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REVIEW ARTICLE

Pharmacology and toxicology of tannins

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Abstract

Tannins are an interesting class of polyphenols, characterized, in almost all cases, by a different degree of polymerization, which, inevitably, markedly influences their bioavailability, as well as biochemical and pharmacological activities. They have been used for the process of tanning to transform hides into leather, from which their name derives. For several time, they have not been accurately evaluated, but now researchers have started to unravel their potential, highlighting anti-inflammatory, antimicrobial, antioxidant and anticancer activities, as well as their involvement in cardiovascular, neuroprotective and in general metabolic diseases prevention. The mechanisms underlying their activity are often complex, but the main targets of their action (such as key enzymes modulation, activation of metabolic pathways and changes in the metabolic fluxes) are highlighted in this review, without losing sight of their toxicity. This aspect still needs further and better-designed study to be thoroughly understood and allow a more conscious use of tannins for human health.

Keywords Ellagitannins · Proanthocyanidins · Gallotannins · Complex tannins · Pharmacological activities · Toxicology

Introduction

Polyphenols are among the most studied natural compounds due to their wide plethora of potential health benefits, which have been investigated for many years now. An important, but often neglected group of polyphenols, are tannins, a heterogenous group of secondary metabolites, whose name derives from the French word "tanin", a phytocomplex rich of these compounds and employed in the process of tanning for transforming hides into leather due to their ability to form cross-linkages with macromolecules (Falcao and Araujo 2018). In the seventeenth century, an Italian chemist, named Giovannetti, investigated the properties of certain substances, known as "astringents", to interact with iron ions. The next century, the German chemist Scheele isolated the acidic compound responsible of this effect, which revealed itself to be gallic acid. On this line, several other compounds have been included in the group of tannins, based on their peculiar effects, by all the nineteenth century. As industrialization rushed, the employment of iron tannate as a more efficient method, in terms of time and costs, in the leather industry dramatically bloomed up to the introduction for general population of plastic-based textiles at half of the twentieth century, which supplanted the majority of the more precious, yet expensive, leather products (Pizzi 2019). Tannins are commonly known for their astringent taste and can be found in almost each part of many plants (i.e., bark, root, leaf, seed, etc.). Plant production of tannins is a defensive strategy against noxious agents due to their ability to complex irreversibly proteins. This characteristic, among many others, are known to beneficially affect both human health as well as cattle welfare (Pizzi 2019). Given their structure complexity, many classifications of tannins have been attempted, though the most accepted one divide these compounds according to their susceptibility to hydrolyzation, either chemical or enzymatic. Therefore, in the group of hydrolysable tannins, we can find gallotannins and ellagitannins, whereas those unhydrolyzable are known as condensed tannins or proanthocyanidins and complex tannins (Watrelot and Norton 2020).

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Noteworthy, flavonoids are definitely the polyphenols that sparked among the others and proved to possess undoubted anti-oxidant, anti-inflammatory, anti-cancer, anti-rheumatic, anti-microbial and neuroprotective activities (Cirmi et al. 2016, 2018; Mannucci et al. 2021; Marino et al. 2015; Maugeri et al. 2019; Musumeci et al. 2020), exploited also in clinical settings (Mannucci et al. 2018, 2017). Furthermore, coumarins, anthocyanins and lignans represent well-studied plant secondary metabolites, arising from the same biosynthetic pathway as flavonoids, which are known for their anti-cancer, vasoprotective and neuroprotective activities (Bruni et al. 2019; Smeriglio et al. 2016; Talarek et al. 2017).

Therefore, this review aims at gathering the recent evidence on the pharmacological properties of tannins, with an eye on their toxicological profile.

Chemistry, biochemistry and sources

Tannins are found in plant extracts as water-soluble polyphenols, with different molecular sizes and complexity. Tannins having molecular weight between 500 and 3000 Da are effective tanning agents, while low-molecular-weight (< 500 Da) and high molecular weight (> 3000) phenolic compounds are ineffective. Tannins are classified into two groups namely, hydrolyzable tannins (ellagitannins and gallotannins) and condensed tannins (proanthocyanidins and oligo-polymeric complex tannins) (Fig. 1). Hydrolyzable tannins contain glucose, and hydroxyl groups, which are esterified by gallic acid or hexahydroxydiphenic acid. Moreover, hydrolyzable tannins can be characterized in three main types based on the presence as unit constituent structure of gallic acid, ellagic acid and on both previous reported compounds. Hydrolyzable tannins are also modified with sugars and coffee acids or combined to create dimers, trimers, and multimers (such as polygonanin A, helioscopinin A, pentagalloyl glucose davicratinic acids B). Condensed tannins (such as proanthocyanidins) are oligomers or polymers based on the presence of flavan-3-ols, characterized by C-4 → C-8 or C-4 → C-6 (although it is less frequent) bonds between the monomeric units, forming the so-called B-type proanthocyanidins. The A-type proanthocyanidins are characterized by the presence of a further linkage between C-2 → C-7 of the basic flavan-3-ol units. Condensed tannins are more complex than hydrolyzable tannins, occur by the polymerization of flavan-3-ols and flavan-3,4-diols based on the presence of common structural units such as (−)-epicatechin, (+)-catechin, (−)-epigallocatechin gallate, (−)-epicatechin gallate and (+)-gallocatechin. They cannot be hydrolyzed by enzymatic with alkali, and acid treatment or long-term storage. Often, they condense to form the so-called red tannins, a water-insoluble polymer product.

Tannins are found in wines and tea, as well as a number of plants used as food and feed. Millets, barley, beans, peas,

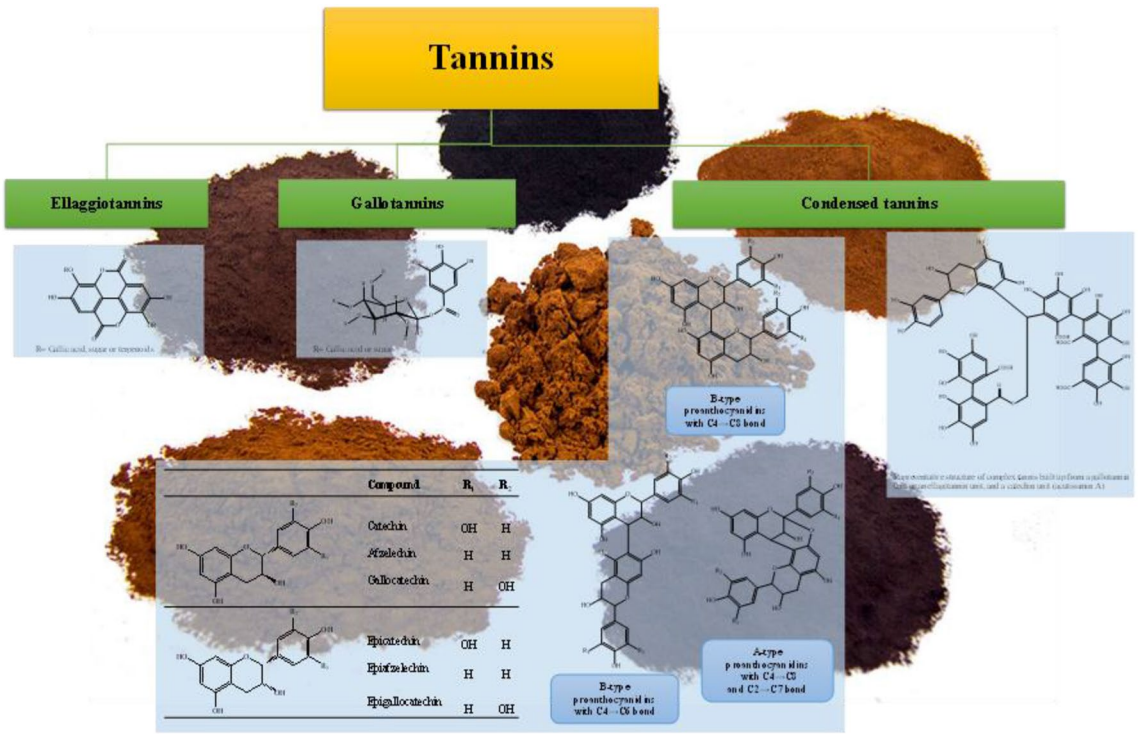

Fig. 1 Schematic representation of tannins classification

carobs, and other legumes, grapes, apples, strawberries, blackberries, cranberries, raspberries, plums, hawthorns, peaches, pears and persimmons, are among them (Chung et al. 1998).

Pharmacokinetics of tannins

The pharmacokinetics of tannins are influenced by their structural complexity. Indeed, the first step of absorption is highly influenced by the molecular weight and degree of polymerization of tannins, being only monomeric polyphenols easily absorbed, while more complex ones need to be firstly hydrolized (Zhang et al. 2016). In these regards, the in vitro metabolization of extracts from *Cistus* spp., widely spread in the Mediterranean area, recently showed higher total phenolic content, antioxidant activities and diabetes-related enzyme inhibitions than non-digested samples, supporting the relevance of proper breakage of complex molecules like proanthocyanidins to unleash their full potential (Inan et al. 2021). On the other hand, ferritin or chitosan nanoparticles, as well as solid self-double-emulsifying drug delivery system have been investigated to improve the absorption of proanthocyanidins and overcome metabolization discrepancy, proving to be valuable alternative strategies for delivering tannins (Tian et al. 2020; Yu et al. 2018; Zhang et al. 2019). Contrariwise, the ellagitannins present in pine cones of *Pinus koraiensis*, along with other polyphenols (i.e., apigenin, phloretin, quercetin, myricetin and chlorogenic acid), have been studied after in vitro metabolization to mimic the physiological digestion process. It was shown that the biotransformation ellagitannins undergo, along with the other compounds, diminish their bioavailability as well as their antioxidant capacity, thus corroborating the need of proper strategies if employing ellagitannin as nutraceuticals (Wang et al. 2019). Nevertheless, it is known that the wide majority of tannins are extensively metabolized by the colonic bacterial flora, rather than hydrolized by gastric acid (Kawabata et al. 2019). Indeed, an experimental study showed that a microbiota metabolite of the ellagitannin geraniin, namely urolithin A, hindered in a stronger manner the LPS-induced polarization of murine J774.1 macrophages, lowering both nitric oxide (NO) and reactive oxygen species (ROS) production as well as pro-inflammatory cytokines, inducing autophagy and hampering mTOR signalling pathway, than unmetabolized compound (Boakye et al. 2018). Therefore, it is still under debate whether polymeric or monomeric tannins may act stronger than each other.

Once absorbed, unaltered or modified by microbiota, tannins hence undergo to different metabolic routes in the liver (Zeng et al. 2020). In this regard, the metabolization of red wine extract or grape seed proanthocyanidin-rich extract (GSPE), administered to rats, showed that the former brought a plasma peak of flavan-3-ol monomers, whereas the latter of microbiota-derived 5-carbon side chain ring fission metabolites. These compounds were present also in the urine of rats after the ingestion of both extracts. Interestingly, given the different polymerization degree of proanthocyanidins present in the two extracts, the different profile of metabolization and hence catabolites detected can be explained, although being still challenging to thoroughly understand the metabolic fate of proanthocyanidins in an in vivo setting (Pereira-Caro et al. 2020).

Metabolic dysregulations have been investigated in clinical studies for their role in the metabolization and hence bioavailability of tannins. In particular, *Eugenia dysenterica* DC (cagaita) juice, rich in ellagitannin, was provided to healthy volunteers and to dysglycemic ones with metabolic syndrome. Along with glucose-lowering effect and reduced post-prandial glycemia and insulin response of cagaita juice, the study clarified that alteration of metabolic conditions did not alter the rate of metabolization of ellagitannin or the principal metabolite, namely urolithin A (Araujo et al. 2021). A human clinical trial aimed at the investigation of gallotannin-metabolites pharmacokinetics and the modulation of intestinal microbiota in healthy individuals, lean and obese, after 6 weeks of daily mango pulp consumption, demonstrated that lean subjects showed greater areas under curve of different metabolites, especially 4-*O*-methyl-gallic acid. Moreover, cumulative urinary excretion of gallotannin-metabolites significantly increased in both lean and obese individuals after mango consumption. Regarding microbiota, mango pulp brought in obese subjects an increase of tannase-producing bacteria (*Lactococcus lactis*) and a decrease of obesity-related strands (*Clostridium leptum* and *Bacteroides thetaiotaomicron*), whereas in lean ones increased faecal levels of butyric and valeric acids, thus suggesting that body mass index is a relevant discriminant in the pharmacokinetics of gallotannins (Barnes et al. 2019).

Pharmacology of tannins

Tannins have been extensively studied in attempt to discover their possible health advantages. Indeed, tannins were reported to have several biological effects for human wellness. The main pharmacological activities, discussed in this review in the following sections, are also reported in Tables 1, 2, 3, 4, 5, 6 and 7, as regards the in vitro and in vivo evidence, and in Table 8, for the human studies.

