

Supplementary Data

Supplemental Table: A summary of recent studies that have focused on PAs and their associated health benefits.

Aging-Related Diseases	PAs	PAs Origins	Model Organisms	Molecular Targets	Reference
Cancer	Grape seed procyanidin (GSP) (>98%)	Grape seeds	Multi-drug resistance (MDR)1-overpressing paclitaxel resistant ovarian cancer cells	GSP reversed P-glycoprotein (P-gp) associated multi-drug resistance (MDR) by inhibiting the function and expression of P-gp through down-regulation of NF- κ B and MAPK/ERK pathway mediated Y-box binding protein 1 (YB-1) nuclear translocation	1
Cancer	Procyanidin C1	Cinnamomi cortex (CC)	Human lung adenocarcinoma A549 cells	Inhibitory effect on transforming growth factor (TGF)- β -induced epithelial-to-mesenchymal transition (EMT)	2
Cancer	Procyanidin B2-3,3'-di-O-gallate (B2G2)	Chemically synthesized, gram-scale quantities	Human prostate cancer PCa, PC3 and 22Rv1 cells	B2G2 induced apoptosis by inhibiting NF- κ B and activator protein1 (AP1) transcriptional activity and nuclear translocation of signal transducer and activator of transcription3 (STAT3)	3
Cancer	Oligomeric procyanidin, average degree of polymerization (DP) = 3.9	French cider apple (<i>Malus domestica</i>)	Human esophageal adenocarcinoma OE33 and esophageal epithelial (HEECs) cells	Induction of cell cycle arrest and apoptosis via JNK mediated activation of c-Jun	4
Cancer	Acetylated procyanidin B1	Chemically synthesized	Human cervical adenocarcinoma HeLa-S3 cell	Inhibitory effect on HeLa S3 cell proliferation	5
Cancer	Procyanidin A2	American cranberry (<i>Vaccinium macrocarpon</i> Ait.)	Human hepatocytes	Stimulatory effect on main drug metabolizing enzymes namely five forms of cytochromes P450 (CYP) except CYP2A6	6
Cancer	Flavan-3-ol, <i>Vitis labrusca</i> seed extract (VLE)	Grape seeds (<i>Vitis labrusca</i>)	Human liver cancer HepG2 and breast cancer MCF-7 cells	Induction of p53 and peroxisome proliferator-activated receptor (PPAR) related DNA damage and accompanied NO production	7
Cancer	Epigallocatechin-3-gallate (EGCG), procyanidin B2-3, 3'-di-O-gallate (B2)	Chemically synthesized	Human invasive breast cancer cell MDA-MB-231 and immortalized human keratinocyte cell HaCaT	Attenuation of DNA methyltransferases (DNMTs), a key epigenetic enzyme, and DNMT target genes E-cadherin, Maspin and BRCA1	8
Cancer	Standardized GSPE (90% procyanidins)	White grapes (<i>Vitis vinifera</i> L.)	Lung neoplastic cells NSCLC, A549, H520, H1299, BEAS-2B and the bronchial premalignant cell line	Antineoplastic effect through the modulation of oncomirs miR-19a and -19b, mRNA and protein levels of insulin-like growth factor II receptor (IGF-2R) and phosphatase and tensin homolog (PTEN)	9

