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THE ANTI-COVID19 POTENTIAL OF THE ELLAGIC ACID AND THE POMEGRANATE POLYPHENOLS

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ABSTRACT

The ellagic acid (EA) is the main compound associated with the beneficial effects of pomegranate. EA has a clinical antiviral effect against the influenza virus, the herpes virus, the poxviruses, and the HIV-1 virus. Similarly to HIV, SARS-CoV-2 is a RNA virus relying on the reverse transcriptase for its multiplication. Recent docking simulation studies showed that EA has the second highest affinity to the ACE-2-receptors which makes it a strong candidate for the prevention and treatment of the SARS-CoV-2 infection. EA could be a promising agent to prevent and ameliorate the damaging effects in the infected individuals.

The pomegranate polyphenols have a potent anti-inflammatory effect which achieves decreasing of the pro-inflammatory cytokines and inflammatory mediators by regulating the mitogen-activated protein kinases pathway. This effect is explained by the inhibition of some inflammatory markers such as NF-κ-B, TNFα and COX-2.

Through its capacity to neutralize ROS, pomegranate extracts seem to be capable of directly addressing the respiratory inflammation observed in respiratory viral infections through inhibition of neutrophil ROS and methylperoxydase. Data from our previous studies as well as the data available from other sources is convincing that the pomegranate extract could be used as an anti-inflammatory and antioxidant agent to improve the host immune response and serve as a preventive agent to acquiring COVID-19.

Key words: COVID-19, ellagic acid, pomegranate

INTRODUCTION

The SARS-CoV-2 novel coronavirus is the causative agent of the coronavirus disease (COVID-19). COVID-19 poses a significant burden due to the long recovery where pathological changes in multiple organ systems persist after the acute respiratory involvement stage of the disease has passed.

Scientists are intensively looking for new compounds with potential anti-COVID activity. Recently published data point to the potent activity of plant polyphenolic extracts and their potential to become a multipronged approach in the prevention and recovery of COVID-19.

The ellagic acid (EA) is the main compound associated with the beneficial effects of pomegranate. EA has a clinical antiviral effect against the influenza virus, the herpes virus, the poxviruses, and the HIV-1 virus. Similarly to HIV, SARS-CoV-2 is a RNA virus relying on the reverse transcriptase for its multiplication. Recent docking simulation studies showed that EA has the second highest affinity to the ACE-2-receptors which makes it a strong candidate for the prevention and treatment of the SARS-CoV-2 infection. EA could be a promising agent to prevent and ameliorate the damaging effects in the infected individuals.

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COVID-19 infection pathology

The disease progression is markedly different from that caused by the related coronavirus infections SARS-CoV-1 and MERS, even though the SARS-CoV-2 infection also occurs mainly through the respiratory route and viral entry into the host cells is facilitated by binding to the ACE2 receptor (6, 7). With the unfolding of the global COVID-19 pandemic, it has emerged that COVID-19 is not limited to acute infection of the respiratory tract, but is a multi-organ disease with pathological changes lasting many months after the acute phase (6-8).

Deregulated neutrophils in COVID-19 have been suggested to act as disseminators of the local inflammatory response to the rest of the body, leading to a severe systemic disease and organ damage. (9) Neutrophil activation and regulation is regulated by oxidative stress levels, which in COVID-19 appear to follow from the depletion of host antioxidant defenses similar to other viral diseases (9,10).

In support of this hypothesis for the involvement of reactive oxygen species (ROS) in COVID-19 pathogenesis, the levels of superoxide dismutase 3 (SOD3) in the lungs of elderly patients and children may be a factor for the different disease progressions in these age groups (9). Ageing, preexistent cardiovascular pathology or metabolic disorders such as type II diabetes (T2D) seem to be risk factors for a more severe disease progression. Ageing is associated with a decreased capacity of the cells to maintain their redox balance and to repair subcellular components such as mitochondria, through autophagy. This results in chronic low-grade inflammation, or 'inflamm-ageing' (6, 11). Atherosclerosis, hypertension, obesity, T2D, dementia and ageing itself are not only comorbidity factors for worse SARS-CoV-2 infection outcomes, but are also emerging as diseases with significant ROS involvement (6). Therefore, proactive control of pro-inflammatory conditions, or the limitation of chronic inflammatory conditions may alleviate the COVID-19 symptoms and aid recovery.