Antioxidant activity

The majority of tannins' actions are largely determined by their structure and degree of polymerization. Tannins such as pentagalloylglucose, geraniin, kaki-tannin, procyanidins B1

Table 1 Antioxidant effects of tannins assessed in vitro and in vivo

Compound/extract	Experimental model	Effects	References
Grape seed extract/grape seed proanthocyanidin-rich extract	Luteinized and tumour granulosa cells	ROS↓	Barbe et al. (2019)
	LPS-stressed Caco-2 cells	ROS ↓; ROO^- ↓; antioxidant defence enzymes ↑; mitochondrial membrane potential ↑	Nallathambi et al. (2020)
	CAF-fed rats	ROS ↓; MPO ↓; iNOS ↓; IL-1β ↓; intestinal permeability ↓; ZO-1 ↑	Gil-Cardoso et al. (2017)
	Steroid-exposed male rats	NADPH oxidase ↓; ROS ↓; MDA ↓	Tousson et al. (2018)
Proanthocyanidin A2	PDGF-induced VSMCs proliferation	NADPH oxidase ↓; ROS ↓	Zhang et al. (2018a)
Proanthocyanidin-enriched fractions of strawberry 'San Andreas' and blackberry 'Black Satin'	LPS-stimulated RAW 264.7 macrophages	ROS↓; NO synthase↓; PTGS2, IL1B, IL6 expression↓	Van de Velde et al. (2019)
Proanthocyanidin-rich extracts of *Empetrum nigrum*, *Vaccinium uliginosum* and *V. vitis-idaea*	LPS-stimulated RAW 264.7 macrophages	ROS ↓; NO ↓; NOS2, COX2 expression ↓;	Esposito et al. (2019)
Cassia abbreviata root extract	Juglone-stressed *Caenorhabditis elegans*	ROS ↓; GSH ↑; MDA ↓; ALT, AST and GGT activity ↓	Sobeh et al. (2018)
Praecoxin A (from *Melaleuca ericifolia*)	CCl_4-induced hepatotoxicity in mice	MDA ↓; GSH ↑; SOD ↑; COX2 and CASP3↓	Al-Sayed et al. (2019)
	Scopolamine-injured Korl:ICR mice; B35 neuroblastoma cells	BDNF ↑; antioxidant defence systems ↑	Park et al. (2019)
Gallotannin-enriched extract isolated from Galla Rhois	H_2O_2-stressed HepG2 cells	ROS ↓; apoptosis ↓	Go et al. (2017)
Pentagalloylglucose	AGE-stressed mesangial cells	ROS ↓; Nrf2/HO-1 pathway ↑; JAK2/STAT3 pathway ↓	Tong et al. (2021)
Pistachio green hull, *Marrubium vulgare* L., *Cytinus hypocistis* and *C. ruber* extracts	Cell-free models	Antioxidant activity ↑; reducing power ↑	Hayat et al. (2020), Maisetta et al. (2019) and Noorolahi et al. (2020)
Sorghum spp.	LPS-stimulated RAW 264.7 macrophages	Antioxidant activity ↑; inflammation ↓	Hong et al. (2020)

and B3, tellimagrandins I and II, pedunculagin, isoterchebin, mallotusinic acid, chebulinic acid have been shown to prevent lipid peroxidation and to scavenge free radicals (Jerez et al. 2007; Okuda 2005; Tian et al. 2012). A GSPE, and its main component proanthocyanidin B2 were able to reduce ROS levels in primary luteinized granulosa cells and the tumour granulosa cell line (Barbe et al. 2019). Moreover, GSPE was also able to exert interesting antioxidant effects in lipopolysaccharide (LPS)-stressed human Caco-2 colon cells, where it significantly reduced ROS and mitochondrial superoxide production, up-regulated antioxidant enzyme gene expression, as well as restored mitochondrial function by increasing mitochondrial membrane potential (Nallathambi et al. 2020). GSPE was assessed also in vivo in cafeteria diet (CAF)-fed rats, a diet plan which mimics the same human regimen characterized by tasty but unhealthy food products (Lalanza and Snoeren 2021). In this study, GPSE reduced ROS production and myeloperoxidase (MPO) activity due to high fat/carbohydrate given to the animals, as well as iNOS and IL-1β expression; moreover, GSPE ameliorated damaged intestinal barrier, as observed by lower LPS plasma levels and increased zonulin-1 expression respect to CAF group (Gil-Cardoso et al. 2017). In addition, GSPE ameliorated cardiac toxicity induced by the anabolic steroid boldenone in male rats, via the inhibition of NADPH oxidases, thus reducing ROS and molondialdehyde (MDA) levels in cardiac tissues of injured rats (Tousson et al. 2018). Proanthocyanidin A2 proved to be a valuable antioxidant agent in platelet-derived growth factor (PDGF)-induced vascular smooth muscle cells proliferation, an in vitro model of several cardiovascular pathological condition, where it inhibited abnormal cell proliferation induced by PDGF via a mechanism involving the reduction of NAD(P)H oxidase activation and intracellular ROS generation (Zhang et al. 2018a). Proanthocyanidin-enriched fractions of strawberry 'San Andreas' and blackberry 'Black Satin' were able to reduce ROS generation in LPS-stimulated RAW 264.7 macrophages, NO production and the expression of the inducible

Table 2 Anti-inflammatory activities of tannins assessed in vitro and in vivo

Compound/extract	Experimental model	Effects	References
Proanthocyanidin	Cisplatin-injured rats	NF-κβ/TLR-4 pathway ↓; COX2, IL-1β, IL-6 and TNF-α ↓; NO and ROS levels↓	El-Shitany and Eid (2017)
Proanthocyanidins from *Iris lactea*	High-fat-diet/streptozocin (STZ)-injured mice	Lipid metabolism ↑; hepatic steatosis ↓	Tie et al. (2020)
Urolithin B	LPS-activated BV2 microglial cells	NO ↓; pro-inflammatory cytokines ↓; IL-10 ↑	Lee et al. (2019)
	Polyinosinic–polycytidylic acid- or lipoteichoic acid-stimulated BV2 microglial cells	NO, TNF-α, and IL-6 production ↓; ROS and NADPH oxidase ↓; HO-1 and Nrf2/ARE signalling ↑; AMPK ↑; NF-κB ↓	
	LPS-stressed bone marrow-derived macrophages	NF-κB and TLR4 ↓; ROS and DNA damages ↓; calcium influx ↓; MAPK and PI3k activation ↓	Abdelazeem et al. (2021)
	Coronary ligation in rats	Cardiac functionality ↑; infarct areas and myocyte size ↓; cardiac fibrosis and inflammation ↓; JAK2/STAT3 and Smad2/3 signalling ↓	Gao et al. (2020a)
Urolithin A and B	STZ-induced diabetic rats	Fractalkine ↓; hemodynamic parameters and contractility ↑	Savi et al. (2017)
Urolithins (from strawberry)	High-fat diet-fed rats	Body weight gain and adipose tissues ↓; oxidized glutathione, triglycerides and total cholesterol blood plasma levels ↓	Zary-Sikorska et al. (2020)
Urolithin A and B	High-fat diet-fed rats	Dysbiosis ↓; body weight and serum lipid levels ↓	Abdulrahman et al. (2021)
Gallotannin	2-Deoxy-D-glucose (2DG)-stressed primary chondrocytes	2DG-induced dedifferentiation ↓; ER-stress-induced COX-2 unglycosylation ↓; p38 kinase inositol-requiring enzyme 1 (IRE1) pathways ↓	Kim et al. (2019)

form of NO synthase, along with inflammatory-related genes (i.e., PTGS2, IL1B, IL6) (Van de Velde et al. 2019). Similarly, proanthocyanidin-rich extracts of *Empetrum nigrum* (crowberry), *Vaccinium uliginosum* (bog blueberry), and *V. vitis-idaea* (low-bush cranberry or lingonberry), wild berry species endemic to the circumpolar Artic, inhibited ROS production and inflammatory markers (i.e., NO levels, NOS2, cyclooxygenase-2—COX2—gene expression) in LPS-stimulated RAW 264.7 macrophages (Esposito et al. 2019). *Cassia abbreviata* root extract is rich in polyphenolic compounds, particularly proanthocyanidins, and it was demonstrated to possess relevant antioxidant potential in cell-free tests, to reduce ROS production in juglone-stressed *Caenorhabditis elegans*, as well as to ameliorate hepatic biomarkers (i.e., increase of glutathione—GSH—levels and reduction of MDA contents, along with ALT, AST and GGT activities) in D-galactosamine-induced hepatotoxicity in rats (Sobeh et al. 2018).

Praecoxin A, an ellagitannin from *Melaleuca ericifolia*, ameliorated CCl_4-induced hepatotoxicity in mice, by improving liver enzymes functionality and reducing MDA levels. Moreover, praecoxin A enhanced antioxidant machinery, increasing GSH content and superoxide dismutase activity, parallelly hampering inflammation and apoptosis via COX-2 and caspase-3, respectively (Al-Sayed et al. 2019).

A gallotannin-enriched extract isolated from Galla Rhois (GEGR), consisting of gallotannin, gallic acid and methyl gallate, showed great radical scavenging activity and reducing power in cell-free tests, along with protecting hydrogen peroxide-stressed HepG2 cells, by reducing ROS formation and hampering apoptotic machinery (Go et al. 2017). Moreover, GEGR was shown to protect Korl:ICR mice from the administration of scopolamine, as a model of cognitive impairment, as well as B35 neuroblastoma cells, enhancing their antioxidant defence systems. In addition, in this in vivo model, GEGR increased the impaired secretion of brain-derived neurotrophic factor, along with its signalling pathway, protecting from cell death and enhancing survival during cognitive impairment (Park et al. 2019). Pentagalloylglucose, a gallotannin polyphenolic compound, protected mesangial cells from advanced glycated end products oxidative stress, as a model of diabetic renal injury, inhibiting

Table 3 Anti-cancer effects of tannins assessed in vitro and in vivo

Compound/extract	Experimental model	Effects	References
Proanthocyanidin polymer-rich fraction of *Stryphnodendron adstringens*	HeLa, SiHa, and C33A cells; BALB/c mice with Ehrlich solid tumours	Cell viability and migration ↓; ROS and mitochondrial impairment ↑	Kaplum et al. (2018)
Chinese bayberry leaves proanthocyanidin	Cisplatin-resistant A2780/CP70 ovarian cancer cells	Angiogenesis (HIF-1α and VEGF) ↓; G1 cell cycle arrest (c-Myc, cyclin D1 and CDK4 levels ↓); ROS ↓; Akt/mTOR/p70S6K/4E-BP-1 pathway ↑	Zhang et al. (2018b)
Proanthocyanidin B2	Xenograft and diethyl-nitrosamine (DEN)-induced hepatocellular carcinoma (HCC) mouse models	Akt pathway ↓; cell proliferation ↓	Liu et al. (2020)
Lipophilic grape seed proanthocyanidin	PC3 cells; PC3-derived mouse xenograft model	G1 cell cycle arrest; cyclin D1 and CDK 4 ↓; p21 and p27 ↑	Chen and Yu (2019)
Red rice germ and bran proanthocyanidin-rich extracts	HepG2 cells	Cell viability ↓; block of cell cycle in G2/M phase; cyclin B1 and cdc25 expression ↓; apoptosis ↑; cleavage of PARP-1, caspase-8 and caspase-3 ↑	Upanan et al. (2019)
Red rice germ and bran proanthocyanidin-rich extracts	A549 cells	TNF-α-induced A549 cell death ↑; apoptosis autophagy, and invasion ↑; MAPKs, Akt, NF-κB, and AP-1 ↓	Subkamkaew et al. (2019)
Myrciaria jaboticaba (jabuticaba) seed extract	1,2 Dimethyl hydrazine-induced colon carcinogenesis in rats	Pro-inflammatory markers ↓; anti-apoptotic factors↓; pro-apoptotic factors ↑; aberrant crypt foci ↓; gut microbiota ↑	do Carmo et al. (2021)
1,2,3,4,6-Penta-*O*-galloyl-β-D-glucose	HCT-116 and HT-29 colon cancer cells	Apoptosis ↑; clonogenic activity ↓; modulation of p53 and p21, cyclin E, CDK2, Bcl-2 and caspase-3/7	Kawk et al. (2018)

Table 4 Neuroprotective effects of tannins assessed in vitro and in vivo

Compound/Extract	Experimental model	Effects	References
Proanthocyanidins	Rotenone-stressed SH-SY5Y neuroblastoma cell	Oxidative stress ↓; cleavage of caspase-9, caspase-3 and poly ADP-ribose polymerase ↓; p38, JNK, and ERK signalling factors ↓	Ma et al. (2018)
Grape seed proanthocyanidin-rich extract	STZ-injured rats	Cognitive function and hippocampal long-term potentiation ↑; MDA ↓; SOD and GSH ↑; hippocampal AKT and ERK activities ↑	Gao et al. (2020b)
	Neonatal hypoxic-ischemic (HI) brain injury in rats	Brain damages ↓; neurobehavioral outcomes ↑; Bax expression ↓; cleavage of caspase-3 ↓	Tu et al. (2019)
Ginkgo biloba proanthocyanidin extract	Sprague-Dawley rats subjected to cerebral ischemia–reperfusion (I/R) injury	Neurological dysfunctions ↓; average infarct size ↓; MDA ↓; SOD ↓	Yao et al. (2020)
Proanthocyanidin B2	High-glucose-cultured dorsal root ganglion neurons collected from rats	ROS ↓; apoptosis ↓; cell viability and normal neurites outgrow ↑; transactive response DNA binding protein 43 (TPD-43) expression ↑	Zhang et al. (2018c)
Urolithin A	STZ-induced diabetic mouse model	Tau phosphorylation ↓; Aβ deposition ↓; cognitive impairment ↓; transglutaminase type 2 (TGM2) expression ↓	Lee et al. (2021)
	H_2O_2-stressed SK-N-MC neuroblastoma cells	ROS ↓; cell viability ↑; Bax/Bcl-2 ratio ↓; cytochrome c, cleaved caspase-9, cleaved caspase-3, and cleaved PARP expressions ↓; p38 phosphorylation ↓	Kim et al. (2020b)
	H_2O_2-stressed Neur-2a neuroblastoma cells	ROS ↓; CAT, SOD, GPx activities ↑; GSH content ↑	Casedas et al. (2020)
	SH-SY5Y cells; APP-transfected SY5Y-APP695 cells	MMP and ATP-levels ↓; mitochondrial biogenesis and respiration genes ↑	Esselun et al. (2021)

