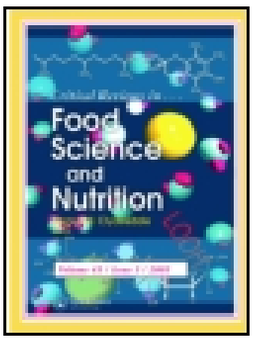

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Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Ye Peng, Renyou Gan, Huabin Li, Mingxuan Yang, David Julian McClements, Ruichang Gao & Quancai Sun (2020): Absorption, metabolism, and bioactivity of vitexin: recent advances in understanding the efficacy of an important nutraceutical, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2020.1753165

To link to this article: https://doi.org/10.1080/10408398.2020.1753165

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https://doi.org/10.1080/10408398.2020.1753165

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REVIEW

Absorption, metabolism, and bioactivity of vitexin: recent advances in understanding the efficacy of an important nutraceutical

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ABSTRACT

vitexin, an apigenin-8-C-glucoside, is widely present in numerous edible and medicinal plants. vitexin possesses a variety of bioactive properties, including antioxidation, anti-inflammation, anti-cancer, neuron-protection, and cardio-protection. Other beneficial health effects, such as fat reduction, glucose metabolism, and hepatoprotection, have also been reported in recent studies. This review briefly discusses the absorption and metabolism of vitexin, as well as its influence on gut microbiota. Recent advances in understanding the pharmacological and biological effects of vitexin are then reviewed. Improved knowledge of the absorption, metabolism, bioactivity, and molecular targets of vitexin is crucial for the better utilization of this emerging nutraceutical as a chemopreventive and chemotherapeutic agent.

KEYWORDS

flavonoid C-glycosides; food components; gut microbiota; protective effects; vitexin

Introduction

Naturally-occurring flavonoids, which are present in numerous plant species, have been reported to exhibit a range of health benefits, such as the ability to prevent chronic conditions like obesity, diabetes, and cardiovascular diseases (Cao et al. 2011; Choi et al. 2014; Xiao et al. 2016). Almost all flavonoids are glycosides that have sugar groups bound to a hydroxyl (*O*-glycosides) or carbon (*C*-glycosides) group on an aglycone. Compared to flavonoid *O*-glycosides, flavonoid *C*-glycosides exhibit more diverse biological activities since they are more stable and resistant to acidic, alkaline, and enzymatic hydrolysis (Xiao et al. 2016). Flavonoid *C*-glycosides are present in various plants, including, but not limited to, mung bean (Cao et al. 2011; Luo et al. 2016), beetroot (Ninfali et al. 2017), hawthorn (Liang et al. 2007), otter flowers (Ngwoke et al. 2017), passion flowers (Colomeu et al. 2017; Shuayprom et al. 2016), bamboo (Yang et al. 2017), and gaillardia (Moharram et al. 2017). These plants have been historically consumed as food and used as medicine in Asia for 3000 years (Ganesan and Xu 2018; Kumar et al. 2012). Today they are still widely used for detoxification, the treatment of digestive disorders, skin diseases, heart stroke, inflammation, and various other dysfunctions (Ganesan and Xu 2018; Kumar et al. 2012).

In the past two decades, vitexin has received considerable attention from researchers because of its diverse biological activities, such as antioxidant, anti-inflammatory, anti-cancer, anti-microbial, neuron-protective, and cardio-protective effects (Al-Jeboory and Dizaye 2006; An et al. 2012; Borghi et al. 2013; Choi et al. 2006; Je et al. 2014; Krcatovic et al. 2008; Min et al. 2015). The effects of vitexin are related to multiple systems, including the immune, nervous, respiratory, heart and vascular, and endocrine systems (Al-Jeboory and Dizaye 2006; An et al. 2012; Borghi et al. 2013; Choi et al. 2006; Je et al. 2014; Krcatovic et al. 2008; Min et al. 2015). More recently, vitexin has been revealed to exhibit several novel beneficial effects related to fat metabolism, glucose homeostasis, and hepatoprotection (Duncan et al. 2017; Peng et al. 2019d; Wu et al. 2017; Yang et al. 2017). To better understand the potential of this compound as a nutraceutical ingredient, we collected and critically reviewed recent literature (2016 to the present) based on Web of Science Core Collection and PubMed searches. In the current review, we first briefly summarize the absorption and metabolism of vitexin, then discuss its influence on the gut microbiota, and finally highlight the latest observations about the bioactivities of vitexin and related molecular mechanisms.

Absorption and metabolism of vitexin

Within the upper gastrointestinal tract, *C*-glycoside vitexin is only absorbed to a relatively small extent (4.9-5.8%) and is largely resistant to molecular transformations (Bai et al. 2017; Gao et al. 2016; Wang et al. 2012). Consequently, the

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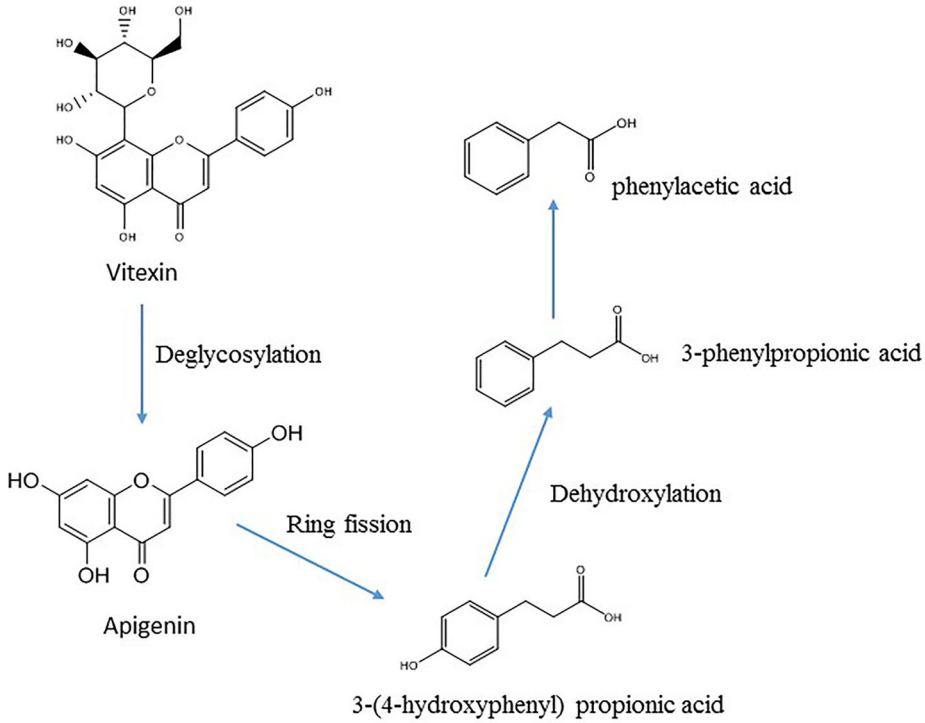

Figure 1. Possible metabolic pathways of vitexin by gut microbiota in the intestine (Hein et al. 2008). Vitexin transforms to the aglycone structure and the glucose moiety is cleaved by the bacteria. The aglycone structure was then degraded to small phenolic acids including 3-(4-hydroxyphenyl) propionic acid, phenylacetic acid, and 3-phenylpropionic acid, through ring fission, and dehydroxylation reactions.

crucial metabolic transformation of this flavonoid glycoside takes place in the colon, where the gut microbiota play significant roles in degrading it (Hein et al. 2008). The transformation of *C*-glucosides is dependent on the presence of specific bacteria for key degradation steps, such as the cleavage of the *C*-*C* bond (Liao et al. 2017). For example, the intestinal *Lachnospiraceae* strain is able to deglycosylate the *C*-glycoside vitexin, while *Eubacterium cellulosolvens* cannot (Hein et al. 2008). In fermentation with a human fecal sample, the degradation of vitexin is likely to take place via the formation of the aglycone structure, with the glucose moiety primarily cleaved by the bacteria. The aglycone structure is further degraded to small phenolic acids – including 3-(4-hydroxyphenyl) propionic acid, phenylacetic acid, and 3-phenylpropionic acid – through ring fission and dehydroxylation reactions (Figure 1) (Braune and Blaut 2012; Liao et al. 2017). In future, it will be important to carry out more studies to identify the key bacteria strains responsible for vitexin degradation.

The microbial transformation products of vitexin may exert considerable effects on gut microbiota, which could alter the health of the host. Some studies have reported an influence of phenolic compounds on microbiota composition (Etxeberria et al. 2013). Other studies, however, have shown that a prebiotic effect on the microbiota was not achievable when vitexin was consumed in typical dietary concentrations (~20 mg/day), even though it could be metabolized by the human gut microorganisms (Hein et al. 2008). Nevertheless, higher concentrations of vitexin, or vitexin interactions with other food components, might influence microbiota composition (Hein et al. 2008) (Figure 2).

The first-pass metabolism effects of vitexin after exposure to the liver, stomach, and intestine have been reported to be 5.2%, 31.3%, and 94.1%, respectively (Xue et al. 2014). Since the liver is important for the metabolization of many compounds, the relatively low first-pass effect of vitexin in this organ would be expected to result in a low in vivo bioavailability of vitexin. Two recent studies, however, suggested that vitexin-soybean phospholipid nanocomplexes could improve the bioavailability of vitexin in vitro (Gu et al. 2017; Luo et al. 2017) (Figure 3).

Biological effects of vitexin

As mentioned earlier, the major reported beneficial activities of vitexin include antioxidant, neuroprotective, cardio-protective, anti-inflammatory, anti-cancer, fat and glucose metabolism, antivirus, and antibacterial effects. Vitexin has also been reported to have some other potential health benefits, such as nicotine cessation, hair regeneration, and nociception (Bedell et al. 2019; Luo et al. 2018a; Zhu et al. 2016). The biological properties and related molecular targets of vitexin from in vitro and in vivo studies are summarized in Tables 1 and 2.

Antioxidant activity of vitexin

Oxidative stress is induced by the excessive generation of reactive oxygen species (ROS), which causes high toxicity and physical damage to cells (Peng, Sun, and Park 2019b). Long-term oxidative stress accelerates aging-related functional losses and further contributes to many chronic

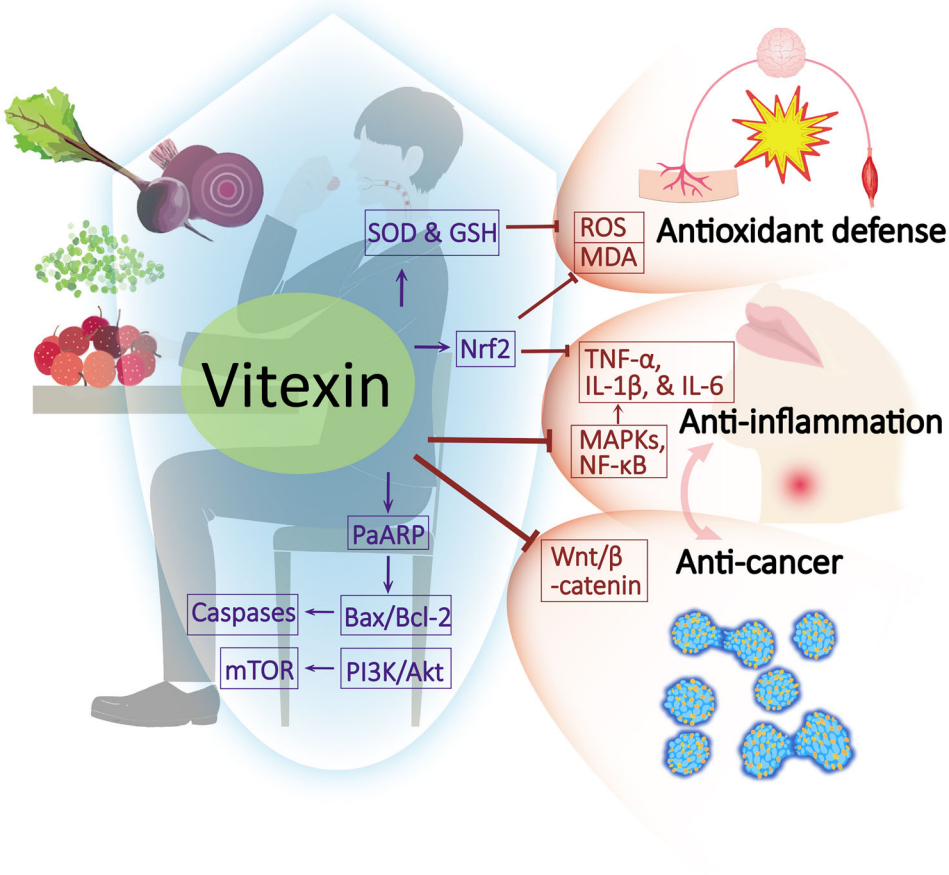

Figure 2. The main pathways involved in vitexin associated-beneficial activities including antioxidant defense, anti-inflammation, and anti-cancer. SOD, superoxide dismutase; GSH, glutathione; ROS, reactive oxygen species; MDA, malondialdehyde; Nrf2, nuclear factor erythroid 2-related factor 2; TNF-α, tumor necrosis factor α; IL-1β, interleukin 1β; IL-6, interleukin 6; MAPKs, mitogen-activated protein kinases; NF-κB, nuclear factor κB; PARP, poly(ADP-ribose) polymerase; Bax, B-cell lymphoma 2-associated X; Bcl-2, B-cell lymphoma 2; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin;- promotion;- inhibition.

disorders (Papalia, Barreca, and Panuccio 2017; Peng et al. 2019a; Xiao et al. 2016). Indeed, many prooxidants, such as H_2O_2, glutamate, and ox-LDL, have been shown to induce cellular dysfunctions and diseases (Lu et al. 2018; Malar et al. 2018a; Wu et al. 2017; Zhu et al. 2016). Vitexin has been shown to be a potent oxygen radical scavenger that generates a strong antioxidant defense (An et al. 2016). Recent studies have focused on the beneficial effects of vitexin on oxidative stress-induced chronic disorders, such as neurodegeneration, myocardial injury, liver injury, and insulin resistance, both in vitro and in vivo (Chen et al. 2016; Malar et al. 2018a; Malar et al. 2018b; Zhang et al. 2017b). In general, vitexin increases cell viability and/or alleviates tissue damage by enhancing their resistance against oxidative stress inducers. The ability to reduce intracellular ROS and malondialdehyde (MDA) levels has been found to be key to the protective effects of vitexin (Chen et al. 2016; Malar et al. 2018a; Malar et al. 2018b; Zhang et al. 2017b). The reduction of ROS and MDA by vitexin has recently been attributed to an increase of antioxidant enzyme activities (such as superoxide dismutase, heme oxygenase, NAD(P)H quinone oxidoreductase 1, and glutathione), as well as to the upregulation of antioxidant response proteins (such as nuclear factor erythroid 2-related factor 2 (Nrf2) and AMP-activated protein kinase) (AMPK) (Malar et al. 2018a; Malar et al. 2018b; Zhang et al. 2017b). In summary, vitexin can be considered as a potent antioxidant that helps prevent oxidative-stress-induced disorders.