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Cancer	Purified white grape pomace extract (PWGPE)	Grape pomace (<i>Zalema</i>)	Human colon adenocarcinoma cell Caco-2	Inhibitory effect on Caco-2 cell proliferation	10
Cancer	Flavonoids extracted from <i>Orostachys japonicus A. Berger</i> (FEOJ)	<i>Orostachys japonicus A. Berger</i>	U937 human leukemic cancer cell	Induction of caspase-dependent cancer cell apoptosis through the suppression of mitochondrial membrane potential, BLC-2, XIAP proteins and p38 MAPK signaling	11
Cancer	Trimeric PAs, hexamer and the cocoa flavanol extract	Cocoa liquor and chocolates	Colorectal cancer cell (CRC)	Inhibitory effect on colorectal cancer cell growth through the regulation of Akt kinase pathway	12
Cancer	Cocoa procyanidins	Non-alkalized cocoa powder	Human ovarian cancer OAW42 and OVCAR3 cells	Suppression of the growth of ovarian cancer <i>in vitro</i> while stimulation of the viability of normal dermal fibroblasts, affecting cell cycle and the expression of P-glycoprotein (P-gp)	13
Cancer	Procyanidin A2	Chemically synthesized	Human alveolar epithelial A549 cell	Temporal inhibition of chemokine eotaxin-3 (CCL26) production	14
Cancer	Leucoselect® Phytosome® grape seed procyanidin extract (LP, Indena S.p.A., Milan, Italy)	A formulation of lower procyanidin oligomers from grape seeds (<i>Vitis vinifera L.</i>)	Human lung premalignant and malignant cells, bronchoalveolar lavage (BAL) cell	Stimulatory effect on the production of prostacyclin synthase (PTGIS)/PGI2 and 15-lipoxygenase-2 (15-LOX-2)/15-HETE	15
Cardiovascular diseases	Grape seed procyanidin extract (GSPE)	White grape seeds (<i>Vitis vinifera L.</i>)	Spontaneously hypertensive rats (SHR), a model of genetically hypertensive rats and normotensive Wistar-Kyoto rats	GSPE significantly reduced the systolic and diastolic blood pressure of spontaneously hypertensive rats while did not affect blood pressure of normotensive Wistar-Kyoto rats	16
Cardiovascular diseases	Cacao liquor procyanidin extract (CLPr)	Cacao liquor	L6 myotubes to myoblasts	Low-DP procyanidins stimulated glucose uptake by glucose transporter 4 translocation through AMP-activated protein kinase (AMPK)-dependent pathway in skeletal muscle; high-DP procyanidins mainly inhibited the activity of α -glucosidase in small intestine	17
Cardiovascular diseases	Low-molecular-weight procyanidin rich grape seed extract (LM-GSPE)	White grape seeds (<i>Vitis vinifera L.</i>)	Male spontaneously hypertensive rats (SHR)	LM-GSPE presented antihypertensive effects in an endothelium dependent manner, which is related to the bioavailability of endothelium-derived nitric oxide and prostacyclin	18
Cardiovascular diseases	Grape seed procyanidin B2 (GSPB2) (> 90%)	Grape seeds liquid-solid extraction	Male C57BLKS/J <i>db/db</i> and age-matched <i>db/m</i> mice	Regulation of the expression of key proteins involved in cardiac fibrosis and proliferation	19

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Cardiovascular diseases	Procyanidin C1 (Pro C1)	Chemically synthesized	Phenylephrine-constricted endothelium-intact thoracic aortic rings, denuded thoracic aortic rings	Vasorelaxant effect on phenylephrine-constricted endothelium-intact thoracic aortic rings, regulating calcium-dependent NO/cyclic guanosine monophosphate (cGMP) pathway	20
Cardiovascular diseases	(-)-epicatechin and its derived dimer procyanidin B2 (> 98%)	Chemically synthesized	Isolated rat heart mitochondria	Inhibitory effect on the oxidative phosphorylation of isolated rat heart mitochondria in a substrates dependent manner	21
Cardiovascular diseases	Oligopin® (OP, Purextract, Dax, France), low molecular weight procyanidins	French maritime pine bark (FMPB)	Eligible patients were recruited from the outpatient clinics of Hospital Universitari Sant Joan de Reus	Improvement of lipid cardiovascular profile, increasing high density lipoprotein-cholesterol (HDL-c) in stage-I-hypertensive subjects	22
Cardiovascular diseases	Procyanidin B2-3,3'-di- O-gallate (B2G2)	Grape seeds	Human umbilical vein endothelial cells (HUVECs) and prostate microvascular endothelial cells (HPMECs)	B2G2 inhibited growth and induced death in both HUVECs and HPMECs, causing G1 arrest in cell cycle. B2G2 also inhibited the motility and invasiveness of both HUVECs and HPMECs via the VEGFR2/PI3K/Akt and integrin signaling	23
Cardiovascular diseases	Grape seed procyanidin extract (GSPE)	White grape seeds (<i>Vitis vinifera L.</i>)	Male 8-week-old Wistar rats fed with cafeteria or standard diet	Regulation of levels of endothelium-derived NO and endothelial prostacyclin	24
Cardiovascular diseases	Grape seed procyanidin extract (GSPE)	Grape seeds liquid-solid extraction	Male Sprague-Dawley rats exposed to intermittent chronic hypoxia for 4 weeks to mimic a severe hypoxic pulmonary hypertension (HPH) condition and pulmonary artery smooth muscle cells (PASMCs)	GSPE prevented HPH via antioxidant and antiproliferative mechanisms, up-regulating superoxide dismutase (SOD) and suppressing malondialdehyde (MDA), NOX4, reactive oxygen species (ROS) and pulmonary artery smooth muscle cells (PASMCs) proliferation; GSPE also suppressed the increase of phospho-STAT3, cyclin D1, cyclin D3 and Ki67 in PASMCs caused by hypoxia	25
Obesity	Cacao liquor procyanidin (CLPr) extract	Cacao beans (<i>Theobroma cacao</i>)	C57BL/6 mice exposed to high-fat diet	Suppression of high-fat diet-induced hyperglycemia, glucose intolerance and lipid deposits via the activation of AMP-activated protein kinase α (AMPK α), translocation of glucose transporter 4 (GLUT4) and up-regulation of uncoupling protein (UCP)-1	26
Obesity	Epicatechin-(4 β →6)-epicatechin-(2 β →O→7, 4 β →8)-catechin (EEC)	Peanut skin (<i>Arachis hypogaea L.</i>)	A cholesterol micellar solution	Hypocholesterolaemia activity via regulating the micelle degradation in the intestine	27
Obesity	Flavangenol® (72.5% polyphenols, pine bark extracts, Toyo Shinyaku Co.), procyanidin B1	Flavangenol is a trademark for several pine bark extracts obtained from the pine trees (<i>Pinus maritima</i>)	Male metabolic syndrome model animal (TSOD) and control of TSOD (TSNO) mice; HepG2 cells	Flavangenol®, especially procyanidin B1 as the major components, suppressed fat accumulation and induced the mRNA expression of fatty acid oxidative enzymes	28