Antioxidant and anti-inflammatory activity of the pomegranate extract

Pomegranate (*Punica granatum*) is an edible fruit known for its antioxidant and anti-inflammatory properties, which have been applied in traditional medicine (12). These are due predominantly to polyphenolic substances present in both the edible and non-edible parts of the plant. These polyphenols are mainly representatives of the hydrolysable ellagitannins (ETs) group and the anthocyanins, condensed tannins that give the fruit its brilliant red color (12). ETs are a class of more than 500 compounds commonly found in many plant families, including edible berries and nuts. They consist of multiple units of ellagic acid (EA) attached to a sugar or a sugar alcohol core and are hydrolyzed after ingestion. The resultant EA is further converted to urolithins by the gut flora (11, 13). In the pomegranate extract, tens of ET compounds have been identified, but the highest concentration of ETs is due to punicalagins, and a smaller proportion is contributed by punicalin and free EA (12, 14). All these components, as well as the extract itself have shown a good antioxidant and anti-inflammatory activity in a range of experimental systems.

Antioxidant and anti-inflammatory effects of EA and its downstream metabolites

The generation of reactive oxygen species is important in promoting inflammation, therefore, the compounds with antioxidant activity are often

anti-inflammatory as well. Numerous studies have tested pomegranate extracts, purified ETs, EA and urolithins for improvement of chronic inflammatory conditions, including autoimmune disorders, neurodegenerative conditions, respiratory distress and viral infection and their outcomes are summarized 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)*

Compound tested	Experimental system	Findings	Reference
pomegranate extract	human consumption of capsules	↑ antioxidant capacity of plasma (ORAC) within 30 min	(35)
pomegranate extract	Alzheimer's disease transgenic R1.40 mice model	non-significant ↓ TNFα, IL-1 and COX2	(13)
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	(33)
pomegranate juice	hyperoxia rat model	↓ neutrophil infiltration, albumin leak, ROS, apoptotic bodies in lungs, IL-1β, IL-6	(20)
pomegranate leaf ethanolic extract	intranasal application in asthma mouse model	↓ IL-1β, IL-5, inflammatory cell infiltration in lung, mucous glycoprotein secretion	(18)
pomegranate peel extract	neutrophil culture and LPS-stimulated mice	x MPO activity in neutrophils, ↓ lung invasion of inflammatory cells	(17)
pomegranate peel extract	LPS-induced RAW264.7 macrophages	↓ TLR4 expression, ↓ IL-1β, IL-6, TNFα, NO, PGE2, ROS production, x nuclear translocation of NFκB nuclear translocation	(32)
walnut methanolic extract	human aorta endothelial cells (HAEC)	↓TNFα-induced VCAM1 and ICAM1 expression	(15)
walnut methanolic extract	KS483 osteoblastic cells line	nodule formation induced	(15)
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	(24)
corilagin	HSV-1 infected mice	↓ numbers of inflammatory cells in the brain, ↓ neuronal degeneration and interstitial edema	(24)
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	(27)
punicalagin	Jurkat cells	x T cell activation by NFAT	(26)
punicalagin	activated CD4+ murine splenic lymphocytes	↓ IL-2 mRNA and protein	(26)
punicalagin	PMA-induced ear edema in mice	↓ hyperplasia and inflammatory cell infiltration	(26)
punicalagin	LPS-induced RAW264.7 macrophages	↓ TLR4 expression, ↓ IL-1β, IL-6, TNFα, NO, PGE2, ROS production, x nuclear translocation of NFκB nuclear translocation	(32)
ellagic acid	human aorta endothelial cells (HAEC)	↓TNFα-induced VCAM1 and ICAM1 expression	(15)

