti et al. (2020)
Neuroprotective (chemoprotective, memory): anti-inflammatory, antioxidant, anticholinesterase, anti-stress benefits for memory, particularly when combined with exercise; anti-anxiety, anti-seizure; anti-Alzheimer's potential; chemoprotective against cisplatin, mercury	Chua (2013); Sharma et al. (2013); Al-Dhabi et al. (2015); Qu et al. (2014); Cheng et al. (2016); Habtemariam (2016); Ramalingayya et al. (2016 &

chloride, doxorubicin, manganese, copper and cadmium neurotoxicity	2017); Abdel-Aleen & Khaleel (2017); Almutairi et al. (2017); Budzynska et al. (2019); Mostafa et al. (2019); Nkpaa et al. (2019); Pan et al. (2019a); Ramalingayya et al. (2019); Yasar et al. (2019); Asgharian et al. (2020); Celik et al. (2020); Ishola et al. (2020); Mahendra et al. (2020); Arowoogun et al. (2021); Fidelis et al. (2021); Islam et al. (2021b); Sun et al. (2021b)
Neuroprotective: benefits in Huntington's disease studies; synergistic effect of rutin and selenium combination	Abdelfattah et al. (2020); Cordeiro et al. (2020 & 2021)
Sexual function (male): anti-stress protective effect on testicular function; protective effect on sperm integrity (*Hypericum* species); protective against cisplatin and mercuric-chloride toxicity; also mitigate titanium dioxide nanoparticle reproductive toxicity	Abarikwu et al. (2013, 2016 & 2017a); Aksu et al. (2017); Salem et al. (2017); Jahan et al. (2018a); Mehfooz et al. (2018); Hussein et al. (2019); Kolarevic et al. (2019); Kandemir et al. (2020); Oboh et al. (2020)
Chemoprotective: antioxidant, anti-inflammatory against testicular damage due to cadmium and busulfan	Abarikwu et al. (2013, 2017b & 2020)
Gynaecology: antioxidant and anti-inflammatory, anti-ischaemic for ovarian function; benefits for polycystic ovarian syndrome and endometriosis; cervical cancer (rutin-fucoidan complex)	Jahan et al. (2016b & 2018b); Hu et al. (2017); Nayki et al. (2018); Deepika et al. (2019a); Talebi et al. (2021)
Bone metabolism: cellular protection; stimulant activity on bone structure; anti-osteoporotic potential; supportive for vitamin D and alkaline phosphatase enzyme activity; Rutin nanosuspension shows potential for osteoporosis management with enhanced bioavailability	Hyun et al. (2014); Al-Dhabi et al. (2015); Na et al. (2016); Ganeshpurkar & Saluja (2017); Wang et al. (2017d); Abdel-Naim et al. (2018); Xiao et al. (2019); Gera et al. (2020); Lee et al. (2020a)
Radioprotective: good activity against radiation-induced haematopoietic (blood cell production, bone marrow) damage; photoprotective against UV radiation	Li et al. (202g); Ranjan et al. (2021)
Dental care: protect periodontal tissue and support stem cell regeneration techniques; curcumin and rutin (single or combined) antioxidant benefits for hyperglycemic-associated periodontitis	Zhao et al. (2019a & 2020b); Iova et al. (2021)
Anticancer: this natural dietary polyphenol has promising anticancer potential that can be incorporated into functional foods, dietary supplements, and pharmaceuticals for both cancer prevention and treatment	Farha et al. (2020)

Anticancer: active against various cancer cell lines e.g. leukaemia, melanoma, brain (glioma), lung, colon and liver cancer cells	Al-Dhabi et al. (2015); Guon & Chung (2016); Vijay et al. (2016); Ganeshpurkar & Saluja (2017); Pandey et al. (2018); Imani et al. (2020)
Anticancer (synergist and chemoprotective); synergistic activity in combination with anticancer drugs, can decrease drug resistance and side effects of chemotherapy; protect against oxaliplatin neurotoxicity (ovarian cancer, plus increase drug sensitivity); also cisplatin reproductive, haematological, liver and kidney toxicity; 5-fluorouracil induced intestinal mucositis; radiosensitizing effect on colon cancer	Azevedo et al. (2013); Jahan et al. (2018a); Fideles et al. (2020); Lins et al. (2020); Prasad & Prasad (2021); Satari et al. (2021)
