Table 12.2 Pharmacological activity of bioactive chemicals in the *Piper* genus

Class of Compound: Compound and Properties	Resources
Piperine alkaloids: Piperine, piplartine (piperlongumine), pellitorine	
Piperine	
Pharmacological properties (general): antimicrobial, antioxidant, anti-inflammatory, immunomodulatory, protective effect on many body systems eg. respiratory tract, heart and vascular system, liver and renal function, metabolic dysfunction and significant anticancer potential	Srinivasan (2007); Meghwal & Goswami (2013); Shityakov et al. (2019); Tiwari et al. (2020)
Bioavailability: lipophilic nature makes it difficult to dissolve limiting its bioavailability in the body; nano-delivery can increase solubilisation, as well as to promote controlled release to specific sites; piperine showed increased oral bioavailability from black pepper using a nanosuspension formulation; sustained-release matrix piperine pellets also substantially enhance piperine bioavailability	Zafar et al. (2019); Zhu et al. (2020a); Quijia et al. (2021); Zhang et al. (2021a); Tiwari et al. (2020)
Bioavailability: piperine absorption can be enhanced by co-administration with vitamins and minerals; piperine-iron combination has potential to enhance iron bioavailability and absorption	Fernandez-Lazaro et al. (2020)
Bioavailability (dietary influence): capsaicin/piperine improves carotenoid uptake, while curcumin is inhibitory; carotenoids are lipid soluble spice ingredients with low bioavailability and their intestinal absorption is crucial to their metabolism	Shilpa et al. (2021)
Bioavailability (turmeric): piperine can significantly enhance curcumin absorption; this combination has been incorporated into numerous formulations for the clinical treatment of COVID, cancer, asthma, liver disorders, arthritis, nervous system function, parasitic conditions (eg. malaria) and diabetes	Smilkov et al. (2019) [see also separate sections below]
Drug bioavailability: piperine can promote bioavailability/permeation of nasal drug delivery strategies; piperine has potent drug-enhancement potential and can reduce the side effects of many conventional drug therapies. Piperine can influence a wide variety of drugs i.e. NSAIDs, antidiabetics, analgesics, antihistamines, antiretrovirals, antimicrobials, anti-epileptics and other conventional	Srinivasan (2007); Venkatesh et al. (2011); Shao et al. (2015); Bedada et al. (2016); Chavarria et al. (2016); Lee et al. (2018); Rather & Bhagat (2018); Gerber et al. (2019); Shityakov et al. (2019); Tiwari et al. (2020); Afreen et al.

drugs e.g. theophylline (respiratory antispasmodic), propranolol (blood pressure and cardiac disorders) and anti-inflammatory drugs (i.e. nimesulide, diclofenac and ibuprofen)	(2021); Bakshi et al. (2021)
Inflammation and immune system: immunomodulatory, antioxidant, anti-inflammatory; potentiate natural immunity against infection, immunosuppressant; potential for use in immune-mediated disorders; also for treatment of endotoxic shock; anti-allergic (hayfever); anti-anaphylactic potential	Pathak & Khandelwal (2007); Bae et al. (2010); Aswar et al. (2015); Kumar et al. (2015); Pan et al. (2015); Lu et al. (2016); Rodgers et al. (2016); Soutar et al. (2017); Yasir et al. (2018); Qiao et al. (2020); Tiwari et al. (2020); Gholijani et al. (2021)
Anti-inflammatory, analgesic, anti-arthritic: useful in combinations with curcuminoids for osteoarthritis; potential for treatment of osteoarthritis and rheumatoid arthritis; clinical trial of turmeric extract, black pepper and ginger showed comparable activity to naproxen for treating chronic knee osteoarthritis; significant analgesic, nerve repair and anti-inflammatory activity eg. against spinal disc herniation and sciatica	Umar et al. (2013); Ying et al. (2013); Tasleem et al. (2014); Panahi et al. (2016b); Bhalekar et al. (2017); Ren & Liang (2018); Panthong et al. (2020); Heidari-Beni et al. (2020); Tiwari et al. (2020); Yu et al. (2021a & 2021b); Quijia et al. (2021)
Musculoskeletal (injury): anti-inflammatory, healing potential for tendon injuries	Gong et al. (2018)
Anti-sepsis: antibacterial and anti-inflammatory; active against *Escherichia coli*	Bae et al. (2010); Liang et al. (2016); Liew et al. (2020)
Anti-inflammatory (drug delivery): metal-piperine nanoformulations (zirconium- and titanium-based) had enhanced anti-inflammatory and antioxidant effects	AbouAitah et al. (2021)
Lupus erythematosus (inflammatory autoimmune disease): piperine plus resveratrol showed various benefits for SLE treatment but were not curative; piperine did not enhance resveratrol activity	Pannu & Bhatnagar (2019 & 2020)
Ocular function (eye disorders): anti-cataract (steroid protective); protect retinal function in diabetes	Vurmaz et al. (2019); Zhang et al. (2021b)
Bone and disc protection: support bone structure; protective against intervertebral degeneration	Deepak et al. (2015); Li et al. (2015a); Kim et al. (2018)
Haematology: radioprotective against blood cell damage [see below]; anti-anaemic (black pepper and piperine), active against inflammation-induced anaemia; increased iron bioavailability with black pepper methanol extracts	Fernandez-Lazaro et al. (2020); Banerjee et al. (2021a)
Dental and oral care: enhance periodontal repair for oral disorders; anti-inflammatory for oral lichen planus with anticancer potential; enhance activity of curcumin	Hie et al. (2009); Dong et al. (2015); Martins et al. (2015); Guimaraes-Stabili et al.