Anti-inflammatory activity of vitexin

The anti-inflammatory activity of vitexin has gained increasing interest in recent in vitro and in vivo studies (Jiang et al. 2019; Kim, Nam, et al. 2018; Lee, Hossaine, and Park 2016; Lu et al. 2018; Rosa et al. 2016; Schuster et al. 2016; Venturini et al. 2018; Wang et al. 2019; Yang et al. 2017). At the cell culture level, vitexin has been shown to ameliorate lipopolysaccharide (LPS)-induced inflammatory responses and injury in RAW 264.7 mouse macrophage and INS-1 rat insulin secreting cells by reducing the release of NO and prostaglandin E2 (PGE2) (Lee, Hossaine, and Park 2016; Rosa et al. 2016; Schuster et al. 2016; Wang et al. 2017; Yang et al. 2017). In these processes, vitexin downregulated the release of inflammatory cytokines (TNF-α, IL-1β, and IL-6) and enzymes (iNOS, MMP-1, MMP-3, and MMP-13) (Kim, Oh, et al. 2018; Lu et al. 2018; Nikfarjam et al. 2017; Xie et al. 2018; Yang et al. 2019). The downregulation of these pro-inflammatory factors by vitexin might be

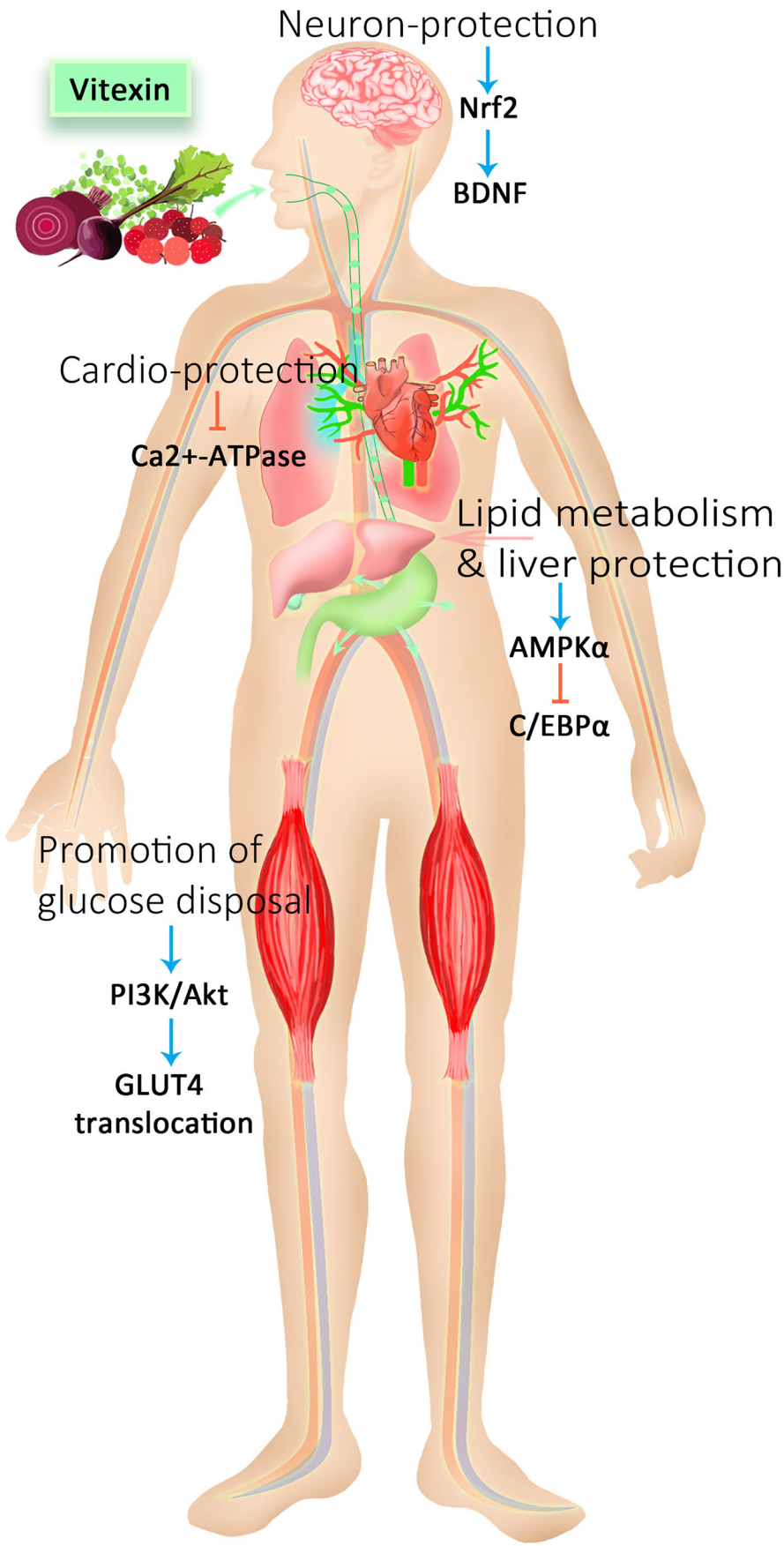

Figure 3. The key molecular biomarkers involved in the protective effects of vitexin on neuron, cardiovascular, and liver and its regulation on fat and glucose metabolism. Nrf2, nuclear factor erythroid 2-related factor 2; BDNF, brain-derived neurotrophic factor; AMPKα, AMP-activated protein kinase α; C/EBPα, CCAAT/enhancer binding protein α; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; GLUT4, glucose transporter type 4;- promotion;- inhibition.

Table 1. In vitro effects of vitexin in the treatment of various disorders.

Bioactive effects	Models	Dose (μM)	Duration (hrs)	Effects	Suggested mechanisms	References
Neuron-protection	Human PC12 pheochromocytoma neurosecretory cells	10- 100	24	↑ cell viability; ↓ neuroinflammation	↓ TNF-α & IL-6; ↑ SOD & GSH; ↓ ROS; ↓ Caspase-3; ↓ BACE, cytosolic calcium excitotoxicity, NR2B, & TRPV1	(Chen et al. 2016)
	Primary cortical neurons (Oxygen glucose deprivation model OGD)	10	2.5	↑ neuronal injury; ↑cell viability; ↓ lactate dehydrogenase	↓ cytosolic calcium excitotoxicity; ↑ Bcl-2/Bax; ↓ Caspase-3	(Min et al. 2017)
	SH-SY5Y human neuroblastoma	10-40	2	↑cell viability; ↓ cell apoptosis	↑ Bcl-2/Bax; ↓ Caspase 3; ↑ PI3K & Akt	(Hu, Li, and Wang 2018)
	Rat brain microvascular endothelial cells (RBMECs)	10^5	24	↓ F-actin stress fiber formation	↓ NKCC1; ↑ ZO-1	(Luo et al. 2018b)
	H4 human neuroglioma	100	24	↑cell viability	↑ SOD & GPx; ↓ Caspase-3 & Bax; ↑ VEGF; ↓ p38	(Lyu et al. 2018)
	Neuro-2a neuroblastoma (Glutamate)	50	26	↑ cell viability; ↓ cell shrinkage; ↓ macromolecular damage; ↓ loss of mitochondrial membrane potential; ↓ ROS & NO	↑ Nrf-2, HO-1, & NQO-1; ↓ Calpain & NMDA receptor; ↓ cyclophilin-D; ↑ BiP; ↓ GADD153	(Malar et al. 2018a)
	Neuro-2a neuroblastoma (Amyloid beta (Aβ))	50	26	↑ cell viability; ↓ lipid peroxidation, protein oxidation, & loss of mitochondrial membrane potential	↑ Nrf-2 & HO-1; ↑ LXR-α, APOE, & ABCA-1; ↓ cyclophilin-D; ↓ MDA; ↑ BiP; ↓ GADD153; ↑ Bcl-2/Bax; ↓ Caspase-3	(Malar et al. 2018b)
	Human brain microvascular endothelial cells (cerebral ischemia reperfusion I/R injury)	10^{-3}	24	↑ cell viability; ↓ lipid peroxidation & loss of mitochondrial membrane potential; ↓ NO & $ONOO^-$	↑ eNOS; ↓ iNOS; ↑ Akt ↓ LDH; ↓ Caspase-3; ↓ TNF-α, IL-6, and IL-1β; ↑ Claudin-5 & ZO-1; ↓ MMP-2 & MMP-9	(Cui et al. 2019)
Cardio-protection	Human umbilical vein endothelial cells (ox-LDL)	20	24	↑ cell viability; ↓ cell inflammation; ↓ endothelial injury; ↓ ROS; ↑ cell autophygy	↑ Bcl-2/Bax; ↓ Caspase- 3; ↓ TNF-α, IL-1β, & IL-6; ↑ SOD; ↓ MDA; ↓ E-selectin, VCAM1, & ICAM1; ↑ AMPKα; ↓ mTOR; ↑ Beclin1 & LC3-II; ↓ p62	(Zhang et al. 2017b)
	H9c2 rat cardiomyocytes	100-200	4	↓ cell apoptosis; ↓ cell autophagy	↓ LDH, CK, & MDA; ↑ Bcl-2/Bax; ↓ Caspase-3; ↑ SOD; ↓ Beclin1; ↑ p62; ↑ Akt; ↑ mTOR	(Tang, Yang, and Zhang 2017)
	Human induced pluripotent stem cells- derived cardiomyocytes (isoproterenol)	7-23	24	↓ arrhythmic; ↓ irregular/immature field potentials; ↓ abnormal cell beating rate	N/A	(Pahlavan et al. 2018)
Inflammation responses (include anti-allergic effect)	RAW 264.7 mouse macrophage (LPS)	15	18	↑ depigmentation; ↓ cell inflammation; ↓ NO	↓ iNOS; ↓ NF-κB	(Lee, Hossaine, and Park 2016)
	RAW 264.7 mouse macrophage (LPS)	100	28	↓ cell inflammation	↓ IL-6; ↓ iNOS	(Schuster et al. 2016)
	RAW 264.7 mouse macrophage (LPS)	25-100	26	↓ cell inflammation; ↓ (reduce the release of) NO & PGE2	↓ TNF-α & IL-1β; ↑ IL-10; ↓ p38, ERK1/2, & JNK (MAPKs)	(Rosa et al. 2016)
	Human peripheral blood neutrophils	25	5-7	↓ cell inflammation; ↓ NO	↓ TNF-α; ↓ MPO	(Nikfarjam et al. 2017)
	INS-1 rat insulin secreting cells (LPS)	50	24	↓ cell injury & apoptosis	↓ HMGB1↓ p38; ↓ Caspase-3; ↑ Bcl-2	(Wang et al. 2017)
	RAW 264.7 mouse macrophage (LPS)	25-50	1	↓ cell inflammation; ↓ NO	↓ iNOS; ↓ p38 & JNK	(Yang et al. 2017)
	Human corneal epithelial cells (hyperosmolar stress, HOS)	10-25	24	↑ cell viability; ↓ cell inflammation	↓ TNF-α, IL-1β, & IL-6; ↓ p38, ERK1/2, & JNK (MAPKs)	(Kim, Oh, et al. 2018)
	Jurkat CD4+ T lymphocytes, HEK293T human T-lymphoblastoid, & RBL-2H3 rat mast cells	30-100	3	↓ T-cell proliferation; ↓ mast cell degranulation	↓ calcium release-activated calcium (CRAC) currents; ↓ β-hexosaminidase	(Kim, Nam, et al. 2018)
	RAW 264.7 mouse macrophage (LPS)	50	1	↓ cell inflammation;	↑ Nrf2 & HO-1; ↓ TNF-α & IL-1β	(Lu et al. 2018)
	Rat osteoarthritis chondrocytes (IL-1β)	N/A	N/A	↓ cell inflammation; ↓ ER stress	↓ BiP & PDI; ↓ CHOP; ↓ NF- κB; ↓ TNF-α & IL-6	(Xie et al. 2018)
	Human osteoarthritis chondrocytes (IL-1β)	10-50	24	↑ cell viability; ↓ NO & PGE_2	↓ IL-6 & TNF-α, ↓ MMP-1, MMP-3, & MMP-13; ↓ HIF-1α	(Yang et al. 2019)
	Mouse hematopoietic bone marrow monocytic/ macrophage (BMM) cells (receptor activator of nuclear factor-κB ligand (RANKL))	25-50	48	↓ osteoclast formation; ↓ preosteoclast fusion; ↓ F-actin ring formation; ↓ bone resorption	↓ c-Fos, Nfatc1, Dcstamp, Acp5, & Ctsk; ↓ p38 & ERK1/2 (MAPKs)	(Jiang et al. 2019)
	3T3-L1 mouse preadipocytes	25-50	48	↓ adipocyte differentiation; ↓ TG	↓ FAS, ACC, & PPARγ	(Yang et al. 2017)

(*continued*)

Table 1. Continued.