ellagic acid	KS483 osteoblastic cells line	nodule formation induced	(15)
ellagic acid	mice on high fat diet	↓ aortic lesions, plasma cholesterol and triglyceride, ↓sICAM1 and E-selectin expression, ↑Nrf2, HO-1 protein and aortic NOS activity	(16)
ellagic acid	human umbilical vein endothelial cells (HUVEC)	Nrf2-mediated cytoprotection, ↑HO-1 protein	(16)
ellagic acid	human Caco-2 intestinal cells	↓NFκB activation after LPS stimulation, ↑IκB-α phosphorylation and IL-8 secretion after IL-1β stimulation	(34)
ellagic acid	in combination with oseltamivir and isoprinosine in influenza A infected mice	↑ glutathione reductase activity, ↓ TBARS in blood plasma and lungs during infection	(36)
ellagic acid	LPS-induced RAW264.7 macrophages	↓ TLR4 expression, ↓ IL-1β, IL-6, TNFα, NO, PGE2, ROS production, x nuclear translocation of NFκB nuclear translocation	(32)
ellagic acid	Caco-2 and HT-29/B6 intestinal cells	↑ transepithelial resistance, ↓ caludin-4, -7, -15 expression	(50)
urolithin A	experimental autoimmune encephalomyelitis	↓ demyelination and inflammatory infiltrating cells, reduce severity of disease, ↓ activation of dendritic cells and CNS microglia	(28)
urolithin A	bone marrow-derived dendritic cells and SIM-A9 microglia	↓ IL-1β, IL-6, TNFα, ↑ IL-10	(28)
urolithin A	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	(31)
urolithin A	Caco-2 and HT-29/B6 intestinal cells	x TNF-α induced drop in transepithelial resistance	(50)
urolithins	LPS-stimulated BV2 microglia	↓ NO, TNFα and IL-6, improved SH-SY5Y neuronal cell viability in H_2O_2	(13)

The chronic inflammatory conditions are associated with immune cell invasion of the tissues and often lead to tissue damage, including fibrosis. EA supports the endothelial function not only by reducing the oxidative stress but also by decreasing the TNF-α induced endothelial expression of VCAM1 and ICAM1 (15, 16). These molecules serve to increase the 'stickiness' of the blood vessel endothelium to the circulating monocytes in the early steps of inflammation and atherosclerosis, therefore, lowering their expression will reduce the entry of the inflammatory cells in tissues. A reduction in immune cell invasion was achieved by using pomegranate extract, punicalagin or urolithin A in the lungs, CNS and other inflammation sites in a variety of rodent model systems**. (Table 1)** (17-28).

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. The viral infections are also able to induce the secretion of these molecules (10, 24, 29, 30). The studies presented in **Table 1** show a general trend of decrease in the levels of these pro-inflammatory markers as a result of treatment with plant polyphenol-rich extracts or with their purified components and downstream metabolites (13, 18, 24, 25, 27, 28, 31, 32). These results were achieved in various tissues subject to inflammatory stimuli and pretreated with pomegranate extracts, ETs (corilagin or punicalagin) and urolithin A.

The nuclear factor NFκB has been described as a "matchmaker between inflammation, IBD, cancer and diabetes" (21) and it is under its regulation that IL-6, TNF-α and IL-1beta levels increase in a chronic disease. It appears that the pomegranate polyphenolic extracts and their components restrict the secretion of the pro-inflammatory molecules listed above by reducing NFκB activity (21-24). The details of the interaction between plant ETs and the regulatory components of NFκB remain to be established. Being potent antioxidants, the plant extracts and their components were also able to restrict the generation of reactive oxygen and nitrogen species (ROS and NOS), and to increase the overall tissue antioxidant capacity in a multitude of experimental settings. **(Table 1)** (13, 16, 17, 19, 20, 21, 22, 23, 24, 25, 27, 31, 32, 35, 36)

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) point to the potential benefits of using plant polyphenolic extracts as part of the supportive treatment for neuro-inflammation after COVID-19, a serious and long-term complication (7, 8).