in supporting bone structure after dental trauma treatment of periodontitis	(2019); Yang et al. (2019)
Oral care: precancerous mouth and throat lesions (oral submucous fibrosis) curcumin–lycopene–piperine combination gave excellent clinical results	Mahato et al. (2019)
Oral care: stimulation of salivary secretion, useful for treating dry mouth (xerostomia)	Houghton et al. (2020)
Antiviral: active against hepatitis B; inhibition of Ebola and Dengue virus in studies; antiviral activity of curcumin (*Curcuma longa*), Green tea (catechins) and piperine (*Piper nigrum*) or combination treatments, with potential to inhibit entry of SARS-CoV-2 virus in host cell, reduce transmission and improve immunity; bilosomes (piperine incorporated into bile salt based nano vesicles) considerably improved its antiviral activity	Jiang et al. (2013); Maurya et al. (2020); Nag & Chowdhury (2020); Rout et al. (2020); Miryan et al. (2020 & 2021); Junior et al. (2021); Kumar et al. (2021a); Peter et al. (2021); Zakaria et al. (2021)
Antiviral (COVID clinical trial): curcumin–piperine tables (525 mg:2.5 mg) twice daily gave significant results with improvement in symptomology and clinical response to treatment, reduced hospital time and fewer deaths; another trial proposes a higher dosage rate curcumin–piperine capsules (500 mg:5 mg 3x daily; piperine; total 1500 mg curcumin and 15 mg piperine/daily)	Askari et al. (2021); Pawar et al. (2021)
Antibacterial: broad-spectrum activity; includes activity against *Clostridium botulinum* and *Staphylococcus aureus*; also *Chromobacterium violaceum*; synergistic with gentamicin and ciprofloxacin against MRSA; synergistic with amikacin and streptomycin against *Salmonella enterica* biofilm (16-fold reduction of the minimum inhibitory concentration)	Sampath et al. (2011); Meghwal & Goswami (2013); Khameneh et al. (2015); Zhai et al. (2016); Maitra & Shilpi (2017); Mgbeahuruike et al. (2019b); Shityakov et al. (2019); Vazquez-Martínez et al. (2020); Tokam Kuate et al. (2021)
Anti-aflatoxin: active against *Aspergillus flavus, A. parasiticus*; animal studies showed reduced activity of mycotoxin and decreased liver injury; prevents the activation of aflatoxin (a pro-carcinogen) markedly reducing its toxicity; curcumin–piperine also shows good activity	Gagini et al. (2010); Caceres et al. (2017); Buitimea-Cantua et al. (2020); Zarev et al. (2020)
Antimicrobial: activity against *Enterobcter aerogenes, E. coli, Salmonella enterica, Proteus mirabilis* and *Bacillus cereus*; antifungal and substantial anti-*Candida* potential (*Piper guineense*) eg. for use in treating oral candidiasis and difficult to treat strains	Mgbeahuruike et al. (2018 & 2019a); Priya & Pandian (2020); Thakre et al. (2021)
Antimycobacterial: active against *M. tuberculosis*; good	Hegeto et al. (2018 & 2019);

anti-tuberculosis potential, combines well with antibiotics (eg. rifampin, streptomycin) which can enhance activity	Murase et al. (2019); Tiwari et al. (2020); Calsavara et al. (2021); Ma et al. (2021)
Antibacterial (synergist): piperine showed synergistic effects against *Staphylococcus aureus* when combined with rifampicin and tetracycline; piperine plus rifampicin also active against *Pseudomonas aeruginosa*	Mgbeahuruike et al. (2019b)
Antimicrobial (fungicidal: plant pathogens): piperine and essential oil derivatives showed a broad-spectrum of activity eg. *Rhizoctonia solani, Fusarium graminearum, Phomopsis adianticola, Gloeosporium theae-sinensis,* with notable activity against *Alternaria tenuis, Phytophthora capsici*	Wang et al. (2020b)
Cosmetic and skin disorders: re-pigmentation properties (melanogenesis); potential for treatment of vitiligo (loss of skin pigmentation); clinical use in combination with UVB radiation has given excellent results for treating facial vitiligo; clinical efficacy of *Piper nigrum* extract was better than pure piperine suggesting additional synergistic natural components (travoprost solution further enhanced activity)	Srinivasan (2007); Shafiee et al. (2018); Mihaila et al. (2019)
Cosmetic: radioprotectant; UV photoprotection for skin	Verma et al. (2017)
Skin disorders: anti-inflammatory against atopic dermatitis; topical creams with piperine-loaded lipid nanocarriers have been developed for the management of atopic dermatitis	Choi et al. (2020); Kumar et al. (2021b)
Gastrointestinal system: anti-ulcer, antidiarrheal, carminative, sialagogue (increase saliva flow), enhance pancreatic enzyme activity and nutritional absorption processes; anti-inflammatory antioxidant for treatment of colitis, combination with curcumin-piperine was useful for ulcerative colitis	Srinivasan (2007); Ahmad et al. (2012); Meghwal & Goswami (2013); Butt et al. (2013); Gupta et al. (2015); Hu et al. (2015); Li et al. (2015d); Shityakov et al. (2019); Guo et al. (2020); Quijia et al. (2021)
Anti-*Helicobacter*: gastroprotective anti-ulcer; prevention of gastric cancer	Tharmalingam et al. (2014 & 2016); Toyoda et al. (2016)
ENT (swallowing reflex): treatment of dysphagia; black pepper oil and capsaicin are very useful for this condition; anti-coughing (antitussive) properties of pectic-polysaccharide-piperine combination	Butt et al. (2013); Rofes et al. (2014); Khawas et al. (2017); Alvarez-Berdugo et al. (2018)
Cardiovascular system: antioxidant anti-inflammatory cardioprotective, anti-hypertensive (vascular relaxation); anticholesterol, antifibrotic; prevention of cardiac damage following ischaemia and promote	Taqvi et al. (2008); Srinivasan (2007); Diwan et al. (2013); Meghwal & Goswami (2013); Dutta et al. (2014); Liu et al.

recovery; enhanced cardioprotective properties of curcumin against drug side effects (chemoprotective against cyclophosphamide cardiotoxicity); protective against diabetic cardiac damage	(2014); Ma et al. (2014); Dhivya et al. (2017); Chakraborty et al. (2017); Ma et al. (2017); Li et al. (2020); Wang et al. (2020c); Guo et al. (2021); Viswanadha et al. (2021)
Anticoagulant (drug interaction): may reduce the plasma concentration and anti-coagulation efficacy of warfarin, which needs to be investigated in a clinical setting	Zayed et al. (2020)
Thyroid function: inhibition of thyroid function; regulation of raised thyroid stimulating hormone and thyroid (T3, T4) hormone levels	Panda & Kar (2003); Vijayakumar & Nalini (2006)
Metabolic syndrome: benefits from clinical use of curcuminoid-piperine combinations; benefit lipid metabolism and obesity (piperine-catechin/EGCG combination enhanced activity); also anti-cholesterol properties with turmeric (or curcumin); enhancement of intestinal barrier function and inhibit intestinal fatty acid absorption linked to anti-obesity activity; immunomodulatory and anti-inflammatory potential for obesity-related diabetes	BrahmaNaidu et al. (2014); Shah et al. (2011); Neyrinck et al. (2013); Tu et al. (2014); Panahi et al. (2014 & 2015); Miyazawa et al. (2018); Liu et al. (2020a); Saberi-Karimian et al. (2020); Oruganti et al. (2021); Wang et al. (2021)
Metabolic disorders: antidiabetic, anti-hyperglycaemic and anticholesterol; good blood sugar regulation and lipid-lowering activity; cellular pancreatic protective properties; antifibrotic in pancreatitis; piperine-supplemented *Curcuma longa* extract was effective in clinical trials; piperine combined with *Piper longum* oil or quercetin-turmeric for the treatment of diabetes and metabolic syndrome; other combinations of resveratrol-alpha-tocopherol, and phytosomal curcumin-phosphatidylserine-piperine, showed clinical benefits for metabolic syndrome	Vijayakumar & Nalini (2006); Srinivasan (2007); Atal et al. (2012); Kaur & CM (2012); Kaur et al. (2016); Kumar et al. (2013a); Maeda et al. (2018); Panahi et al. (2018); Choi et al. (2019); Cicero et al. (2020); Pastor et al. (2020); Magana-Barajas et al. (2021); Neta et al. (2021); Tupe et al. (2021); Yuan et al. (2021)
Antidiabetic (synergist): enhance drug treatment; bioenhancing activity with metformin and nateglinide; microemulsion containing piperine (permeation enhancer) and albumin (stabilizer) for oral delivery of insulin with improved hypoglycaemic activity	Sama et al. (2012); Atal et al. (2016); Kaur et al. (2021)
Hormonal function (male): improved testosterone levels	Vijayakumar & Nalini (2006)
Liver function: hepatoprotective; antifbrotic, chemoprotective; protect against fatty liver and toxin damage; clinical benefits for NAFLD (non-alcoholic	Srinivasan (2007); Jwa et al. (2012); Sethiya et al. (2015); Tunsophon & Chootip (2016);