Bioactive effects	Models	Dose (μM)	Duration (hrs)	Effects	Suggested mechanisms	References
Lipid metabolism & liver function						
	HepG2 human hepatoma & Hepa1–6 mouse hepatoma (H_2O_2)	50	4	↓ oxidative stress; ↑ cell viability; ↓ ROS	N/A	(Wu et al. 2017)
	3T3-L1 mouse preadipocytes	50	192	↓ adipocyte differentiation; ↓ TG	↑ AMPKα; ↓ C/EBPα & FAS	(Peng et al. 2019d)
Glucose metabolism	HepG2 human hepatoma (high glucose)	50	60	↓ hyperglycemia; ↓ oxidative stress; ↓ ROS & O_2^-	↓ JNK & p38; ↑ Nrf2	(Duncan et al. 2017)
Anti-cancer	MCF-7 human breast adenocarcinoma	1.5-3	48	↓ cell proliferation; ↑ cell apoptosis;	↓ Bcl-2/Bax; ↑ Caspase-7, −8, & −9	(Czemplik et al. 2016)
	SK-Hep1 human hepatoma & Hepa1-6 mouse hepatoma	50-150	24	↑ cell apoptosis; ↓ autophagy	↓ LC3-II; ↓ JNK & Erk1/2; ↓ Bcl-2; ↑ Caspase-3 & cleave Caspase-3	(He et al. 2016)
	T24 human bladder carcinoma	6	24 & 48	↑ cell apoptosis; ↓ cell proliferation	↑ Bax; ↓ survivin (BIRC5); ↓ β-catenin (CTNNB1); ↑ Caspase-8 & −3	(Scarpa et al. 2016)
	HeLa human cervical carcinoma	50-100	24	↑ cell apoptosis	↓ Bcl-2/Bax; ↑ Caspase-3	(Girish, Kumar, and Prasada Rao 2016)
	HCT-116 human colorectal carcinoma	10-50	24	↓ cell proliferation; ↑ ROS-induced autophagy	↑ JNK; ↓ HSF-1 transactivation; ↓ Hsp90 & Hsp27; ↑ Beclin-1, LC3-I, & LC3-II; ↑ ApoL1	(Bhardwaj et al. 2017)
	HCT-116^{DR} human colorectal carcinoma	10-50	24	↑ cell apoptosis; ↓ cell viability; ↓ autophagy	↓ MDR-1; ↑ Caspase-9 & −3; ↑ BID & Bax; ↓ Atg5 & Beclin-1; ↓ LC3-I, & LC3-II	(Bhardwaj et al. 2018)
	HCT-116 & LoVo human colorectal carcinoma	2.5-10	3-24	↑ cell apoptosis; ↓ cell viability	↑ p53 & PUMA; ↓ Akt; ↑ Bax mitochondrial translocation & Caspase-3	(Chen et al. 2018)
	A375, Sk-Mel-5, & Sk-Mel-28 human malignant melanoma	10-20	24-72	↑ cell apoptosis & G2/M cell cycle arrest; ↓ cell viability; ↓ colony number; ↑ ROS	↑ PARP; ↓ Bcl-2/Bax; ↑ p53 & p21; ↑ ATM, ATR, & CHK2	(Liu et al. 2018)
	LN-18 human glioblastoma	20-80	24-48	↑ cell apoptosis & G2/M cell cycle arrest; ↓ cell viability	↑ PARP; ↓ Akt & mTOR	(Zhang et al. 2018)
	A549 human non-small cell lung carcinoma	20-40	48	↓ cell viability; ↑ cell apoptosis; ↑ LDH release; ↓ mitochondrial membrane potential & mitochondrial cytochrome c	↓ Bcl-2/Bax; ↑ cleave Caspase-3; ↓ PI3K, Akt & mTOR	(Liu et al. 2019)
Anti-virus	NBL-2 dog kidney epithelial cells	N/A	36	↑ infected cell viability; ↓ H1N1 influenza virus replication	N/A	(Ding and Liu 2019)
Others	Human dermal papilla cells	0.1	24	↑ cell proliferation; ↑ colony growth; ↑ hair shaft elongation	↑ LEF1 & Wnt5a; ↓ Dkk1; ↑ β -catenin; ↓ AXIN2	(Luo et al. 2018a)

↑ - increase; ↓ - decrease; N/A, not available.

Acronymes: ABCA-1, ATP-binding cassette transporter-1; ACC, acetyl-CoA carboxylase; AChE, acetylcholinesterase; ACP5, acid phosphatase 5; Akt, protein kinase B; ALP, alkaline phosphatase; AMPKα, AMP-activated protein kinase α; APOE, apolipoprotein E; ApoL1, apolipoprotein L1; Atg5, autophagy protein 5; ATM, ataxia-telangiectasia mutated, ATR, ATM-and Rad3-related; AXIN2, axis inhibition protein 2; BACE, β-secretase 1; Bax, B-cell lymphoma 2-associated X; Bcl-2, B-cell lymphoma 2; BID, BH3-interacting domain death agonist; BiP, binding immunoglobulin protein; C/EBPα, CCAAT/enhancer binding protein α; c-Fos, activator protein 1; CHK2, Checkpoint kinase 2; CHOP, CCAAT-enhancer-binding protein homologous protein; CK, creatine kinase; CRAC, Ca^{2+} entry through store-operated Ca^{2+} release-activated Ca^{2+} (Ca^{2+} channel); Ctsk, Cathepsin K; Dcstamp, dendrocyte expressed seven transmembrane protein; Dkk1, dickkopf-1; eNOS, endothelial nitric oxide synthase; E-selectin, CD62 antigen-like family member E; ERK1/2, extracellular signal-regulated kinase 1/2; FAS, fatty acid synthase; GADD153, growth arrest DNA damage-inducible gene 153; GPx, glutathione peroxidase; GSH, glutathione; HIF-1α, hypoxia-inducible factor 1α; HMGB1, high mobility group protein B1; HO-1, heme oxygenase; HSF-1, heat shock factor 1; Hsp27, heat shock protein 27; Hsp90, heat shock protein 90; ICAM1, intercellular adhesion molecule 1; IL-1β, interleukin 1β; IL-6, interleukin 6; IL-10, interleukin 10; iNOS, inducible nitric oxide synthase; LC3, microtubule-associated protein 1 A/1B-light chain 3; LC3-I, cytosolic LC3; LC3-II, LC3-phosphatidylethanolamine conjugate; LDH, lactate dehydrogenase; LEF1, lymphoid enhancer-binding factor 1; LXR-α, liver X receptor-α; MAP1LC3B, microtubule-associated proteins 1 A/1B light chain 3B; MAPKs, mitogen-activated protein kinases; MDA, malondialdehyde; MDR-1, multi-drug resistance 1; MMPs, matrix metalloproteinases; MPO, myeloperoxidase; mTOR, mammalian target of rapamycin; Nfatc1, nuclear factor of activated T-cells 1; NF-κB, nuclear factor κB; NKCC1, Na^+-K^+-Cl^- co-transporter1; NMDAR, N-methyl-D-aspartate receptor; NQO-1, NAD(P)H quinone oxidoreductase 1; NR2B, N-methyl D-aspartate receptor subtype 2B; Nrf2, nuclear factor erythroid 2-related factor 2; ox-LDL, oxidized low-density lipoprotein; p21, cyclin-dependent kinase inhibitor 1; p38, mitogen-activated protein kinase; p53, tumor suppressor p53; p62, sequestosome 1; PARP, poly(ADP-ribose) polymerase; PI3K, phosphoinositide 3-kinase; PPARγ, peroxisome proliferatoractivated receptor γ; PUMA, p53 upregulated modulator of apoptosis; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF-α, tumor necrosis factor α; TRPV1, transient receptor potential cation channel subfamily V member 1; VCAM1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; Wnt5a, Wnt family member 5a; ZO-1, tight junction protein-1.

Table 2. In vivo effects of vitexin in the treatment of various disorders.

Bioactive Effects	Species (sex)	Models	Dose (mg/kg/d)	Duration (d)	Effects	Suggested Mechanisms	References
Neuron-protection	Swiss albino mice (M)	Epilepsy seizure (Pilocarpine)	10 p.o.	15	↓ frequency of convulsion; ↓ flexion; ↑ latency period; ↓ hind limb extension phase; ↑ neuron survival; ↓ NO	↑ AChE & DBH; ↓ hippocampus glutamate; ↑ GABA; ↑ SOD, catalase, & GSH; TBARS; ↓ NMDAR & mGluR1	(Aseervatham et al. 2016)
	Sprague – Dawley rats (M)	Retinal damage (Isoflurane)	10 i.p.	30 min	↑ neuron survival	↓ cleaved PARP; ↓ cleaved Caspase 3	(Chen et al. 2016)
	Postnatal day (P9) C57BL/6J mice (M & F)	Right common carotid artery hypoxic-ischemic	60 i.p.	3	↓ hypoxic-ischemic neuronal injury; ↓ brain infarction; ↓ brain atrophy; ↓ neuronal apoptosis	↓ CaMKII; ↓ NF-κB; ↑ Bcl-2/Bax; ↓ Caspase 3	(Min et al. 2017)
	C57BL/6J mice (M)	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) challenges	50 i.p.	15	↑ neurobehavior protection; ↓ bradykinesia	↑ PI3K & Akt; ↑ Bcl-2/Bax; ↓ Caspase 3	(Hu, Li, and Wang 2018)
	Sprague-Dawley rats (M)	Streptozotocin challenges	1 p.o.	56	↑ spatial learning & memory retention; ↑ cortical gyrification; ↓ neuron damage; ↑ glucose metabolism; ↑ neurotransmission	↓ TBARS; ↑ SOD; ↓ GPx; ↑ brain insulin, amylin, & testosterone; ↑ DPA	(Nurdiana et al. 2018)
	Postnatal day (P7) Sprague-Dawley rats (M & F)	Right common carotid artery ligation & hypoxic injury	45 i.p.	1-23	↓ hypoxic-ischemic neuronal injury; ↓ blood-brain barrier damage; ↓ duration and frequence of seizures	↓ NKCC1; ↑ ZO-1; ↓ IL-1β, IL-6, & TNF-α	(Luo et al. 2018b)
	Sprague-Dawley rats (M)	Sevoflurane challenges	50	4	↓ neuronal apoptosis	↓ Caspase-3 & Bax; ↓ MDA; ↑ SOD & GPx; ↑ HIF-1α; ↑ VEGF; ↓ p38	(Lyu et al. 2018)
	Sprague-Dawley rats (M)	Middle cerebral artery occlusion	2 i.p.	1	↓ brain infarction; ↓ neuronal apoptosis; ↓ oxidative damage; ↓ LDH, MDA, & NO	↑ Ki67 & Bcl-2/Bax; ↓ Caspase 3; ↓ TNF-α & IL-6; ↑ IL-10; ↑ mTOR; ↑ PPARγ; ↓ Sequestosome-1; ↓Belclin 1	(Jiang, Dai, and Cui 2018)
	DBA/2 Swiss albino mice & Sprague-Dawley rats (M)	Sleep disturbances challenge	??? 50 *p.o.*	3	↓ sleep disorders; ↑ hippocampal neurogenesis; ↑ memory	↑ BDNF; ↑ doublecortin; ↓ COX-2; ↑ Iba-1; ↑ Mela R1; ↓ Tau protein	(Kim et al. 2019)
Cardio-protection	Sprague-Dawley rats (M)	Myocardial ischemia/reperfusion injury	3-6 *i.p.*	7-14	↓ myocardial damage; ↓ myocardial infarction; ↑ myocardial diastolic function; ↓ myocardial reactive fibrosis; ↑ tension-systaltic aorta	↑ NADPH & SOD; ↓ MDA; ↓ Epac1 & Rap1; ↑ Bcl-2/Bax	(Che et al. 2016)
	Sprague-Dawley rats (M)	Isoproterenol challenge	6 i.p.	7	↑ antioxidant capacity; ↑ myocardial preservation	↓ LDH, CK, & AST; ↑ SOD; ↓ MDA	(Bai et al. 2016)
	Sprague-Dawley rats (M)	Doxorubicin challenge	30 p.o.	28	↓ myocardial injury & inflammation; ↑ antioxidant capacity	↓ LDH & CK; ↓ NF-κB, TNF-α, IL-1β, & IL-6; ↑ SOD; ↓ MDA; ↑ FOXO3; ↓ Caspase 3	(Sun et al. 2016)
	C57BL/6 mice	Myocardial ischemia reperfusion (MI/R) injury	4-6	3 hr	↓ myocardial infarction; ↑ heart beat	↓ LC3-II & Beclin1; ↓ MDA; ↑Akt; ↑ mTOR	(Tang, Yang, and Zhang 2017)
	Wistar albino rats (M)	Aluminum challenge	2 i.p.	84	↓ cardiac necrosis, infarction, & ion levels; ↓ oxidative damage	↓ Ca^{2+}-ATPase; ↓ JNK; ↓ NF-κB; ↓ cytochrome C & Caspase-9; ↓ LDH & CK; ↓ MDA	(Cheng et al. 2017)
	Wistar albino rats (M)	Isoproterenol challenge	1.5 *p.o.*	28	↓ myocardial injury; ↓ oxidative damage & lipid peroxidation; ↓ ER stress induced myocyte apoptosis	↓ LDH & CK; ↑ SOD & CAT; ↓ MDA; ↓ BiP & CHOP; ↓ Mst1 & Yap; ↓ Caspase-9, 7, & 3; ↑ Bcl-2/Bax	(Ashokkumar et al. 2018)
	Sprague-Dawley rats (M)	Streptozotocin challenge	1	42		↓ MDA & GPx; ↑ SOD	(Nurdiana et al. 2017)

(*continued*)

Table 2. Continued.

