Supplementary Table 1: Chemical formulas, molecular weights, and classification of ellagitannins present in red raspberries.

Compound Name	Classification	Molecular Formula	Molecular Weight,g/mol	Origin
casuarictin	Monomer	$C_{41}H_{28}O_{26}$	936.6	Casuarictin | C41H28O26 | CID 73644 - PubChem
sanguiin H-6	Dimer	$C_{82}H_{54}O_{52}$	1870.3	Sanguiin H 6 | C82H54O52 | CID 16130897 - PubChem
lambertianin C	Oligomer/Trimer	$C_{121}H_{80}O_{76}$	2749.9	Lambertianin C | C121H80O76 | CID 155903165 - PubChem
Sanguiin H-10	Oligomer	$C_{68}H_{48}O_{44}$	1569.1	Sanguiin H 10 | C68H48O44 | CID 131752591 - PubChem
potentillin	Monomer	$C_{41}H_{28}O_{26}$	936.6	Potentillin | C41H28O26 | CID 452242 - PubChem
pedunculalagin	Monomer	$C_{34}H_{24}O_{22}$	784.5	Pedunculagin | C34H24O22 | CID 442688 - PubChem
nobotanin A	Dimer	$C_{75}H_{52}O_{48}$	1721.2	SID 319428190 - PubChem
lambertianin D	Tetramer	$C_{164}H_{106}O_{104}$	3740.5	Lambertianin D | C164H106O104 | CID 44460483 - PubChem

Supplementary Table 2.Summary of in vitro evidence on ellagitannins and their metabolites across different disease domains

Study type	Disease	Evidence source	Main mechanisms of action	Limitations	Overall appraisal	Ref.
In vitro studies	Cardiovascular protection	Samples:HUVECs, macrophages, etc.; experimental Treatments: ellagic acid or urolithin A added under stimuli such as ox-LDL or oxidative stress	Antioxidant / anti-inflammatory: reduce ROS, inhibit NF-κB activation,and attenuate oxidative stress– and inflammation-induced injury; endothelial protection: activate PI3K/Akt/eNOS, upregulate eNOS and NO, downregulate LOX-1 expression, and improve endothelium-dependent vasodilation;anti-atherosclerotic: via miR-27/ERK/PPAR-γ and miR-33/ERK/AMPKα/SREBP-1 pathways, promote cholesterol efflux and inhibit cholesterol uptake	Mainly acute in vitro models; supraphysiological concentrations of ellagic acid and urolithins; do not reflect inter-individual variability in gut microbiota.	Provides key molecular-target evidence that ellagic acid/urolithin A exert antioxidant, anti-inflammatory, endothelial-protective, and anti-atherosclerotic effects, forming a mechanistic basis for subsequent animal and clinical investigations	92, 98, 102, 103, 105, 106
	Antidiabetic Effects	Samples:pancreatic β-cells,high-glucose and/or insulin-resistant adipocytes,etc.; Treatments: ellagic acid and urolithins.	Improve β-cell function: ellagic acid enhances insulin secretion from β-cells under high-glucose conditions;Increase insulin sensitivity and regulate energy metabolism: urolithin A activates AMPK and mitochondria-related pathways, increases glucose uptake, and attenuates inflammation and oxidative stress.	Use of single cell–type models; tested compound concentrations exceed physiological levels.	Demonstrates that ellagic acid and urolithins can ameliorate disordered glucose metabolism via dual mechanisms—preservation of pancreatic islet function and enhancement of insulin sensitivity—thereby providing direct mechanistic evidence to support nutritional interventions for metabolic syndrome and type 2 diabetes.	86, 117

Supplementary Table 2.(Contd.)

Study type	Disease	Evidence source	Main mechanisms of action	Limitations	Overall appraisal	Ref.
In vitro studies	Anti-Alzheimer's activity	Samples: BACE1 enzymatic activity models, neuronal cell lines, etc.; Treatments: ellagic acid, urolithins, and ellagitannin-rich extracts.	Antioxidant / anti-inflammatory: scavenging of ROS, suppression of pro-inflammatory mediators, and attenuation of neuroinflammation and oxidative damage. Anti-Aβ generation: ellagic acid selectively inhibits β-secretase (BACE1) activity, thereby reducing Aβ production. Targeting protein kinases: urolithin A anchors to the active site of DYRK1A via key side-chain interactions, inhibits its activity, and thus interferes with AD-related aberrant phosphorylation signalling.	Most studies are based on ellagitannins extracted from pomegranate or on purified urolithins, with limited direct evidence for red raspberry–derived preparations; single-target in vitro models do not recapitulate the complexity of the brain microenvironment.	Converging evidence on multiple critical targets (e.g. BACE1, DYRK1A) supports the potential neuroprotective and anti-Alzheimer's capacity of ellagic acid and urolithins.	130 – 133, 136, 137

Supplementary Table 2.(Contd.)