CONCLUSIONS

The pomegranate extracts, containing a multitude of EA-derivatives, appear to act through different mechanisms to maintain endothelia integrity, to restrict inflammatory cell activation and tissue invasion and to supplement the antioxidant systems in the body. Supplementation with these bioactive compounds may therefore be especially beneficial to individuals with high risk factors for severe COVID-19 progression, e.g. ageing, T2D, cardiovascular pathology, atherosclerosis, neurodegenerative diseases, etc.

REFERENCES

1. Abarova, S.; Tancheva, L.; Nikolov, R.; Serkedjieva, J.; Pavlova, E.; Bramanti, A.; Nicoletti, F.; Tzvetkov, N. T. Preventive Effect of a Polyphenol-Rich Extract from Geranium Sanguineum L. on Hepatic Drug Metabolism in Influenza Infected Mice. *Sci Pharm* 2020, 88, 45. (in press)
2. Tancheva, L., Drug metabolism and oxidative stress during Influenza Virus Infection. Experimental approaches for antioxidant protection, Monography, Publisher Eagle, Silistra, 2019, 111 papers, ISBN 978-619-7424-22-5
3. Serkedjieva, J.; Stefanova, T.; Krumova, E.; Tancheva, L. Protective Effect of Polyphenol Rich Extract on Acute Lung Injury in Influenza Virus Infected Mice, *Biotechnol Biotechnol Equip*, 2009, 23:3, 1355-1359
4. Serkedjieva, J.; Krumova, E.; Stefanova, T. H.; Tancheva, L. Pulmonary protection of a plant polyphenol extract in influenza virus-infected mice, *J Infect*, 2009, 59, 6, S426
5. Encheva, E.; Tancheva, L.; Abarova, S.; Serkedjieva, J.; Ivantcheva, S. Modulation of hepatic drug metabolism in influenza infected mice. Preventive effect of polyphenols isolated from Geranium sanguineum L., *Toxicol Lett*, 2010, 196, S214-S215
6. Ganji, R. and P.H. Reddy, Impact of COVID-19 on Mitochondrial-Based Immunity in Aging and Age-Related Diseases. *Front Aging Neurosci*, 2021, 12(614650),
7. Raman, B.; Cassar, M. P.; Tunnicliffe, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine*, 2021, 31:100683
8. Tancheva, L.; Petralia, M. C.; Miteva, S.; Dragomanova, S.; Solak, A.; Kalfin, R.; Lazarova, M.; Yarkov, D.; Ciurleo, R.; Cavalli, E.; et al. Emerging Neurological and Psychobiological Aspects of COVID-19 Infection. *Brain Sci* 2020, 10, 852.
9. Laforge, M.; Elbim, C.; Frère, C.; et al. Tissue damage from neutrophil-induced oxidative stress in COVID-19. *Nat. Rev. Immunol.* 2020, 20(9): 515-516,.
10. Fratta Pasini, A. M.; Stranieri, C.; Cominacini, L.; Mozzini, C. Potential Role of Antioxidant and Anti-Inflammatory Therapies to Prevent Severe SARS-Cov-2 omplications. *Antioxidants* 2021, *10*, 272.
11. D'Amico, D.; Andreux, P.; Valdés, P.; Singh, A., Rinsch, C.; Auwerx, J. Impact of the Natural Compound Urolithin A on Health, Disease, and Aging. *Trends Mol Med,* 2021, 27(7): 687-699
12. Wu, S.; Tian, L. Diverse Phytochemicals and Bioactivities in the Ancient Fruit and Modern