Anticancer: active in brain cancer (glioma); protective against copper-induced brain damage; rutin-loaded nanoparticles enhance ability to cross the blood-brain barrier and show potential for brain tumour treatments	da Silva et al. (2020a); Arowoogun et al. (2021); Pandian et al. (2021)
Anticancer: active against kidney cancer; enhanced bioavailability & anticancer activity when combined with ionic liquids	Caparica et al. (2020)
Radioprotective: combination with podophyllotoxin shows enhanced anti-inflammatory and protective activity including radioprotective against radiation exposure for blood cells, bone marrow (haemopoietic), liver, lung and gastrointestinal tract	Verma et al. (2017); Yashavarddhan et al. (2017); Dutta et al. (2018); Kalita et al. (2019); Nadella et al. (2019); Yu & Yamashita (2019); Bajaj et al. (2020); Verma et al. (2020)
Radioprotective: protective for brain tissue; radioprotective against; potential for radio-iodine therapy; UVA skin damage; sunscreen potential	Goncalves et al. (2013); Al-Dhabi et al. (2015); Ganeshpurkar & Saluja (2017); Patil et al. (2017); Gegotek et al. (2018 & 2019); Thabet & Moustafa (2018)
Chemoprotective: protective against arsenic contamination, also lead and manganese toxicity	Sharma et al. (2013); Sarkozi et al. (2015); Nkpaa et al. (2019)
Antiparasitic (rutin source: *Terminalia catappa*): anthelmintic activity against gastrointestinal parasite of livestock e.g. buffalo (paramphistomosis)	Minsakorn et al. (2021)
Antiparasitic: antimalarial, synergistic with chloroquine and artesunate (artequine); immunomodulatory with significant protective benefits on immune and inflammatory responses	Ganeshpurkar & Saluja (2017); Olanlokun et al. (2021)
Anti-Leishmania: potent potential against leishmania parasites	Chauhan et al. (2018); da Silva et al. (2019)
Taxifolin (dihydroquercetin; flavonoid)	
Pharmacological properties (summary): antioxidant, anti-inflammatory, immunomodulatory; neuroprotective,	Aminimoghadamfarouj et al. (2011); Xie et al. (2017); Sunil &

antidiabetic, cardioprotective; anticancer	Xu (2019)
Antibacterial: *Staphylococcus epidermidis* (skin bacteria) and *Streptococcus sobrinus* (dental pathogen)	Sunil & Xu (2019)
Antibacterial: active against MRSA (antibiofilm)	Wang et al. (2021c)
Anti-mycobacterial: active against tuberculosis bacteria (*M. tuberculosis*)	Sunil & Xu (2019)
Antifungal: reduction in *Candida* pathogenicity	Mishra et al. (2017)
Food preservation: antioxidant, antimicrobial; improved the hygienic quality of sausages without significant effect on the growth of lactic acid bacteria; sausages inoculated with the taxifolin plus starter cultures (*Leuconostoc carnosum* or *Pediococcus pentosaceus* and *Staphylococcus xylosus*) showed improved shelf life	Rokaityte et al. (2019); Gustiene et al. (2019)
Antiviral: active against coxsackievirus	Galochkina et al. (2016)
Anti-inflammatory and anti-allergy (good activity)	Pan et al. (2019b)
Anti-gout: significant anti-hyperuricaemic activity	Adachi et al. (2017); Kondo et al. (2021)
Cosmetic and skin disorders: anti-inflammatory, anti-allergy, treatment of dermatitis and psoriasis; promote skin regeneration after injury; good potential for use in skincare cosmetics; UV protection (radioprotectant) against skin cancer; active against cadmium toxicity in skin cells	Oi et al. (2012); Shubina & Shatalin (2012); Kim et al. (2015b); Moon et al. (2019); Sunil & Xu (2019); Yuan et al. (2020a); Micek et al. (2021); Di et al. (2021)