Table 5 Anti-microbial activities of tannins assessed in vitro and in vivo

Compound/extract	Experimental model	Effects	References
36 polyphenols and 4 terpenoids	*H. pylori*	Antibacterial activity; unaltered viability of MKN-28 cells	Funatogawa et al. (2004)
Chebulagic acid and punicalagin	Human cytomegalovirus (HCMV), hepatitis C virus (HCV), dengue virus (DENV), measles virus (MV), and respiratory syncytial virus (RSV)	Viral attachment, penetration, and spread ↓	Lin et al. (2013)
Proanthocyanidins from *Pelargonium sidoides* DC root extract	*Staphylococcus aureus, S. epidermidis, Aggregatibacter actinomycetemcomitans* and *E. coli;* LPS-stressed gingival fibroblast cell	Bacterial growth ↓; IL-8 and PGE2 (fibroblasts) ↓; IL-6 (leukocytes) ↓ IL-1β, iNOS, and surface presentation of CD80 and CD86 (LPS + IFNgamma-treated macrophages) ↓; IL-1β and COX-2 expression (LPS-treated leukocytes) ↓	Jekabsone et al. (2019)
	Porphyromonas gingivalis and *S. salivarus*	Antioxidant activity ↑; *Porphyromonas gingivalis* ↓; *S. salivarus* ↑	Savickiene et al. (2018)
Cranberry proanthocyanidin-chitosan composite nanoparticles	*E. coli*	Bacterial growth ↓	Alfaro-Viquez et al. (2019)
Grape seed proanthocyanidin-chitosan composite nanoparticles	*E. coli* and *S. aureus*	Bacterial growth ↓	Ding et al. (2021)
Maytenus imbricata root proanthocyanidins	Mayaro virus (MAYV)	Viral activity ↓	Ferraz et al. (2019)
22 ellagitannins	*Clostridiales perfringens, E. coli* and *S. aureus*	Bacterial growth ↓	Puljula et al. (2020)
Pentagalloyl glucose (from *Schinus terebinthifolia* leaves)	Carbapenem-resistant *Acinetobacter baumannii*; *Pseudomonas aeruginosa* and *S. aureus*	Bacterial growth ↓	Dettweiler et al. (2020)
Ellagitannins, gallotannins and semi-synthetic derivatives	Herpes simplex virus-infected Madin–Darby bovine kidney (MDBK) mono-layers	Viral replication ↓	Vilhelmova-Ilieva et al. (2019)

Table 6 Anti-diabetic effects of tannins assessed in vitro and in vivo

Compound/extract	Experimental model	Effects	References
Eugenia jambolana bark extract	Cell-free models	Alfa-amylase activity ↓	Tong et al. (2021)
Pharbitis nil (SOA) and Ipomoea batatas (YGM) extract extract	Cell-free models	Alfa-glucosidase activity ↓	Matsui et al. (2001)
Strawberry, raspberry, blueberry, blackcurrant, or red cabbage extracts	Cell-free models	Alfa-amylase activity ↓; Alfa-glucosidase activity ↓	McDougall et al. (2005)
Grape seed procyanidins extract	STZ-induced diabetic rats; L6E9 myotubes and 3T3-L1 adipocytes	Hyperglycaemia (in vivo) ↓; glucose uptake, p38, PI3K and GLUT4 (in vitro) ↑	Pinent et al. (2004)
Diospyros kaki 'Hachiya' tannins	High fat diet-fed type 2 diabetic NSY/Hos mice	Faecal bile acid excretion ↑; plasma cholesterol, triglyceride, and insulin levels ↓; fatty liver ↓;3-hydroxy-3-methylglutaryl-coenzyme A reductase and sterol regulatory element-binding protein 2 expression ↑; uncoupling protein-1 (UCP1) and the UCP3 expression ↑	Matsumoto and Yokoyama (2012)

ROS formation and promoting Nrf2/HO-1 pathway activation and parallelly blocking JAK2/STAT3 one (Tong et al. 2021). Gallotannins present in a pistachio green hull extract, rich in galloyl-*O*-hexoside, galloyl-shikimic acid, galloylquinic acid and gallic acid, interestingly scavenged radical species and reduced ferric ions in cell-free models (Noorolahi et al. 2020). Similarly, the extracts of *Marrubium vulgare* L. leaves, an endemic plant of the North-East of Morocco, and that of *Cytinus hypocistis* and *C. ruber* showed antioxidant effects in several abiotic assays (Hayat et al. 2020; Maisetta et al. 2019). The plants of the genus *Sorghum* have also been shown to possess antioxidant activity in cell-free assays, as well as reducing inflammatory status in murine RAW 264.7 cells exposed to lipopolysaccharide (Hong et al. 2020). Table 1 reports the studies on the antioxidant effects of tannins.

Anti-inflammatory activity

Proanthocyanidin was shown to protect rats against cisplatin-induced oxidative liver damage through the inhibition of the inflammatory NF-κB/TLR-4 pathway and related factors (i.e., COX2, IL-1β, IL-6 and TNF-α) as well as reducing both oxidative stress markers (i.e., ROS, NO, MDA) and increasing those antioxidant (i.e., catalase, superoxide dismutase and glutathione peroxidase) NO and ROS levels in this in vivo experimental model (El-Shitany and Eid 2017). Proanthocyanidins from *Iris lactea* improved dysregulated lipid metabolism and hepatic steatosis in high-fat-diet/streptozocin (STZ)-induced type 2 diabetes mellitus in mice, with procyanidin B3 and procyanidin B1 potentially being the most active players among the other in *I. lactea* extract (Tie et al. 2020).

In LPS-activated BV2 microglial cells, urolithin B, a metabolite of ellagitannins, inhibited NO production and pro-inflammatory cytokines, while increased anti-inflammatory cytokine IL-10; in polyinosinic–polycytidylic acid- or lipoteichoic acid-stimulated BV2 microglial cells, urolithin B inhibited NO, TNF-α, and IL-6 production. These effects were achieved by the reduction of ROS levels and NADPH oxidase expression, and by upregulating the antioxidant hemeoxygenase-1 expression via Nrf2/ARE signalling, along with hampering NF-κB pathway and stimulating AMPK phosphorylation, as antioxidant and anti-inflammatory processes (Lee et al. 2019). In LPS-stressed bone marrow-derived macrophages, urolithin B inhibited NF-κB activation by targeting TLR4 signalling pathway, along with hindering ROS production, DNA double-strand breaks, calcium influx, and MAPK and PI3K activation (Abdelazeem et al. 2021). In a rat model of myocardial infarction due to coronary ligation, urolithin B protected cardiac functionality, reducing infarct areas and myocyte size as well as attenuated cardiac fibrosis and inflammation, via inhibiting the phosphorylation of JAK2/STAT3 and Smad2/3 signalling molecules (Gao et al. 2020a). In another rat model of STZ-induced diabetic rats to induce cardiac dysfunction, urolithin A and B decreased the release of the pro-inflammatory cytokine fractalkine, preventing the early inflammatory response of cardiac cells to hyperglycaemia, along with enhancing hemodynamic parameters and contractility, thus restoring cardiac performance (Savi et al. 2017).

The urolithins from the metabolization of strawberry ellagitannins were claimed to be responsible for the reduction of the inflammatory status given by a high-fat diet in rats. In particular, a decreased body weight gain and adipose tissues, along with lowered oxidized glutathione,

Table 7 Miscellaneous activities of tannins assessed in vitro and in vivo

Compound/extract	Experimental model	Effects	References
Corilagin	Bleomycin-induced mice lung fibrosis	Fibrosis ↓; apoptosis ↓; membrane breakdown, effluence of lamellar bodies and thickening of the respiratory membrane ↓; MDA, IKKalpha, p-IKKalpha, NF-κB P65, TNF-α and IL-1β ↓; I-kappaB expression ↑; TGF-beta1 production and alpha-SMA expression ↓	Wang et al. (2014)
Ellagitannins from *Phyllanthus muellerianus* (Kuntze) Exell	HaCaT human keratinocytes and NHDF dermal fibroblasts	Cellular energy status ↑; biosynthesis of collagen ↑	Agyare et al. (2011)
Terminalia chebula extracts	Fibroblast (L929) and keratinocytes cells	Cell proliferation ↑; free-radical production ↓	Singh et al. (2014)
Chinese plant extracts	HaCaT human keratinocytes and NHDF dermal fibroblasts	Cell viability and cellular proliferation ↑	Wang et al. (2013)
Tannic acid	Porcine aorta in vitro model	Elastin stabilization ↑	Isenburg et al. (2004, 2005)
Rhus coriaria (Sumac) leaves extract	Isolated rabbit heart tissues (ischemia model)	Coronary perfusion pressure ↓; ventricular contracture ↓; left ventricular developed pressure ↑; Creatinine kinase (CK) and lactate dehydrogenase (LDH) outflow ↓; cytoprotective 6-ketoprostaglandin F (1α) (6-keto-PGF (1α)) ↑; TNF-α ↓; vasorelaxant activity ↑	Beretta et al. (2009)
Extracts and purified tannins from *Geum japonicum*	Isolated rat thoracic aorta; anesthetized normotensive and hypertensive rats	Relaxion of phenylephrine-precontracted aortic rings; mean arterial blood pressure ↓	Xie et al. (2007)
Digallic acid, gallic acid, germin D, praecoxin A and 1-desgalloyl rugosin F	Papillary muscle from Male Sprague–Dawley rats	Propranolol-induced negative inotropic contractile response ↓	Lee et al. (2010)
Guazuma ulmifolia bark procyanidins	Sugar-fed hypertensive rats	Systolic arterial pressure and the heart rate (per os) ↓; arterial hypotension (i.v.) ↑; vasorelaxant effects ↑	Magos et al. (2008)
Grape seed proanthocyanidins	Isoproterenol-induced myocardial injury in Wistar albino rats	AST, ALT, LDH and CK ↓; GSH, GPx, GST, SOD and CAT ↑; myocardial injury ↓	Karthikeyan et al. (2007)

triglycerides and total cholesterol blood plasma levels were observed after strawberry ellagitannin-rich extract administration to rats (Zary-Sikorska et al. 2020). Moreover, in the same experimental model, urolithin A and B restored dysbiosis caused by the unhealthy dietary plan, along with body weight and serum lipid levels (Abdulrahman et al. 2021).

In primary chondrocytes stressed with 2-deoxy-D-glucose (2DG), as inhibitor of glucose metabolism and inducer of endoplasmic reticulum stress, gallotannin inhibited 2DG-induced dedifferentiation and endoplasmic reticulum-stress-induced COX-2 unglycosylation while regulating differentiation and inflammation via the endoplasmic reticulum-stress-induced p38 kinase pathway downstream from the inositol-requiring enzyme 1 downstream signalling pathway (Kim et al. 2019). Table 2 summarizes the papers investigating the anti-inflammatory effects of tannins.

Anti-cancer activity

Apple proanthocyanidins and red wine proanthocyanidins have been shown to inhibit colon cancer progression in vivo; hence, a tannin-rich diet may have beneficial effects on the colon (Serrano et al. 2009). Anti-tumour effect was found for the macrocyclic dimers such as oenothein B and woodfordin C, macrocyclic trimers including oenothein A and woodfordin D; the macrocyclic tetramer woodfordin F; cyclic dimers, such as agrimoniin, coriariin A and C, cornusiin A, hirtellins A and B, rugosins D and E, isorugosin D and tamarixinin; monomer tellimagrandin II. As evidenced by the increase of IL-1 production from human peripheral macrophages, the effect is due to the immunological response of the host animals (Okuda 2005; Okuda and Ito 2011).

Proanthocyanidin polymer-rich fraction of *Stryphnodendron adstringens* reduced cell viability and

Table 8 Clinical trials on the effects of tannin-rich extracts

Extract	Participants	Duration	Intake	Effects	References
Mangifera indica L. (mango) pulp	12 lean subjects and 12 obese subjects (aged 18–65)	6 weeks	400 g/daily	Lean: systolic blood pressure ↓ Obese: hemoglobin A1c, plasminogen activator inhibitor-1, IL-8 and monocyte chemoattractant protein-1 ↓	Fang et al. (2018)
	10 IBD patients	8 weeks	200–400 g/daily	Simple Clinical Colitis Activity Index score ↓; IL-8, growth-regulated oncogene (GRO) and granulocyte macrophage colony-stimulating factor (GM-CSF) ↓	Kim et al. (2020b)
Proanthocyanidin-standardized cranberry juice	Double-blind, randomized, placebo-controlled trial on 522 *H. pylori*-positive adults	8 weeks	44 mg proanthocyanidin/240-mL serving/twice daily	Bacterial infection ↓	Li et al. (2021)

significantly inhibited the migration of cervical cancer cell lines, including HeLa, SiHa, and C33A cells. In addition, the extract increased oxidative stress (i.e., increase of ROS and loss of mitochondrial potential) of cervical cell lines, along with promoting apoptosis, effects also observed in BALB/c mice with Ehrlich solid tumours (Kaplum et al. 2018). Chinese bayberry leaves proanthocyanidin showed anti-proliferative effects on cisplatin-resistant A2780/CP70 ovarian cancer cells, through a mechanism involving the inhibition of angiogenesis and induction of G1 cell cycle arrest. In particular, it lowered ROS levels and targeted Akt/mTOR/p70S6K/4E-BP-1 pathway, reducing the expression of both HIF-1α and VEGF, thus inhibiting angiogenesis. On the other hand, it reduced the expressions of c-Myc, cyclin D1 and CDK4, thus promoting cell cycle arrest. In addition, it hampered tube formation in HUVECs and lessened wound healing in A2780/CP70 cells (Zhang et al. 2018b). Proanthocyanidin B2 was shown to directly bind and inhibit AKT activity and downstream signalling, thereby suppressing tumour cell proliferation and metabolism in vitro and in a xenograft and diethyl-nitrosamine-induced hepatocellular carcinoma mouse models, thus proving to be a novel allosteric AKT inhibitor with potent anti-tumour efficacy (Liu et al. 2020). Lipophilic grape seed proanthocyanidin (LGSP) exerts anti-proliferative and pro-apoptotic effects on PC3 human prostate cancer cells, via a mechanism involving caspases 3 and 9, as well as PARP activation. Moreover, LGSP brought a block in G1 phase of cell cycle of PC3 cells, as supported by the inhibition of cyclin D1 and CDK 4 and increase of p21 and p27. These results were also reflected in vivo in a PC3-derived mouse xenograft model, where LGSP inhibited tumour mass growth (Chen and Yu 2019). The proanthocyanidin-rich fractions obtained from red rice germ and bran extract showed anti-proliferative activity in both on hepatocellular carcinoma HepG2 cells and lung adenocarcinoma A549 cells. In the former line, it reduced cell viability, by blocking cell cycle in G2/M phase and confirmed by the reduction of cyclin B1 and cdc25 expression, along with inducing apoptosis, as confirmed by the cleavage of PARP-1, caspase-8 and caspase-3 (Upanan et al. 2019). In the latter line, proanthocyanidin-rich fractions enhanced TNF-α-induced A549 cell death, by inducing both apoptosis and autophagy, and invasion, reducing activation of MAPKs, Akt, NF-κB, and AP-1 (Subkamkaew et al. 2019).