fatty liver disease) in combination with curcumin; chemoprotective against paracetamol toxicity, also steroid-induced liver dysfunction	Mirhafez et al. (2019); Mohammadi et al. (2019a); Panahi et al. (2019); Morsy et al. (2020); Saberi-Karimian et al. (2020); Shu et al. (2021); Vurmaz & Atay (2021)
Hepatoprotective: enhancement of the activity of silybin suggests excellent hepatoprotective synergism with Milk Thistle supplements; also complexes of piperine-phospholipid, and phytosomal curcumin-phosphatidylserine-piperine, showed enhanced bioavailability and liver protective activity; piperine can also enhance the hepatoprotective properties of ursolic acid (which has poor bioavailability)	Bi et al. (2019); Cicero et al. (2020); Biswas et al. (2021a & 2021b); Quijia et al. (2021)
Liver cancer: anticancer for hepatic carcinoma; curcumin-piperine-taurine combination shows potential clinical benefits in some cancer patients	Hatab et al. (2019); Tiwari et al. (2021)
Hepatoprotective: active against cyanotoxin damage; enhanced activity of thymoquinone	Abdel-Daim et al. (2019)
Gall bladder function: anti-lithic activity (prevent cholesterol gallstones), which can be enhanced by combination with curcumin	Li et al. (2015c); Song et al. (2015)
Note: *Piper longum* has hepatoprotective effects and can prevent the formation of cholesterol gallstones	Xu et al. (2013); Sharma and Sahu et al. (2016)
Kidney function: diuretic; protective anti-inflammatory, antioxidant, immunomodulatory and anti-ischaemic properties; protective for diabetic nephropathy and lupus nephritis; protective against lead acetate nephrotoxicity	Srinivasan (2007); Kakalij et al. (2016); Samra et al. (2016); Sudjarwo et al. (2017); Peng et al. (2018); Mohammadi et al. (2019b)
Genitourinary tract and fertility: anti-implantation and anti-fertility activity; male contraceptive potential	Srinivasan (2007); Chinta & Periyasamy (2016); Chinta et al. (2017)
Gynaecology: antibacterial, anti-inflammatory for bacterial endometritis (*Staphylococcus aureus*) and mastitis (breast inflammation)	Zhai et al. (2016); Yu et al. (2020)
Respiratory tract: anti-asthmatic (combines well with curcumin); anti-allergy; anti-tussive potential for treating coughing (pectic polysaccharide-piperine combination); protective against inflammatory lung injury; piperine-curcumin combination for clinical treatment of sulphur-mustard lung damage	Srinivasan (2007); Kim & Lee (2009); Lu et al. (2016); Panahi et al. (2016a); Khawas et al. (2017); Chauhan et al. (2018)
Respiratory Tract (tuberculosis): antimicrobial, piperine is active against *Mycobacterium tuberculosis*; also shows a synergistic effect with rifampicin to improve treatment of tuberculosis	Sharma et al. (2014)

Neuroprotective: anxiolytic, antidepressant, memory support and enhancement; ACh inhibition; MAO inhibition with derivatives showing potent activity; potential treatment of Alzheimer's disease and multiple sclerosis; potential protection against neurological damage due to anticancer agents eg. streptozotocin in animal studies (piperine combines well with donepezil) Note: Monoamine oxidase inhibitors prevent the breakdown of neurotransmitters (i.e. serotonin, melatonin, epinephrine, norephinephrine, dopamine, tyramine and phenethylamine). They are used in the treatment of emotional disorders (depression, anxiety, stress and personality disorders), neurological problems such as Parkinson's disease and for migraine prophylaxis.	Srinivasan (2007); Fu et al. (2010); Al-Baghdadi et al. (2012); Butt et al. (2013); Pragnya et al. (2014); Elnaggar et al. (2015); Yang et al. (2015); Chavarria et al. (2016); Wang et al. (2016a); Ren et al. (2017); Etman et al. (2018); Khalili-Fomeshi et al. (2018); Ren & Zuo (2019); Wang et al. (2019c); Wang et al. (2019a & 2020a); Chavarria et al. (2020); Dhiman et al. (2020); Khatami et al. (2020); Liu et al.(2020b); Roshanbakhsh et al. (2020); Tiwari et al. (2020); Nasrnezhad et al. (2021); Nazifi et al. (2021); Quijia et al. (2021)
Neuroprotective: active against cyanotoxin damage; enhanced activity of thymoquinone	Abdel-Daim et al. (2019)
Neuroprotective: neurodegenerative disorders; anti-Parkinsonian activity (gold nanoparticles showed enhanced activity), including protection against experimental rotenone and iron toxicity in combination with quercetin; protection in Huntington's disease (neurodegenerative brain disorder)	Liu et al. (2013); Liu et al. (2016); Singh & Kumar (2016 & 2017); Guo et al. (2018); Ren & Zuo (2019); Sharma et al. (2020); Li et al. (2021); Srivastav et al. (2020); Salman et al. (2020); Wang et al. (2020d)
Neuroprotective (nerve damage): enhanced piperine activity with curcumin and dexibuprofen for peripheral neuropathy; support nerve repair and anti-inflammatory processes in spinal disc damage and sciatica	Di Pierro & Settembre (2013); Yu et al. (2021a & 2021b)
Neuroprotective anti-ischaemic: preventive effect on brain damage due to ischaemic stroke	Hua et al. (2019a); Zou et al. (2019); Hua et al. (2019b); Kaushik et al. (2021)
Neuroprotective (natural product bioactivity): nanoformulations show excellent clinical potential for enhancement of the herbal treatment of neurodegenerative disorders (eg. piperine, curcumin, quercetin, resveratrol, ferulic acid, *Ginkgo biloba*, *Nigella sativa*) some of which have been used in combination therapies eg. piperine can enhance the	Huang et al. (2013); Wightman et al. (2014); Li et al. (2015b); Jangra et al. (2016); Singh & Kumar (2016); Xu et al. (2016); Rinwa & Kumar (2017); Moradi et al. (2020)

