Ellagic Acid and Polyphenols of Punica *granatum L.*

Subjects: Neurosciences

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Pomegranate (*Punica granatum* L.) is a rich source of polyphenols, including ellagitannins and ellagic acid. The plant is used in traditional medicine, and its purified components can provide anti-inflammatory and antioxidant activity and support of host defenses during viral infection and recovery from disease. Pomegranate extracts, ellagitannins and ellagic acid are promising agents to target the SARS-CoV-2 virus and to restrict the host inflammatory response to viral infections, as well as to supplement the depleted host antioxidant levels during the stage of recovery from COVID-19.

Punica granatum | COVID-19 | polyphenols | ellagitannins | ellagic acid | neurodegeneration | antioxidant activity

1. Antioxidant and Anti-Inflammatory Activity of Pomegranate Extract

The anti-inflammatory and antioxidant properties of pomegranate are attributed predominantly to the polyphenolic substances present in both the edible and non-edible parts of the plant. These polyphenols are mainly anthocyanins, condensed tannins that give the fruit its brilliant red color and hydrolysable ellagitannins (ETs) [1]. The ETs are regarded as the main contributors to the antioxidant effects of pomegranate extracts, and their concentration is much higher in pomegranate plants compared to other plants [2][3][4]. ETs consist of one or multiple units of EA attached to a sugar or a sugar alcohol core. In pomegranate extract, numerous ET compounds have been identified, the punicalagins (PUN) being the most abundant, and a smaller portion is contributed by their hydrolysis products, punicalin and free EA [5][6][7]. Purified ETs, as well as the pomegranate polyphenol extract itself, have shown good antioxidant and anti-inflammatory activity in a range of experimental systems. Numerous articles have examined their effect on chronic inflammatory conditions, including autoimmune disorders, neurodegenerative conditions, respiratory distress and viral infection. The studies show a general trend of decrease in the levels of pro-inflammatory markers after treatment with plant polyphenol-rich extracts or with their purified components and downstream metabolites [7][8][9][10][11][12][13][14]. The data show that pre-treatment with pomegranate extracts, ETs (corilagin or punicalagin) and urolithin A are associated with anti-inflammatory effects in various tissues [15][16].

2. Antioxidant and Anti-Inflammatory Effects of EA and Its Metabolites

ETs undergo hydrolysis during fruit processing or after ingestion. Therefore, ET-rich plants or plant extracts can be a nutritional source of EA. The resultant EA is further converted to urolithins by the gut flora [7][17]. The urolithins and their conjugates show higher bioavailability compared to the EA precursor and thus can be expected to exert systemic effects [18][19]. However, the human population can be divided into three different metabotypes according to the urolithin profile measured after ingestion of ET-containing foods or extracts, which may result in a high variability of the effects associated with urolithin treatment in vivo [18][19][20][21].

Chronic inflammatory conditions are associated with immune cell invasion of the tissues and often lead to tissue damage, including fibrosis. The ET corilagin and EA have been shown to be able to interfere with hypertrophic scar formation and lung fibrosis by regulating levels of TGF-β1 via activity of lysyl oxidase homolog 2 enzyme (LOXL2) and the remodeling of the extracellular matrix by matrix metalloproteinases (MMPs) [22][23]. EA supports endothelial function not only by directly reducing oxidative stress but also by decreasing the TNF-α-induced endothelial expression of vascular cell adhesion molecule 1 (VCAM1) and intracellular adhesion molecule 1 (ICAM1) [24][25]. A reduction in immune cell invasion was achieved by using pomegranate extract, PUN or urolithin A in the lungs, CNS and other inflammation sites in a variety of rodent model systems. The positive effects of ETs and related metabolites on inhibiting the invasion of CNS tissues with immune cells and the decreased activation of resident immune cells (e.g., microglia) points to the potential benefits of using plant polyphenolic extracts as part of supportive treatment for neuro-inflammation after COVID-19, a serious and long-term complication [26][27].

In addition to infiltrating the inflamed tissues, activated immune cells release pro-inflammatory cytokines (including TNF-α, IL-1β and IL-6) and pro-inflammatory molecules, such as NO, which can also influence chemotaxis. Viral infections are also able to induce the secretion of these molecules [9][28][29][30]. The SARS-CoV-2 proteins nsp9 and nsp10 may stimulate chemotaxis via IL-6 and IL-8 by interfering with NFκB signaling [31][32].

The nuclear factor NFκB has been described as a “matchmaker between inflammation, inflammatory bowel disease, cancer and diabetes” [13], and it is under its regulation that IL-6, TNF-α and IL-1β levels increase in chronic diseases. Viral infection can also be an activator for NFκB. It appears that pomegranate polyphenolic extracts and their components restrict the secretion of pro-inflammatory molecules listed above by reducing NFκB activity [5][33][34][35]. A comparative study testing three ETs (urolithin A, *iso*-urolithin A and urolithin B), along with their respective glucuronides, on lipopolysaccharide (LPS)-induced inflammation in vitro showed that urolithin A was the most effective in reducing the levels of TNF-alpha, while its glucuronide conjugate did not have any effect [15].