Myrciaria jaboticaba (jabuticaba) seed extract, rich in ellagitannin, proved its anti-cancer properties in 1,2 dimethyl hydrazine-induced colon carcinogenesis in rats, where it promoted a reduction of pro-inflammatory markers, decreased the gene expression of anti-apoptotic factors along with increasing the expression of pro-apoptotic ones. Moreover, the seed extract weakened colon cancer initiation and progression by diminishing aberrant crypt foci, while recovering normal gut microbiota (do Carmo et al. 2021).

A gallotannin from Galla Rhois, namely 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose, induced cytotoxicity and decreased proliferation of HCT-116 and HT-29 colon cancer cells, via increasing apoptosis and lowering clonogenic activity. The mechanisms underlying the activity of the compound involved p53 and p21 induction, coupled to a modulation of cyclin E, CDK2, Bcl-2 and caspase-3/7, cell-cycle- or apoptosis-related proteins (Kawk et al. 2018). In Table 3, the papers discussed above in this section are summarized.

Neuroprotective activity

Proanthocyanidins were investigated in rotenone-stressed SH-SY5Y neuroblastoma cell lines, a known in vitro model of Parkinson's disease. These compounds reduced rotenone-induced oxidative stress, as well as apoptotic biomarkers (i.e., cleavage of caspase-9, caspase-3 and poly ADP-ribose polymerase), through the suppression of p38, JNK, and ERK signalling factors (Ma et al. 2018). GPSE was assessed in an in vivo model of Alzheimer's disease (AD), a sporadic AD rat model induced by intracerebroventricular injection of STZ, where it prevented the impairment of cognitive function and hippocampal long-term potentiation, decreased the levels of MDA, increased those of SOD and GSH, along with protecting hippocampal AKT and ERK activities (Gao et al. 2020b). *Ginkgo biloba* proanthocyanidin extract (GPE), more than its single components, reduced neurological dysfunctions in male Sprague–Dawley rats subjected to cerebral ischemia–reperfusion (I/R) injury, lowering average infarct size and concentrations of both MDA and super oxide dismutase (SOD) (Yao et al. 2020). In a similar in vivo model of neonatal hypoxic-ischemic brain injury, pre-treatment of rats with GPSE diminished brain damages and improved neurobehavioral outcomes, along with suppressing apoptosis through the inhibition of Bax expression and cleavage of caspase-3, typically augmented in ischemic tissues (Tu et al. 2019). Proanthocyanidin B2 was investigated on high-glucose-cultured dorsal root ganglion neurons collected from rats, as a model of hyperglycaemia-induced neuronal damage, showing that it hindered neurotoxic effects caused by the glucose challenge reducing both ROS levels and apoptosis, thus increasing cell viability and normal neurites outgrow, via the induction of the transactive response DNA binding protein 43 (TPD-43) expression, factor known for its protective role in neuronal development (Zhang et al. 2018c).

Urolithin A, a metabolite of ellagitannin by gut microbiota, was investigated in a STZ-induced diabetic mouse model for AD in which high glucose content brings elevated mitochondrial ROS levels and impairment of mitochondrial calcium influx. This induces the expression of amyloid beta (Aβ)-producing enzymes, such as amyloid precursor protein (APP) and β-secretase-1, along with its production. In particular, urolithin A hampered Tau phosphorylation, Aβ deposition, and cognitive impairment, via a mechanism involving transglutaminase type 2 expression (Lee et al. 2021). Furthermore, urolithin A protected SK-N-MC neuroblastoma cells from hydrogen peroxide-induced oxidative stress, reducing ROS levels and restoring cell viability, hampering apoptotic machinery decreasing Bax/Bcl-2 ratio, cytochrome c, cleaved caspase-9, cleaved caspase-3, and cleaved PARP expressions. In addition, it blocked the phosphorylation of the p38 mitogen-activated protein kinase (MAPK) pathway (Kim et al. 2020b). Similarly, Urolithin A showed antioxidant effects in mouse Neuro-2a neuroblastoma cells stressed with hydrogen peroxide, in which the metabolite decreased ROS levels and enhanced antioxidant defence systems, such as CAT, SOD, GPx activities and GSH content (Casedas et al. 2020). In SH-SY5Y cells and in their APP-transfected counterpart (SY5Y-APP695), characterized by an increased production of AB peptide as a model of early AD, urolithin A reduced MMP and ATP-levels, while increased the expression of mitochondrial biogenesis and respiration genes (Esselun et al. 2021). Studies on the neuroprotective effects of tannins are summarized in Table 4.

Anti-microbial activity

Tannins have been shown to have antibacterial activity against a variety of human gastrointestinal infections. Ellagitannins were found to be effective antimicrobials against *Staphylococcus bacterium, Candida albicans,* and *Campylobacter jejuni* (Serrano et al. 2009). Gallotannins displayed bactericidal effects against *Streptococcus mutans*, *S. salivarius*, and *Actinomyces viscosus* (Singh et al. 2005). Hydrolysable tannins also showed antibacterial activity against *H. pylori* (Funatogawa et al. 2004). Moreover, tannins demonstrated to have cytoprotective and cicatrizing properties in rats with stomach ulcers, by forming a mechanical barrier and regenerating the mucosa (Vasconcelos et al. 2010)... Cranberry (*Vaccinium* spp.) proanthocyanidins are long known to inhibit *Escherichia coli* adherence to human uroepithelium (Howell et al. 1998). Recently, the anti-microbial activity of cranberry extract was evaluated in a small clinical trial, where the extract showed the maximum anti-adhesive effect against *E. coli* after 6–8 h from administration, thus suggesting its role aginst urinary tract infections. Interestingly, this effect was ascribable to the metabolized products derived from proanthocyanidins, namely urolithins, as assessd by gas cromatogrpahy of urine samples (Peron et al. 2017). On this line, it was demonstrated that the anti-adhesive effect of cranberry extract has to be attributed to the whole phytocomplex, as assessed by flow cytometric adhesion assay. More specifically, this was due to the inhibition of the interaction between fimbrin D-mannose-specific adhesin with the host cell bladder epithelium and the bacteria, highest for B-ring substituted flavones and flavonols from cranberry extracts (Scharf et al. 2020).

Pelargonium sidoides DC root extract and its proanthocyanidin fraction showed interesting anti-bacterial activity against *Staphylococcus aureus*, *S. epidermidis*, *Aggregatibacter actinomycetemcomitans* and *E. coli*, strands commonly involved in periodontal disease. Moreover, both elements were able to hinder LPS-induced death of fibroblasts, release of IL-8 and prostaglandin E2 from fibroblasts and IL-6 from leukocytes, blocked expression of

IL-1β, iNOS, as well as surface presentation of both CD80 and CD86 in LPS + IFN-γ-treated macrophages, and IL-1β and COX-2 expression in LPS-treated leukocytes (Jekabsone et al. 2019). Interestingly, the proanthocyanidin fraction possessed stronger antioxidant activity than the whole extract, along with preserving commensal bacterial strand as *S. salivarius* (Savickiene et al. 2018). Dimeric tannins exerted anti-bacterial activity against methicillin-resistant *S. aureus*. The complex tannin theasinensin A provided a reduction in MIC values of oxacillin, penicillin G, ampicillin, and streptomycin (Hatano et al. 2005; Okuda and Ito 2011). Proanthocyanidins have also been bound to chitosan to formulate bioactive nanoparticle to be employed as anti-bacterial agents. In these regards, cranberry proanthocyanidin–chitosan composite nanoparticles showed to efficiently agglutinate extra-intestinal pathogenic *E. coli* and inhibit its gut epithelial cell invasion (Alfaro-Viquez et al. 2019), while grape seed proanthocyanidins-chitosan nanoparticles demonstrated bacterial inhibitory effects against *E. coli* and *S. aureus*, along with their strong antioxidant activity (Ding et al. 2021). Proanthocyanidin, extracted from the root of *Maytenus imbricata*, also proved to be effective as antiviral agents against Mayaro virus, a sublethal arbovirus transmitted by mosquitoes. In particular, proanthocyanidin exerted significant virucidal activity and caused moderate effect during both adsorption and virus internalization stage, though being effective only before infection (Ferraz et al. 2019).

Several ellagitannins were tested for their anti-bacterial activity against *Clostridiales perfringens, E. coli* and *S. aureus*, with the latter being the most sensitive to the former being the least. Notably, the molecular size and the flexibility of ellagitannin were important factors in their anti-bacterial activity (Puljula et al. 2020).

Pentagalloyl glucose, extracted from *Schinus terebinthifolia* leaves, showed bactericidal properties against carbapenem-resistant *Acinetobacter baumannii*, an alarming multidrug-resistant gram-negative pathogen, along with *Pseudomonas aeruginosa* and *S. aureus*, promoting its use against cutaneous infection (Dettweiler et al. 2020). Anti-herpes simplex virus activity of several ellagitannins, gallotannins and semi-synthetic derivatives was assessed in Madin-Darby bovine kidney mono-layers, showing that the former compounds exerted a significantly stronger activity against virus replication, respect with the others (Vilhelmova-Ilieva et al. 2019). Dimeric ellagitannins oenothein B, coriariin A, and agrimoniin showed anti-HIV effect (Okuda and Ito 2011). Hydrolysable tannins, chebulagic acid and punicalagin inhibited human cytomegalovirus, hepatitis C virus, dengue virus, measles virus, and respiratory syncytial virus infections (Lin et al. 2013).

In Table 5, the studies investigating the anti-microbial effects of tannins are reported.

Anti-diabetic effects

Tannins have antidiabetic effect by delaying intestinal glucose absorption and exerting an insulin-like effect on insulin-sensitive tissues, and by regulating the antioxidant environment of pancreatic β-cells to delay the onset of insulin-dependent diabetes mellitus (Serrano et al. 2009). Inhibition of α-amylase and α-glucosidase activity results in a reduction in glucose levels. In an in vitro human starch digestion model, hydrolysable tannins, vescalagin, acutissimin A/B, epiacutissimin A/B, grandinin/roburin E, hexagalloyl glucose, and heptagalloyl glucose were found to inhibit α-amylase (Tong et al. 2014). Tannins have also been demonstrated to suppress the activity of intestinal α-glucosidase (Matsui et al. 2001). The amount of α-glucosidase inhibition is proportional to the proanthocyanidin level, whereas hydrolysable tannins block α-amylase (McDougall et al. 2005). In vitro, grape seed procyanidin preparations showed insulinomimetic characteristics (Pinent et al. 2004; Serrano et al. 2009). In type 2 diabetic mice fed a high-fat diet, kaki-tannin avoided a rise in plasma total cholesterol, non-HDL cholesterol, triglycerides, and insulin. Furthermore, kaki-tannin consumption reduced fatty liver and increased cholesterol metabolism genes (Matsumoto and Yokoyama 2012). Polyphenols' ability to interact directly or indirectly with adipose tissues appears to be responsible for the anti-obesity effects of polyphenol-rich diets. The studies on the anti-diabetic effects of tannins are gathered in Table 6.

Other activities

In a pulmonary fibrosis animal model, the effect of corilagin on lung injury produced by bleomycin exposure was examined. Bleomycin-induced lung fibrosis was avoided by corilagin, which also reduced the amount of apoptotic lung cells and inhibited membrane breakdown in lung epithelial cells. The production of pro-inflammatory cytokines was dramatically reduced. Its anti-oxidative, anti-inflammatory, and anti-apoptotic properties, as well as suppression of TGF-1 expression and ECM production, were credited with this lung-protective effect (Wang et al. 2014). Ellagitannins, such as geraniin, corilagin, and furosin, have been identified as active chemicals with potent wound-healing abilities (Agyare et al. 2011). There have also been studies on the possible wound healing capabilities of pentagalloylglucose, trigalloylglucose, and gallic acid (Singh et al. 2014; Wang et al. 2013).

Tannins protect the heart by stabilizing pericardial tissue, inhibiting elastin enzymatic degradation, and reducing the calcification of glutaraldehyde-fixed aortic walls (Isenburg et al. 2004, 2005; Jastrzebska et al. 2006). Through the interplay of various factors such as endothelial nitric

oxide synthase activation, cyclooxygenase pathway activation, TNF-α inhibition, and scavenging of free radicals and reactive oxygen species, hydrolysable tannins, in particular, have anti-ischemic and an endothelium-dependent vasorelaxant effect (Beretta et al. 2009). In rat aortic rings that had been pre-contracted with the 1-adrenergic receptor agonist phenylephrine, hydrolysable tannins elicited strong NO- and cGMP-mediated vasorelaxation (Xie et al. 2007). Tannic acid also relaxed precontracted human coronary arteries and rat aortic rings in an endothelial and NO-dependent manner, which was accompanied by a rise in vascular GMP levels (Flesch et al. 1998). Propranolol-induced negative inotropism was inhibited by hydrolysable tannins, and the relative order of potency of the studied hydrolysable tannins indicated that the galloyl group in the tannin structure is critical for the negative inotropic action (Lee et al. 2010). Proanthocyanidins have long-acting antihypertensive and vasorelaxant characteristics associated to endothelium-related variables involving nitric oxide (Magos et al. 2008) as well as a substantial role in heart protection against isoproterenol-induced myocardial infarction (Karthikeyan et al. 2007). The studies on the activities discussed in this section are reported in Table 7.