Bioactive Effects	Species (sex)	Models	Dose (mg/kg/d)	Duration (d)	Effects	Suggested Mechanisms	References
Glucose metabolism					↑ islets regeneration; ↓ blood glucose; ↑ glucose disposal; ↓ insulin resistance; ↓ TG; ↓ pancreas injury		
	Sprague-Dawley rats (M)	LPS challenge	5-10 *i.p.*	7	↓ islet tissue damage; ↓ islet cell apoptosis; ↓ HMGB1	↓ TNF-α; ↓ p38; ↓ Caspase 3; ↑ Bcl-2	(Wang et al. 2017)
	Swiss-Webster mice (M)	Streptozotocin challenge	20-40 *p.o.*	62	↑ reproductive organ weight; ↓ testicular pathological structure damage; ↑ (restore) sperm quality	↑ Testosterone; ↓ GnRH; ↑ LH & FSH	(Li et al. 2019)
Lipid metabolism & liver function	Wistar albino rats (M)	High-fat diet challenge	2 p.o.	56	↓ TC, TG, & LDL-C; ↑ HDL-C; ↓ ROS	↑ CAT, SOD, & GPx; ↓ MDA	(Belguith-Hadriche et al. 2016)
	Wistar albino rats (M)	Acetaminophen (paracetamol) or cholesterol challenge	1 p.o.	7	↓ liver injury; ↓ hepatocytes necrosis	↓ ALT, AST, & ALP	(Hashem et al. 2016)
	ICR mice (M)	Acetaminophen challenge	10 p.o.	7	↓ liver injury; ↓ oxidative stress	↓ ALT, AST, & LDH; ↓ MDA; ↑ GSH, GPx, SOD, & CAT; ↓ JNK & ERK1/2 (MAPKs); ↑ Nrf2	(Wu et al. 2017)
	Swiss-Webster mice (M)	High-fat diet challenge	3-6 *p.o.*	56	↓ body weight; ↓ blood glucose; ↓ TC; ↓ oxidative stress	↓ GR & GPx; ↑ GSH	(Lorizola et al. 2018)
	C57BL/6J mice (M)	High-fat diet challenge	10 p.o.	56	↓ body weight; ↓ TG;	↑ adiponectin; ↑ Glut4, mTOR, IRS-1, & InsR	(Seyedan et al. 2019)
	C57BL/6J mice (M)	High-fat diet challenge	5 p.o.	74	↓ body weight; ↓ TG; ↓ blood glucose	↑ AMPKα; ↓ C/EBPα & FAS	(Peng et al. 2019d)
Anti-inflammation	Swiss-Webster mice (M)	Ymosan, carrageenan, fMLP, or LPS challenges	15-30 *p.o.*	5-7 hrs	↓ peritonitis (by reducing neutrophil counts in peritoneal cavity/ inhibiting neutrophil migration to); ↓ NO	↓ TNF-α & IL-1β	(Rosa et al. 2016)
	Swiss-Webster mice (M)	Ovalbumin challenge	1-5 *p.o.*	5	↓ allergic asthma; ↓ airway inflammation; ↓ leukocyte infiltration into the airway; ↓ edema	↓ IgE; ↓ IL-4, IL-5, & IL-13	(Rosa et al. 2017)
	Swiss-Webster mice (M)	Ovalbumin challenge	0.2-5 *p.o.*	5	↓ allergic asthma; ↓ leukocyte infiltration, mucus production, & pulmonary edema; ↓ airway inflammation	↓ IgE; ↓ IL-4, IL-5, & IL-13	(Venturini et al. 2018)
	C57BL/6J mice (M)	LPS challenge	10 i.p.	1	↓ lung edema; ↓ lung water content; ↓ pulmonary inflammation & injury; ↑ NO; ↓ ROS; ↑ phagocytic activity	↑ Nrf2; ↑ HO-1; ↓ NLRP3; ↓ TNF-α, IL-1β, & IL-6	(Lu et al. 2018)
	Sprague-Dawley rats (M)	LPS challenge	10 i.p.	1	↓ kidney injury; ↓ serum creatinine & BUN	↓ KIM-1 & NGAL; ↑ AMPKα; ↑ FOXO3a	(Wang et al. 2019)
	C57BL/6J mice (M)	LPS challenge	5-15 *i.p.*	7	↓ inflammatory osteolysis; ↓ osteoclast formation	↓ p38 & ERK1/2 (MAPKs)	(Jiang et al. 2019)
Anti-cancer	C57BL/6J mice (M)	Hepatocellular carcinoma challenge	2 p.o.	28	↓ tumorigenesis; ↑ liver cell apoptosis and necrosis; ↓ autophagy	↓ Ki-67 & MMP-2; ↓ LC3-II	(He et al. 2016)
	BALB/c pathogen free athymic nude mice (M)	Colorectal carcinoma challenge	25-100 *p.o.*	28 (3 days/week)	↓ tumor growth & size	↑ JNK;↑ LC3-II; ↑ ApoL1	(Bhardwaj et al. 2017)
	BALB/c pathogen free athymic nude mice (M)	Colorectal carcinoma challenge	40 i.p.	14 (every other day)	↓ tumor growth & size	↑ p53 & PUMA	(Chen et al. 2018)
	BALB/c pathogen free athymic nude mice (F)	Melanoma challenge	40-80 *i.p.*	17 (twice per day)	↓ tumor growth & size	↑ PARP; ↓ Bcl-2/Bax	(Liu et al. 2018)

	BALB/c pathogen free athymic nude mice (M)	Lung carcinoma challenge	1-2 *i.p.*	28	↓ tumor growth & size	↓ Bcl-2/Bax; ↑ cleave Caspase-3; ↓ PI3K, Akt & mTOR	(Liu et al. 2019)
Anti-bacteria & anti-virus	BALB/c pathogen free athymic nude mice (F)	P. aeruginosa challenge	5.5 *i.p.*	3	↓ pathogen swarming motility; ↓ biofilm forming capability; ↓ surface adhered pathogen	N/A	(Das et al. 2016)
Others	Wistar albino rats (M)	Nicotine challenge	60 i.p.	30 min	↓ locomotor activity	N/A	(Bedell et al. 2019)
	ICR mice (M)	Incision-induced mechanical hyperalgesia	10-20 *i.p.*	90 min	↑ paw withdrawal threshold; ↓ paw swelling; ↓ locomotive activity	N/A	(Zhu et al. 2016)

ICR mice – Institute of Cancer Research mice; M – male; F - female; ↑ - increase; ↓ - decrease; N/A, not available; *p.o.*, Per os (oral administration); *i.p.*, intraperitoneal injection.

Acronymes: AChE, acetylcholinesterase activity, Akt, protein kinase B; ALP, alkaline phosphatase; AMPKα, AMP-activated protein kinase α; ApoL1, apolipoprotein L1; AST, aspartate aminotransferase; Bax, B-cell lymphoma 2-associated X; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; BiP, binding immunoglobulin protein; BUN, blood urea nitrogen; CaMKII, Ca^{2+}/Calmodulin-dependent protein kinase II; CAT, catalase; C/EBPα, CCAAT/enhancer binding protein α; CHOP, CCAAT-enhancer-binding protein homologous protein; CK, creatine kinase; COX-2, cyclooxygenase-2; DBH, dopamine b-hydroxylase activity; DPA, docosapentaenoic acid; FAS, fatty acid synthase; fMLP, n-formyl-methionyl-leucyl-phenylalanine; FOXO3, forkhead-box O3; FSH, follicular stimulating hormone; GABA, gamma-aminobutyric acid; GLUT4, glucose transporter type 4; GnRH, gonadotropin-releasing hormone; GPx, glutathione peroxidase; GR, glucocorticoid receptor; GSH, glutathione; HDL-C, high-density lipoprotein cholesterol; HIF-1α, hypoxia inducible factor 1α; HMGB1, high mobility group box 1; HO-1, heme oxygenase; Iba-1, ionized calcium binding adaptor molecule 1; IgE, immunoglobulin E; IL-1β, interleukin 1β; IL-6, interleukin 6; InsR, insulin receptor; IRS-1, insulin receptor substrate 1; JNK, c-Jun N-terminal kinases; Ki-67, antigen Ki-67; KIM-1, kidney injury molecule-1; LC3-II, LC3-phosphatidylethanolamine conjugate; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; LPS, lipopolysaccharide; MAPKs, mitogen-activated protein kinases; MDA, malondialdehyde; Mela R1, melatonin receptor 1; mGluR1, metabotropic glutamate receptor 1; MMP-2, matrix metalloproteinase 2; Mst1, macrophage stimulating 1; mTOR, mammalian target of rapamycin; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor κB; NGAL, neutrophil gelatinase-associated lipocalin; NKCC1, Na^{+}-K^{+}-Cl^{-} co-transporter1; NLRP3, nucleotide-binding domain and leucine-rich repeat PYD-containing protein 3; NMDAR, N-methyl-D-aspartate receptor; Nrf2, nuclear factor erythroid 2-related factor 2; p21, cyclin-dependent kinase inhibitor 1; p38, mitogen-activated protein kinase; p53, tumor suppressor p53; PARP, poly(ADP-ribose) polymerase; PI3K, phosphoinositide 3-kinase; PPARγ, peroxisome proliferatoractivated receptor γ; PUMA, p53 upregulated modulator of apoptosis; Rap1, Ras-proximate-1; SOD, superoxide dismutase; TBARS, thiobarbituric-acid reacting substances; TC, total cholesterol; TG, triglycerides; TNF-α, tumor necrosis factor α; Ulk1, Unc-51 like autophagy activating kinase 1; VEGF, vascular endothelial growth factor; Yap, yes-associated protein 1; ZO-1, tight junction protein-1.

Hossaine, and Park 2016; Xie et al. 2018). Excessively high calcium ion (Ca^{2+}) transition though the endoplasmic reticulum membrane Ca^{2+} channel in T lymphocytes and mast cells leads to the secretion of inflammatory mediators and further contributes to allergic responses (Kim, Nam, et al. 2018). Vitexin was found to alleviate allergies by inhibiting calcium release-activated calcium currents and β-hexosaminidase, which suggests the importance of Ca^{2+} transition as the target for the amelioration of inflammation (Kim, Nam, et al. 2018). Immunoglobulin E (IgE) is another important biomarker for allergic disorders (Galli and Tsai 2012). Interestingly, two in vivo studies revealed that vitexin inhibited the release of IgE into serum, which resulted in the amelioration of ovalbumin-induced allergic asthma [49, 57]. Moreover, the release of IL-4, IL-5, and IL-13 in the bronchoalveolar lavage fluid was reduced by vitexin (Rosa et al. 2017; Venturini et al. 2018). Other animal studies have shown that vitexin ameliorated peritonitis, lung edema, kidney injury, and inflammatory osteolysis by regulating targets commonly found in cell culture results (Jiang et al. 2019; Lu et al. 2018; Rath et al. 2016; Wang et al. 2019).

Anti-cancer effect of vitexin

Vitexin has also been shown to be a potent compound in the inhibition of carcinogenesis and tumor growth (Ganesan and Xu 2017). It exerts antineoplastic effects on cancer in various organs and systems, including the liver, colon, breast, skin, bladder, lung, *etc.* (Ganesan and Xu 2017). In recent years there have been many studies focusing on the inhibitory effects of vitexin on tumor progression for these cancers and cancer cell lines. Additionally, more mechanisms have been explored.

Consistent in different cancer cells, vitexin induced cell apoptosis and inhibited cell proliferation by the prolongation of G2 cell-cycle arrest, the reduction of the Bcl-2/Bax ratio, and by increasing the expression of caspase-7, −8, −9, and -3 (Czemplik et al. 2016; Girish, Kumar, and Prasada Rao 2016; He et al. 2016; Liu et al. 2019; Scarpa et al. 2018; Scarpa et al. 2016; Zhang et al. 2018). Another study suggested that vitexin acted as a matrix metalloproteinase (MMP) inhibitor, which are important regulators of tumor proliferation and invasion (He et al. 2016). Vitexin has also been reported to upregulate poly (ADP-ribose) polymerase (PARP), an enzyme responsible for programed cell death. As a previous study revealed, the inhibition of PARP suppressed the cell apoptosis pathway, with enhanced Bcl-2 and reduced Bax, which suggests an important role of PARP in vitexin-mediated tumor suppression (Kalmar-Nagy et al. 2013; Liu et al. 2018; Zhang et al. 2018). β-catenin and survivin are two key components of the Wnt/β-catenin pathway contributing to cancer cell proliferation and survival (Shang, Hua, and Hu 2017). These components have been shown to be inhibited by vitexin in T24 human bladder carcinoma (Scarpa et al. 2016). In addition, vitexin upregulated tumor suppressors: p53, p53 upregulated modulator of apoptosis (PUMA), and several serine/threonine kinases, *i.e.,* ataxia-telangiectasia mutated kinase (ATR), Rad3-related kinase

(ATM), and Checkpoint kinase 2 (CHK2) (Chen et al. 2018; Liu et al. 2018). Since p53 was reported to inhibit β-catenin and survivin, the inhibition of the two proteins might contribute to the activation of p53 and PUMA by vitexin (Sadot et al. 2001).