Respiratory tract: anti-inflammatory, antioxidant; protective against chemotherapy (cisplatin) and cigarette/exhaust (benzo[a]pyrene) tissue damage	Unver et al. (2019); Islam et al. (2021a)
Kidney protective (renoprotective): anti-fibrotic; significant activity against kidney damage due to insecticide (rotenone) and acrylamide (industrial polymer chemical; also produced in high heat cooking processes); also antibiotic (colistin) toxicity (in combination with dapagliflozin); protect against diabetic renal damage	Zhao et al. (2018); Crown et al. (2019); Bedir et al. (2021); Kabel & Salama (2021); Ren et al. (2021a)
Hepatoprotective: protective against acute toxic liver injury; anti-inflammatory, chemoprotective and antifibrotic; active against fatty liver due to various causes e.g. drugs (acetaminophen), fatty diet or alcohol; protective against liver damage due to pesticides and chemotherapy (pazopanib, cisplatin)	Xie et al. (2017); Akinmoladun et al. (2018); Hu et al. (2019); Yang et al. (2019c); Akagunduz et al. (2021); Butt et al. (2021); Ding et al. (2021b); Kurt et al. (2021); Liu et al. (2021b); Zhan et al. (2021)
Hepatoprotective: protective effect against iron overload liver injury and regenerative liver support due to anti-inflammatory, antioxidant, and iron chelation activity	Shubina & Shatalin (2017); Salama & Kabel (2020)
Metabolic disorders: antidiabetic; potential for use in viral pancreatitis; blood sugar regulation, improvement of post-meal rises in blood glucose levels	Galochkina et al. (2016); Xie et al. (2017); Rehman et al. (2019); Gao et l. (2020); Su et al. (2020a);

	Yoon et al. (2020); Kondo et al. (2021)
Metabolic and gastrointestinal tract: anti-obesity, blood sugar regulation, liver function support and gut microbiota modulating properties	Su et al. (2021)
Gastrointestinal tract: gastroprotective; anti-ulcer, support mucosal barrier, inhibition of *Helicobacter pylori*; use of chitosan microparticles for enhanced bioavailability and stability	Eken et al. (2019); Stenger Moura et al. (2019 & 2021)
Gastrointestinal tract: potential use in colonic inflammation (colitis); support colonic microbiota (*Bacteroides, Clostridium* spp., *Sphingobacterium*) and enhance intestinal barrier function	Hou et al. (2021)
Eye function: anti-inflammatory, antioxidant; potential to protect against degenerative disorders such as macular degeneration, diabetic retinopathy and cataract; also inflammatory optic nerve damage and cisplatin-induced optic nerve damage	Xie et al. (2017); Ahiskali et al. (2019a & 2019b); Patil et al. (2019); Liu et al. (2020b); Ahiskali et al. (2021)
Cardioprotective: anti-ischaemic, reduce cholesterol levels; benefits against cardiovascular disorders such as arteriosclerosis and diabetic cardiomyopathy; anti-hypertensive (vasodilatory); protect against environmental toxin damage (phthalate plasticizers ie. DEHP) and heavy metal (chromium) toxicity	Sun et al. (2014); Guo et al. (2015a); Arutyunyan et al. (2016); Plotnikov et al. (2017b); Kim et al. (2018a); Cai et al. (2019); Sunil & Xu (2019); Tang et al. (2019); Zhang et al. (2019e); Zheng et al. (2019); Cao et al. (2020b); Gao et al. (2020a)
Bone structure: potential for bone cell protection and benefits for bone regeneration	Satue et al. (2013); Li et al. (2017a); Wang et al. (2017e); Cai et al. (2018); Sunil & Xu (2019); Zhang et al. (2019b)
Dental care: reduced bone loss and supported bone formation in experimental periodontitis; protective effect on dental pulp stem cells	Fu et al. (2021); Lektemur Alpan et al. (2020 & 2021)