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Obesity	Grape seed procyanidin extract (GSPE)	White grape seeds (<i>Vitis vinifera</i> L.)	Obese female Zucker <i>fa/fa</i> rats	A moderate dose of GSPE down-regulated the expression of inducible nitric oxide synthase (iNOS) and Il-6 and up-regulated the expression of adiponectin in adipocytes	29
Obesity	Grape seed procyanidin extract (GSPE)	Grape seeds	Human colorectal adenocarcinoma cells (Caco-2); wild type (WT) and farnesoid x receptor (<i>Fxr</i>) ^{-/-} mice	GSPE lowered triglyceride levels, selectively modulated intestinal expression of FXR-target genes (e.g. hepatic cholesterol 7 α -hydroxylase (CYP7A1) and fibroblast growth factor 15 (FGF-15)), altering enterohepatic bile acids (BA) recirculation	30
Obesity	Grape seed procyanidin extract (GSPE)	White grape seeds (<i>Vitis vinifera</i> L.)	Female virgin rats (Charles River Laboratories, Spain) were mated with males until impregnation	Increase of adiposity index and the weight of white adipose tissue depots of offspring, via regulating the expression of 238 genes associated with immunity, inflammation, lipid and glucose homeostasis and the metabolism of methyl groups	31
Obesity	Grape seed procyanidin extract (GSPE)	White grape seeds (<i>Vitis vinifera</i> L.)	Fructose-fed male Wistar rats	Inhibitory effect on hepatic lipogenesis via the down-regulation of sterol regulatory element binding protein 1c (SREBP1c) and stearoyl-CoA desaturase 1, targeting the bile acids (BA) homeostasis and non-biliary cholesterol excretion	32
Obesity	Procyanidin A2 (> 99%)	Chemically synthesized	Liver tissue collected from normolipidemic male C57BL/6 mice	Decrease of serum triglyceride <i>in vivo</i> via the epigenetic regulation modulating histone deacetylases and peroxisome proliferator-activated receptor α (PPARA) activity; Cholesterol synthesis and excretion in in various physiological states were also regulated	33
Obesity	Grape seed procyanidin extract (GSPE)	Grape seeds	C57BL/6 mice	Enhancement of <i>de novo</i> bile acid biosynthesis, regulating intestinal expression of IBABP and FGF15 and hepatic expression of CYP7A1 and SREBP1c	34
Obesity	Grape seed procyanidin extract (GSPE): monomers (68.68 \pm 0.02%), dimers (26.16 \pm 0.01%) and trimers (5.16 \pm 0.02%)	Grape seeds	Farnesoid x receptor (<i>Fxr</i>) ^{-/-} mice	GSPE selectively regulated intestinal <i>Fxr</i> target genes involved in bile acids (BA) uptake and transport, up-regulating both gene and protein expression of hepatic cholesterol 7 α -hydroxylase (Cyp7A1)	35
Obesity	Grape seed procyanidin (GSP)	Chemically synthesized	3T3-L1 preadipocyte cell line	Decrease of intracellular lipid accumulation in induced 3T3-L1 cells, targeting miR-483-5p and peroxisome proliferator-activated receptor γ (PPARG)	36
Diabetes	<i>Cinnamomum cassia</i> extract (CC-E) and <i>Cinnamomum tamala</i> extract (CT-E) PAs enriched	<i>Cinnamomum cassia</i> and <i>Cinnamomum tamala</i>	8-week-old diabetic (<i>db/db</i>) mice	CC-E promoted lipid accumulation in the adipose tissues and liver, whereas CT-E improved the insulin concentration in the blood and pancreas	37