Study type	Disease	Evidence source	Main mechanisms of action	Limitations	Overall appraisal	Ref.
In vitro studies	Anticancer effects	Samples: HT-29 colon cancer cells, esophageal squamous carcinoma cells, UMUC3 bladder cancer cells, hepatocellular carcinoma cells, etc.; Treatments: ellagitannins, ellagic acid, urolithin A, urolithin B, and related compounds.	Inhibition of proliferation / cell-cycle arrest: induction of G0/G1 or G2/M phase arrest in HT-29 and other cancer cell lines, thereby suppressing cell proliferation. Induction of apoptosis: ellagic acid downregulates RNF6 and upregulates SHP-1, inhibits STAT3 signaling, and promotes apoptosis of tumor cells. Inhibition of migration / invasion: urolithin A suppresses Rac1/Pak1 kinase activity, disrupts actin polymerization, and consequently inhibits the migratory capacity of multiple cancer cell types. Inactivation of oncogenic signaling: urolithin B inactivates Wnt/β-catenin signaling, reduces the expression of β-catenin, c-Myc, and Cyclin D1, and inhibits the proliferation of hepatocellular carcinoma cells.	All experiments are short-term in vitro studies using relatively high doses; single cell-line models cannot recapitulate the complexity of the tumor microenvironment and the immune system; the use of purified compounds does not fully reflect the forms and exposure patterns associated with dietary intake.	In vitro evidence indicates that ellagitannins and urolithins exhibit broad-spectrum antiproliferative, pro-apoptotic, and anti-migratory potential across multiple tumor types, providing important leads for future research on cancer chemoprevention and adjuvant therapy.	28, 69, 147 – 149

Supplementary Table 3.Summary of Animal models on ellagitannins and their metabolites across different disease domains

Study type	Disease	Evidence source	Main mechanisms of action	Limitations	Overall appraisal	Ref.
Animal models	Cardiovascular protection	Samples: rat myocardial ischemia–reperfusion (I/R) models and myocardial fibrosis models; Treatments: ellagic acid and urolithin A.	Cardiomyocyte protection: activation of PI3K/Akt, attenuation of I/R injury, and reduction of necrosis/apoptosis. Anti-fibrotic effects: Ellagic acid downregulates HDAC1 and inhibits fibroblast proliferation and migration; urolithin A suppresses TGF-β1–induced fibroblast activation and myofibroblast differentiation. Antioxidant / Nrf2-related effects: urolithin A restores Nrf2 and its downstream antioxidant gene expression, thereby reducing myocardial oxidative stress.	Rodent short-term models; doses differ markedly from realistic human dietary exposure; use of free ellagic acid and urolithin rather than food-derived forms; lack of composite models incorporating multiple cardiovascular risk factors.	Animal studies indicate that ellagic acid and urolithin A ameliorate myocardial injury and remodeling through multi-target actions (antioxidant, anti-apoptotic, and anti-fibrotic), providing preclinical evidence for their cardioprotective potential.	107 – 110

Supplementary Table 3.(Contd.)

Study type	Disease	Evidence source	Main mechanisms of action	Limitations	Overall appraisal	Ref.
Animal models	Antidiabetic Effects	Samples: high-fat diet–induced obese mice and models of type 2 diabetes and metabolic syndrome; Treatments: feeding whole red raspberries, raspberry juice concentrates, or raspberry extracts.	Improvement of insulin signalling / glucose homeostasis: enhanced insulin sensitivity and partial restoration of glucose homeostasis. Regulation of adipose tissue and energy metabolism: activation of skeletal muscle AMPKα1, promotion of brown/beige adipocyte formation, and increased energy expenditure. Anti-inflammatory / inflammasome inhibition: suppression of the NLRP3 inflammasome and related inflammatory mediators, thereby alleviating obesity-associated chronic inflammation.	Doses are generally higher than typical human dietary intake; coexistence of multiple polyphenols makes it difficult to attribute effects specifically to ellagitannins; animal models are restricted to particular strains and sexes.	Collectively, these studies indicate that red raspberry polyphenols (including ellagitannins) can improve metabolic phenotype by enhancing insulin sensitivity, improving adipose tissue function, and suppressing inflammation, providing important preliminary evidence to support future clinical interventions [118–122].	118 – 122

Supplementary Table 3.(Contd.)