Reproductive system (male): active against chemical toxicology ie. developmental and reproductive toxicity of the plastizer DBP (di-n-butylphthalate) in animal studies; anti-ischaemic effect on testicular function	Li et al. (2020c); Bedir et al. (2021)
Male hormonal: suppression of hormonal (androgen) production that may have benefits for prostate cancer	Ge et al. (2018); Su et al. (2020b)
Reproductive function (female): chemoprotective against ovarian dysfunction, infertility and hormonal disruption due to the use of antipsychotic drugs	Ince et al. (2021)
Neuroprotective: antioxidant benefits for memory and mental function; anti-amyloid activity; anti-ischaemic on	Aminimoghadamfarouj et al. (2011); Kim et al. (2017);

cerebral function; protect against hypertensive damage to brain tissue (vasoprotective); protect against pesticide (chlorpyrifos) neurotoxicity	Plotnikov et al. (2017a); Saito et al. (2017); Xie et al. (2017); Wang et al. (2018c); Tanaka et al. (2019); Turovskaya et al. (2019); Zhang et al. (2019f); Gunesch et al. (2020); Saito et al. (2021)
Neuroprotective (memory functions): anti-amyloid activity, anti-Alzheimer's potential	Park et al. (2016); Mahdavimehr et al. (2017); Inoue et al. (2019); Tanaka et al. (2019); Saito et al. (2021)
Anticancer: cancer chemopreventive, antitumour, anti-leukaemia; enhance antibiotic activity and cancer cell sensitivity to anticancer drugs (re-sensitizes multidrug resistance of cancer cells) with drug-synergist potential; active against breast, scar carcinoma, brain (glioblastoma), liver, gastric, lung and bone (osteosarcoma) cancer cell lines; protective potential for skin cancer; synergistic anticancer effect with andrographolide	Michael et al. (2010); Manigandan et al. (2015a); Nam et al. (2015); Alzaharna et al. (2017); Kuang et al. (2017); Chen et al. (2018b); Chen et al. (2018c); Haque et al. (2018); Razak et al. (2018); Li et al. (2019c); Sunil & Xu (2019); Zhou et al. (2019); Wang et al. (2020c); Butt et al. (2021); Das et al. (2021); Xie et al. (2021a); Yao et al. (2021b)
Chemoprotective: active against pesticide (rotenone and chlorpyrifos) toxicity, antibiotic (colistin) and environmental toxin damage (phthalate plasticizers ie. DEHP and DBP; cadmium); also chemotherapy (cisplatin) toxicity	Manigandan et al. (2015b); Cai et al. (2019); Crown et al. (2019); Unver et al. (2019); Zhang et al. (2019f); Akinmoladun et al. (2020); Cui et al. (2021); Kabel & Salama (2021)
Radioprotective: antioxidant	Arutyunyan et al. (2016)
Antiparasitic: anti-leishmania; potential for combination with pyrimethamine for Toxoplasmosis	Kumar et al. (2017a); Abugri et al. (2018); da Silva et al. (2019); Sunil & Xu (2019)
Anthocyanins: Anthocyanins derived from anthocyanidins cyanidin and delphinidin, especially the rutinoside and glucoside forms, are typical for may black berry fruits, also black cherries, black rice and black beans	
Cyanidin 3-glucoside (C3G or Cy3G: anthocyanin)	
Pharmacological properties (summary): antioxidant, anti-inflammatory; chemopreventive; protection against age-related diseases; antidiabetic, neuroprotective	Huang et al. (2013); Jo et al. (2015); Olivas-Aguirre et al. (2016)
Bioavailability: C3G normally has poor stability; nanoparticle encapsulation with caseins or chitosan improved C3G stability with good C3G release capacity	Ouyang et al. (2020); Sun et al. (2020e)
Functional food: blue corn, blueberries, black rice, black bean, blackcurrant and other black berries, black cherries	Attaribo et al. (2020); Cerezo et al. (2020); Chatham et al. (2020);