Clinical trials

Human studies have been conducted on pure tannins, extracts, and drinks (Table 8). Tannins have been researched for their effects on metabolic syndrome, cardiovascular disease, plasma lipid profiles, and inflammation. The effect of green tea and grape seed products administration on metabolic syndrome and obesity-related parameters has been reported in several clinical studies. However, non-significant findings were observed (Alexopoulos et al. 2008; Basu et al. 2011; Diepvens et al. 2005; Fukino et al. 2008; Hill et al. 2007; Maki et al. 2009; Matsuyama et al. 2008; Sivaprakasapillai et al. 2009; Zern et al. 2005). Moreover, green tea has been reported to be ineffective in patients with high-grade prostatic intraepithelial neoplasia (Micali et al. 2017). Nevertheless, *Mangifera indica* L. (mango) pulp showed also noteworthy effects against obesity-related biomarkers in another clinical study. In lean subjects, mango pulp administration brough just a reduction of systolic blood pressure, while, in obese ones, haemoglobin A1c and plasminogen activator inhibitor-1, along with IL-8 and monocyte chemoattractant protein-1 were reduced, thus indicating a potential of mango pulp to inhibit obesity-related inflammation and the related chronic conditions (Fang et al. 2018). Interestingly, gallotannins from *Mangifera indica* L. (mango) were also the object of a clinical study aimed at the evaluation of the effect of mango pulp to counteract the symptoms of inflammatory bowel disease. In detail, subjects receiving the nutraceutical showed a significantly improved Simple Clinical Colitis Activity Index, an easy and reliable scoring of the clinical manifestations of colitis, and a decreased plasma levels of pro-inflammatory cytokines (i.e., IL-8, growth-regulated oncogene, GRO, and granulocyte macrophage colony-stimulating factor, GM-CSF). Moreover, mango pulp ameliorated faecal microbial composition by significantly increasing the abundance of *Lactobacillus plantarum*, *L. reuteri* and *L. lactis*, and hence faecal butyric acid production (Kim et al. 2020a). In a double-blind, randomized, placebo-controlled trial on *Helicobacter pylori*-positive adults, the effects of cranberry juice at different proanthocyanidin concentration were evaluated, showing that these juices decreased *H. pylori* infection rate in a dose-dependent manner, outcome reflected also in the percentage of *H. pylori*-negative participants (Li et al. 2021). These results are corroborated by the fact that cranberry juice showed interesting anti-bacterial properties to be exploited in the prophylaxis of recurrent urinary tract infections in young and middle-aged women (Micali et al. 2014).

The effect of polyphenol-rich cocoa on lipid levels has been studied in a number of human trials. The polyphenols in cocoa increase the formation of nitric oxide (Campia and Panza 2008). Hawthorn was utilized as an adjuvant to standard treatment for chronic heart failure in the majority of studies. When compared to placebo, symptoms like shortness of breath and exhaustion improved dramatically with hawthorn administration (Pittler et al. 2008; Sieniawska 2015).

Toxicology of tannins

The toxicity of tannin-rich products has been assessd in different in vitro and in vivo experimental models, as well as in clinical trials (Table 9).

The acute oral toxicity of geraniin and an enriched geraniin-extract of *Nephelium lappaceum* L. peel was recently evaluated following the OECD 423 acute oral toxicity test in rats, where both showed an LD_{50} of 2000 mg/kg b.w. without any relevant adverse events with lower doses (Moorthy et al. 2019). Similarly, the ethyl acetate-soluble proanthocyanidins from *Cocos nucifera* L., widely employed in ayrvedic medicine against menhorragia, were tested for their acute and sub-acute toxicity in female Wistar rats. As for geraniin, these proanthocyanidins showed an LD_{50} at doses higher than 2000 mg/kg b.w., while exposure to lower ones for 28 days (sub-acute assays) displayed no relevant effect (Ekanayake et al. 2019). The safety of *Polypodium feei* root extract was investigated through acute and sub-chronic studies in mice and rats, respectively, which showed that none of the doses tested practically exerted any toxicity, either acutely or sub-chronically. Regarding haematological parameters, only platelet count was altered for high doses of

Table 9 Toxic effects of tannin-rich extracts

Extract	Experimental model	Effects	References
Geraniin (from *Nephelium lappaceum* L. rind)	OECD 423 acute oral toxicity test in rats; 14-day-long toxicity test	$LD_{50} > 2000$ mg/kg b.w.	Moorthy et al. (2019)
Ethyl acetate-soluble proanthocyanidins from *Cocos nucifera* L	OECD 423 acute oral toxicity test in rats; 28-day-long toxicity test	$LD_{50} > 2000$ mg/kg b.w.	Ekanayake et al. (2019)
Polypodium feei root extract	Acute (mice) and 90-day-long sub-chronic (rats) toxicity tests	$LD_{50} > 5000$ mg/kg b.w.	Suwandi et al. (2021)
Eucalyptus robusta Smith (eucalyptus) leachate tannins	Static bioassay test in zebrafish	48 h LC50 values 186 mg·L^{-1} (under no aeration) and 452 mg·L^{-1} (under aeration)	Xie et al. (2022)
Tannin-rich extracts from *Acacia mollissima* (mimosa)	Sea urchin (*Paracentrotus lividus* and *Sphaerechinus granularis*) fertilization assay	Embryogenesis damages at doses < 1 mg·L^{-1}	De Nicola et al. (2007)
Proanthocyanidin-rich extract from *Pinus radiata* (pine) bark (Enzogenol®)	Reverse mutation assays (bacteria); acute (single dose) and sub-acute (14-day-long dosing) toxicity test in rats and dogs; 5-week- and 6-month-long chronic toxicity tests (humans)	No mutagenic activity (bacteria); MTD = 2500 mg/kg/day, NOAEL = 750 mg/kg/day (rats and dogs); no toxicity (humans)	Frevel et al. (2012)
Proanthocyanidin-rich extract from *Pinus radiata* (pine) bark (Oligopin®)	Reverse mutation assay (bacteria) and in mammalian chromosome aberration assay (human lymphocytes); acute and 90-day-long sub-chronic toxicity tests in rats	NOAEL = 1000 mg/kg/day	Segal et al. (2018)
Grape seed and peel extracts	Reverse mutation test (bacteria); toxicity test in rats	Slightly mutagenic (5 mg/plate, bacteria); $LD_{50} > 5000$ mg/kg b.w. (rats)	Lluis et al. (2011)
	4-week-long chornic toxicity assay (29 healthy volunteers)	No toxicity	Sano (2017)

the extract, yet in a reversible manner, whereas urea concentrations and stomach lesions remained with high doses. Nevertheless, this study suggested the safety of mid-range doses of this extract (Suwandi et al. 2021). *Eucalyptus robusta* Smith (eucalyptus) leachate tannins are known to impair the viability of fish, as demonstrated by Xie and collaborators (Xie et al. 2022). Zebrafish were exposed to tannic acidand a tannin fraction from the eucalypthus leachate which proved LC_{50} values at 48 h of 92 and 186 mg·L^{-1}, under no aeration, respectively, and 171 and 452 mg·L^{-1}, under aeration, respectively. These noxious effects were counteracted by adding iron salts into the water tanks, thus suggesting that chelation of tannins reduced their toxicity.

The effect on fertilization was investigated for a tannin-rich extracts from *Acacia mollissima* (mimosa), commonly employed a plant material for the tanning process, in a model of sea urchin fertilization, given its high sensitivity against toxicants. Sea urchin embryogenesis was affected at doses higher than 1 mg·L^{-1}, whereas developmental defects were significantly decreased at 0.1 and 0.3 mg·L^{-1}, indicating a hormetic effect of these extracts (De Nicola et al. 2007).

An extract from *Pinus radiata* (pine) bark, rich in proanthocyanidins, is currently commercialized under the name of Enzogenol® and employed for its antioxidant and anti-inflammatory properties. The safety of this extract was investigated in reverse mutation assays, where it showed no mutagenic activity. In addition, acute (single dose) and sub-acute (14-day-long dosing) in rats and dogs showed no effect on body weight, feed consumption or blood composition, yet emesis and diarrhoea occurred in dogs at the highest dose tested with an incidence of 18%. In this study, the maximum tolerated dose (MTD) was 2500 mg/kg/day, while the no observed adverse effect level (NOAEL) was 750 mg/kg/day. Interestingly, consumption of 480 mg/day for 6 months and 960 mg/day for 5 weeks in two human studies showed no effect of either liver, kidneys or blood composition (Frevel et al. 2012). In parallel, another pine bark extract, commercially known as Oligopin® showed no mutagenic activity in a bacterial reverse mutation assay and in mammalian chromosome aberration assay with human lymphocytes. Moreover, neither a single administration of 2000 mg/kg nor a 90-day-long sequential administrations brought any toxic effect in Sprague Dawley rats. The NOAEL of this extract was 1000 mg/kg/day, value similar to that observed for Enzogenol® (Segal et al. 2018). The toxicity of grape seed and peel extracts was evaluated to safely exploit its anti-oxidant and cardioprotective activities. In this study, Wistar rats were treated with increasing concentration of the extract, finding a LD_{50} higher than 5000 mg/kg, while for doses lower than 2000 mg/kg at 72 h of treatment,

no increase in micronucleated erythrocytes was detected, investigated as an index of cytogenetic damage. Moreover, the extract was assessed from 5 to 0.05 mg/plate through the bacterial reverse mutation test, proving to be slightly mutagenic only at the highest concentration, after in vitro metabolization. In addition, neither 19.5 nor 9.7 µg/ml of the extract altered the normal incidence of aberrant metaphases respect to negative controls in human blood leukocytes (Lluis et al. 2011). The safety of a grape seed extract was also investigated in a clinical trial in 29 healthy Japanese adult volunteers, who received 1000, 1500 or 2500 mg of the extract orally for 4 weeks daily. Despite two volunteers showed a dramatic fall of iron plasma concentrations at the second week of treatment, promptly restored at the end of the experimentation, the extract was generally safe as well as being well tolerated in humans (Sano 2017).

In comparison to other elements, less research on tannins toxicity have been conducted, with the majority of them being in vitro and in vivo animal studies, despite the fact that studying tannin toxicity is an essential step in their clinical use. Furthermore, because the existing clinical trials are primarily small sample trials, the results must be validated via better-designed, placebo-controlled investigations, which are meant to further examine the toxicological effects of tannins in humans (Smeriglio et al. 2017).

Conclusions

Consuming fruits and vegetables to improve one's health is unquestionably an important element of living a healthy lifestyle. In this regard, the use of nutraceuticals, which are compounds found in foods that have favourable effects on health, has taken on a prominent role in aiding in the prevention or treatment of diseases, as well as in the amelioration of chronic illnesses and the promotion of lifespan (Maugeri et al. 2019). Their beneficial influence on a variety of health issues, including cancer, inflammation, hypertension, cardiovascular disease, atherosclerosis, obesity, and diabetes, has previously been demonstrated (Mannucci et al. 2021). As a result, tannins, which are plentiful in our everyday food and natural goods, have gained considerable scientific interest. Although recent papers have discussed the potential of tannins, existing epidemiological and clinical data only suggest an association between tannin consumption and health benefits in humans (Smeriglio et al. 2017; Zeng et al. 2020; Zhang et al. 2016).

Therefore, further research is needed to better understand the effect of tannins in certain populations, particularly through properly designed clinical trials (i.e., placebos, standardized phytocomplexes, larger cohorts etc.). On this line, tannins are generally employed as phytocomplexes by general population, who exploits the multitarget potential of the extracts as a pharmacological strategy to deal with diseases (Atanasov et al. 2021; Cirmi et al. 2017; Efferth and Koch 2011). However, the downside is that phytocomplexes can be either more effective or more toxic, thus knowing the exact quali-quantitative composition of tannin-based nutraceuticals is essential. This will allow toxicologist to correctly investigate the harmful effects of whichever extract, understanding the role of each component, as well as the final users, who can safely employ standardized nutraceuticals, with far more less unexpected effects. Moreover, given the peculiar pharmacokinetics of tannins, due to their complex structures, it is necessary to design studies aimed at a thorough comprehension on their metabolic fate, since this will support the study of their toxicological profile. This aspect is still too scarcely investigated, though current results are quite encouraging. Nevertheless, tannins represent a promising class of nutraceuticals with great potentialities, hence defining a definitive risk–benefit profile will lay the foundation of a proper use of tannins in human health.