Recent studies revealed that vitexin exerts antineoplastic effects by inhibiting phosphatidylinositol-3-kinase (PI3K)/Akt (Liu et al. 2019; Zhang et al. 2018). This pathway has been recently considered as another important mediator contributing to cell proliferation, survival, and cancer development (Liu et al. 2019; Zhang et al. 2018). Interestingly, the mammalian target of rapamycin (mTOR), which is known to promote the synthesis of proteins involved in tumorigenesis, was suggested to be directly or indirectly regulated by PI3K/Akt (Porta, Paglino, and Mosca 2014). Moreover, the activation of PI3K/Akt resulted in an enhanced resistance of cancer cells against TNF-α-mediated apoptosis (Porta, Paglino, and Mosca 2014). Thus, PI3K/Akt and its downstream mTOR may be other molecular targets for the prevention of carcinogenesis by vitexin.

An increasing number of publications have suggested that autophagy exhibits dual effects for both cancer development and cancer therapy (Rosenfeldt and Ryan 2011; Yun and Lee 2018). On one hand, abnormal autophagy was reported to maintain cancer cell stemness, induce recurrence, and enhance cell resistance to anticancer reagents, which promotes cancer cell survival and tumor initiation (Yun and Lee 2018). It was revealed that vitexin induced the apoptosis of hepatoma and colorectal carcinoma by reducing autophagic rate and autophagosome formation via the downregulation of Beclin-1, microtubule-associated protein light chain (LC3)-I, LC3-II, and Atg5, the biomarkers involved in autophagy (Bhardwaj et al. 2018; He et al. 2016). Conversely, a basal level of autophagy helped tumor suppression through the clearance of damaged cellular parts and abnormal proteins (Bhardwaj et al. 2017; Yun and Lee 2018). Researchers have also reported that vitexin promoted oxidative stress and induced apolipoprotein L1-mediated autophagic cell death in colon cancer cells (Bhardwaj et al. 2017). All these studies indicate the involvement of autophagy in the anti-cancer effects of vitexin.

Neuron-protection of vitexin

Neuron disorders, including epilepsy seizure, brain infarction, retinal damage, hypoxic-ischemic injury, bradykinesia, depression, and memory loss, are closely associated with the loss of neurons, reduced stress resistance, and inflammation (Aseervatham et al. 2016; Chen et al. 2016; Hu, Li, and Wang 2018; Jiang, Dai, and Cui 2018; Kim et al. 2019; Luo et al. 2018b; Lyu et al. 2018; Malar et al. 2018a; Malar et al. 2018b; Min et al. 2017; Nurdiana et al. 2018). Vitexin attenuated these neuron disorders and improved the learning behaviors in mice and rats mainly by promoting neuron survival, decreasing ROS levels, and reducing the release of pro-inflammatory factors (Aseervatham et al. 2016; Chen et al. 2016; Hu, Li, and Wang 2018; Jiang, Dai, and Cui 2018; Kim et al. 2019; Luo et al. 2018b; Lyu et al. 2018; Malar et al. 2018a; Malar et al. 2018b; Min et al. 2017; Nurdiana et al. 2018). Vitexin also enhanced neuron cell viability by the upregulation of the Bcl-2/Bax ratio and the downregulation of caspases (Chen et al. 2016; Hu, Li, and Wang 2018; Jiang, Dai, and Cui 2018; Lyu et al. 2018). In recent studies, vitexin has been reported to activate the phosphatidylinositol-3-OH kinase (PI3K)-protein kinase B (Akt) pathway (Cui et al. 2019; Hu, Li, and Wang 2018). This pathway can be activated by BDNF and then inhibits apoptotic regulators such as FOXO and p53 (Brunet, Datta, and Greenberg 2001). Moreover, Akt is implicated in the inhibition of cell death as it indirectly increase the expression of Bcl-2, thereby decreasing the release of cytochrome c (Brunet, Datta, and Greenberg 2001). The NMDA receptor is one of the glutamate receptors responsible for Ca^{2+} influx and pass-signaling from one neuron to another (Doshi and Lynch 2009). Glutamate can induce the excessive expression of NMDA and its downstream neuronal protease calpain (Malar et al. 2018a), resulting in cytosolic Ca^{2+}-mediated excitotoxicity, which may induce brain lesions and the pathogenesis of neuron cells (Doshi and Lynch 2009). Pretreatment of vitexin reduced the level of the NMDA receptor and calpain (Malar et al. 2018a), and thus attenuated toxicity by cytosolic Ca^{2+} transaction (Chen et al. 2016; Min et al. 2017).

Considering that lipid peroxidation, protein oxidation, and loss of mitochondrial membrane are typical oxidative damages to neuron cells, their reduction by vitexin has great importance for protecting brain areas from oxidative stress injuries (Cui et al. 2019; Malar et al. 2018a; Malar et al. 2018b). Sleep disorders contribute to neurodegeneration. It has been reported that improved neurogenesis and memory by vitexin alleviated sleep disorders, which lends support to the benefits of vitexin on neurodegenerative diseases (Kim et al. 2019).

Cardio-protection of vitexin

The pathogenesis of cardiovascular disorders, including myocardial infarction, atherosclerosis, and cardiac necrosis, are closely linked to endothelia cell dysfunction, oxidative damage, lipid peroxidation, and inflammation (Bai et al. 2016; Che et al. 2016; Cheng et al. 2017; Glick, Barth, and Macleod 2010; Sun et al. 2016). It has been reported that vitexin protected endothelia cells from oxidized low density lipoproteins (ox-LDL) by enhancing cell viability and physical stress resistance *via* the activation of AMPKα (Zhang et al. 2017b). Autophagy is a process for maintaining cellular balance by the degradation of misfolded proteins or damaged organelles (Glick, Barth, and Macleod 2010). The protective effect of vitexin in endothelia cells may also be attributed to the increased cell autophagy and upregulation of relative genes, such as Beclin1 and light chain 3 II (LC3-II), as well as the downregulation of p62 (Wirawan et al. 2012; Zhang et al. 2017b). However, another study showed the opposite results (Tang, Yang, and Zhang 2017). This study found that vitexin reduced cell autophagy with a reduced level of Beclin 1 and an increased level of p62 in

H9C2 rat cardiomyocytes (Tang, Yang, and Zhang 2017). This inconsistency in results may be attributed to different cell cultures (endothelia cells vs cardio muscle cells), cell injury inducers (ox-LDL vs myocardial ischemia reperfusion injury), dosages of vitexin (20 μM vs 100-200 μM), and/or treatment periods (24 hr vs 4 hr) used in the different studies (Tang, Yang, and Zhang 2017; Zhang et al. 2017a). Since autophagy is a dynamic balancing process for cell survival (Glick, Barth, and Macleod 2010), under different conditions, vitexin may exert different regulatory effects. Vitexin has also been reported to ameliorate isoproterenol-induced abnormal cell beating rate through the extension of field potential durations, an indication of the potential usage of the compound on cardiac arrhythmias (Pahlavan et al. 2018).

Effects of Vitexin on glucose metabolism, lipid metabolism, and liver function

Recently, many researchers have focused on the potential health benefits of vitexin with respect to glucose homeostasis, fat metabolism, and hepatoprotection (Duncan et al. 2017; Li et al. 2019; Nurdiana et al. 2018; Peng et al. 2019d; Wu et al. 2017; Yang et al. 2017). Pancreas injury and/or islet tissue damage usually causes insulin secretion insufficiency or insulin resistance, which leads to impaired glucose disposal and increased blood glucose levels (Peng, Sun, and Park 2019c; Wang et al. 2017). Vitexin has been shown to protect pancreas and islet tissue from toxicity induced by streptozotocin or LPS via the upregulation of Nrf2 and antioxidases (Nurdiana et al. 2017), as well as the inhibition of MAPKs, including JNK and p38 (Duncan et al. 2017). Vitexin also increased GLUT4 translocation from the cytoplasm to the membrane, suggesting the promotion of glucose uptake by vitexin (Seyedan et al. 2019). Another study revealed that vitexin improved diabetes-induced sexual dysfunction and fertility impairments in mice (Li et al. 2019). In this process, vitexin treatment increased reproductive organ weight, attenuated testicular pathological structure damage, restored sperm quality, and improved sex hormonal balance (Li et al. 2019).

As in the mechanism of glucose metabolism, the fat reductive effects of vitexin are attributed to enhanced oxidative stress resistance in liver and adipose tissues. More recently, our research group found that AMPKα was a key molecular target on vitexin-mediated fat reduction (Peng et al. 2019d). Vitexin activated AMPKα, a master in controlling fat accumulation (Sun et al. 2018), and inhibited C/EBPα and FAS, two contributors to lipogenesis and adipocyte differentiation (Peng et al. 2019d). The inhibition of AMPKα by Compound C abolished the reduced fat content in adipocytes, suggesting the involvement of AMPKα in this process (Peng et al. 2019d). Moreover, vitexin exerted protection against liver injury by downregulating ALT, AST, ALP, and LDH, the enzymes involved in liver functions (Wu et al. 2017).

Antimicrobial and antiviral effects of vitexin

Vitexin has been reported to have inhibitory effects on gram negative bacteria, especially *Pseudomonas aeruginosa* and *Bordetella petrii* (Das et al. 2016; Rath et al. 2016). Layers of *P. aeruginosa* cells can easily form surface-attached biofilm on animal and human hosts, leading to cystic fibrosis and infections in the urinary tract, kidney, and intestine (Das et al. 2016). Vitexin has been shown to attenuate the formation of *P. aeruginosa* biofilms mainly through reducing cell adhering ability, specifically by decreasing pathogen-swarming motility and downregulating quorum-sensing regulator proteins (Das et al. 2016). *B. petrii* was also known to induce cystic fibrosis in humans (Rath et al. 2016). A molecular docking study suggested vitexin was a potential drug target against *B. petrii*, although in vitro and in vivo studies are required to further confirm this finding.

Vitexin also exerted the ability to inhibit infection with influenza viruses (Ding and Liu 2019; Sadati et al. 2019). Several studies reported that vitexin acted as an inhibitor of influenza virus neuraminidase, a surface presenting enzymes responsible for virus releasement and replication (Ding and Liu 2019; Li et al. 2002; Sadati et al. 2019).

Other bioactivities of vitexin

Vitexin has also been shown to exhibit a number of other biological activities that may be beneficial to human health. A treatment of 60 mg/kg vitexin for 30 min prior to a nicotine challenge effectively attenuated the locomotive activity of rats, indicating the potential benefits of vitexin on nicotine cessation (Bedell et al. 2019). Another two studies reported that vitexin helped in promoting human dermal papilla cell proliferation, colony growth, and hair shaft elongation by activating the Wnt/β-catenin signaling pathway, which may contribute to human hair growth (Luo et al. 2018a). Moreover, vitexin protected mice from incision-induced mechanical hyperalgesia and promoted their sedation by enhancing the paw withdrawal threshold and reducing paw swelling (Zhu et al. 2016). Another study suggested that the GABAergic pathway was involved in vitexin-mediated sedation in mice (Gazola et al. 2018).

Delivery of vitexin

To have an appreciable impact on human health and well-being, vitexin must be delivered to the target tissues within the human body at sufficiently high levels. Vitexin can be delivered orally through foods, supplements, or pharmaceuticals in a number of ways. It can be consumed as an integral part of vitexin-rich edible plants, such as mung beans, beetroot, or bamboo. Alternatively, it can be isolated from these plants and converted into a bioactive ingredient that can be incorporated into functional foods, supplements, or drugs. Vitexin is a relatively small polar molecule with a molecular weight of 432 Da and a LogP value of 1.28 (chemspider.com). Consequently, it should be relatively easy to dissolve within aqueous-based foods, drinks, or pharmaceuticals.

Alternatively, vitexin could be converted into a powdered form that can then be incorporated into tablets, pills, or capsules for supplement or pharmaceutical applications. The bioavailability and bioactivity of many phytochemicals has been shown to be increased using colloidal delivery systems or by controlling food matrix properties (Goncalves et al. 2018; McClements and Xiao 2017; Sayed, Khurana, and Godugu 2019). Surprisingly, there have been few studies on the development of delivery systems for vitexin, which may be because of its relatively high water-solubility and good stability. In one study, however, vitexin-phospholipid nanocomplexes were shown to have a higher bioavailability than free vitexin (Luo et al. 2017), which highlights the potential of using colloidal delivery systems to enhance its functionality. In this case, the delivery system may be developed to improve the chemical stability of the nutraceutical within a food or supplement product, or to modulate its metabolism and absorption in the gastrointestinal tract after ingestion.