etc. are good resources; silkworm pupae protein plus C3G had a protective on anthocyanin stability with potential for use in food products; black rice C3G increased with air drying (also quercetin)	Damian-Medina et al. (2020); Ratseewo et al. (2020); Simerdova et al. (2020); Neder-Suarez et al. (2021)
Antiviral: active against norovirus; potential against SARS-CoV-2 and dengue virus	Lee et al. (2016c); Islam et al. (2021c); Pitsillou et al. (2021); Rahman et al. (2021c)
Antioxidant: significant antioxidant, anti-inflammatory, and cytoprotective effects against oxidative stress-induced disorders	Tan et al. (2020c); Rahman et al. (2021c)
Anti-inflammatory, antioxidant, immunomodulatory, antiarthritic, analgesic; anti-allergy (black soybean hull extract)	Chen et al. (2017b); Sun & Li (2018); Aloud et al. (2020); Cenk et al. (2021); Hiemori-Kondo et al. (2021)
Skin and cosmetic: anti-inflammatory, anti-allergy, useful for dermatitis, psoriasis; photoprotective (UVA and UVB) for skin cells; skin whitening (depigmentation) potential for black-rings under the eyes (periorbital hyper-pigmentation)	Han et al. (2009); Hu et al. (2016); Wu et al. (2018); Liu et al. (2018b); Sawant & Khan et al. (2020)
Dental: potential for use in chronic periodontitis; effective in combination with erythrosine and photodynamic (light-activated) therapy against *Porphyromonas gingivalis* biofilms	Park et al. (2015); Teerakapong et al. (2017)
Radioprotective: against UV damage of the skin and eye; radioprotective (UVB exposure) properties are enhanced with nanoencapsulation	Lee et al. (2014); Pratheeshkumar et al. (2014); Hu et al. (2016); Silvan et al. (2016); Wang et al. (2016a); Liu et al. (2018b)
Gastrointestinal tract: antioxidant and anti-inflammatory, anti-ulcer, analgesic, gastroprotective (*Prunus cerasus*), modulate digestive functions; maintain intestinal integrity and function; protective benefits for intestinal inflammation (colitis); influence gut microbial balance; active against *Helicobacter pylori* infection; benefits for colonic motility (which can be impaired in pancreatitis)	Olivas-Aguirre et al. (2016); Ferrari et al. (2017); Tan et al. (2019); Gan et al. (2020); Lian & Chen (2020); Raafat et al. (2020)
Gastrointestinal function: prebiotic benefit for gut microbiota (black rice C3G); mitigation of high fat/sugar dietary metabolic dysfunction, inflammation and gut dysbiosis; metabolized by *Bifidobacteria* and *Lactobacillus*; C3G lauryl ester enhanced bioavailability and prebiotic activity	Zhu et al. (2018c); Huang et al. (2020c); Yang et al. (2020d)
Liver function: hepatoprotective; chemoprotective; liver fibrosis prevention; promote triglyceride excretion (via bile); potential use in alcoholic liver dysfunction; also for prevention of liver cancer	Jiang et al. (2015 & 2017); Hashimoto et al. (2017); Mogalli et al. (2018); Pei et al. (2018); Zhou et al. (2020); Matboli et al. (2021); Zhao et al. (2021e); Zhao et al. (2021f)

Urinary tract (antimicrobial): blueberry extract rich in anthocyanins (particularly C3G) were active against urinary tract pathogens e.g. *Psudomonas aeruginosa, Klebsiella pneumoniae*	Cerezo et al. (2020)
Kidney function: anti-inflammatory renoprotective, prevent kidney damage; active against diabetic nephropathy (black rice, purple rice husk, Ligonberry)	Olivas-Aguirre et al. (2016); Qin et al. (2018); Madduma Hewage et a. (2020); Zheng et al. (2020); Wongmekiat et al.(2021)
Eye and vision: benefits visual function, anti-bacterial and anti-inflammatory e.g. bacterial keratitis (corneal inflammation); photoprotective; protective effect on retinal function and diabetic cataract formation; dye component with potential for eye surgical procedures; anti-inflammatory for eye disorders e.g. macular degeneration	Silvan et al. (2016); Wang et al. (2016a & 2017f); Caiado et al. (2017); Jin et al. (2018); Peris et al. (2018); Ercan et al. (2019); Wang et al. (2019d); Li et al. (2020j); Song et al. (2020b); Amato et al. (2021)