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References

Abdelazeem KNM, Kalo MZ, Beer-Hammer S, Lang F (2021) The gut microbiota metabolite urolithin A inhibits NF-kappaB activation in LPS stimulated BMDMs. Sci Rep 11(1):7117. https://doi.org/10.1038/s41598-021-86514-6

Abdulrahman AO, Alzubaidi MY, Nadeem MS, Khan JA, Rather IA, Khan MI (2021) Effects of urolithins on obesity-associated gut dysbiosis in rats fed on a high-fat diet. Int J Food Sci Nutr 72(7):923–934. https://doi.org/10.1080/09637486.2021.1886255

Agyare C, Lechtenberg M, Deters A, Petereit F, Hensel A (2011) Ellagitannins from Phyllanthus muellerianus (Kuntze) Exell.: Geraniin and furosin stimulate cellular activity, differentiation and collagen synthesis of human skin keratinocytes and dermal fibroblasts. Phytomedicine 18(7):617–624. https://doi.org/10.1016/j.phymed.2010.08.020

Alexopoulos N, Vlachopoulos C, Aznaouridis K, Baou K, Vasiliadou C, Pietri P, Xaplanteris P, Stefanadi E, Stefanadis C (2008) The acute effect of green tea consumption on endothelial function in healthy individuals. Eur J Cardiovasc Prev Rehabil 15(3):300–305. https://doi.org/10.1097/HJR.0b013e3282f4832f

Alfaro-Viquez E, Esquivel-Alvarado D, Madrigal-Carballo S, Krueger CG, Reed JD (2019) Proanthocyanidin–chitosan composite nanoparticles prevent bacterial invasion and colonization of gut epithelial cells by extra-intestinal pathogenic *Escherichia coli*. Int J Biol Macromol 135:630–636. https://doi.org/10.1016/j.ijbiomac.2019.04.170

Al-Sayed E, Abdel-Daim MM, Khattab MA (2019) Hepatoprotective activity of praecoxin A isolated from *Melaleuca ericifolia* against carbon tetrachloride-induced hepatotoxicity in mice. Impact on oxidative stress, inflammation, and apoptosis. Phytother Res 33(2):461–470. https://doi.org/10.1002/ptr.6242

Araujo RL, Tomas-Barberan FA, Santos RFD, Martinez-Blazquez JA, Genovese MI (2021) Postprandial glucose-lowering effect of cagaita (*Eugenia dysenterica* DC) fruit juice in dysglycemic subjects with metabolic syndrome: an exploratory study. Food Res Int 142:110209. https://doi.org/10.1016/j.foodres.2021.110209

Atanasov AG, Zotchev SB, Dirsch VM, International Natural Product Sciences T, Supuran CT (2021) Natural products in drug discovery: advances and opportunities. Nat Rev Drug Discov 20(3):200–216. https://doi.org/10.1038/s41573-020-00114-z

Barbe A, Rame C, Mellouk N, Estienne A, Bongrani A, Brossaud A, Riva A, Guerif F, Froment P, Dupont J (2019) Effects of grape seed extract and proanthocyanidin B2 on in vitro proliferation, viability, steroidogenesis, oxidative stress, and cell signaling in human granulosa cells. Int J Mol Sci. https://doi.org/10.3390/ijms20174215

Barnes RC, Kim H, Fang C, Bennett W, Nemec M, Sirven MA, Suchodolski JS, Deutz N, Britton RA, Mertens-Talcott SU, Talcott ST (2019) Body mass index as a determinant of systemic exposure to gallotannin metabolites during 6-week consumption of mango (*Mangifera indica* L.) and modulation of intestinal microbiota in lean and obese individuals. Mol Nutr Food Res 63(2):e1800512. https://doi.org/10.1002/mnfr.201800512

Basu A, Du M, Sanchez K, Leyva MJ, Betts NM, Blevins S, Wu M, Aston CE, Lyons TJ (2011) Green tea minimally affects biomarkers of inflammation in obese subjects with metabolic syndrome. Nutrition 27(2):206–213. https://doi.org/10.1016/j.nut.2010.01.015

Beretta G, Rossoni G, Santagati NA, Facino RM (2009) Anti-ischemic activity and endothelium-dependent vasorelaxant effect of hydrolysable tannins from the leaves of Rhus coriaria (Sumac) in isolated rabbit heart and thoracic aorta. Planta Med 75(14):1482–1488. https://doi.org/10.1055/s-0029-1185797

Boakye YD, Groyer L, Heiss EH (2018) An increased autophagic flux contributes to the anti-inflammatory potential of urolithin A in macrophages. Biochim Biophys Acta Gen Subj 1862(1):61–70. https://doi.org/10.1016/j.bbagen.2017.10.006

Bruni R, Barreca D, Protti M, Brighenti V, Righetti L, Anceschi L, Mercolini L, Benvenuti S, Gattuso G, Pellati F (2019) Botanical sources, chemistry, analysis, and biological activity of furanocoumarins of pharmaceutical interest. Molecules. https://doi.org/10.3390/molecules24112163

Campia U, Panza JA (2008) Flavanol-rich cocoa a promising new dietary intervention to reduce cardiovascular risk in type 2 diabetes? J Am Coll Cardiol 51(22):2150–2152. https://doi.org/10.1016/j.jacc.2008.02.058

Casedas G, Les F, Choya-Foces C, Hugo M, Lopez V (2020) The metabolite urolithin-A ameliorates oxidative stress in neuro-2a cells, becoming a potential neuroprotective agent. Antioxidants (basel). https://doi.org/10.3390/antiox9020177

Chen M, Yu S (2019) Lipophilic grape seed proanthocyanidin exerts anti-proliferative and pro-apoptotic effects on pc3 human prostate cancer cells and suppresses PC3 xenograft tumor growth in vivo. J Agric Food Chem 67(1):229–235. https://doi.org/10.1021/acs.jafc.8b05936

Chung KT, Wong TY, Wei CI, Huang YW, Lin Y (1998) Tannins and human health: a review. Crit Rev Food Sci Nutr 38(6):421–464. https://doi.org/10.1080/10408699891274273

Cirmi S, Bisignano C, Mandalari G, Navarra M (2016) Anti-infective potential of Citrus bergamia Risso et Poiteau (bergamot) derivatives: a systematic review. Phytother Res 30(9):1404–1411. https://doi.org/10.1002/ptr.5646

Cirmi S, Maugeri A, Ferlazzo N, Gangemi S, Calapai G, Schumacher U, Navarra M (2017) Anticancer potential of citrus juices and their extracts: a systematic review of both preclinical and clinical studies. Front Pharmacol 8:420. https://doi.org/10.3389/fphar.2017.00420

Cirmi S, Navarra M, Woodside JV, Cantwell MM (2018) Citrus fruits intake and oral cancer risk: a systematic review and meta-analysis. Pharmacol Res 133:187–194. https://doi.org/10.1016/j.phrs.2018.05.008

De Nicola E, Meric S, Gallo M, Iaccarino M, Della Rocca C, Lofrano G, Russo T, Pagano G (2007) Vegetable and synthetic tannins induce hormesis/toxicity in sea urchin early development and in algal growth. Environ Pollut 146(1):46–54. https://doi.org/10.1016/j.envpol.2006.06.018

Dettweiler M, Marquez L, Lin M, Sweeney-Jones AM, Chhetri BK, Zurawski DV, Kubanek J, Quave CL (2020) Pentagalloyl glucose from Schinus terebinthifolia inhibits growth of carbapenem-resistant *Acinetobacter baumannii*. Sci Rep 10(1):15340. https://doi.org/10.1038/s41598-020-72331-w

Diepvens K, Kovacs EM, Nijs IM, Vogels N, Westerterp-Plantenga MS (2005) Effect of green tea on resting energy expenditure and substrate oxidation during weight loss in overweight females. Br J Nutr 94(6):1026–1034. https://doi.org/10.1079/bjn20051580

Ding Z, Mo M, Zhang K, Bi Y, Kong F (2021) Preparation, characterization and biological activity of proanthocyanidin–chitosan nanoparticles. Int J Biol Macromol 188:43–51. https://doi.org/10.1016/j.ijbiomac.2021.08.010

do Carmo MAV, Fidelis M, de Oliveira PF, Feitoza LQ, Marques MJ, Ferreira EB, Oh WY, Shahidi F, Hellstrom J, Almeida LA, Novaes RD, Granato D, Azevedo L (2021) Ellagitannins from jabuticaba (Myrciaria jaboticaba) seeds attenuated inflammation, oxidative stress, aberrant crypt foci, and modulated gut microbiota in rats with 1,2 dimethyl hydrazine-induced colon carcinogenesis. Food Chem Toxicol 154:112287. https://doi.org/10.1016/j.fct.2021.112287

Efferth T, Koch E (2011) Complex interactions between phytochemicals. The multi-target therapeutic concept of phytotherapy. Curr Drug Targets 12(1):122–132. https://doi.org/10.2174/138945011793591626

Ekanayake CP, Thammitiyagodage MG, Padumadasa S, Seneviratne B, Padumadasa C, Abeysekera AM (2019) Acute and subacute toxicity studies of the ethyl acetate soluble proanthocyanidins of the immature inflorescence of *Cocos nucifera* L. in female Wistar Rats. Biomed Res Int 2019:8428304. https://doi.org/10.1155/2019/8428304

El-Shitany NA, Eid B (2017) Proanthocyanidin protects against cisplatin-induced oxidative liver damage through inhibition of inflammation and NF-kappabeta/TLR-4 pathway. Environ Toxicol 32(7):1952–1963. https://doi.org/10.1002/tox.22418

Esposito D, Overall J, Grace MH, Komarnytsky S, Lila MA (2019) Alaskan berry extracts promote dermal wound repair through modulation of bioenergetics and integrin signaling. Front Pharmacol 10:1058. https://doi.org/10.3389/fphar.2019.01058

Esselun C, Theyssen E, Eckert GP (2021) Effects of urolithin A on mitochondrial parameters in a cellular model of early Alzheimer disease. Int J Mol Sci. https://doi.org/10.3390/ijms22158333

Falcao L, Araujo MEM (2018) Vegetable tannins used in the manufacture of historic leathers. Molecules. https://doi.org/10.3390/molecules23051081

Fang C, Kim H, Barnes RC, Talcott ST, Mertens-Talcott SU (2018) Obesity-associated diseases biomarkers are differently modulated in lean and obese individuals and inversely correlated to plasma polyphenolic metabolites after 6 weeks of mango (*Mangifera indica* L.) consumption. Mol Nutr Food Res. https://doi.org/10.1002/mnfr.201800129

Ferraz AC, Moraes TFS, Nizer W, Santos MD, Totola AH, Ferreira JMS, Vieira-Filho SA, Rodrigues VG, Duarte LP, de Brito Magalhaes CL, de Magalhaes JC (2019) Virucidal activity of proanthocyanidin against Mayaro virus. Antiviral Res 168:76–81. https://doi.org/10.1016/j.antiviral.2019.05.008

Flesch M, Schwarz A, Bohm M (1998) Effects of red and white wine on endothelium-dependent vasorelaxation of rat aorta and human coronary arteries. Am J Physiol 275(4):H1183-1190. https://doi.org/10.1152/ajpheart.1998.275.4.H1183

Frevel MA, Pipingas A, Grigsby WJ, Frampton CM, Gilchrist NL (2012) Production, composition and toxicology studies of Enzogenol(R) Pinus radiata bark extract. Food Chem Toxicol 50(12):4316–4324. https://doi.org/10.1016/j.fct.2012.08.051

Fukino Y, Ikeda A, Maruyama K, Aoki N, Okubo T, Iso H (2008) Randomized controlled trial for an effect of green tea-extract powder supplementation on glucose abnormalities. Eur J Clin Nutr 62(8):953–960. https://doi.org/10.1038/sj.ejcn.1602806

Funatogawa K, Hayashi S, Shimomura H, Yoshida T, Hatano T, Ito H, Hirai Y (2004) Antibacterial activity of hydrolyzable tannins derived from medicinal plants against *Helicobacter pylori*. Microbiol Immunol 48(4):251–261. https://doi.org/10.1111/j.1348-0421.2004.tb03521.x

Gao H, Huang X, Tong Y, Jiang X (2020a) Urolithin B improves cardiac function and reduces susceptibility to ventricular arrhythmias in rats after myocardial infarction. Eur J Pharmacol 871:172936. https://doi.org/10.1016/j.ejphar.2020.172936

Gao WL, Li XH, Dun XP, Jing XK, Yang K, Li YK (2020b) Grape seed proanthocyanidin extract ameliorates streptozotocin-induced cognitive and synaptic plasticity deficits by inhibiting oxidative stress and preserving AKT and ERK activities. Curr Med Sci 40(3):434–443. https://doi.org/10.1007/s11596-020-2197-x

Gil-Cardoso K, Gines I, Pinent M, Ardevol A, Arola L, Blay M, Terra X (2017) Chronic supplementation with dietary proanthocyanidins protects from diet-induced intestinal alterations in obese rats. Mol Nutr Food Res. https://doi.org/10.1002/mnfr.201601039

Go J, Kim JE, Koh EK, Song SH, Kang HG, Lee YH, Kim HD, Hong JT, Hwang DY (2017) Hepatoprotective effect of gallotannin-enriched extract isolated from gall on hydrogen peroxide-induced cytotoxicity in HepG2 cells. Pharmacogn Mag 13(Suppl 2):S294–S300. https://doi.org/10.4103/pm.pm_424_15

Hatano T, Kusuda M, Inada K, Ogawa TO, Shiota S, Tsuchiya T, Yoshida T (2005) Effects of tannins and related polyphenols on methicillin-resistant *Staphylococcus aureus*. Phytochemistry 66(17):2047–2055. https://doi.org/10.1016/j.phytochem.2005.01.013

Hayat J, Akodad M, Moumen A, Baghour M, Skalli A, Ezrari S, Belmalha S (2020) Phytochemical screening, polyphenols, flavonoids and tannin content, antioxidant activities and FTIR characterization of *Marrubium vulgare* L. from 2 different localities of Northeast of Morocco. Heliyon 6(11):e05609. https://doi.org/10.1016/j.heliyon.2020.e05609

Hill AM, Coates AM, Buckley JD, Ross R, Thielecke F, Howe PR (2007) Can EGCG reduce abdominal fat in obese subjects? J Am Coll Nutr 26(4):396S-402S. https://doi.org/10.1080/07315724.2007.10719628

Hong S, Pangloli P, Perumal R, Cox S, Noronha LE, Dia VP, Smolensky D (2020) A comparative study on phenolic content, antioxidant activity and anti-inflammatory capacity of aqueous and ethanolic extracts of sorghum in lipopolysaccharide-induced RAW 264.7 macrophages. Antioxidants (basel). https://doi.org/10.3390/antiox9121297

Howell AB, Vorsa N, Der Marderosian A, Foo LY (1998) Inhibition of the adherence of P-fimbriated *Escherichia coli* to uroepithelial-cell surfaces by proanthocyanidin extracts from cranberries. N Engl J Med 339(15):1085–1086. https://doi.org/10.1056/NEJM199810083391516

Inan Y, Akyuz S, Kurt-Celep I, Celep E, Yesilada E (2021) Influence of in vitro human digestion simulation on the phenolics contents and biological activities of the aqueous extracts from turkish cistus species. Molecules. https://doi.org/10.3390/molecules26175322

Isenburg JC, Simionescu DT, Vyavahare NR (2004) Elastin stabilization in cardiovascular implants: improved resistance to enzymatic degradation by treatment with tannic acid. Biomaterials 25(16):3293–3302. https://doi.org/10.1016/j.biomaterials.2003.10.001