Conclusion

The absorption and metabolic process of vitexin and its multiple bioactivities, including enhancing stress resistance, inflammatory responses, neuron health, cardio-protection, improvement of energy homeostasis, tumor inhibition, and detoxification, were reviewed in this paper. We also discussed its possible molecular mechanisms. However, further studies investigating its upstream regulators or receptors are needed to better understand its mechanisms of bioactivities modulation effects. Moreover, it has been indicated that a nanotechnology-based delivery system can be a promising strategy for improving its bioavailability, which may be an important area of research in the future. Another question is that the bioactivities of vitexin in vivo may not be elicited by itself, but by its metabolites, since it has been metabolized by gut microbiota before entering the bloodstream. Therefore, the question of whether its main metabolites mediate its bioactivities in vivo requires further study. The influence of vitexin on gut microbiota composition together with their correlation with the biological activities are also worthy of further investigation. Overall, vitexin is a promising natural small molecule with a variety of bioactivities. Further investigation, such as clinical studies, and the development of an efficient delivery system are needed to integrate vitexin into effective functional food products.

Funding

This work was supported by Senior Talent Cultivation Program of Jiangsu University (18JDG023); and the Jiangsu "Mass Innovation and Entrepreneurship" (shuang chuang Ph.Ds) Talent Program. No conflict of interest existed.

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References

Al-Jeboory, A. A., and K. E. H. Dizaye. 2006. Cardiovascular effects of vitexin. *Acta Pharmacologica Sinica* 27:e146.

An, F., G. D. Yang, J. M. Tian, and S. H. Wang. 2012. Antioxidant effects of the orientin and vitexin in *Trollius chinensis* Bunge in D-galactose-aged mice. *Neural Regeneration Research* 7 (33):2565–75. doi: 10.3969/j.issn.1673-5374.2012.33.001.

An, F., S. Wang, D. Yuan, Y. Gong, and S. Wang. 2016. Attenuation of oxidative stress of erythrocytes by the plant-derived flavonoids vitexin and apigenin. *Evidence-Based Complementary and Alternative Medicine* 2016:1–732. doi: 10.1155/2016/3401269.

Aseervatham, G. S., U. Suryakala, S., S. Doulethunisha, P. C. Bose, and T. Sivasudha. 2016. Expression pattern of NMDA receptors reveals antiepileptic potential of apigenin 8-C-glucoside and chlorogenic acid in pilocarpine induced epileptic mice. *Biomedicine & Pharmacotherapy* 82:54–64. doi: 10.1016/j.biopha.2016.04.066.

Ashokkumar, R., S. Jamuna, M. S. S. Sadullah, and S. N. Devaraj. 2018. Vitexin protects isoproterenol induced post myocardial injury by modulating hipposignaling and ER stress responses. *Biochemical and Biophysical Research Communications* 496 (2):731–7. doi: 10.1016/j.bbrc.2018.01.104.

Bai, Y., J. Chang, Y. Xu, D. Cheng, H. Liu, Y. Zhao, and Z. Yu. 2016. Antioxidant and myocardial preservation activities of natural phytochemicals from mung bean (*Vigna radiata L.*) seeds. *Journal of Agricultural and Food Chemistry* 64 (22):4648–55. doi: 10.1021/acs.jafc.6b01538.

Bai, Y., Q. Zhang, B. Wang, M. Zhang, Y. Xu, S. Li, Y. Zhao, and Z. Yu. 2017. Plasma pharmacokinetics, bioavailability, and tissue distribution of four *C*-glycosyl flavones from mung bean (*Vigna radiata L.*) seed extracts in rat by ultrahigh-performance liquid chromatography-tandem mass spectrometry. *Journal of Agricultural and Food Chemistry* 65 (27):5570–80.

Bedell, S., J. Wells, Q. F. Liu, and C. Breivogel. 2019. Vitexin as an active ingredient in passion flower with potential as an agent for nicotine cessation: Vitexin antagonism of the expression of nicotine locomotor sensitization in rats. *Pharmaceutical Biology* 57 (1):8–12. doi: 10.1080/13880209.2018.1561725.

Belguith-Hadriche, O., S. Ammar, M. d M. Contreras, M. Turki, A. Segura-Carretero, A. El Feki, F. Makni-Ayedi, and M. Bouaziz. 2016. Antihyperlipidemic and antioxidant activities of edible *Tunisian Ficus carica L.* fruits in high fat diet-induced hyperlipidemic rats. *Plant Foods for Human Nutrition* 71 (2):183–9. doi: 10.1007/s11130-016-0541-x.

Bhardwaj, M., H. J. Cho, S. Paul, R. Jakhar, I. Khan, S. J. Lee, B. Y. Kim, M. Krishnan, T. P. Khaket, H. G. Lee, et al. 2018. Vitexin induces apoptosis by suppressing autophagy in multi-drug resistant colorectal cancer cells. *Oncotarget* 9 (3):3278–91. doi: 10.18632/oncotarget.22890.

Bhardwaj, M., S. Paul, R. Jakhar, I. Khan, J. I. Kang, H. M. Kim, J. W. Yun, S. J. Lee, H. J. Cho, H. G. Lee, et al. 2017. Vitexin confers HSF-1 mediated autophagic cell death by activating JNK and ApoL1 in colorectal carcinoma cells. *Oncotarget* 8 (68):112426–41. doi: 10.18632/oncotarget.20113.

Borghi, S. M., T. T. Carvalho, L. Staurengo-Ferrari, M. S. N. Hohmann, P. Pinge, R. Casagrande, and W. A. Verri. 2013. Vitexin inhibits inflammatory pain in mice by targeting TRPV1, oxidative stress, and cytokines. *Journal of Natural Products* 76 (6):1141–9. doi: 10.1021/np400222v.

Braune, A., and M. Blaut. 2012. Intestinal bacterium *Eubacterium cellulosolvens* deglycosylates flavonoid *C*- and *O*-glucosides. *Applied and Environmental Microbiology* 78 (22):8151–3. doi: 10.1128/AEM.02115-12.

Brunet, A., S. R. Datta, and M. E. Greenberg. 2001. Transcription-dependent and -independent control of neuronal survival by the PI3K–Akt signaling pathway. *Current Opinion in Neurobiology* 11 (3):297–305. doi: 10.1016/S0959-4388(00)00211-7.

Cao, D., H. Li, J. Yi, J. Zhang, H. Che, J. Cao, L. Yang, C. Zhu, and W. Jiang. 2011. Antioxidant properties of the mung bean flavonoids

on alleviating heat stress. *PLoS One* 6 (6):e21071. doi: 10.1371/journal.pone.0021071.

Che, X., X. Wang, J. Y. Zhang, C. F. Peng, Y. L. Zhen, X. Shao, G. L. Zhang, and L. Y. Dong. 2016. Vitexin exerts cardioprotective effect on chronic myocardial ischemia/reperfusion injury in rats via inhibiting myocardial apoptosis and lipid peroxidation. *American Journal of Translational Research* 8 (8):3319–28.

Chen, J. F., J. C. Zhong, Y. Y. Liu, Y. Huang, F. Luo, Y. J. Zhou, X. Pan, S. S. Cao, L. L. Zhang, Y. J. Zhang, et al. 2018. Purified vitexin compound 1, a new neolignan isolated compound, promotes PUMA-dependent apoptosis in colorectal cancer. *Cancer Medicine* 7 (12):6158–69. doi: 10.1002/cam4.1769.

Chen, L. L., B. Zhang, S. Q. Shan, and X. Zhao. 2016. Neuroprotective effects of vitexin against isoflurane-induced neurotoxicity by targeting the TRPV1 and NR2B signaling pathways. *Molecular Medicine Reports* 14 (6):5607–13. doi: 10.3892/mmr.2016.5948.

Cheng, D., R. Wang, C. Wang, and L. Hou. 2017. Mung bean (*Phaseolus radiatus L.*) polyphenol extract attenuates aluminum-induced cardiotoxicity through an ROS-triggered Ca^{2+}/JNK/NF-kappaB signaling pathway in rats. *Food & Function* 8 (2):851–9. doi: 10.1039/C6FO01817C.

Choi, H. J., J. S. Eun, B. G. Kim, S. Y. Kim, H. Jeon, and Y. Soh. 2006. Vitexin, an HIF-1 alpha a inhibitor, has anti-metastatic potential in PC12 cells. *Molecules and Cells* 22 (3):291–9.

Choi, J. S., M. N. Islam, M. Y. Ali, E. J. Kim, Y. M. Kim, and H. A. Jung. 2014. Effects of C-glycosylation on anti-diabetic, anti-Alzheimer's disease and anti-inflammatory potential of apigenin. *Food and Chemical Toxicology* 64:27–33. doi: 10.1016/j.fct.2013.11.020.

Colomeu, T. C., D. De Figueiredo, P. Silva Matos, V. D. Carvalho, N. S. G. Schumacher, D. M. Abram, L. G. R. Fernandes, and R. D. Zollner. 2017. Effect of aqueous leaves extract from passiflora alata curtis and vitexin, isoorientin in co-culture of min6/lymphocytes from nod mice in oxidative stress and cell death. *Annals of Nutrition and Metabolism* 71:391–2.

Cui, Y. H., X. Q. Zhang, N. D. Wang, M. D. Zheng, and J. Yan. 2019. Vitexin protects against ischemia/reperfusion-induced brain endothelial permeability. *European Journal of Pharmacology* 853:210–9. doi: 10.1016/j.ejphar.2019.03.015.

Czemplik, M., J. Mierziak, J. Szopa, and A. Kulma. 2016. Flavonoid *C*-glucosides derived from flax straw extracts reduce human breast cancer cell growth in vitro and induce apoptosis. *Frontiers in Pharmacology* 7:282–94. doi: 10.3389/fphar.2016.00282.

Das, M. C., P. Sandhu, P. Gupta, P. Rudrapaul, U. C. De, P. Tribedi, Y. Akhter, and S. Bhattacharjee. 2016. Attenuation of *Pseudomonas aeruginosa* biofilm formation by vitexin: A combinatorial study with azithromycin and gentamicin. *Scientific Reports* 6 (1):23347. doi: 10.1038/srep23347.

Ding, F., and J. Liu. 2019. Qualitative and quantitative analysis for the chemical constituents of *Tetrastigma hemsleyanum* diels et gilg using ultra-high performance liquid chromatography/hybrid quadrupole-orbitrap mass spectrometry and preliminary screening for anti-influenza virus components. *Evidence-Based Complementary and Alternative Medicine* 2019:9414926.

Doshi, S., and D. R. Lynch. 2009. Calpain and the glutamatergic synapse. *Frontiers in Bioscience* S1 (2):466–76. doi: 10.2741/s38.

Duncan, S. H., M. Schreiner, P. Louis, R. Maul, S. Rohn, F. Yan, Y. Yang, L. Yu, and X. Zheng. 2017. Effects of *C*-glycosides from *Apios americana* leaves against oxidative stress during hyperglycemia through regulating mitogen-activated protein kinases and nuclear factor erythroid 2-related factor 2. *Journal of Agricultural and Food Chemistry* 65 (34):7457–66. doi: 10.1021/acs.jafc.7b03163.

Etxeberria, U., A. Fernández-Quintela, F. I. Milagro, L. Aguirre, J. A. Martínez, and M. P. Portillo. 2013. Impact of polyphenols and polyphenol-rich dietary sources on gut microbiota composition. *Journal of Agricultural and Food Chemistry* 61 (40):9517–33. doi: 10.1021/jf402506c.

Galli, S. J., and M. Tsai. 2012. IgE and mast cells in allergic disease. *Nature Medicine* 18 (5):693–704. doi: 10.1038/nm.2755.

Ganesan, K., and B. J. Xu. 2017. Molecular targets of vitexin and isovitexin in cancer therapy: A critical review. *Annals of the New York Academy of Sciences* 1401 (1):102–13. doi: 10.1111/nyas.13446.

Ganesan, K., and B. J. Xu. 2018. A critical review on phytochemical profile and health promoting effects of mung bean (*Vigna radiata*). *Food Science and Human Wellness* 7 (1):11–33. doi: 10.1016/j.fshw.2017.11.002.

Gao, Y. C., Y. Du, Z. M. Ying, A. J. Leng, W. J. Zhang, Y. H. Meng, C. Y. Li, L. Xu, X. X. Ying, and T. G. Kang. 2016. Hepatic, gastric and intestinal first-pass effects of vitexin-2-O-rhamnoside in rats by ultra-high-performance liquid chromatography. *Biomedical Chromatography* 30 (2):111–6. doi: 10.1002/bmc.3522.

Gazola, A. C., G. M. Costa, S. M. Zucolotto, L. Castellanos, F. A. Ramos, T. C. M. de Lima, and E. P. Schenkel. 2018. The sedative activity of flavonoids from *Passiflora quadrangularis* is mediated through the GABAergic pathway. *Biomedicine & Pharmacotherapy* 100:388–93. doi: 10.1016/j.biopha.2018.02.002.

Girish, T. K., K. A. Kumar, and U. J. S. Prasada Rao. 2016. *C*-Glycosylated flavonoids from black gram husk: Protection against DNA and erythrocytes from oxidative damage and their cytotoxic effect on HeLa cells. *Toxicology Reports* 3:652–63. doi: 10.1016/j.toxrep.2016.08.006.

Glick, D., S. Barth, and K. F. Macleod. 2010. Autophagy: Cellular and molecular mechanisms. *The Journal of Pathology* 221 (1):3–12. doi: 10.1002/path.2697.

Goncalves, R. F. S., J. T. Martins, C. M. M. Duarte, A. A. Vicente, and A. C. Pinheiro. 2018. Advances in nutraceutical delivery systems: From formulation design for bioavailability enhancement to efficacy and safety evaluation. *Trends in Food Science & Technology* 78:270–91. doi: 10.1016/j.tifs.2018.06.011.