ability of resveratrol to increase cerebral blood flow	
Neuroprotective (with curcumin): piperine and curcumin show protective activity in Alzheimer's disease models; hydroxypropyl-β-cyclodextrin improved solubility of the curcumin–piperine combination, its permeability (gastrointestinal tract, blood–brain barrier) and activity (antioxidant, antimicrobial and cholinesterase-inhibition); also enhanced activity with a bioactive self-nanoemulsifying curcumin–piperine delivery system in combination with Black Seed (*Nigella sativa*) oil Note: curcumin has poor intestinal absorption which can be significantly enhanced by piperine	Abdul Manap et al. (2019); Kazi et al. (2020); Stasiłowicz et al. (2020)
Neuroprotective: anticonvulsant, anti-seizure; analgesic and protect against epilepsy associated depression or seizures associated with traumatic brain injury; nanostructured piperine delivery system (copper nano-dots) under investigation for epilepsy treatment	Pal et al. (2011); Bukhari et al. (2013); Chen et al. (2013b); da Cruz et al. (2013); Mao et al. (2014); Mishra et al. (2015); Chavarria et al. (2016); Mao et al. (2017); Anissian et al. (2018); Song et al. (2020); Zhu et al. (2020b)
Bioavailability (drug): anti-epileptic piperine nanoparticles show enhanced dissolution and oral bioavailability; also inhibitory activity on metabolism of some drugs (giving a longer exposure time in the body) although there is also possibility of decreased drug bioavailability interactions	Ren et al. (2019a & 2019b); Ren & Zuo (2019)
Bioavailability (natural products): enhanced bioavailability of nutritional components e.g. curcumin, ginsenoside, oxyresveratrol, CoQ10, β-carotene; flavonoids (EGCG from green tea), alkaloids (e.g. vasicine, sparteine), and cannabidiol	Srinivasan (2007); Ratanavaraporn et al. (2014); Jin et al. (2018); Junsaeng et al. (2019); Izgelov et al. (2020)
Bioavailability (synergist): widely reported for increasing the effect and bioavailability of antibiotics (norfloxacin, ampicillin, metronidazole, ampicillin, oxytetracycline, gatifloxacin), various drugs (phenytoin, pentobarbitone, propranolol/theophylline, rifampicin, losartan potassium, ibuprofen, atenolol), and some vaccines.	Tiwari et al. (2020); Quijia et al. (2021)
Drug enhancement (antimalarial): piperine derivatives have been suggested for enhancement of antimalarial drugs Note: Piperazine, named for its similarity to piperidine (structurally related to piperine), is not derived from *Piper* vines. Piperazine–artemisinin antimalarial drugs are in clinical	Rasoanavio et al. (2011)

use.	
Anticancer activity: antioxidant, antimutagenic, antimetastatic; potent anticancer activity against numerous cancer cell lines, including leukaemia, brain, breast, ovarian (including drug-resistant), prostate, colorectal, lung, liver, melanoma and osteosarcoma cell lines	Selvendiran et al. (2006); Srinivasan (2007); Lu et al. (2012); Lai et al. (2012); Butt et al. (2013); Lee et al. (2013a); Paarakh et al. (2015); Zheng et al. (2016); Gunasekaran et al. (2017); Manayi et al. (2018); Rather & Bhagat (2018); Si et al. (2018); George et al. (2019); Qiu et al. (2019); Yoo et al. (2019); Zadorozhna et al. (2019); Tiwari et al. (2020); Banerjee et al. (2021b); Quijia et al.(2021)
Bioavailability (anticancer drug delivery): investigations of advanced delivery systems (e.g. nanocarrier strategies) to improve drug bioavailability etc.; combination chemotherapy using curcumin-piperine emulsomes showed enhanced activity in colorectal cancer cells	Izgelov et al. (2018); Sedeky et al. (2018); AbouAitah et al. (2020); Bolat et al. (2020)
Bioavailability (drug resistance): piperine and analogues showed potential for ameliorating drug resistance eg. to vincristine in leukaemia chemotherapy; also resistance to colchicine or paclitaxel chemotherapy Note: piperine and black pepper also show anti-leukaemic potential	Khan et al. (2015); Syed et al. (2017 & 2021); Banerjee et al. (2021b): Quarti et al. (2021)
Anticancer (breast cancer): chemoprevention against breast cancer and its recurrence; synergistic with piperlongumine for enhanced activity; natural product combinations (piperine-curcumin is common) show substantial promise for cancer prevention and treatment eg. resveratrol-curcumin-piperine; also piperine-sulphoraphane-thymoquinone combination; nanoformulation enhanced bioavailability, provided an efficient targeted delivery system and reduced dosage requirements; synergist with cisplatin, rapamycin and paclitaxel in breast cancer cell lines; piperine-hesperidin-beevenom were synergistic with tamoxifen	Kakarala et al. (2008); Katiyar et al.(2016); Khamis et al. (2018); Aumeeruddy & Mahomoodally (2019); Mokbel & Mokbel (2019); Burande et al. (2020); Chen et al. (2020); Rad & Hoskin (2020); Schmidt et al. (2020); Fattah et al. (2021); Quijia & Chorilli (2021); Zeleznik et al. (2021)
Note: piperine-free *Piper nigrum* extract also show good anticancer activity in breast cancer cell studies, suggesting a significant synergistic effect of other components in black pepper	Sriwiriyajan et al. (2016)
Anticancer (prostate cancer): nutritional prevention of	Henning et al. (2008); Ouyang