Isenburg JC, Simionescu DT, Vyavahare NR (2005) Tannic acid treatment enhances biostability and reduces calcification of glutaraldehyde fixed aortic wall. Biomaterials 26(11):1237–1245. https://doi.org/10.1016/j.biomaterials.2004.04.034

Jastrzebska M, Zalewska-Rejdak J, Wrzalik R, Kocot A, Mroz I, Barwinski B, Turek A, Cwalina B (2006) Tannic acid-stabilized pericardium tissue: IR spectroscopy, atomic force microscopy, and dielectric spectroscopy investigations. J Biomed Mater Res A 78(1):148–156. https://doi.org/10.1002/jbm.a.30717

Jekabsone A, Sile I, Cochis A, Makrecka-Kuka M, Laucaityte G, Makarova E, Rimondini L, Bernotiene R, Raudone L, Vedlugaite E, Baniene R, Smalinskiene A, Savickiene N, Dambrova M (2019) Investigation of antibacterial and antiinflammatory activities of proanthocyanidins from pelargonium sidoides DC root extract. Nutrients. https://doi.org/10.3390/nu11112829

Jerez M, Touriño S, Sineiro J, Torres JL, Núñez MJ (2007) Procyanidins from pine bark: relationships between structure, composition and antiradical activity. Food Chem 104(2):518–527. https://doi.org/10.1016/j.foodchem.2006.11.071

Kaplum V, Ramos AC, Consolaro MEL, Fernandez MA, Ueda-Nakamura T, Dias-Filho BP, Silva SO, de Mello JCP, Nakamura CV (2018) Proanthocyanidin polymer-rich fraction of stryphnodendron adstringens promotes in vitro and in vivo cancer cell death via oxidative stress. Front Pharmacol 9:694. https://doi.org/10.3389/fphar.2018.00694

Karthikeyan K, Bai BR, Devaraj SN (2007) Cardioprotective effect of grape seed proanthocyanidins on isoproterenol-induced myocardial injury in rats. Int J Cardiol 115(3):326–333. https://doi.org/10.1016/j.ijcard.2006.03.016

Kawabata K, Yoshioka Y, Terao J (2019) Role of intestinal microbiota in the bioavailability and physiological functions of dietary polyphenols. Molecules. https://doi.org/10.3390/molecules24020370

Kawk SH, Kang YR, Kim YH (2018) 1,2,3,4,6-Penta-*O*-galloyl-beta-D-glucose suppresses colon cancer through induction of tumor suppressor. Bioorg Med Chem Lett 28(12):2117–2123. https://doi.org/10.1016/j.bmcl.2018.05.028

Kim SM, Han Y, Yu SM, Kim SJ (2019) Gallotannin attenuates 2deoxyDglucoseinduced dedifferentiation and endoplasmic reticulum stress through inhibition of inositolrequiring enzyme 1 downstream p38 kinase pathway in chondrocytes. Mol Med Rep 20(6):5249–5256. https://doi.org/10.3892/mmr.2019.10773

Kim H, Venancio VP, Fang C, Dupont AW, Talcott ST, Mertens-Talcott SU (2020a) Mango (*Mangifera indica* L.) polyphenols reduce IL-8, GRO, and GM-SCF plasma levels and increase *Lactobacillus* species in a pilot study in patients with inflammatory bowel disease. Nutr Res 75:85–94. https://doi.org/10.1016/j.nutres.2020.01.002

Kim KB, Lee S, Kim JH (2020b) Neuroprotective effects of urolithin A on H_2O_2-induced oxidative stress-mediated apoptosis in

SK-N-MC cells. Nutr Res Pract 14(1):3–11. https://doi.org/10.4162/nrp.2020.14.1.3

Lalanza JF, Snoeren EMS (2021) The cafeteria diet: a standardized protocol and its effects on behavior. Neurosci Biobehav Rev 122:92–119. https://doi.org/10.1016/j.neubiorev.2020.11.003

Lee H, Lee JY, Suh MH, Sim SS, Lee MW, Kim CJ (2010) Hydrolysable tannins depress cardiac papillary muscle contraction and propranolol-induced negative inotropism. Fitoterapia 81(7):820–825. https://doi.org/10.1016/j.fitote.2010.05.002

Lee G, Park JS, Lee EJ, Ahn JH, Kim HS (2019) Anti-inflammatory and antioxidant mechanisms of urolithin B in activated microglia. Phytomedicine 55:50–57. https://doi.org/10.1016/j.phymed.2018.06.032

Lee HJ, Jung YH, Choi GE, Kim JS, Chae CW, Lim JR, Kim SY, Yoon JH, Cho JH, Lee SJ, Han HJ (2021) Urolithin A suppresses high glucose-induced neuronal amyloidogenesis by modulating TGM2-dependent ER-mitochondria contacts and calcium homeostasis. Cell Death Differ 28(1):184–202. https://doi.org/10.1038/s41418-020-0593-1

Li ZX, Ma JL, Guo Y, Liu WD, Li M, Zhang LF, Zhang Y, Zhou T, Zhang JY, Gao HE, Guo XY, Ye DM, Li WQ, You WC, Pan KF (2021) Suppression of Helicobacter pylori infection by daily cranberry intake: a double-blind, randomized, placebo-controlled trial. J Gastroenterol Hepatol 36(4):927–935. https://doi.org/10.1111/jgh.15212

Lin LT, Chen TY, Lin SC, Chung CY, Lin TC, Wang GH, Anderson R, Lin CC, Richardson CD (2013) Broad-spectrum antiviral activity of chebulagic acid and punicalagin against viruses that use glycosaminoglycans for entry. BMC Microbiol 13:187. https://doi.org/10.1186/1471-2180-13-187

Liu G, Shi A, Wang N, Li M, He X, Yin C, Tu Q, Shen X, Tao Y, Wang Q, Yin H (2020) Polyphenolic proanthocyanidin-B2 suppresses proliferation of liver cancer cells and hepatocellular carcinogenesis through directly binding and inhibiting AKT activity. Redox Biol 37:101701. https://doi.org/10.1016/j.redox.2020.101701

Lluis L, Munoz M, Nogues MR, Sanchez-Martos V, Romeu M, Giralt M, Valls J, Sola R (2011) Toxicology evaluation of a procyanidin-rich extract from grape skins and seeds. Food Chem Toxicol 49(6):1450–1454. https://doi.org/10.1016/j.fct.2011.03.042

Ma J, Gao SS, Yang HJ, Wang M, Cheng BF, Feng ZW, Wang L (2018) Neuroprotective effects of proanthocyanidins, natural flavonoids derived from plants, on rotenone-induced oxidative stress and apoptotic cell death in human neuroblastoma SH-SY5Y cells. Front Neurosci 12:369. https://doi.org/10.3389/fnins.2018.00369

Magos GA, Mateos JC, Paez E, Fernandez G, Lobato C, Marquez C, Enriquez RG (2008) Hypotensive and vasorelaxant effects of the procyanidin fraction from Guazuma ulmifolia bark in normotensive and hypertensive rats. J Ethnopharmacol 117(1):58–68. https://doi.org/10.1016/j.jep.2008.01.015

Maisetta G, Batoni G, Caboni P, Esin S, Rinaldi AC, Zucca P (2019) Tannin profile, antioxidant properties, and antimicrobial activity of extracts from two Mediterranean species of parasitic plant Cytinus. BMC Complement Altern Med 19(1):82. https://doi.org/10.1186/s12906-019-2487-7

Maki KC, Reeves MS, Farmer M, Yasunaga K, Matsuo N, Katsuragi Y, Komikado M, Tokimitsu I, Wilder D, Jones F, Blumberg JB, Cartwright Y (2009) Green tea catechin consumption enhances exercise-induced abdominal fat loss in overweight and obese adults. J Nutr 139(2):264–270. https://doi.org/10.3945/jn.108.098293

Mannucci C, Navarra M, Calapai F, Squeri R, Gangemi S, Calapai G (2017) Clinical pharmacology of *Citrus bergamia*: a systematic review. Phytother Res 31(1):27–39. https://doi.org/10.1002/ptr.5734

Mannucci C, Calapai F, Cardia L, Inferrera G, D'Arena G, Di Pietro M, Navarra M, Gangemi S, Ventura Spagnolo E, Calapai G (2018) Clinical pharmacology of *Citrus aurantium* and *Citrus sinensis* for the treatment of anxiety. Evid Based Complement Altern Med 2018:3624094. https://doi.org/10.1155/2018/3624094

Mannucci C, Casciaro M, Sorbara EE, Calapai F, Di Salvo E, Pioggia G, Navarra M, Calapai G, Gangemi S (2021) Nutraceuticals against oxidative stress in autoimmune disorders. Antioxidants (basel). https://doi.org/10.3390/antiox10020261

Marino A, Paterniti I, Cordaro M, Morabito R, Campolo M, Navarra M, Esposito E, Cuzzocrea S (2015) Role of natural antioxidants and potential use of bergamot in treating rheumatoid arthritis. PharmaNutrition 3(2):53–59. https://doi.org/10.1016/j.phanu.2015.03.002

Matsui T, Ueda T, Oki T, Sugita K, Terahara N, Matsumoto K (2001) Alpha-Glucosidase inhibitory action of natural acylated anthocyanins. 1. Survey of natural pigments with potent inhibitory activity. J Agric Food Chem 49(4):1948–1951. https://doi.org/10.1021/jf001251u

Matsumoto K, Yokoyama S (2012) Induction of uncoupling protein-1 and -3 in brown adipose tissue by kaki-tannin in type 2 diabetic NSY/Hos mice. Food Chem Toxicol 50(2):184–190. https://doi.org/10.1016/j.fct.2011.10.067

Matsuyama T, Tanaka Y, Kamimaki I, Nagao T, Tokimitsu I (2008) Catechin safely improved higher levels of fatness, blood pressure, and cholesterol in children. Obesity (silver Spring) 16(6):1338–1348. https://doi.org/10.1038/oby.2008.60

Maugeri A, Cirmi S, Minciullo PL, Gangemi S, Calapai G, Mollace V, Navarra M (2019) Citrus fruits and inflammaging: a systematic review. Phytochem Rev 18(4):1025–1049. https://doi.org/10.1007/s11101-019-09613-3

McDougall GJ, Shpiro F, Dobson P, Smith P, Blake A, Stewart D (2005) Different polyphenolic components of soft fruits inhibit alpha-amylase and alpha-glucosidase. J Agric Food Chem 53(7):2760–2766. https://doi.org/10.1021/jf0489926

Micali S, Isgro G, Bianchi G, Miceli N, Calapai G, Navarra M (2014) Cranberry and recurrent cystitis: more than marketing? Crit Rev Food Sci Nutr 54(8):1063–1075. https://doi.org/10.1080/10408398.2011.625574

Micali S, Territo A, Pirola GM, Ferrari N, Sighinolfi MC, Martorana E, Navarra M, Bianchi G (2017) Effect of green tea catechins in patients with high-grade prostatic intraepithelial neoplasia: results of a short-term double-blind placebo controlled phase II clinical trial. Arch Ital Urol Androl 89(3):197–202. https://doi.org/10.4081/aiua.2017.3.197

Moorthy M, Khoo JJ, Palanisamy UD (2019) Acute oral toxicity of the ellagitannin geraniin and a geraniin-enriched extract from *Nephelium lappaceum* L. rind in Sprague Dawley rats. Heliyon 5(8):e02333. https://doi.org/10.1016/j.heliyon.2019.e02333

Musumeci L, Maugeri A, Cirmi S, Lombardo GE, Russo C, Gangemi S, Calapai G, Navarra M (2020) Citrus fruits and their flavonoids in inflammatory bowel disease: an overview. Nat Prod Res 34(1):122–136. https://doi.org/10.1080/14786419.2019.1601196

Nallathambi R, Poulev A, Zuk JB, Raskin I (2020) Proanthocyanidin-rich grape seed extract reduces inflammation and oxidative stress and restores tight junction barrier function in Caco-2 colon cells. Nutrients. https://doi.org/10.3390/nu12061623

Noorolahi Z, Sahari MA, Barzegar M, Ahmadi Gavlighi H (2020) Tannin fraction of pistachio green hull extract with pancreatic lipase inhibitory and antioxidant activity. J Food Biochem 44(6):e13208. https://doi.org/10.1111/jfbc.13208

Okuda T (2005) Systematics and health effects of chemically distinct tannins in medicinal plants. Phytochemistry 66(17):2012–2031. https://doi.org/10.1016/j.phytochem.2005.04.023

Okuda T, Ito H (2011) Tannins of constant structure in medicinal and food plants—hydrolyzable tannins and polyphenols related to tannins. Molecules 16(3):2191–2217. https://doi.org/10.3390/molecules16032191

Park JW, Kim JE, Kang MJ, Choi HJ, Bae SJ, Kim SH, Jung YS, Hong JT, Hwang DY (2019) Anti-oxidant activity of gallotannin-enriched extract of galla rhois can associate with the protection of the cognitive impairment through the regulation of BDNF signaling pathway and neuronal cell function in the scopolamine-treated ICR mice. Antioxidants (basel). https://doi.org/10.3390/antiox8100450

Pereira-Caro G, Gaillet S, Ordonez JL, Mena P, Bresciani L, Bindon KA, Del Rio D, Rouanet JM, Moreno-Rojas JM, Crozier A (2020) Bioavailability of red wine and grape seed proanthocyanidins in rats. Food Funct 11(5):3986–4001. https://doi.org/10.1039/d0fo00350f

Peron G, Sut S, Pellizzaro A, Brun P, Voinovich D, Castagliuolo I, Dall'Acqua S (2017) The antiadhesive activity of cranberry phytocomplex studied by metabolomics: intestinal PAC-A metabolites but not intact PAC-A are identified as markers in active urines against uropathogenic *Escherichia coli*. Fitoterapia 122:67–75. https://doi.org/10.1016/j.fitote.2017.08.014

Pinent M, Blay M, Blade MC, Salvado MJ, Arola L, Ardevol A (2004) Grape seed-derived procyanidins have an antihyperglycemic effect in streptozotocin-induced diabetic rats and insulinomimetic activity in insulin-sensitive cell lines. Endocrinology 145(11):4985–4990. https://doi.org/10.1210/en.2004-0764