Gu, C. B., Z. W. Liu, X. H. Yuan, W. Li, Y. G. Zu, and Y. J. Fu. 2017. Preparation of vitexin nanoparticles by combining the antisolvent precipitation and high pressure homogenization approaches followed by lyophilization for dissolution rate enhancement. *Molecules* 22 (11):e2038. doi: 10.3390/molecules22112038.

Hashem, A. N., M. S. Soliman, M. A. Hamed, N. F. Swilam, U. Lindequist, and M. A. Nawwar. 2016. *Beta vulgaris* subspecies cicla var. flavescens (*Swiss chard*): flavonoids, hepatoprotective and hypolipidemic activities. *Die Pharmazie* 71 (4):227–32.

He, J. D., Z. Wang, S. P. Li, Y. J. Xu, Y. Yu, Y. J. Ding, W. L. Yu, R. X. Zhang, H. M. Zhang, and H. Y. Du. 2016. Vitexin suppresses autophagy to induce apoptosis in hepatocellular carcinoma via activation of the JNK signaling pathway. *Oncotarget* 7 (51):84520–32. doi: 10.18632/oncotarget.11731.

Hein, E. M., K. Rose, G. van't Slot, A. W. Friedrich, and H. U. Humpf. 2008. Deconjugation and degradation of flavonol glycosides by pig cecal microbiota characterized by fluorescence in situ hybridization (FISH). *Journal of Agricultural and Food Chemistry* 56 (6):2281–90. doi: 10.1021/jf073444o.

Hu, M., F. M. Li, and W. D. Wang. 2018. Vitexin protects dopaminergic neurons in MPTP-induced Parkinson's disease through PI3K/Akt signaling pathway. *Drug Design, Development and Therapy* Volume 12:565–73. doi: 10.2147/DDDT.S156920.

Je, H. G., S. M. Hong, H. D. Je, U. D. Sohn, Y. S. Choi, S. Y. Seo, Y. S. Min, S. J. Chung, Y. K. Shin, T. J. Lee, et al. 2014. The inhibitory effect of vitexin on the agonist-induced regulation of vascular contractility. *Die Pharmazie* 69 (3):224–8.

Jiang, J.,. J. C. Dai, and H. Cui. 2018. Vitexin reverses the autophagy dysfunction to attenuate MCAO-induced cerebral ischemic stroke via mTOR/Ulk1 pathway. *Biomedicine & Pharmacotherapy* 99:583–90. doi: 10.1016/j.biopha.2018.01.067.

Jiang, J.,. Y. Jia, X. Lu, T. Zhang, K. Zhao, Z. Fu, C. Pang, and Y. Qian. 2019. Vitexin suppresses RANKL-induced osteoclastogenesis and prevents lipopolysaccharide (LPS)-induced osteolysis. *Journal of Cellular Physiology* 234 (10):17549–12. doi: 10.1002/jcp.28378.

Kalmar-Nagy, K.,. P. Degrell, A. Szabo, K. Sumegi, I. Wittmann, F. Gallyas, Jr., and B. Sumegi. 2013. PARP inhibition attenuates acute kidney allograft rejection by suppressing cell death pathways and activating PI-3K-Akt cascade. *PLoS One* 8 (12):e81928. doi: 10.1371/journal.pone.0081928.

Kim, G. H., K. Lim, H. S. Yang, J. K. Lee, Y. Kim, S. K. Park, S. H. Kim, S. Park, T. H. Kim, J. S. Moon, et al. 2019. Improvement in neurogenesis and memory function by administration of *Passiflora incarnata L.* extract applied to sleep disorder in rodent models. *Journal of Chemical Neuroanatomy* 98:27–40. doi: 10.1016/j.jchemneu.2019.03.005.

Kim, H. J., Y. R. Nam, E. J. Kim, J. H. Nam, and W. K. Kim. 2018. *Spirodela polyrhiza* and its chemical constituent vitexin exert anti-allergic effect via ORAI1 channel inhibition. *The American Journal of Chinese Medicine* 46 (06):1243–61. doi: 10.1142/S0192415X18500659.

Kim, Y.-H., T. Oh, E. Park, N.-H. Yim, K. Park, W. Cho, and J. Ma. 2018. Anti-inflammatory and anti-apoptotic effects of *Acer palmatum* Thumb. extract, KIOM-2015EW, in a hyperosmolar-stress-induced in vitro dry eye model. *Nutrients* 10 (3):e282. doi: 10.3390/nu10030282.

Krcatovic, E., G. Rusak, N. Bezic, and M. Krajacic. 2008. Inhibition of tobacco mosaic virus infection by quercetin and vitexin. *Acta Virol* 52:119–24.

Kumar, D., V. Arya, Z. A. Bhat, N. A. Khan, and D. N. Prasad. 2012. The genus *Crataegus*: Chemical and pharmacological perspectives. *Revista Brasileira de Farmacognosia* 22 (5):1187–200. doi: 10.1590/S0102-695X2012005000094.

Lee, S. J., M. D. Hossaine, and S. C. Park. 2016. A potential anti-inflammation activity and depigmentation effect of *Lespedeza bicolor* extract and its fractions. *Saudi Journal of Biological Sciences* 23 (1): 9–14. doi: 10.1016/j.sjbs.2015.01.016.

Li, Y. L., S. C. Ma, Y. T. Yang, S. M. Ye, and P. P. But. 2002. Antiviral activities of flavonoids and organic acid from *Trollius chinensis Bunge*. *Journal of Ethnopharmacology* 79 (3):365–8. doi: 10.1016/S0378-8741(01)00410-X.

Li, Z. M., N. Liu, Y. P. Jiang, J. M. Yang, J. Zheng, M. Sun, Y. X. Li, T. Sun, J. Wu, and J. Q. Yu. 2019. Vitexin alleviates streptozotocin-induced sexual dysfunction and fertility impairments in male mice via modulating the hypothalamus-pituitary-gonadal axis. *Chem Biol Interact* 297:119–29. doi: 10.1016/j.cbi.2018.10.013.

Liang, M., W. Xu, W. Zhang, C. Zhang, R. Liu, Y. Shen, H. Li, X. Wang, X. Wang, Q. Pan, et al. 2007. Quantitative LC/MS/MS method and in vivo pharmacokinetic studies of vitexin rhamnoside, a bioactive constituent on cardiovascular system from hawthorn. *Biomedical Chromatography* 21 (4):422–9.

Liao, M., X. Cheng, X. Diao, Y. Sun, and L. Zhang. 2017. Metabolites identificaion of two bioactive constituents in *Trollius ledebourii* in rats using ultra-high-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry. *Journal of Chromatography B-Analytical Technologies in the Biomedical and Life Sciences* 1068–1069:297–312. doi: 10.1016/j.jchromb.2017.10.061.

Liu, N. A., K. S. Wang, M. Qi, Y. J. Zhou, G. Y. Zeng, J. Tao, J. D. Zhou, J. L. Zhang, X. Chen, and C. Peng. 2018. Vitexin compound 1, a novel extraction from a Chinese herb, suppresses melanoma cell growth through DNA damage by increasing ROS levels. *Journal of Experimental & Clinical Cancer Research* 37 (1):e269. doi: 10.1186/s13046-018-0897-x.

Liu, X. L., Q. F. Jiang, H. M. Liu, and S. X. Luo. 2019. Vitexin induces apoptosis through mitochondrial pathway and PI3K/Akt/mTOR signaling in human non-small cell lung cancer A549 cells. *Biological Research* 52 (1):e7. doi: 10.1186/s40659-019-0214-y.

Lorizola, I., C. Furlan, M. Portovedo, M. Milanski, P. Botelho, R. Bezerra, B. Sumere, M. Rostagno, and C. Capitani. 2018. Beet stalks and leaves (*Beta vulgaris L.*) protect against high-fat diet-induced oxidative damage in the liver in mice. *Nutrients* 10 (7):e872. doi: 10.3390/nu10070872.

Lu, Y., T. Yu, J. Y. Liu, and L. N. Gu. 2018. Vitexin attenuates lipopolysaccharide-induced acute lung injury by controlling the Nrf2 pathway. *PLoS One* 13 (4):e0196405. doi: 10.1371/journal.pone.0196405.

Luo, J., M. Chen, Y. Liu, H. Xie, J. Yuan, Y. Zhou, J. Ding, Z. Deng, and J. Li. 2018a. Nature-derived lignan compound VB-1 exerts hair growth-promoting effects by augmenting Wnt/beta-catenin signaling in human dermal papilla cells. *PeerJ* 6:e4737. doi: 10.7717/peerj.4737.

Luo, J., W. Cai, T. Wu, and B. Xu. 2016. Phytochemical distribution in hull and cotyledon of adzuki bean (*Vigna angularis L.*) and mung bean (*Vigna radiate L.*), and their contribution to antioxidant, anti-inflammatory and anti-diabetic activities. *Food Chemistry* 201: 350–60. doi: 10.1016/j.foodchem.2016.01.101.

Luo, W. D., J. W. Min, W. X. Huang, X. Wang, Y. Y. Peng, S. Han, J. Yin, W. H. Liu, X. H. He, and B. W. Peng. 2018b. Vitexin reduces epilepsy after hypoxic ischemia in the neonatal brain via inhibition of NKCC1. *Journal of Neuroinflammation* 15 (1):e186. doi: 10.1186/s12974-018-1221-6.

Luo, Y. J., Z. L. Wang, D. L. Shi, Z. Q. Luo, and N. L. Yu. 2017. Preparation, characterization, and physicochemical properties of vitexin-phospholipid nano-complex. *Nanoscience and Nanotechnology Letters* 9 (12):2067–75. doi: 10.1166/nnl.2017.2542.

Lyu, Z. P., J. Cao, J. Wang, and H. M. Lian. 2018. Protective effect of vitexin reduces sevoflurane-induced neuronal apoptosis through HIF-1 alpha, VEGF and p38 MAPK signaling pathway in vitro and in newborn rats. *Experimental and Therapeutic Medicine* 15: 3117–23. doi: 10.3892/etm.2018.5758.

Malar, D. S., M. I. Prasanth, R. B. Shafreen, K. Balamurugan, and K. P. Devi. 2018a. *Grewia tiliaefolia* and its active compound vitexin regulate the expression of glutamate transporters and protect Neuro-2a cells from glutamate toxicity. *Life Sciences* 203:233–41. doi: 10.1016/j.lfs.2018.04.047.

Malar, D. S., V. Suryanarayanan, M. I. Prasanth, S. K. Singh, K. Balamurugan, and K. P. Devi. 2018b. Vitexin inhibits A beta(25-35) induced toxicity in Neuro-2a cells by augmenting Nrf-2/HO-1 dependent antioxidant pathway and regulating lipid homeostasis by the activation of LXR-alpha. *Toxicology in Vitro* 50:160–71. doi: 10.1016/j.tiv.2018.03.003.

McClements, D. J., and H. Xiao. 2017. Designing food structure and composition to enhance nutraceutical bioactivity to support cancer inhibition. *Seminars in Cancer Biology* 46:215–26. doi: 10.1016/j.semcancer.2017.06.003.

Min, J. W., J. J. Hu, M. He, R. M. Sanchez, W. X. Huang, Y. Q. Liu, N. B. Bsoul, S. Han, J. Yin, W. H. Liu, et al. 2015. Vitexin reduces hypoxia-ischemia neonatal brain injury by the inhibition of HIF-1 alpha in a rat pup model. *Neuropharmacology* 99:38–50. doi: 10.1016/j.neuropharm.2015.07.007.

Min, J. W., W. L. Kong, S. Han, N. Bsoul, W. H. Liu, X. H. He, R. M. Sanchez, and B. W. Peng. 2017. Vitexin protects against hypoxic-ischemic injury via inhibiting Ca^{2+}/Calmodulin-dependent protein kinase II and apoptosis signaling in the neonatal mouse brain. *Oncotarget* 8 (15):25513–24. doi: 10.18632/oncotarget.16065.

Moharram, F. A., R. El-Dib, M. S. Marzouk, S. M. El-Shenawy, and H. A. Ibrahim. 2017. New apigenin glycoside, polyphenolic constituents, anti-inflammatory and hepatoprotective activities of *Gaillardia grandiflora* and *Gaillardia pulchella* aerial parts. *Pharmacognosy Magazine* 13 (50):244–S249. doi: 10.4103/pm.pm_344_16.

Ngwoke, K. G., C. Ezenkwu, D. L. Ajaghaku, and P. Proksch. 2017. Vitexin with its derivatives is responsible for the cholinomimetic properties of *Penianthus longifolius* extract which stimulates muscarinic receptors. *Natural Products Journal* 7:231–6.

Nikfarjam, B. A., F. Hajiali, M. Adineh, and M. Nassiri-Asl. 2017. Anti-inflammatory effects of quercetin and vitexin on activated human peripheral blood neutrophils - The effects of quercetin and vitexin on human neutrophils. *J Pharmacopuncture* 20:127–31.

Ninfali, P., E. Antonini, A. Frati, and E. S. Scarpa. 2017. *C*-Glycosyl flavonoids from *Beta vulgaris Cicla* and betalains from *Beta vulgaris rubra*: Antioxidant, anticancer and antiinflammatory activities-A review. *Phytotherapy Research* 31 (6):871–84. doi: 10.1002/ptr.5819.