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Diabetes	Grape seed procyanidin B2 (GSPB2)	Grape seeds	Male C57BLKS/J <i>db/db</i> and their nondiabetic <i>db/m</i> littermates	Decrease of protein levels of milk fat globule EGF-8 (MFG-E8), phospho-ERK1/2, phospho-Akt and phospho-GSK-3 β in the kidney of <i>db/db</i> mice	38
Diabetes	Grape seed procyanidin extract (GSPE)	White grape seeds (<i>Vitis vinifera</i> L.)	INS-1E pancreatic β -cell line	High molecular weight GSPE components enhanced the pro-apoptotic effect of high glucose and showed clear antiproliferative effect under high levels of glucose, insulin and palmitate, but not basal conditions	39
Diabetes	Oligomeric procyanidins and cinnamtannin A2, a tetrameric procyanidin	Cacao liquor	Male ICR mice	Cinnamtannin A2 activated insulin receptor and insulin receptor substrate-1, increasing glucagon-like peptide-1 (GLP-1) and insulin secretion in the plasma	40
Diabetes	Cacao liquor procyanidin (CLPr)	Cacao liquor	Male ICR and C57BL/6 mice; L6 myoblasts (passage 27-37)	CLPr improved glucose tolerance by promoting GLUT4 translocation to the plasma membrane of skeletal muscle	41
Diabetes	Grape seed procyanidin extract (GSPE)	White grape seeds (<i>Vitis vinifera</i> L.)	Zucker fatty (ZF) rats: 5-week-old lean and obese female Zucker <i>fa/fa</i> rats	GSPE limited the synthesis and secretion of insulin and modulated factors involved in apoptosis	42
Diabetes	Procyanidin-B2	Cinnamon (<i>Cinnamomum zeylencium</i>)	Male Wistar-NIN (WNIN) rats	Delay of diabetic cataract via inhibiting the accumulation of advanced glycation end products (AGE) in diabetic rats	43
Diabetes	Procyanidin-B2 (PCB2)	Cinnamon (<i>Cinnamomum zeylencium</i>)	Streptozotocin-induced diabetic rats	Cinnamon and PCB2-fraction down-regulated advanced glycation end products (AGE), ameliorated diabetes mediated renal malfunction in rats as seen the reduced urinary albumin and creatinine	44
Diabetes	Procyanidin	Chemically synthesized	Sprague Dawley (SD) rats	Neuroprotective effect on type 2 diabetes mellitus-middle cerebral artery occlusion (MCAO), via down-regulating the expression level of SATA1 involved in the kinase/signal transducer and activator of transcription (JAK/STAT) pathway	45
Diabetes	Grape seed procyanidin B2 (GSPB2) (> 95%)	Grape seeds	Diabetic <i>db/db</i> mice	Protective effect on diabetic pancreas and islet, improving the level of insulin and homeostatic model assessment-insulin resistance (HOMA-IR) while reducing the level of milk fat globule epidermal growth factor-8 (MFG-E8), pro-inflammatory cytokines interleukin-1 β (IL-1 β) and pyrin domain containing 3 (NLRP3)	46