prostate cancer which may have significant synergistic effects with other natural products e.g. green tea catechins and curcumin (other bioactive natural products include lycopene, epigallocatechin gallate, sulforaphane, indole-3-carbinol, resveratrol, quercetin, zinc)	et al. (2013); Samycutty et al. (2013); Zheng et al. (2016); George et al. (2019); Mokbel et al. (2019); Jonnalagadda et al. (2021)
Anticancer (synergist): drug enhancement e.g. docetaxel, paclitaxel, topotecan, mitomycin C; may help with multidrug resistance eg. chemosensitizing activity with doxorubicin; enhances the effect of temozolomide against drug-resistant glioma cell lines and paclitaxel against cervical cancer cells	Li et al. (2011a); Li et al. (2016); Khan et al. (2015); Raza et al. (2016); Han et al. (2017); Li et al. (2017); Li et al. (2018); Xie et al. (2019); Burande et al. (2020); Ding et al. (2020); Jeong et al. (2020); Wojtowicz et al. (2021)
Anticancer (drug side effects): chemoprotective; significant protection against doxorubicin cardiac toxicity	Yan et al. (2019)
Radiotherapy: piperine is a potent radioprotective agent (more active than curcumin at lower dose); enhance radiosensitization of cancer cells; sensitizes radiation-resistant colon cancer cells to radiotherapy; synergistic with curcumin showing enhanced haematological protective properties against blood cell damage	Shaheer et al. (2020); Ghelishli et al. (2019); Singh et al. (2021b)
Chemopreventive: significant chemoprotective properties; reduce the toxicity of environmental pollutants (eg. cadmium, arsenic) and cyanotoxin (enhanced activity with thymoquinone)	Srinivasan (2007); Li et al. (2011b); Manayi et al. (2018); Rather & Bhagat (2018); Abdel-Daim et al. (2019); Zadorozhna et al. (2019); Dey et al. (2020); Verma et al. (2020)
Antitoxin: ant-venom activity	Shenoy et al. (2013 & 2014); Christian Bharathi et al. (2018)
Antiparasitic: antiamoebic activity; antifilarial (piperine derivatives); anti-*Trypanosoma* (nanoformulations enhanced antiparasitic activity); piperine (and analogues; also capsaicin) show anti-leishmania activity with potential for drug development	Freire-deLima et al. (2008); Ferreira et al. (2011); Vieira-Araujo et al. (2018); Rather & Bhagat (2018); Rani et al. (2020); Joardar et al. (2021); Quijia et al. (2021)
Antiparasitic: anthelmintic against goat gastrointestinal nematodes	Da Silva et al. (2021c)
Anti-*Leishmania*: piperine-amphotericin B synergistic nanoparticle formulation showed significant inhibition of the parasite	Ray et al. (2021)
Antimalarial potential: piperine-curcumin has	Neto et al. (2013);

significant potential as an antimalarial treatment that is likely to an effect similar to chloroquine ie. restrict parasite development, enhance immune response against the parasite and reduce parasitaemia; there is also a synergistic activity piperine–curcumin plus chloroquine (additive effect to reduce parasite levels), but not artemisinin	Thiengsusuk et al. (2018); Khairani et al. (2021)
Pesticidal: insect repellent, pesticidal and contributes to the antiparasitic efficacy of Black Pepper extracts	Ahmad et al. (2012); Butt et al. (2013)
Pesticide (acaricide): tick larvicide; nanoscale zinc oxide–piperine formulation was active against cattle ticks	Kancharna et al. (2020); da Silva et al. (2021a)
Insecticide: mosquito larvicidal activity (derivatives under investigation for commercial use)	Samuel et al. (2016); Tantawy et al. (2020)
Piplartine (piperlongumine)	
Pharmacological properties:	
Bioavailability: nanoformulations increased water solubility, bioavailability and reduced toxicity, thereby enhancing therapeutic efficacy eg. anticancer potential	Tripathi & Biswal (2020)
Antimicrobial: activity against *Enterobacter aerogenes, E. coli, Salmonella enterica, Proteus mirabilis* and *Bacillus cereus,* antifungal and anti-candida potential (*Piper guineense*)	Mgbeahuruike et al. (2018 & 2019a)
Antimicrobial synergist: active with conventional antibiotics; piperlongumine showed synergistic effects against *Staphylococcus aureus* when combined with rifampicin.	Mgbeahuruike et al. (2019b)
Antiviral: active against Zika virus	Lu et al. (2021b)
Immunomodulatory: pro-oxidant immune suppressant	Liang et al. (2020)
Anti-sepsis: anti-inflammatory activity	Huang et al. (2021a)
Anti-inflammatory, analgesic; antiarthritic; potential for rheumatoid arthritis and osteoarthritis	Bezerra et al. (2013); Seo et al. (2014); Sun et al. (2015a); Sun et al. (2015b); Xiao et al. (2016); Xu et al. (2018); Ye et al. (2020)
Gastrointestinal system: antiulcer and gastroprotective; potential use for colonic inflammation (colitis), Crohn's disease and cancer prevention	Burci et al. (2013); Huang et al. (2020); Kwak et al. (2020)
Liver function: strong hepatoprotective and antifibrotic activities	Bezerra et al. (2013); Chilvery et al. (2020)
Metabolic disorders: anti-inflammatory, anti-diabetic	Bezerra et al. (2013); Xu et al.(2021)
Cardiovascular: cardioprotective; anti-fibrosis, active	Bao & Borjihan (2012); Son et

against cardiac hypertrophy (enlarged heart) often associated with heart failure; vascular protective, anti-inflammatory activity; anti-ischaemic; antiplatelet aggregation (anticoagulant), anti-atherosclerotic, protect against vascular calcification; reduce cholesterol levels; antihypertensive	al. (2012); Bezerra et al. (2013); Lee et al. (2013b and 2013c); Ku et al. (2014a); Wang et al. (2016b); Yoval-Sanchez et al. (2020); Gu et al. (2021); Shi et al. (2021); Ye et al. (2021b)
Respiratory tract: reduce inflammation and lung injury due to cigarette smoke exposure; potential use in COPD (chronic obstructive pulmonary disease) and asthma	Lu et al. (2019); Sant'Ana et al. (2020)
Skin disorders: anti-inflammatory with potential for psoriasis	Thatikonda et al. (2020)
Neuroprotective: acetylcholinesterase inhibition; anxiolytic, analgesic (pain-relief), anti-stress activity; antidepressant, anti-Parkinsonian; neuroprotective analogues are under investigation; protective against stroke (ischaemic brain damage)	Al-Baghdadi et al. (2012); Bezerra et al. (2013); Liu et al. (2013); Yang et al. (2014); Peng et al. (2015); Yadav et al. (2015a & 2015b); Wang et al. (2016a); Wiemann et al. (2017); Li et al. (2019); Zhang et al. (2019a);
Neuroprotective: anti-inflammatory, immunomodulatory against encephalomyelitis, with potential for multiple sclerosis; neuroprotective potential of anti-inflammatory antioxidant derivatives with blood-brain barrier permeability	Gu et al. (2017); Ji et al. (2021)
Anticancer activity: significant contribution to anticancer activity of Black Pepper (*Piper nigrum*); anti-inflammatory, immunomodulatory; potent anticancer activity (cytotoxic, antitumor, antimetastatic, genotoxic, antiangiogenic) against numerous cell lines, particularly breast and ovarian cancer; also osteosarcoma (bone cancer), pancreas, skin, gall bladder (biliary cancer), gastric, colorectal, lung, thyroid, liver, eye (retinal), brain, head and neck cancers; potential for preventive effects against some forms of cancer; piplartine derivatives also under evaluation eg. NBFTA against glioblastoma	Kumar et al. (2013b); Wang et al. (2014); Wu et al. (2014); de Lima Moreira et al. (2016); Fofaria et al. (2016); Meegan et al. (2017); Srivastava et al. (2017); Farooqi et al. (2018); Piska et al. (2018); Carvalho et al. (2019a); Chen et al. (2019a); Fan et al. (2019); Mohammad et al. (2019); Turkez et al.(2019); Cheng et al. (2020); Delaney et al. (2020); Henrique et al. (2020); Lv et al. (2020); Talabnin et al. (2020); Turrini et al. (2020); Zhou et al. (2020); Allaman-Pillet & Schorderet (2021); Conde et al. (2021); Kumar & Agnihotri