Respiratory Tract: anti-inflammatory, anti-allergy (rhinitis); protection of lung tissue in infection (sepsis) and acute respiratory distress	Han et al. (2009); Fu et al. (2014); Ma et al. (2015a); Yan et al. (2015b); Ma et al. (2019b)
Cardioprotective: protective effect in cardiovascular disease; antioxidant, anti-ischaemic, vasorelaxant, anti-hypertensive; anti-inflammatory and anti-thrombotic; anti-atherosclerotic potential; benefits for cholesterol levels; antioxidant, anti-haemolytic; protective against doxorubicin cardiotoxicity	Du et al. (2015); Olivas-Aguirre et al. (2016); Isaak et al. (2017); Petroni et al. (2017); Yao et al. (2017); Aloud et al. (2018 & 2020); Li et al. (2018e); Wang et al. (2020k); Ouyng et al. (2021); Shan et al. (2021)
Metabolic function: anti-obesity (regulate energy metabolism); antidiabetic and pancreatic support, antioxidant, antifibrotic and protective against ethanol toxicity in pancreatic tissue; confers protection against age-related diseases, metabolic syndrome, type 2 diabetes and its side effects including kidney and cardiovascular damage; enhance exercise performance	Bhaswant et al. (2015); Cesna et al. (2015); Lee et al. (2015b); Matsukawa et al. (2015); Olivas-Aguirre et al. (2016); Zheng et al. (2016b); Fratantonio et al. (2017); Li et al. (2017b); Matsukawa et al. (2017); You et al. (2017); Zhou et al. (2017); Ajay Krishna et al. (2018); Li et al. (2018e); Spinola et al. (2019); Jia et al. (2020b); Molonia et al. (2020); Tan et al. (2020d); Yoon et al. (2020); Zheng et al. (2020); Sasikumar et al. (2021); Xue et al. (2021); Zhao et al. (2021f)
Metabolic (enzyme inhibition): legume (*Vigna unguiculata*) anthocyanins Cyanidin and cyanidin-3-glucoside inhibit digestive enzyme (pancreatic lipase), which reduces fat absorption	Vijayaraj et al. (2019)

Neuroprotective: antioxidant, anti-inflammatory, preventive and/or therapeutic activities in a wide range of disorders, such as cerebral ischemia, Alzheimer's disease, Parkinson's disease, multiple sclerosis, and cancer (glioblastoma); protective against aging neurological disability; support learning capacity and memory protection; anti-ischaemic; very bioavailable in brain tissue; C3G-rich *Oryza sativa* extract improves memory function	Bhuiyan et al. (2011); Nasri et al. (2012); Thummayot et al. (2014); Fornasaro et al. (2016); Yang et al. (2018a); Joo et al. (2019); Sukprasansap et. al. (2019); Zhang et al. (2019i); Liu et al. (2020e); Carballeda-Sangiao et al. (2021)
Neuroprotective (chemoprotective): protective against neurotoxins e.g. lipopolysaccharide, hydrogen peroxide, ethanol, kainic acid, acrolein, glutamate, and scopolamine	Zhang et al. (2019i)
Reproductive system: phytoestrogen; chemoprotective against acrylamide (carcinogen) and glycidamide (genotoxin) food contamination; protective against lead toxicity on hormonal function	Nanashima et al. (2017); Sun et al. (2018b); Wen et al. (2018)
Reproductive system (male): chemoprotective; protective against cadmium-induced testicular damage and endocrine (hormonal) dysfunction	Jiang et al. (2018); Li et al. (2019e & 2020i)
Bone structure: potential prevention of osteoporosis, benefits for rheumatoid arthritis and dental inflammation (periodontitis)	Park et al. (2015); Hu et al. (2021)
Musculoskeletal: nutritional-based reduction of muscle inflammation and oxidative stress; cyanidin provides dietary protection against development/progression of muscular dystrophy	Saclier et al. (2020)