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Diabetes	Grape seed procyanidin B2 (GSPB2)	Grape seeds liquid-solid extraction	Rat mesangial cells (HBZY-1)	GSPB2 inhibited apoptosis in rat mesangial cells treated with glucosamine (GlcN) under high-dose conditions, suppressed oxidative stress by elevating the activity of glutathione peroxidase and superoxide dismutase, activated the expression of peroxisome proliferator-activated receptor γ (PPARG) co-activator-1 α (PGC-1 α), silent mating type information regulation 2 homologue 1 (SIRT1) and AMP-activated protein kinase (AMPK)	47
Diabetes	Procyanidin B2	Chemically synthesized	HK-2 human renal proximal tubular epithelial cell line	Pretreatment with procyanidin B2 reversed the high glucose induced epithelial mesenchymal transition (EMT)-associated changes, up-regulated the expression of E-cadherin and down-regulated the expression level of vimentin and α SMA, decreased the phosphorylation of small mothers against decapentaplegic (SMAD)2, 3 and P38, and up-regulated the expression of phosphorylatedSMAD7	48
Diabetes	Procyanidin A2 (PCA2)	Chemically synthesized	NMRI male mice	PCA2 strongly prevented islet cell apoptosis, reduced mRNA expression of pancreatic and duodenal homeobox 1 (<i>Pdx1</i>) and glucose transporter 2 (<i>Glut2</i>) and the antioxidant level in pancreas tissue induced by bisphenol A	49
Diabetes	ChoronoCare® black soybean seed coat extract (BE, Fujicco, Hyogo, Japan): 68.7% polyphenols and 40.7% flavan-3-ols	Black soybean seed	Male ICR mice	Trimeric and tetrameric procyanidins, especially cinnamtannin A2, suppressed acute hyperglycaemia, activated both insulin- and AMP-activated protein kinase (AMPK) signaling and induced GLUT4 translocation in muscle	50
Diabetes	Epicatechin-(4 β →6)-epicatechin-(2 β →O→7, 4 β →8)-catechin (EEC)	Peanut skin (<i>Arachis hypogaea</i> L.)	Caco-2 cell	Procyanidin dimer EEC, compared to (+)-catechin, inhibited α -amylase activity and glucose transport in Caco-2 cells	51
Diabetes	A-type procyanidin trimer cinnamtannin-1 (CT1) and its methylated products (MPs)	<i>Cinnamomum tamala</i>	Palmitic acid-treated INS-1 cell	Compared to CT1, O-methyl derivatives of CT1 presented less protective capacity on a palmitic acid-induced pancreatic β -cell apoptosis model, which might be attributed to the obstructed formation of quinone intermediate and thus antioxidant ability	52

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Diabetes	Trimeric procyanidin oligomers	<i>Cinnamomum tamala</i> (CT-E) and <i>Cinnamomum cassia</i> (CC-E)	INS-1 pancreatic β -cells exposed to palmitic acid (PA) or H ₂ O ₂ to induce lipotoxicity and oxidative stress	Trimer procyanidins cpd3, cpd4 and cpd6 dose-dependently increased the cell viability, decreased reactive oxygen species (ROS) accumulation in H ₂ O ₂ -treated β -cells and increased glucose-stimulated insulin secretion in PAs treated β -cells	53
Diabetes	Procyanidin (OPC)	Not mentioned	Sprague-Dawley rat bone marrow mononuclear cell and endothelial progenitor cell (EPCs) exposed to high glucose (HG)	OPC significantly reduced the level of oxidative stress related products, up-regulated the expression of vascular endothelial growth factor receptor-2 (VEGFR-2), Protein kinase B (AKT), NF- κ B protein and down-regulated the expression of NF- κ B inhibitor α (I κ B- α)	54
Diabetes	Grape seed procyanidin B2 (GSPB2)	Grape seeds liquid-solid extraction	Podocytes injured in rats with diabetic nephropathy (DN)	GSPB2 protected podocytes from high glucose-induced mitochondrial dysfunction and apoptosis via the AMP-activated protein kinase (AMPK)-SIRT1-PGC-1 α axis <i>in vitro</i>	55
Oxidation	Procyanidin B2 (PB2)	Cocoa flavonoids	Human colonic Caco-2 cell	PB2 induced the expression and activity of glutathione S-transferase P1 (GSTP1), nuclear translocation of the transcription factor NF-erythroid 2-related factor (NRF2), extracellular signal-regulated protein kinases (ERKs) and p38 mitogen-activated protein kinase (MAPK)	56
Oxidation	Grape seed procyanidins extract (GSPE)	Grape seeds liquid-solid extraction	Adult Kunming mice administered with dietary cadmium (Cd)-incorporated diet	GSPE attenuated cadmium-induced lipid peroxidation and renal damage, probably associated with the expression of BAX and BCL-2	57
Oxidation	A specific blend of resveratrol (3,5,40-trihydroxystilbene) and procyanidin	One capsule of supplement contains 8 mg transresveratrol and 133 mg grape (<i>Vitis vinifera</i> L.) extract from a patented production process	50 human subjects (25 treated with supplements and 25 with placebo)	Short term treatment of resveratrol and procyanidin improved clinical features induced by chronoaging or photoaging, including skin hydration, elasticity, roughness levels and systemic oxidative stress levels	58
Oxidation	Procyanidin C1	White grape seeds (<i>Vitis vinifera</i> L.)	Rat aortic endothelial cells (RAECs)	Procyanidin C1 induced NO production in RAECs via both Ca ²⁺ -dependent Ca ²⁺ -activated K ⁺ (BK _{Ca}) channel-mediated hyperpolarization and Ca ²⁺ -independent PI3K/Akt pathways	59