	(2021); Kung et al. (2021); Lu et al. (2021a); Tripathi & Biswal (2020)
Anticancer (drug delivery): micelle liposome formulations for enhanced piplartine bioavailability and drug delivery system; nanoemulsion modification with chitosan and sodium alginate for topical delivery in skin cancer models; ruthenium–piplartine complexes show potential for colon cancer; platinum–piplartine complex as an anti-leukaemia treatment	Baliza et al. (2019); Carvalho et al. (2019b); Oliveira et al.(2019); Giacone et al. (2020); Zhang et al. (2020); Tripathi & Biswal (2020)
Anticancer (drug delivery): cancer nanomedicine developed from human serum ie. converting total blood serum into chemotherapy nanoparticles (loaded with piperlongumine or paclitaxel/ gemcitabine) with enhanced anti-tumour activity	Thayath et al. (2021)
Anticancer: piperlongumine analogues have been extensively studied for cancer therapy	Zhu et al. (2021)
Anticancer (synergist): ability to enhance chemotherapy drugs e.g. 5-fluorouracil, also enhanced curcumin activity; combined with doxorubicin in prostate, cervical and breast cancer cell lines, and with oxaliplatin in gastric and colorectal cancer; synergistic with gemcitabine in lung cancer cell studies; enhanced activity of paclitaxel in a cervical and intestinal cancer cells	Jyothi et al. (2009); Bezerra et al. (2013); Piska et al. (2019); Zhang et al. (2019b); Chen et al. (2019b); Chen et al. (2019c); Rawat et al. (2020); Seber et al. (2020); Tripathi & Biswal (2020); Ye et al. (2021a)
Anticancer (synergist): the alkaloid combination piperlongumine plus sanguinarine (4:1 ratio) was synergistic in lung cancer cell studies (increased apoptosis, anti-metastasis); piperlongumine is synergistic with piperine in breast cancer cell studies	Chen et al. (2020); Halas-Wisniewska et al. (2020)
Anticancer (drug resistance): piperlongumine (and harmine) showed potential for overcoming chemotherapy resistance and reducing likelihood of cancer relapse	Machado et al. (2020)
Anticancer (immunomodulation): pro-oxidant, immune suppressant potential; cancer immunotherapy potential (immune supportive)	Fan et al. (2020); Liang et al. (2020); Afolabi et al. (2021)
Radiotherapy (radiosensitisation): enhance sensitivity of colorectal cancer cells to radiation treatment	Wang et al. (2019b)
Antiparasitic: piplartine is active against *Leishmania, Trypanosoma* and *Schistosoma* parasites; potential for use in synergistic drug combinations to treat schistosomiasis	Bezerra et al. (2013); Veiga-Santhos et al. (2013); Campelo et al. (2017); Moreira et al. (2018); Mengarda et al. (2020); Ticona et al. (2020); da Silva

	et al. (2021b); Peixoto et al. (2021)
Antimalarial: anti-plasmodial activity; combination with cinnamides suggested for malaria treatment	Araujo-Vilges et al. (2017); Da Silva et al. (2020)
Molluscicidal: activity against snail vector for trypanosoma	Rapado et al. (2013)
Pellitorine	
Pharmacological properties: antimicrobial, anti-inflammatory, antiparasitic, pesticidal	
Antimicrobial: antibacterial; enhanced activity of erythromycin against *Staphylococcus aureus*	Reddy et al. (2004); Ahirrao et al. (2020)
Anti-sepsis, anti-inflammatory potential	Ku et al. (2014b); Ngo et al. (2017); Liew et al. (2020)
Cardiovascular system: vascular protective and significant anti-inflammatory activity; antithrombotic	Ku et al. (2013); Lee et al. (2014)
Cholesterol levels (trans-pellitorine): hypolipidaemic and anti-lipidogenic potential	Rohm et al. (2015); Lieder et al. (2017 & 2019)
Bioavailability: good absorption via the gut and bioavailable across blood-brain barrier	Veryser et al. (2016)
Analgesic	Olah et al. (2017)
Cosmetic: good skin penetration qualities (sourced from *Anacyclus pyrethrum*)	Veryser et al. (2014)
Antiparasitic: antimalarial potential; antiplasmodial against *Plasmodium* spp., synergistic with other components in *Zanthoxylum heitsii, Z. zanthoxyloides* and *Achillea ptarmica*	Althaus et al. (2014); Goodman et al. (2016 & 2019)
Anti-Leishmania activity	Peixoto et al. (2021)
Pesticidal: insecticidal; mosquito larvicidal and adulticidal; active against date palm weevil larvae	Park et al. (2002); Perumalsamy et al. (2013); Moussavi et al. (2015); Hussain et al. (2017)
Larvicidal: very toxic to honeybee larvae	Miranda et al. (2003)
Neuroprotective: Ach inhibition with potential for enhancing memory and learning functions	Khatami et al. (2020)
Neurological function (trans-pellitorine): anti-inflammatory and tingling qualities; active on trigeminal nerve	Walker et al. (2016);
Anticancer: cytotoxic activity; active against leukaemia and breast cancer cell lines	Ee et al. (2010); Takooree et al. (2019)
Phenolics:	
Eupomatenoids (also found in *Eupomatia* and *Aristolochia*)	
Antimicrobial: eupomatenoids demonstrate a significant level of antimicrobial activity; antibacterial	Pessini et al. (2003); De Campos et al. (2005);