Chemoprotective: lead and cadmium toxicity; doxorubicin cardiotoxicity	Petroni et al. (2017); Wen et al. (2018); Li et al. (2020i)
Anticancer studies: chemoprotective; good protective activity on gastrointestinal tract, particularly oesophageal and colon cancer; active in lung, liver, melanoma, bone (osteosarcoma), breast, brain (glioma), cervical, ovarian and prostate cancer cell lines; also potential for use in treatment of oral cancer; potential for dietary sources to improve chemotherapy resistance of lung cancer cells	Serafino et al. (2004); Chen et al. (2006); Kocic et al. (2011); Zikri et al. (2009); Xu et al. (2010); Zeng et al. (2012); Long et al. (2013); Chen et al. (2016a); Li et al. (2016b); Olivas-Aguirre et al. (2016); Wang et al. (2016b); Cho et al. (2017); Ereminas et al. (2017); Hosseini et al. (2017); Mazewski et al. (2018); Liang et al. (2019a); Ma & Ning (2019); Yin et al. (2019); Atashi et al. (2020); Baster et al. (2020); Jongsomchai et al.(2020); Chen et al. (2021g); Eguchi et al. (2021); Li et al. (2021d); Matboli et al. (2021)

Anticancer (synergist): C3G enhanced activity of cisplatin in cervical cell cancer studies; C3G combined well with chloroquin as an anti-tumour agent	Li et al. (2021d); Wet et al. (2021b)
Anticancer (fruit/grain extracts): C3G-rich Haskap fruit (*Lonicera caerulea*) had protective effects in lung cancer studies; chemoprotective against tobacco nitrosamine; contribute to anticancer properties of Blackbean seed coat extracts; contribute to anticancer activity of purple rice husk extract, potential prevention of prostate cancer	Amararathna et al. (2020); Yeewa et al. (2020); Wei et al. (2021b); Punvittayagul et al. (2021)
Cyanidin 3-rutinoside (C3R or Cy3R: anthocyanin)	
Antioxidant, anti-inflammatory: inhibition of allergic inflammation	Jo et al. (2015); Thilavetch et al. (2016); Jeon (2019)
Anti-inflammatory: C3R plus cyanidin 3-glucosylrutinoside were major anthocyanins in tart Cherry juice with anti-inflammatory and anti-gout activity	Schlesinger et al. (2021)
Metabolic function: pancreatic protective properties; benefits for metabolic syndrome; antidiabetic, with potential anti-obesity benefits; anti-glycation properties	Akkarachiyasit et al. (2010); Adisakwattana et al. (2011); He & Lu (2013); Wu et al. (2013); Thilavech et al. (2016 & 2017); Zheng et al. (2016b); Choi et al. (2017); Choi et al. (2018)
Gastrointestinal tract: anti-inflammatory; enzyme inhibition that reduces fat absorption (anti-lipid activity)	Thilavech & Adisakwattana (2019)
Cardiovascular: cardioprotective; benefits for cholesterol levels; vasorelaxant properties	Thilavech et al. (2017); Thilavech & Adisakwattana (2019); Lee et al. (2020d)
Eye and vision: support eye function with potential for enhancing night vision (stimulate regeneration of rhodopsin)	Kanwal et al. (2012)
Neuroprotective: anti-Alzheimers potential	Saithong et al. (2018)
Hormonal influence: phytoestrogen	Nanashima et al. (2017)
Anticancer: good potential for protective activity on gastrointestinal tract particularly oesophageal and oral cancer; active in lung cancer cell lines; also in leukaemia studies, with potential for use in combination therapies to prevent relapse	Chen et al. (2006); Feng et al. (2007); Zikri et al. (2009); Kocic et al. (2011); Kochling et al. (2013); Knobloch et al. (2016);
Anticancer: Sweet Cherry extracts contain bioactive anthocyanins (rutin + C3R) with anti-angiogenesis (inhibition of cancer blood vessel growth) properties	De Leo et al. (2021)

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