The ability of ETs and EA to regulate cytokine levels may be beneficial to counteract the deregulation of immunity induced by SARS-CoV-2.

The studies demonstrating the antioxidant and anti-inflammatory properties of plant extracts containing ellagitannins or of purified ellagitannins and downstream metabolites (ellagic acid or urolithins) are listed in **Table 1**.

Table 1. Antioxidant and anti-inflammatory properties of in vitro and in vivo application of plant extracts containing ellagitannins or application of purified ellagitannins and downstream metabolites (ellagic acid or urolithins). ↑: increased; ↓: decreased; x: counteracted.

Compound Tested	Experimental System	Findings	References
pomegranate extract	human consumption of capsules	↑ antioxidant capacity of plasma (ORAC) within 30 min	[36]
	Alzheimer’s disease transgenic R1.40 mice model	non-significant ↓ TNFα, IL-1 and COX2	[37]
pomegranate flower extract	Zucker diabetic fatty rat	↓ interstitial and perivascular collagen accumulation in heart, expression of collagen I, collagen III, fibronectin, ET1, ETA, ETB, x NFκB activity	[38]
pomegranate juice	hyperoxia rat model	↓ neutrophil infiltration, albumin leak, ROS, apoptotic bodies in lungs, IL-1β, IL-6	[39]
pomegranate leaf ethanolic extract	intranasal application in asthma mouse model	↓ IL-1β, IL-5, inflammatory cell infiltration in lung, mucous glycoprotein secretion	[8]
pomegranate peel extract	neutrophil culture and LPS-stimulated mice	x MPO activity in neutrophils, ↓ lung invasion of inflammatory cells	[40]
	LPS-induced RAW264.7 macrophages	↓ TLR4 expression, ↓ IL-1β, IL-6, TNFα, NO, PGE2, ROS production, x nuclear translocation of NFκB nuclear translocation	[14]
walnut methanolic extract	human aorta endothelial cells (HAEC)	↓ TNFα-induced VCAM1 and ICAM1 expression	[24]
	KS483 osteoblastic cells line	nodule formation induced	
corilagin	HSV-1 infected MV-2 microglia cells	↓ secretion of NO, TNFα, IL-1β, ↑ secretion of IL-10, cytochrome c, caspase-3, -8, -9 and -12	[9]
	HSV-1 infected mice	↓ numbers of inflammatory cells in the brain, ↓ neuronal degeneration and interstitial	

Compound Tested	Experimental System	Findings	References
		edema	
punicalagin	acute respiratory distress mouse model	↓ inflammatory cell lung invasion, alveolar wall thickening, pulmonary congestion, ↓ TNFα, IL-1β, and IL-6 levels, MPO activity, TLR4 expression, x phosphorylation of IκBα and NFκB p65	[11]
	Jurkat cells	T cell activation by NFAT	[41]
	activated CD4+ murine splenic lymphocytes	↓ IL-2 mRNA and protein	
	PMA-induced ear edema in mice	↓ hyperplasia and inflammatory cell infiltration	
	LPS-induced RAW264.7 macrophages	↓ TLR4 expression, ↓ IL-1β, IL-6, TNFα, NO, PGE2, ROS production, x nuclear translocation of NFκB nuclear translocation	[14]
ellagic acid	human aorta endothelial cells (HAEC)	↓ TNFα-induced VCAM1 and ICAM1 expression	[24]
	KS483 osteoblastic cells line	nodule formation induced	
	mice on high fat diet	↓ aortic lesions, plasma cholesterol and triglyceride, ↓sICAM1 and E-selectin expression, ↑ Nrf2, HO-1 protein and aortic NOS activity	[25]
	human umbilical vein endothelial cells (HUVEC)	Nrf2-mediated cytoprotection, ↑ HO-1 protein	
	human Caco-2 intestinal cells	↓ NFκB activation after LPS stimulation, ↑ IκB-α phosphorylation and IL-8 secretion after IL-1β stimulation	[42]
	in combination with oseltamivir and isoprinosine in influenza A infected mice	↑ glutathione reductase activity, ↓ TBARS in blood plasma and lungs during infection	[33]
	LPS-induced RAW264.7 macrophages	↓ TLR4 expression, ↓ IL-1β, IL-6, TNFα, NO, PGE2, ROS production, x nuclear translocation of NFκB nuclear translocation	[14]
	Caco-2 and HT-29/B6 intestinal cells	↑ transepithelial resistance, ↓ caludin-4, -7, -15 expression	[43]