Functional Food Pomegranate (Punica Granatum). *Molecules* 2017, *22*, 1606.
13. DaSilva, N.A.; Nahar, P. P.; Ma, H.; Eid, A.; Wei, Z.; Meschwitz, S.; Zawia, N. H.; Slitt, A. L.; Seeram, N. P. Pomegranate ellagitannin-gut microbial-derived metabolites, urolithins, inhibit neuroinflammation in vitro. *Nutr Neurosci*, 2019 22(3): 185-195
14. Haidari, M.; Ali, M.; Ward Casscells, S. 3rd; Madjid, M. Pomegranate (Punica granatum) purified polyphenol extract inhibits influenza virus and has a synergistic effect with oseltamivir. *Phytomedicine*, 2009.16(12): 1127-1136,
15. Papoutsi, Z.; Kassi, E.; Chinou, I.; Halabalaki, M.; Skaltsounis, L. A.; Moutsatsou, P. Walnut extract (Juglans regia L.) and its component ellagic acid exhibit anti-inflammatory activity in human aorta endothelial cells and osteoblastic activity in the cell line KS483. *Br. J. Nutr* 2008 99(4): 715-722,
16. Ding, Y.; Zhang, B.; Zhou, K.; Chen, M. et al., Dietary ellagic acid improves oxidant-induced endothelial dysfunction and atherosclerosis: role of Nrf2 activation. *Int J Cardiol*, 2014, 175(3): 508-514,
17. Bachoual, R.; Talmoudi, W.; Boussetta, T.; Braut, F.; El-Benna, J. An aqueous pomegranate peel extract inhibits neutrophil myeloperoxidase in vitro and attenuates lung inflammation in mice. *Food Chem Toxicol*, 2011, 49(6): 1224-1228,
18. de Oliveira, J.F.; Garreto, D. V.; da Silva, M. C.; Fortes, T. S.; de Oliveira, R. B.; Nascimento, F. R.; Da Costa, F. B.; Grisotto, M. A.; Nicolete, R. Therapeutic potential of biodegradable microparticles containing Punica granatum L. (pomegranate) in murine model of asthma. *Inflamm Res*, 2013, 62(11): 971-980,
19. Aleksandrova, S.; Tancheva, L.; Dragomanova, S.; Alova, L.; Stefanova, M.; Georgieva, A.; Simeonova, L.; Pavlova, E.; Kalfin, R. Preventive effect of ellagic acid on cognitive disorders in two mouse models of oxidative stress (influenza infection and scopolamine-induced dementia), *Amino Acids*, 2015, (8), 1651-1651
20. Tancheva, L. P.; Lazarova, M. I.; Alexandrova, A. V.; Dragomanova, S. T.; Nicoletti, F.; Tzvetanova, E. R.; Hodzhev, Y. K.; Kalfin, R. E.; Miteva, S. A.; Mazzon, E.; et al. Neuroprotective Mechanisms of Three Natural Antioxidants on a Rat Model of Parkinson's Disease: A Comparative Study. *Antioxidants* 2020, *9*, 49.
21. Murzakhmetova, M.; Moldakarimov, S.; Tancheva, L.; Abarova, S.; Serkedjieva, J. Antioxidant and prooxidant properties of a polyphenol-rich extract from Geranium sanguineum L. in vitro and in vivo, 2008, *Phytother Res*, 22, 6, 746-751
22. Tancheva, L. P.; Popatanasov, A. B.; Dragomanova, S. T.; Tzvetanova, E. R.; Aleksandrova, S. M.; Alova, L. G.; Stefanova, S. M.; Kalfin, R. E. New mechanisms in preventive effect of ellagic acid on cognition in mice with Alzheimer's disease type dementia, *Bulg. Chem. Commun* 2018, 50, 20-24
23. Abarova, S.; Koynova, R.; Tancheva, L.; Tenchov. B. A novel DSC approach for evaluating protectant drugs efficacy against dementia. *Biochim Biophys Acta Mol Basis Dis*, 2017, 1863(11), 2934-2941.
24. Guo, Y.J.; Zhao, L.; Li, X. F.; Mei, Y. W.; Zhang, S. L.; Tao, J. Y.; Zhou, Y.; Dong, J. H. Effect of Corilagin on anti-inflammation in HSV-1 encephalitis and HSV-1 infected microglias. *Eur J Pharmacol*, 2010, 635 (1-3): 79-86
25. Husari, A.; Khayat, A.; Bitar, H.; Hashem, Y.; Rizkallah, A.; Zaatari, G.; El Sabban, M. Antioxidant activity of pomegranate juice reduces acute lung injury secondary to hyperoxia in an animal model, *BMC Res Notes*, 2014, 7(1): 664
26. Lee, S.I.; Kim, B. S.; Kim, K. S.; Lee, S.; Shin, K. S.; Lim, J. S. Immune-suppressive activity of punicalagin via inhibition of NFAT activation., *Biochem Biophys Res Commun*, 2008, 371(4): 799-803
27. Peng, J.; Wei, D.; Fu, Z.; Li, D.; Tan, Y.; Xu, T.; Zhou, J.; Zhang, T. Punicalagin ameliorates lipopolysaccharide-induced acute respiratory distress syndrome in mice. *Inflammation*, 2015, 38(2): 493-499
28. Shen, P.X.; Li, X.; Deng, S. Y.; Zhao, L; Zhang, Y. Y.; Deng, X.; Han, B.; Yu, J.; Li, Y.; Wang, Z. Z.; Zhang, Y.; Urolithin A ameliorates experimental autoimmune encephalomyelitis by targeting aryl