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Oxidation	Procyanidin B2 (> 95%)	Not mentioned	CCl ₄ -treated (hepatotoxicity) male ICR mice	Protective effect on hepatic injury by elevating the antioxidative defense potential, decreasing the expression of TNF- α , IL-1 β , cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and the translocation of nuclear factor-kappa B (NF- κ B) p65, and suppressing the inflammatory response via apoptosis-related <i>Bax</i> and <i>Bcl-xL</i> signaling	60
Oxidation	Grape seed procyanidin B2 (GSPB2)	Grape	Granulosa cell	GSPB2 decreased the expression of transcription factor forkhead box protein O1 (FoxO1), improved granulosa cell viability, up-regulated the expression of autophagy gene LC3-II, and reduced granulosa cell apoptosis rate	61
Oxidation	Procyanidin (PCA) (> 95%)	Pine needles	Broiler chicks	PCA prevented lipopolysaccharide (LPS)-induced oxidative stress response <i>in vivo</i> and improved the morphology of the small intestine, via increasing the activity of antioxidant enzymes and scavenging free radical activity	62
Oxidation	Proanthocyanidin analogue, the geometry of one catechin molecule in procyanidin B3, a dimer of (+)-catechin, is constrained to be planar	Chemically synthesized	Non-aqueous system using galvinoxyl radical as an oxyl radical species	The radical scavenging activity of procyanidin was 3.8 times more potent than (+)-catechin, with the potent of proanthocyanidin analogue 1 further increased to 1.9 times that of procyanidin B3	63
Inflammation	Crude polyphenolic extract (CPE) and its procyanidin fractions from defatted grape seeds	Grape seeds (<i>Campbell Early</i>)	HepG2 cells with oxidative damage induced by tert-butyl hydroperoxide (TBHP)	The oligomeric procyanidin fraction (OPF) and the polymeric procyanidin fraction (PPF) presented cytoprotective effect against oxidative damage by modulating reactive oxygen species (ROS) production, glutathione (GSH) level, malondialdehyde (MDA) formation and antioxidant enzyme activity	64
Inflammation	Grape seed procyanidin extract (GSPE)	White grape seeds (<i>Vitis vinifera L.</i>)	A rat model of septic shock by intraperitoneal injection of lipopolysaccharide (LPS) derived from <i>Escherichia coli</i> to Wistar female rats	Several doses of GSPE alleviated acute inflammation triggered by lipopolysaccharide (LPS) in rats at systemic and local levels by down-regulating the expression of Il-6 and iNOS	65