(including activity against MRSA and mycobacteria) and antifungal (particularly against skin dermatophytes)	Koroishi et al. (2008); Marcal et al. (2010); Lemos et al. (2013); Scodro et al. (2013)
Anti-tuberculosis: eupomatenoid-5 shows potential synergistic effect with anti-tuberculosis drugs	Lopes-Ortiz et al. (2014); Ghiraldi-Lopes et al. (2017)
Anticancer: eupomatenoid-5 (source: *Piper regnellii*) shows tumour-inhibitory properties; also antitumour potential eupomatoid-6 and derivatives eg. activity against oral cancer (source: *Piper rivinoides*)	Morelli et al. (2014); Longato et al. (2011 & 2015); Fonseca et al. (2020)
Anti-venom: eupomatenoid-7 (*Aristolochia elegans*) was active against scorpion venom	Zamilpa et al. (2014)
Antiparasitic: eupomatenoid-5 (*Piper regnellii*) shows anti-*Trypanosoma* activity; also anti-*Leishmania*	Pelizzaro-Rocha et al. (2011); Garcia et al. (2013); Peixoto et al. (2021)
Insecticidal: eupomatenoid-6 (*Piper solmsianum*) potent mosquito larvicidal activity	Macedo et al. (2018)
Hydroxychavicol	
Pharmacological properties (general): antioxidant, anti-inflammatory, antimicrobial, anticancer	Gundala & Aneja (2014)
Antimicrobial: excellent antifungal properties; anti-candida; potentiate antifungal activity of 5-fluorocytosine, potential for treating oral candida infections	Ali et al. (2010 & 2016); Himratul-Aznita et al. (2016); Singh et al. (2018)
Antibacterial: active against *Mycobacterium tuberculosis*	Chen et al. (2013a);
Antifungal: broad-spectrum activity against skin fungal infections, including dermatophytes causing onychomycosis (nail infections), *Candida* and *Tinea*	Ali et al. (2016)
Antimicrobial (synergist): antibiotic synergist; sensitize bacteria to clinically used antibiotics thereby enhancing their activity eg. against drug resistant *E. coli*	Singh et al. (2021a)
Antifungal (plant pathogens): biogenic synthesized silver nanoparticles containing *Piper betle* (eugenol, chavicol, hydroxychavicol) showed significant antifungal activity against *Alternaria brassicae* and *Fusarium solani.*	Khan et al. (2020)
Dental: active against oral bacteria and oral candida infections, with potential for use in mouth/dental infections, ingredient for mouthwashes etc.	Sharma et al. (2009); Himratul-Aznita et al. (2016)
Anti-ulcer activity: prevent ulceration leading to stomach cancer	Gundala & Aneja (2014)
Immunomodulatory, anti-inflammatory (analogues demonstrate potent activity): potential for treating arthritis and gout (xanthine-oxidase inhibition)	Murata et al. (2009); Min et al. (2009); Pandey et al. (2010); Gundala & Aneja (2014);

	Nishiwaki et al. (2018)
Anti-arthritic: contribute to activity of *Piper kadsura* as an anti-inflammatory, antioxidant and anti-arthritis medicine	Huang et al. (2021b)
Neuroprotective and cerebrovascular system: protective against memory loss; anti-inflammatory activity, acetylcholinesterase inhibition	Pandey & Bani (2010)
Metabolic disorders: anti-obesity potential: inhibition pancreatic lipase (source: *Eugenia polyantha*)	Kato et al. (2013)
Cardiovascular disorders: aantithrombotic potential (anti-platelet aggregation)	Chang et al. (2007); Chen et al. (2013a)
Bone support: osteoprotective against steroid-induced bone loss; anti-osteoporosis; promote bone growth (osteogenesis: *Piper betle* leaf extract)	Mishra et al. (2021)
Anticancer: antimutagenic, shows activity in leukaemia, oral, skin, stomach, pancreatic, colon, breast and prostate cancer; analogues show antiproliferative and antileukaemic activity; can promote sensitivity of leukaemia cells to chemotherapy treatment	Bhide et al. (1991); Chen et al. (2000); Chang et al. (2002); Bhattacharya et al. (2005); Rai et al. (2011); Biswas et al. (2012); Chakraborty et al. (2012); Maity et al. (2012); Paranjpe et al. (2013); Yadav et al. (2014); Guha Majumdar & Subramanian (2019); Paul et al. (2019); Hemamalini et al. (2020); Looi et al. (2020); Rajedadram et al. (2021)
Anticancer (brain and CNS): active against glioma cells; synergistic with gamma-tocotrienol	Abdul Rahman et al. (2014 & 2019)
Anticancer (Betel leaf): *Piper betle* leaf (rich source of hydroxychavicol: 26%) antimutagenic, chemoprotective and inhibition of prostate and oral cancer cells	Gundala & Aneja (2014); Singh et al. (2018); Chang et al. (2019)
Radioprotective: synergistic with chavibetol, also immunomodulatory	Gundala & Aneja (2014)
Anticancer (synergist): synergistic with curcumin against leukaemia cells (enhanced apoptosis); synergistic with buthionine sulfoximine	Chowdhury et al. (2013); Chaudhuri et al. (2014)
Allylpyrocatechol	
Pharmacological properties (general): significant antioxidant and cytoprotective; anti-inflammatory, antimicrobial	
Bioavailability: low water solubility with development of strategies to enhance bioavailability	Okonogi et al. (2020 & 2021)
Antiarthritic: potential for rheumatoid arthritis, inhibition of bone and cartilage damage; also potential	De et al. (2017 & 2018)