Study type	Disease	Evidence source	Main mechanisms of action	Limitations	Overall appraisal	Ref.
Animal models	Anti-Alzheime-r's activity	Samples: rat models of Alzheimer's disease, APP/PS1 and 3xTg-AD transgenic mice, and models of subarachnoid hemorrhage, traumatic brain injury (TBI), and radiation-induced brain injury; Treatments: ellagic acid and urolithins.	Cognitive and behavioral improvements: attenuation of learning and memory deficits in Alzheimer's models. Anti-Aβ / anti-inflammatory effects: reduction of Aβ burden, inhibition of microglial activation, and decreased release of pro-inflammatory cytokines. Mitochondrial / autophagy and BBB protection: urolithin A improves mitochondrial function and autophagy, helps maintain blood–brain barrier integrity, and reaches brain concentrations of approximately 10% of plasma levels.	Most studies employ early-stage or preventive intervention models, and efficacy in advanced disease stages remains unclear; routes and forms of administration differ substantially from typical dietary exposure.	Results across multiple models consistently demonstrate that ellagic acid and urolithins exert neuroprotective, anti-inflammatory, and cognition-improving effects, providing important preclinical evidence for their use as nutritional interventions in AD and other neurodegenerative diseases	134 – 139
	Anticancer effects	Samples: murine models bearing hepatocellular carcinoma xenografts; Treatment: administration of urolithin B.	Tumor suppression and signaling: urolithin B significantly inhibits tumor growth in hepatocellular carcinoma xenograft models and, in vivo, inactivates Wnt/β-catenin signaling, leading to reduced expression of associated oncogenic proteins.	Do not adequately mimic the chronic progression of human tumors or the contribution of the immune system; administered doses are relatively high, and long-term safety as well as potential interactions remain unclear.	animal evidence supports a certain level of in vivo antitumor activity of urolithin B, but the findings are still at an exploratory preclinical stage	149

Supplementary Table4. Summary of Human studies on ellagitannins and their metabolites across different disease domains

Study type	Disease	Evidence source	Main mechanisms of action	Limitations	Overall appraisal	Ref.
Human studies	Cardiovascular protection	Samples: healthy older adults; Treatments:: approximately 4 months of urolithin A supplementation.	Reductions in multiple plasma biomarkers related to cardiovascular risk, including sphingolipids, and improvements in mitochondrial function and related health indicators.	Small sample size and short follow-up duration; endpoints limited to biomarkers rather than cardiovascular events; intervention used high-purity urolithin A rather than food-based sources.	Preliminary evidence suggests that urolithin A can improve cardiometabolic risk profiles and mitochondrial health in humans, but its clinical cardioprotective effects still need to be confirmed in large-scale, long-term studies	111
	Antidiabetic Effects	Samples:individuals with type 2 diabetes (T2DM) and prediabetes with overweight/obesity (PreDM-O); Treatments: single intake or 4-week intake of 125–250 g frozen red raspberries.	Glycemic and insulinemic responses: co-ingestion of 250 g red raspberries with a high-fat meal reduced postprandial glucose peak and AUC;In PreDM-O participants, both doses significantly lowered postprandial insulin AUC, whereas effects in established T2DM were limited.Inflammation: some studies reported short-term reductions in inflammatory biomarkers.	Small sample sizes and short intervention periods; lack of evidence on long-term outcomes such as complications; whole-fruit interventions preclude precise quantification of actual ellagitannin/urolithin intake.	The findings indicate that red raspberries can improve postprandial glucose and insulin responses, particularly benefiting individuals with prediabetes or early metabolic dysregulation, whereas evidence for long-term glycemic control in established T2DM remains insufficient	118, 123, 124

Supplementary Table 4. (Contd.)

Study type	Disease	Evidence source	Main mechanisms of action	Limitations	Overall appraisal	Ref.
	Anti-Alzheime-r's activity	At present, no randomized controlled trials have been conducted in which ellagic acid, urolithins, or ellagitannins serve as the primary intervention.	—	Direct clinical intervention data are lacking; the optimal dose, formulation, safety profile, and appropriate follow-up duration have yet to be defined.	In the neurological field, the evidence remains confined to mechanistic and preclinical studies, and potential clinical applications will require support from future clinical research.	—
Human studies	Anticancer effects	Samples:patients with colorectal cancer and individuals at high risk of colorectal cancer; Treatments:supplementation with ellagitannin extracts or ellagitannin-rich foods.	Favorable modulation of oncogene expression; Reductions in systemic and local inflammatory biomarkers.	Most studies are short-term with small sample sizes and lack hard clinical endpoints such as cancer incidence, recurrence, and survival; interventions predominantly involve pomegranate or walnuts, with no dedicated trials specifically targeting red raspberry–derived ellagitannins.	Existing evidence confirms that urolithins can "reach colonic tissue and modulate the local microenvironment," but large-scale clinical trials are still required to substantiate their clinical anticancer efficacy	151 - 153