hydrocarbon receptor. *EBioMedicine,* 2021, 64(103227): 30
29. Checconi, P.; De Angelis, M.; Marcocci, M. E. et al. Redox-Modulating Agents in the Treatment of Viral Infections. *Int J Mol Sci,* 2020, 21(11):4084.
30. Khomich, O.A.; Kochetkov, S. N.; Bartosch, B.; Ivanov, A.V.; et al., Redox Biology of Respiratory Viral Infections, 2018. *Viruses*, 10(8)
31. Abdelazeem, K.N.M.; Kalo, M. Z.; Beer-Hammer, S.; Lang, F. The gut microbiota metabolite urolithin A inhibits NF-κB activation in LPS stimulated BMDMs. *Sci Rep,* 2021, 11(1): 7117
32. Du, L.; Li, J.; Zhang, X.; Wang, L.; Zhang, W.; Yang, M.and Hou, C. Pomegranate peel polyphenols inhibits inflammation in LPS-induced RAW264.7 macrophages via the suppression of TLR4/NF-κB pathway activation. *Food Nutr Res*, 2019, 63
33. Huang, T.H.; Yang, Q.; Harada, M.; Li, G.Q; Yamahara, J.; Roufogalis, B.; Li, Y Pomegranate flower extract diminishes cardiac fibrosis in Zucker diabetic fatty rats: modulation of cardiac endothelin-1 and nuclear factor-kappaB pathways. *J Cardiovasc Pharmacol,* 2005, 46, 856-862
34. Romier, B.; an De Walle, J.; During, A.; Larondelle, Y.;, Schneider, Y. J. Modulation of signalling nuclear factor-kappaB activation pathway by polyphenols in human intestinal Caco-2 cells. *Br J Nutr,* 2008, 3, 542-551
35. Mertens-Talcott, S.U.; Jilma-Stohlawetz, P.; Rios, J.; Hingorani, L.; Derendorf, H. Absorption, metabolism, and antioxidant effects of pomegranate (Punica granatum l.) polyphenols after ingestion of a standardized extract in healthy human volunteers. *J Agric Food Chem*, 2006, 54, 8956-8961
36. Pavlova, E.L.; Simeonova, L. S. and Gegova, G. A. Combined efficacy of oseltamivir, isoprinosine and ellagic acid in influenza A(H3N2)-infected mice. *Biomed Pharmacother,* 2018, 98: 29-35