Nurdiana, S., Y. M. Goh, A. Hafandi, S. M. Dom, A. Nur Syimal'ain, N. M. Noor Syaffinaz, and M. Ebrahimi. 2018. Improvement of spatial learning and memory, cortical gyrification patterns and brain oxidative stress markers in diabetic rats treated with Ficus deltoidea leaf extract and vitexin. *Journal of Traditional and Complementary Medicine* 8 (1):190–202. doi: 10.1016/j.jtcme.2017.05.006.

Nurdiana, S., Y. M. Goh, H. Ahmad, S. M. Dom, N. Syimal'ain Azmi, N. S. Noor Mohamad Zin, and M. Ebrahimi. 2017. Changes in pancreatic histology, insulin secretion and oxidative status in diabetic rats following treatment with *Ficus deltoidea* and vitexin. *BMC Complementary and Alternative Medicine* 17 (1):e290. doi: 10.1186/s12906-017-1762-8.

Pahlavan, S., M. S. Tousi, M. Ayyari, A. Alirezalu, H. Ansari, T. Saric, and H. Baharvand. 2018. Effects of hawthorn (*Crataegus pentagyna*) leaf extract on electrophysiologic properties of cardiomyocytes derived from human cardiac arrhythmia-specific induced pluripotent stem cells. *The FASEB Journal* 32 (3):1440–51. doi: 10.1096/fj.201700494RR.

Papalia, T., D. Barreca, and M. R. Panuccio. 2017. Assessment of antioxidant and cytoprotective potential of Jatropha (*Jatropha curcas*) grown in southern Italy. *International Journal of Molecular Sciences* 18 (3):e660. doi: 10.3390/ijms18030660.

Peng, Y., Q. Sun, and Y. Park. 2019b. The bioactive effects of chicoric acid as a functional food ingredient. *Journal of Medicinal Food* 22 (7):645–52. doi: 10.1089/jmf.2018.0211.

Peng, Y., Q. Sun, and Y. Park. 2019c. Chicoric acid promotes glucose uptake and Akt phosphorylation via AMP-activated protein kinase α-dependent pathway. *Journal of Functional Foods* 59:8–15. doi: 10.1016/j.jff.2019.05.020.

Peng, Y., Q. Sun, R. Gao, and Y. Park. 2019a. AAK-2 and SKN-1 are involved in chicoric-acid-induced lifespan extension in *Caenorhabditis elegans*. *Journal of Agricultural and Food Chemistry* 67 (33):9178–86. doi: 10.1021/acs.jafc.9b00705.

Peng, Y., Q. Sun, W. Xu, Y. He, W. Jin, L. Yuan, and R. Gao. 2019d. Vitexin ameliorates high fat diet-induced obesity in male C57BL/6J mice via the AMPKalpha-mediated pathway. *Food & Function* 10 (4):1940–7. doi: 10.1039/C9FO00148D.

Porta, C., C. Paglino, and A. Mosca. 2014. Targeting PI3K/Akt/mTOR signaling in cancer. *Frontiers in Oncology* 4:64. doi: 10.3389/fonc.2014.00064.

Rath, S. N., M. Ray, A. Pattnaik, and S. K. Pradhan. 2016. Drug target identification and elucidation of natural inhibitors for *Bordetella pertii*: An in silico study. *Genomics & Informatics* 14 (4):241–254. doi: 10.5808/GI.2016.14.4.241.

Rosa, S. I. G., F. Rios-Santos, S. O. Balogun, and D. T. D. Martins. 2016. Vitexin reduces neutrophil migration to inflammatory focus by down-regulating pro-inflammatory mediators via inhibition of p38, ERK1/2 and JNK pathway. *Phytomedicine* 23 (1):9–17. doi: 10.1016/j.phymed.2015.11.003.

Rosa, S. I. G., F. Rios-Santos, S. O. Balogun, D. A. T. de Almeida, A. S. Damazo, T. C. D. da Cruz, E. Pavan, R. D. S. Barbosa, T. D. C. Alvim, I. M. Soares, et al. 2017. Hydroethanolic extract from *Echinodorus scaber Rataj* leaves inhibits inflammation in ovalbumin-induced allergic asthma. *Journal of Ethnopharmacology* 203:191–199. doi: 10.1016/j.jep.2017.03.025.

Rosenfeldt, M. T., and K. M. Ryan. 2011. The multiple roles of autophagy in cancer. *Carcinogenesis* 32 (7):955–963. doi: 10.1093/carcin/bgr031.

Sadati, S. M., N. Gheibi, S. Ranjbar, and M. S. Hashemzadeh. 2019. Docking study of flavonoid derivatives as potent inhibitors of influenza H1N1 virus neuraminidase. *Biomedical Reports* 10 (1):33–38. doi: 10.3892/br.2018.1173.

Sadot, E., B. Geiger, M. Oren, and A. Ben-Ze'ev. 2001. Down-regulation of beta-catenin by activated p53. *Molecular and Cellular Biology* 21 (20):6768–6781. doi: 10.1128/MCB.21.20.6768-6781.2001.

Sayed, N., A. Khurana, and C. Godugu. 2019. Pharmaceutical perspective on the translational hurdles of phytoconstituents and strategies to overcome. *Journal of Drug Delivery Science and Technology* 53:101201. doi: 10.1016/j.jddst.2019.101201.

Scarpa, E. S., E. Antonini, F. Palma, M. Mari, and P. Ninfali. 2018. Antiproliferative activity of vitexin-2-O-xyloside and avenanthramides on CaCo-2 and HepG2 cancer cells occurs through apoptosis induction and reduction of pro-survival mechanisms. *European Journal of Nutrition* 57 (4):1381–1395. doi: 10.1007/s00394-017-1418-y.

Scarpa, E. S., M. Emanuelli, A. Frati, V. Pozzi, E. Antonini, G. Diamantini, G. Di Ruscio, D. Sartini, T. Armeni, F. Palma, et al. 2016. Betacyanins enhance vitexin-2-O-xyloside mediated inhibition of proliferation of T24 bladder cancer cells dagger. *Food & Function* 7 (12):4772–4780. doi: 10.1039/C6FO01130F.

Schuster, R., W. Holzer, H. Doerfler, W. Weckwerth, H. Viernstein, S. Okonogi, and M. Mueller. 2016. Cajanus cajan- a source of PPARgamma activators leading to anti-inflammatory and cytotoxic effects. *Food & Function* 7 (9):3798–3806. doi: 10.1039/C6FO00689B.

Seyedan, A., Z. Mohamed, M. A. Alshagga, S. Koosha, and M. A. Alshawsh. 2019. *Cynometra cauliflora Linn*. attenuates metabolic abnormalities in high-fat diet-induced obese mice. *Journal of Ethnopharmacology* 236:173–182. doi: 10.1016/j.jep.2019.03.001.

Shang, S.,. F. Hua, and Z. W. Hu, 2017. The regulation of β-catenin activity and function in cancer: Therapeutic opportunities. *Oncotarget* 8 (20):33972–33989. doi: 10.18632/oncotarget.15687.

Shuayprom, A., D. Sanguansermsri, P. Sanguansermsri, I. H. Fraser, and N. Wongkattiya, 2016. Quantitative determination of vitexin in *Passiflora foetida Linn*. leaves using HPTLC. *Asian Pacific Journal of Tropical Biomedicine* 6 (3):216–220. doi: 10.1016/j.apjtb.2015.11.006.

Sun, Q., J. Lin, Y. Peng, R. Gao, and Y. Peng, 2018. Flubendiamide enhances adipogenesis and inhibits AMPKα in 3T3-L1 adipocytes. *Molecules* 23 (11):e2950. doi: 10.3390/molecules23112950.

Sun, Z., B. Yan, W. Y. Yu, X. P. Yao, X. J. Ma, G. L. Sheng, and Q. Ma, 2016. Vitexin attenuates acute doxorubicin cardiotoxicity in rats via the suppression of oxidative stress, inflammation and apoptosis and the activation of FOXO3a. *Experimental and Therapeutic Medicine* 12 (3):1879–1884. doi: 10.3892/etm.2016.3518.

Tang, Z. B., L. Yang, and X. S. Zhang, 2017. Vitexin mitigates myocardial ischemia reperfusion-induced damage by inhibiting excessive autophagy to suppress apoptosis via the PI3K/Akt/mTOR signaling cascade. *RSC Advances* 7 (89):56406–56416. doi: 10.1039/C7RA12151B.

Venturini, C. L., A. Macho, K. Arunachalam, D. A. T. de Almeida, S. I. G. Rosa, E. Pavan, S. O. Balogun, A. S. Damazo, and D. T. D. Martins, 2018. Vitexin inhibits inflammation in murine ovalbumin-induced allergic asthma. *Biomedicine & Pharmacotherapy* 97:143–151. doi: 10.1016/j.biopha.2017.10.073.

Wang, C. L., T. Y. Li, L. Zhang, Y. T. Zhu, K. Z. Zhu, and Z. Y. Li, 2019. Vitexin alleviates lipopolysaccharide-induced acute kidney injury via triggering AMPK/FOXO3a signaling pathway in newborn rats. *Latin American Journal of Pharmacy* 38:558–564.

Wang, F., J. Yin, Y. Ma, H. Jiang, and Y. Li, 2017. Vitexin alleviates lipopolysaccharide-induced islet cell injury by inhibiting HMGB1 release. *Molecular Medicine Reports* 15 (3):1079–1086. doi: 10.3892/mmr.2017.6114.

Wang, Y. J., C. H. Han, A. J. Leng, W. J. Zhang, H. F. Xue, Y. H. Chen, J. J. Yin, D. R. Lu, and X. X. Ying, 2012. Pharmacokinetics of vitexin in rats after intravenous and oral administration. *African Journal of Pharmacy and Pharmacology* 6 (31):2368–2373. doi: 10.5897/AJPP12.534.

Wirawan, E., S. Lippens, T. Vanden-Berghe, A. Romagnoli, G. M. Fimia, M. Piacentini, and P. Vandenabeele, 2012. Beclin1: A role in membrane dynamics and beyond. *Autophagy* 8 (1):6–17. doi: 10.4161/auto.8.1.16645.

Wu, H., G. Zhang, L. Huang, H. Pang, N. Zhang, Y. Chen, and G. Wang, 2017. Hepatoprotective effect of polyphenol-enriched fraction from *Folium Microcos* on oxidative stress and apoptosis in acetaminophen-induced liver injury in mice. *Oxidative Medicine and Cellular Longevity* 2017:1–14. doi: 10.1155/2017/3631565.

Xiao, J., E. Capanoglu, A. R. Jassbi, and A. Miron, 2016. Advance on the flavonoid *C*-glycosides and health benefits. *Crit Rev Food Sci Nutr* 56 (sup1):S29–S45. doi: 10.1080/10408398.2015.1067595.

Xie, C. L., J. L. Li, E. X. Xue, H. C. Dou, J. T. Lin, K. Chen, H. Q. Wu, L. Wu, J. Xuan, and Q. S. Huang, 2018. Vitexin alleviates ER-stress-activated apoptosis and the related inflammation in chondrocytes and inhibits the degeneration of cartilage in rats. *Food & Function* 9 (11):5740–5749. doi: 10.1039/C8FO01509K.

Xue, H. F., Z. M. Ying, W. J. Zhang, Y. H. Meng, X. X. Ying, and T. G. Kang, 2014. Hepatic, gastric, and intestinal first-pass effects of vitexin in rats. *Pharmaceutical Biology* 52 (8):967–971. doi: 10.3109/13880209.2013.874464.

Yang, H., J. Huang, Y. Mao, L. Wang, R. Li, and C. Ha, 2019. Vitexin alleviates interleukin-1beta induced inflammatory responses in chondrocytes from osteoarthritis patients: Involvement of HIF-1alpha pathway. *Scandinavian Journal of Immunology* 90 (2):e12773. doi: 10.1111/sji.12773.

Yang, J. H., M. H. Choi, S. H. Yang, S. S. Cho, S. J. Park, H. J. Shin, and S. H. Ki, 2017. Potent anti-inflammatory and antiadipogenic properties of Bamboo (*Sasa coreana Nakai*) leaves extract and its major constituent flavonoids. *Journal of Agricultural and Food Chemistry* 65 (31):6665–6673. doi: 10.1021/acs.jafc.7b02203.

Yun, C. W., and S. H. Lee, 2018. The roles of autophagy in cancer. *International Journal of Molecular Sciences* 19 (11):e3466. doi: 10.3390/ijms19113466.

Zhang, G. N., D. Y. Li, H. Chen, J. C. Zhang, and X. Y. Jin, 2018. Vitexin induces G2/M-phase arrest and apoptosis via Akt/mTOR signaling pathway in human glioblastoma cells. *Molecular Medicine Reports* 17:4599–4604.

Zhang, S. L., C. L. Guo, Z. G. Chen, P. Y. Zhang, J. H. Li, and Y. Li, 2017b. Vitexin alleviates ox-LDL-mediated endothelial injury by inducing autophagy via AMPK signaling activation. *Molecular Immunology* 85:214–221. doi: 10.1016/j.molimm.2017.02.020.

Zhang, S., Y. Xie, J. Wang, Y. Geng, Y. Zhou, C. Sun, and G. Wang, 2017a. Development of an LC-MS/MS method for quantification of two pairs of isomeric flavonoid glycosides and other ones in rat plasma: Application to pharmacokinetic studies. *Biomedical Chromatography* 31 (10):e3972. doi: 10.1002/bmc.3972.

Zhu, Q., L. N. Mao, C. P. Liu, Y. H. Sun, B. Jiang, W. Zhang, and J. X. Li, 2016. Antinociceptive effects of vitexin in a mouse model of postoperative pain. *Scientific Reports* 6 (1):e19266. doi: 10.1038/srep19266.