Pittler MH, Guo R, Ernst E (2008) Hawthorn extract for treating chronic heart failure. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD005312.pub2

Pizzi A (2019) Tannins: prospectives and actual industrial applications. Biomolecules. https://doi.org/10.3390/biom9080344

Puljula E, Walton G, Woodward MJ, Karonen M (2020) Antimicrobial Activities of Ellagitannins against Clostridiales perfringens, *Escherichia coli*, *Lactobacillus plantarum* and *Staphylococcus aureus*. Molecules. https://doi.org/10.3390/molecules25163714

Sano A (2017) Safety assessment of 4-week oral intake of proanthocyanidin-rich grape seed extract in healthy subjects. Food Chem Toxicol 108(Pt B):519–523. https://doi.org/10.1016/j.fct.2016.11.021

Savi M, Bocchi L, Mena P, Dall'Asta M, Crozier A, Brighenti F, Stilli D, Del Rio D (2017) In vivo administration of urolithin A and B prevents the occurrence of cardiac dysfunction in streptozotocin-induced diabetic rats. Cardiovasc Diabetol 16(1):80. https://doi.org/10.1186/s12933-017-0561-3

Savickiene N, Jekabsone A, Raudone L, Abdelgeliel AS, Cochis A, Rimondini L, Makarova E, Grinberga S, Pugovics O, Dambrova M, Pacauskiene IM, Baseviciene N, Viskelis P (2018) Efficacy of proanthocyanidins from *Pelargonium sidoides* root extract in reducing *P. gingivalis* viability while preserving oral commensal *S. salivarius*. Materials (basel). https://doi.org/10.3390/ma11091499

Scharf B, Schmidt TJ, Rabbani S, Stork C, Dobrindt U, Sendker J, Ernst B, Hensel A (2020) Antiadhesive natural products against uropathogenic *E. coli*: what can we learn from cranberry extract? J Ethnopharmacol 257:112889. https://doi.org/10.1016/j.jep.2020.112889

Segal L, Penman MG, Piriou Y (2018) Evaluation of the systemic toxicity and mutagenicity of OLIGOPIN(R), procyanidolic oligomers (OPC) extracted from French Maritime Pine Bark extract. Toxicol Rep 5:531–541. https://doi.org/10.1016/j.toxrep.2018.03.013

Serrano J, Puupponen-Pimia R, Dauer A, Aura AM, Saura-Calixto F (2009) Tannins: current knowledge of food sources, intake, bioavailability and biological effects. Mol Nutr Food Res 53(Suppl 2):S310-329. https://doi.org/10.1002/mnfr.200900039

Sieniawska E (2015) Activities of tannins-from in vitro studies to clinical trials. Nat Prod Commun 10(11), 1877–1884. https://www.ncbi.nlm.nih.gov/pubmed/26749816

Singh D, Singh D, Choi SM, Zo SM, Painuli RM, Kwon SW, Han SS (2014) Effect of extracts of terminalia chebula on proliferation of keratinocytes and fibroblasts cells: an alternative approach for wound healing. Evid Based Complement Altern Med 2014:701656. https://doi.org/10.1155/2014/701656

Singh IP, Bharate SB, Bhutani KK (2005) Anti-HIV natural products. Curr Sci 89(2), 269–290. http://www.jstor.org/stable/24110574

Sivaprakasapillai B, Edirisinghe I, Randolph J, Steinberg F, Kappagoda T (2009) Effect of grape seed extract on blood pressure in subjects with the metabolic syndrome. Metabolism 58(12):1743–1746. https://doi.org/10.1016/j.metabol.2009.05.030

Smeriglio A, Barreca D, Bellocco E, Trombetta D (2016) Chemistry, pharmacology and health benefits of anthocyanins. Phytother Res 30(8):1265–1286. https://doi.org/10.1002/ptr.5642

Smeriglio A, Barreca D, Bellocco E, Trombetta D (2017) Proanthocyanidins and hydrolysable tannins: occurrence, dietary intake and pharmacological effects. Br J Pharmacol 174(11):1244–1262. https://doi.org/10.1111/bph.13630

Sobeh M, Mahmoud MF, Abdelfattah MAO, Cheng H, El-Shazly AM, Wink M (2018) A proanthocyanidin-rich extract from Cassia abbreviata exhibits antioxidant and hepatoprotective activities in vivo. J Ethnopharmacol 213:38–47. https://doi.org/10.1016/j.jep.2017.11.007

Subkamkaew C, Limtrakul Dejkriengkraikul P, Yodkeeree S (2019) Proanthocyanidin-rich fractions from red rice extract enhance TNF-alpha-induced cell death and suppress invasion of human lung adenocarcinoma cell A549. Molecules. https://doi.org/10.3390/molecules24183393

Suwandi DW, Rostinawati T, Muchtaridi M, Subarnas A (2021) Safety assessment of the *Polypodium feei* root extract: acute and subchronic studies. Toxicol Rep 8:696–704. https://doi.org/10.1016/j.toxrep.2021.03.013

Talarek S, Listos J, Barreca D, Tellone E, Sureda A, Nabavi SF, Braidy N, Nabavi SM (2017) Neuroprotective effects of honokiol: from chemistry to medicine. BioFactors 43(6):760–769. https://doi.org/10.1002/biof.1385

Tian Y, Zou B, Li C-M, Yang J, Xu S-F, Hagerman AE (2012) High molecular weight persimmon tannin is a potent antioxidant both ex vivo and in vivo. Food Res Int 45(1):26–30

Tian Y, Mao X, Sun R, Zhang M, Xia Q (2020) Enhanced oral bioavailability of oligomeric proanthocyanidins by a self-double-emulsifying drug delivery system. Food Sci Nutr 8(7):3814–3825. https://doi.org/10.1002/fsn3.1673

Tie F, Wang J, Liang Y, Zhu S, Wang Z, Li G, Wang H (2020) Proanthocyanidins ameliorated deficits of lipid metabolism in type 2 diabetes mellitus via inhibiting adipogenesis and improving mitochondrial function. Int J Mol Sci. https://doi.org/10.3390/ijms21062029

Tong WY, Wang H, Waisundara VY, Huang D (2014) Inhibiting enzymatic starch digestion by hydrolyzable tannins isolated from *Eugenia jambolana*. LWT Food Sci Technol 59(1):389–395

Tong J, Fang J, Zhu T, Xiang P, Shang J, Chen L, Zhao J, Wang Y, Tong L, Sun M (2021) Pentagalloylglucose reduces AGE-induced inflammation by activating Nrf2/HO-1 and inhibiting the JAK2/STAT3 pathway in mesangial cells. J Pharmacol Sci 147(4):305–314. https://doi.org/10.1016/j.jphs.2021.08.006

Tousson E, Elgharabawy RM, Elmasry TA (2018) Grape seed proanthocyanidin ameliorates cardiac toxicity induced by boldenone undecylenate through inhibition of NADPH oxidase and reduction in the expression of NOX_2 and NOX_4. Oxid Med Cell Longev 2018:9434385. https://doi.org/10.1155/2018/9434385

Tu X, Wang M, Liu Y, Zhao W, Ren X, Li Y, Liu H, Gu Z, Jia H, Liu J, Li G, Luo L (2019) Pretreatment of grape seed proanthocyanidin extract exerts neuroprotective effect in murine model of neonatal hypoxic-ischemic brain injury by its antiapoptotic

property. Cell Mol Neurobiol 39(7):953–961. https://doi.org/10.1007/s10571-019-00691-7

Upanan S, Yodkeeree S, Thippraphan P, Punfa W, Wongpoomchai R, Limtrakul Dejkriengkraikul P (2019) The proanthocyanidin-rich fraction obtained from red rice germ and bran extract induces HepG2 hepatocellular carcinoma cell apoptosis. Molecules. https://doi.org/10.3390/molecules24040813

Van de Velde F, Esposito D, Grace MH, Pirovani ME, Lila MA (2019) Anti-inflammatory and wound healing properties of polyphenolic extracts from strawberry and blackberry fruits. Food Res Int 121:453–462. https://doi.org/10.1016/j.foodres.2018.11.059

Vasconcelos PC, Andreo MA, Vilegas W, Hiruma-Lima CA, Pellizzon CH (2010) Effect of Mouriri pusa tannins and flavonoids on prevention and treatment against experimental gastric ulcer. J Ethnopharmacol 131(1):146–153. https://doi.org/10.1016/j.jep.2010.06.017

Vilhelmova-Ilieva N, Jacquet R, Deffieux D, Pouysegu L, Sylla T, Chassaing S, Nikolova I, Quideau S, Galabov AS (2019) Anti-herpes simplex virus type 1 activity of specially selected groups of tannins. Drug Res (stuttg) 69(7):373–374. https://doi.org/10.1055/a-0640-2557

Wang R, Lechtenberg M, Sendker J, Petereit F, Deters A, Hensel A (2013) Wound-healing plants from TCM: in vitro investigations on selected TCM plants and their influence on human dermal fibroblasts and keratinocytes. Fitoterapia 84:308–317. https://doi.org/10.1016/j.fitote.2012.12.020

Wang Z, Guo QY, Zhang XJ, Li X, Li WT, Ma XT, Ma LJ (2014) Corilagin attenuates aerosol bleomycin-induced experimental lung injury. Int J Mol Sci 15(6):9762–9779. https://doi.org/10.3390/ijms15069762

Wang L, Li X, Wang H (2019) Physicochemical properties, bioaccessibility and antioxidant activity of the polyphenols from pine cones of Pinus koraiensis. Int J Biol Macromol 126:385–391. https://doi.org/10.1016/j.ijbiomac.2018.12.145

Watrelot AA, Norton EL (2020) Chemistry and reactivity of tannins in *Vitis* spp.: a review. Molecules. https://doi.org/10.3390/molecules25092110

Xie YW, Xu HX, Dong H, Fiscus RR, But PP (2007) Role of nitric oxide in the vasorelaxant and hypotensive effects of extracts and purified tannins from *Geum japonicum*. J Ethnopharmacol 109(1):128–133. https://doi.org/10.1016/j.jep.2006.07.015

Xie Z, Wang M, Deng Y, Li J, Li J, Pang W, Xie L, Jiang D, Huang Z, He T, Yang G (2022) Acute toxicity of eucalyptus leachate tannins to zebrafish and the mitigation effect of Fe(3+) on tannin toxicity. Ecotoxicol Environ Saf 229:113077. https://doi.org/10.1016/j.ecoenv.2021.113077

Yao J, Qiao H, Jin Z, Wang R, Huang H, Fang L, Chen Y, Tai K, Chen Y, Doeppner TR, Chen Z, Kuchta K (2020) Ginkgo biloba and its constituent 6-hydroxykynurenic-acid as well as its proanthocyanidins exert neurorestorative effects against cerebral ischemia. Planta Med 86(10):696–707. https://doi.org/10.1055/a-1146-2861

Yu HL, Feng ZQ, Zhang JJ, Wang YH, Ding DJ, Gao YY, Zhang WF (2018) The evaluation of proanthocyanidins/chitosan/lecithin microspheres as sustained drug delivery system. Biomed Res Int 2018:9073420. https://doi.org/10.1155/2018/9073420

Zary-Sikorska E, Fotschki B, Jurgonski A, Kosmala M, Milala J, Kolodziejczyk K, Majewski M, Ognik K, Juskiewicz J (2020) Protective effects of a strawberry ellagitannin-rich extract against pro-oxidative and pro-inflammatory dysfunctions induced by a high-fat diet in a rat model. Molecules. https://doi.org/10.3390/molecules25245874

Zeng YX, Wang S, Wei L, Cui YY, Chen YH (2020) Proanthocyanidins: components, pharmacokinetics and biomedical properties. Am J Chin Med 48(4):813–869. https://doi.org/10.1142/S0192415X2050041X

Zern TL, Wood RJ, Greene C, West KL, Liu Y, Aggarwal D, Shachter NS, Fernandez ML (2005) Grape polyphenols exert a cardioprotective effect in pre- and postmenopausal women by lowering plasma lipids and reducing oxidative stress. J Nutr 135(8):1911–1917. https://doi.org/10.1093/jn/135.8.1911

Zhang L, Wang Y, Li D, Ho CT, Li J, Wan X (2016) The absorption, distribution, metabolism and excretion of procyanidins. Food Funct 7(3):1273–1281. https://doi.org/10.1039/c5fo01244a

Zhang L, Shao J, Zhou Y, Chen H, Qi H, Wang Y, Chen L, Zhu Y, Zhang M, Chen L, Du Y, Zhong M, Shi X, Li Q (2018a) Inhibition of PDGF-BB-induced proliferation and migration in VSMCs by proanthocyanidin A2: involvement of KDR and Jak-2/STAT-3/cPLA2 signaling pathways. Biomed Pharmacother 98:847–855. https://doi.org/10.1016/j.biopha.2018.01.010

Zhang Y, Chen S, Wei C, Rankin GO, Rojanasakul Y, Ren N, Ye X, Chen YC (2018b) Dietary compound proanthocyanidins from Chinese bayberry (*Myrica rubra* Sieb. et Zucc.) leaves inhibit angiogenesis and regulate cell cycle of cisplatin-resistant ovarian cancer cells via targeting Akt pathway. J Funct Foods 40:573–581. https://doi.org/10.1016/j.jff.2017.11.045

Zhang YP, Liu SY, Sun QY, Ren J, Liu HX, Li H (2018c) Proanthocyanidin B2 attenuates high-glucose-induced neurotoxicity of dorsal root ganglion neurons through the PI3K/Akt signaling pathway. Neural Regen Res 13(9):1628–1636. https://doi.org/10.4103/1673-5374.237174

Zhang Y, Dong Y, Li X, Wang F (2019) Proanthocyanidin encapsulated in ferritin enhances its cellular absorption and antioxidant activity. J Agric Food Chem 67(41):11498–11507. https://doi.org/10.1021/acs.jafc.9b03903