Compound Tested	Experimental System	Findings	References
urolithin A	experimental autoimmune encephalomyelitis	↓ demyelination and inflammatory infiltrating cells, reduce severity of disease, ↓ activation of dendritic cells and CNS microglia	[12]
	bone marrow-derived dendritic cells and SIM-A9 microglia	↓ IL-1β, IL-6, TNFα, ↑ IL-10	
	inflammatory bowel disease model LPS-stimulated BMDM	↓IκB-α phosphorylation, IL-1β, IL-2, IL-6, IL-12, TNFα, NOS2, double-stranded DNA breaks, superoxide production, MAPK and PI3K activation, proinflammatory miRNAs	[13]
	Caco-2 and HT-29/B6 intestinal cells	x TNF-α induced drop in transepithelial resistance	[44]
urolithins	LPS-stimulated BV2 microglia	↓ NO, TNFα and IL-6, improved SH-SY5Y neuronal cell viability in H_2O_2	[7]

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constituent punicalin (IC_{50} of 0.06 mg/mL), suggesting synergism with other components in the plant extract [48].

Pomegranate leaf ethanolic extract showed antiviral activity against Zika virus and *herpes simplex* virus type 2 (HSV-2) [47], while a pomegranate phenolic extract showed inhibitory activity against influenza [5], and extracts from the fruit (juice and peel) were active against hepatitis C virus (HCV) and SARS-CoV-2 [47][48]. Similarly, promising results against a range of viruses were obtained with purified components of these extracts, the dominant pomegranate ET punicalagin/punicalin fraction and the ET hydrolysis product EA (**Table 2**). Chebulagic acid, another ET from the Japanese medicinal plant *Geranium thunbergii,* also exerts broad antiviral activity with effects similar to punicalagin [57][58][59]. These ETs both seemingly interact with viral glycoproteins and glycosaminoglycan molecules on the host cell surface, which assist the entry into host cells for a range of viruses [46][50].

The antiviral effect of purified EA against viruses such as Zika, HRV-2, HRV-3, HRV-4 and influenza has been suggested to occur by disrupting the virus's interaction with the host cell surface [5][34][35]. EA may also be the dominant antiviral substance in pomegranate leaf extract, according to Acquadro et al. [35], as punicalagins and punicalins are not present in detectable concentrations in the leaves of the plant.

The effects of EA on the virus may extend to other mechanisms, as in human immunodeficiency virus-1 (HIV-1) infection, this phytochemical restricted viral replication by inhibition of the viral integrase, but not protease [55]. In hepatitis B virus (HBV) infection, on the other hand, EA restricted viral proliferation by preventing hepatitis Be antigen (HBeAg) secretion [56].

Table 2. Antiviral properties of plant extracts containing ellagitannins or of purified ellagitannins and downstream metabolites (ellagic acid or urolithins). DENV: Dengue virus; HBV: Hepatitis B virus; HCMV: Human

cytomegalovirus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HRV: Human rhinovirus; HSV: Herpes simplex virus; MV: Measles virus; RSV: Respiratory syncytial virus.

Compound Tested	Viral Target	Molecular Mechanism	References
ellagic acid	influenza A	synergistic effect on antioxidant defenses with oseltamivir and isoprinosine	[33]
pomegranate polyphenol extract, punicalagin	influenza A influenza B	synergistic effect on viral proliferation inhibition with oseltamivir	[5]
pomegranate leaf ethanolic extract	HSV-2 Zika	reduces viral proliferation in cells	[35]
pomegranate peel extract and fruit juice	HCV	inhibition of NS3/4A protease activity	[47]
pomegranate peel extract, punicalin	SARS-CoV-2	binds to SARS-CoV-2 S-glycoprotein and inhibits binding to ACE2	[48]
Rhodiola rosea extract	Ebola	inhibits viral entry in cells	[45]
punicalagin and Zn(II)	SARS-CoV-2	inhibition of 3CL protease, synergistic effect with Zn(II)	[49]
chebulagic acid, punicalagin	SARS-CoV-2	non-competitive inhibition of 3CL protease	[50]
	HSV-1	inhibits viral entry in cells and cell-to-cell spread via viral glycoprotein and host glucosaminoglycans interaction	[46]
	HCMV HCV DENV MV RSV	inhibits viral attachment to cells	[51]
geraniin	SARS-CoV-2	binds SARS-CoV-2 S-glycoprotein receptor binding domain	[52]
corilagin	SARS-CoV-2	binds to SARS-CoV-2 S-glycoprotein and inhibits binding to ACE2	[53]
	SARS-CoV-2	inhibits activity of RNA-dependent RNA polymerase nsp12	[54]

Compound Tested	Viral Target	Molecular Mechanism	References
ellagic acid	Zika	hypothetical interaction with cell surface to prevent viral infection	[35]
	HIV-1	blocks viral integrase but not protease	[55]
	HRV2 HRV3	reduces viral proliferation in cells	[34]
	HBV	blocks HBeAg secretion from cells	[56]
	Ebola	inhibits viral entry in cells	[45]

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