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Inflammation	Procyanidin trimer C1	Chemically synthesized	Murine macrophage cell line RAW264.7	Procyanidin C1 promoted anti-inflammatory activity in macrophages, through the inhibition of mitogen-activated protein kinase (p38 and c-Jun N-terminal kinase) and NF- κ B signaling	66
Inflammation	Procyanidin dimer B2 (Pro B2)	Chemically synthesized	Murine macrophage cell line RAW264.7	Pro B2 down-regulated toll-like receptor 4 (TLR4) signal transduction in macrophages; Pro B2-treated macrophages inactivated naïve T cells by inhibiting lipopolysaccharide (LPS)-induced interferon- γ and interleukin (IL)-2 secretion through IL-1 receptor-associated kinase (IRAK)-M protein signaling	67
Inflammation	Procyanidin trimer C1	Chemically synthesized	Murine macrophage cell line RAW264.7	Procyanidin C1 regulated innate and adaptive immunity by activating macrophage and Th1 polarization, via NF- κ B and mitogen-activated protein kinases (MAPK) pathways	68
Inflammation	Oligomeric procyanidin fraction (OPF) and polymeric procyanidin fraction (PPF)	Defatted grape seeds (<i>Campbell Early</i>)	HepG2 cell	PPF significantly increased the expression of nuclear factor erythroid 2-related factor 2 (Nrf2), inhibiting ROS production and inducing heme oxygenase-1 (HO-1) and NAD(P): Quinone oxidoreductase 1 (NQO1) expression	69
Inflammation	Procyanidin B2 (PCB2)	Chemically synthesized	Human umbilical vein endothelial cell (HUVECs)	PCB2 suppressed the activation of pyrin domain containing 3 (NLRP3) inflammasome, lipopolysaccharides (LPS)-induced production of reactive oxygen species (ROS) and the transcriptional activity of activator protein-1 (AP-1)	70
Inflammation	Procyanidin extract	Grape seeds	Crossbred pigs	Dietary addition of procyanidin improved feed efficiency and anti-inflammatory cytokines (interleukin) IL-1 β , IL-6 and tumor necrosis factor (TNF)- α	71
Inflammation	Procyanidin B2 (epicatechin-(4 β →8)-epicatechin)	Chemically synthesized	Lipopolysaccharide (LPS)-primed THP-1-human monocytes	Procyanidin B2 inhibited inflammasome activation, inactivating NF- κ B signaling through its inhibition of p65 nuclear expression and DNA binding, and (interleukin) IL-1 β secretion during lipopolysaccharide (LPS)-induced acute inflammation	72

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Inflammation	Procyanidin B1	Not mentioned	Human monocyte cell line (THP1)	Procyanidin B1 suppressed the expression of tumor necrosis factor (TNF)- α , phosphorylated p38 mitogen-activated protein kinases (MAPK) and NF- κ B, the transcription of myeloid differentiation factor (MD)-2, TNF receptor-associated factor (TRAF)-6 and NF- κ B, competing with lipopolysaccharides (LPS) to bind to the toll-like receptor (TLR)-4-MD-2 heterodimer to suppress the downstream activation of p38 MAPK and NF- κ B signaling	73
Inflammation	Procyanidin A2, B1 and B2	Chemically synthesized	Human lung epithelial cells (A549)	Procyanidin A2 inhibited the production of eotaxin-1 (CCL11) that is linked with airway inflammation, while Procyanidin B1 and B2 elicited no effect	74
Articular cartilage degeneration and heterotopic cartilage formation	Procyanidin B3 (97%)	Grape seed extract (82% proanthocyanidins)	The mouse chondrogenic ATDC5 cell line and primary epiphyseal chondrocytes isolated from 5-day-old mice	Procyanidin B3 prevented osteoarthritis progression and heterotopic cartilage formation, probably through the suppression of inducible nitric oxide synthase (iNOS)	75
Neurodegeneration	Procyanidin B1	Yokukansan, a traditional Japanese (Kampo) medicine, derived from <i>Uncaria hook</i>	Amyloid β oligomer pre-treated rat primary cultured cortical neurons	Procyanidin B1 inhibited amyloid β oligomer-induced neuronal death in a dose-dependent manner, suppressing the activation of caspase-3, -8, and -9	76
Neurodegeneration	Procyanidin B2 (PB)	Not mentioned	Adult male Sprague-Dawley rats	PB attenuated neurological deficits and blood-brain barrier (BBB) disruption in a rat model of cerebral ischemia, associated with activation of NF-erythroid 2-related factor (<i>Nrf-2</i>) pathway	77
Neurodegeneration	Gallotannin, a class of hydrolyzable tannins consisting of gallic acid and a sugar moiety	Tannin-rich plants	Cell-free models, micro-organelles or H ₂ O ₂ activated cell bodies	Gallotannins were neuroprotective partially attributed to their antioxidant property, blocking the accumulation of nitrites, inhibiting the expression and activity of heme oxygenase 1 (HO-1), and decreasing the degradation of poly (ADP ribose) glycohydrolase (PARP)	78

Supplemental References

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