for combination with anti-arthritic drugs e.g. methotrexate to prevent drug side effects such as liver toxicity	
Blood chemistry: anti-haemolysis	Iyer et al. (2013)
Antibacterial: antibiofilm; significant antibacterial against oral (dental) pathogens *Streptococcus sanguinis S. intermedius, S. mutans*, *Candida albicans* (source: *Piper betle*); bioavailability enhancement strategies (nanoemulsification, polymeric micelles) for antimicrobial oral products; active against *S. aureus*; active against oral bacteria (prevent halitosis)	Ramji et al. (2002); Hussain et al. (2016); Kurnia et al. (2020); Okonogi et al. (2020 & 2021); Phumat et al. (2020)
Gastrointestinal function: antioxidant, anti-inflammatory, anti-ulcer	Yadav et al. (2013)
Thyroid function: benefits for thyrotoxicosis	Panda et al. (2019)
Radioprotective: antioxidant cellular protective properties	Rathee et al. (2006); Mula et al. (2008)
4-nerolidylcatechol (4NC; also found spelt nerolidylcathecol)	
Pharmacological properties:	
Anti-inflammatory, antioxidant, antiulcerogenic, analgesic	Mendanha da Cunha et al. (2013)
Antimicrobial: potent antifungal activity (source: *Piper umbellatum*)	Tabopda et al. (2008); Roersch (2010)
Skin fungi: antidermatophyte activity; nanoparticles designed for enhanced activity against *Microsporum canis* (source: *Piper umbellatum*)	Freitas et al. (2020); Greatti et al. (2020)
Antiparasitic: antiplasmodial, antimalarial (source: *Piper betle*, traditional use as antimalarial remedy)	Pinto et al. (2009); Al-Adhroey et al. (2010); Rocha e Silva et al. (2011 & 2015); Tamura et al. (2020)
Radioprotective: antioxidant and protective against UVB skin damage	Fernandes et al. (2013)
Anticancer: significant antioxidant activity, induce apoptosis; active against various cancer cell lines, particularly prostate cancer, anti-melanoma, anti-leukaemia; analogy under investigation for development of anticancer drugs	Desmarchelier et al. (1997); Mongelli et al. (1999); Sacoman et al. (2008); Brohem et al. (2012); Mendanha da Cunha et al. (2013); Lopes et al. (2013); Cortez et al. (2015); Benfica et al. (2017); Alves-Fernandes et al. (2019 & 2020)
Chemoprotective: antigenotoxic, protective effect against toxicity of cyclophosphamide	Valadares et al. (2007)

(immunosuppressive anticancer drug)	
Antivenom, antitoxic: inhibition of snake venom toxicity	Nunez et al. (2005)
Insecticidal: mosquito larvicide	Mongelli et al. (2002)
Diterpenes	
Phytol: sourced from chlorophyll and can be metabolised to phytanic acid (which, in turn, can form pristanic acid); which can occur in ruminants but not in human metabolism	Roca-Saavedra et al. (2017)
Bioavailability: phytol is a highly hydrophobic compound that is poorly bioavailable in the body. The development biocompatible/biodegradable nanocarrier drug delivery systems aim to solve the problem.	Lima (2020)
Pharmacy and biotechnology: phytol has been used as a precursor for the manufacture of synthetic forms of vitamin E and vitamin K1; production of adjuvants for use in vaccine formulations; used in production of fertiliser supplements and gasoline	Lim et al. (2006); Islam et al. (2015); Eraky et al. (2016)
Antimicrobial: substantial antifungal, antibacterial activity; anti-biofilm activity (*Piper betle*); potential for combination therapy with antimicrobial drugs e.g. cefotaxime; derivatives show anti-mycobacterial potential and potential for use in overcoming drug-resistance	Pejin et al. (2014); Upadhyay et al. (2014); Islam et al. (2015); Lee et al. (2016b); Srinivasan et al. (2017); Ramanathan et al. (2018); Islam et al. (2018)
Anti-Candida: broad-spectrum anti-candida activity (against *C. albicans, C. parapsilosis, C. tropicalis, C. krusei*); development of phytol-loaded nanoparticles to solve bioavailability problem of insolubility in water; good potential for treatment of vaginal candidiasis	Lima et al. (2020)
Aquaculture: useful antimicrobial and immune stimulant for ornamental (goldfish) fish farming	Saha & Bandyopadhyay (2020)
Anti-inflammatory, antioxidant, analgesic, antispasmodic	Srinivasan et al. (2017); Islam et al. (2018)
Immunomodulatory: anti-allergic; immunostimulant and supportive (*Peperomia pellucida*)	Eraky et al. (2016); Lee et al. (2016a); Islam et al. (2018)
Antipyretic	Islam (2019)
Metabolic function: antidiabetic, lipid lowering and anti-obesity potential	Islam et al. (2015); An et al. (2018); Islam et al. (2018)
Hair care: facilitate hair growth and prevent hair loss; antidandruff	Prabavathy et al. (2014); Islam et al. (2015)
Cosmetic: skin tonic; skin whitening (anti-melanogenesis) properties; treatment of hyperpigmentation disorders	Mahalingam et al. (2003); Ko & Cho (2018)
Nervous system: anxiolytic, sedative; anticonvulsant;	Costa et al. (2014); Pereira

antidepressant; anti-cholinesterase and experimental anti-Alzheimer's potential	Costa et al. (2014); Sathya et al. (2017 & 2020); Islam et al. (2018)
Cerebrovascular: anti-inflammatory benefits for encephalomyelitis with potential use in multiple sclerosis	Blum et al. (2018)
Anticancer: cytotoxic, antitumour, antimutagenic, anti-teratogenic, antibiotic-chemotherapeutic; antileukaemic; active against brain tumour (glioblastoma); breast, lung and liver cancer cells	Islam et al. (2015); Kim et al. (2015); Gliszczynska et al. (2017); Thakor et al. (2017); Alencar et al. (2018); Facchini et al. (2018); Itoh et al. (2018); Sakthivel et al. (2018); de Alencar et al. (2019); Islam et al. (2018)
Anticancer (also metabolites phytanic acid and pristanic acid): chemopreventive against cancer development	Bobe et al. (2020)
Skin cancer: synergistic effect with β-caryophyllene and aromadendrene oxide 2 (*Paramburus missonis* essential oil)	Pavithra et al. (2018)
Phytol derivatives (phytol-derived γ-butyrolactones): cytotoxic activity against cancer cell lines ie. leukaemia, lung and colon carcinoma (including doxorubicin-resistant cells)	Gliszczynska et al. (2021)
Note: γ-Butyrolactones: these aromatics have strong antitumor, antibiotic, antifungal and antiviral properties. They influence food fragrances and taste (fruits, vegetables and cheese), as well as alcoholic drinks such as wine, sherry, and whisky. They also play a significant role in the world of insects (sex attractant pheromones and good antifeedant activity).	Gliszczynska et al. (2021)
Antiparasitic: antischistosomal properties against *Schistosoma* worms; anti-trypanosoma	De Moraes et al. (2014); Islam et al. (2015); Eraky et al. (2016); Islam et al. (2018)
Anti-parasitic (crop pest; root-knot nematode): phytol accumulation (a precursor of tocopherols) in nematode-parasitized roots enhanced resistance to pest damage, possibly via tocopherol (vitamin E) production	Fujimoto et.al. (2021)
Insecticidal: active against white fly eggs and nymphs (*Petiveria alliaceae* ethanolic extracts).	Cruz-Estrada et al. (2013)
Insecticidal: vermin repellent; mosquito repellent and	Kim et al. (2012); Methew &

larvicide	Thoppil (2011); Cantrell et al. (2016)
Insecticidal: contribute to strong activity of *Cleome serrata* against sweet potato weevil and *Jatropha curcas* against houseflies	McNeil et al. (2012); Chauhan et al. (2015)

Resources

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