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File: ■ Pomegranate (*Punica granatum*, Lythraceae)
■ Vascular Adhesion Factor
■ Systematic Review/Meta-analysis

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RE: Systematic Review on Cardiovascular Adhesion Factors of Pomegranate Juice

Asgary S, Karimi R, Joshi T, et al. Effect of pomegranate juice on vascular adhesion factor: a systematic review and meta-analysis. *Phytomedicine*. January 2021;80:153359. doi: 10.1016/j.phymed.2020.153359.

The interior lining of blood vessels, made up of endothelial cells, has many metabolic and signaling functions. The endothelium maintains balance between vasoconstriction and dilation; it also plays a significant role in regulating thrombogenesis and the proliferation and migration of smooth muscle cells. Endothelial dysfunction (EDF) disrupts physical systems and can lead to diseases like diabetes, atherosclerosis, and high blood pressure (BP). Inflammation occurs when leukocytes migrate to exterior cells and adhere. Adhesion molecules (AMs) including intercellular AM-1 (ICAM-1), vascular AM-1 (VCAM-1), interleukin (IL)-6, and E-selectin,* are each, at high serum levels, risk factors for atherosclerosis and cardiovascular (CV) disease (CVD). CVD, obesity, and insulin resistance are signs of endothelial damage. High cholesterol, low-density lipoprotein, and triglyceride levels; low levels of high-density lipoprotein; high BP; hyperinsulinemia; hyperglycemia; and smoking are risk factors for EDF. In vivo models point to key roles for nuclear and intracellular signaling in EDF's pathogenesis.

Many plant-derived compounds are potentially able to limit endothelial damage through various mechanisms and can reduce expression of adhesion molecules. Such plant-derived products can reduce oxidative stress in endothelial cells by modulating expression of enzymes involved in antioxidant effects and promoting endothelium-dependent vascular relaxation via nitric oxide production. Polyphenols (e.g., catechin, resveratrol, epigallocatechin gallate, curcumin, quercetin, etc.) are important plant compounds related to endothelial protection, inhibiting pro-angiogenic agents like vascular endothelial growth factor and matrix metalloproteinases. Polyphenols may suppress pro-inflammatory mediators, e.g., ILs and tumor necrosis factor-α. Other benefits may include higher intracellular calcium levels and suppression of xanthine oxidase and protein kinase C activity, thus reducing superoxide radical and redox-sensitive gene expression and protecting endothelial cells.

Pomegranate (POM; *Punica granatum*, Lythraceae) is an important crop in India and Iran, where it has been used as food and in traditional medicines for centuries. POM is rich in polyphenols in all plant parts. In vitro, in vivo, and clinical trials (CTs) report POM's numerous benefits to the CV system, including improved endothelial function and lower BP. POM fruit juice (POMj) has been found to boost blood flow to the heart and reduce risk of heart attack. Changes in vascular reactivity to catecholamines were reported after POMj. In some studies, POM reduced EDF by modulating levels of ICAM-1, VCAM-1, E-selectin, and IL-6.

The authors present a systematic review (SR) and meta-analysis (MA) of randomized controlled CTs (RCTs) of POM effects on AMs. A search of electronic databases from inception to July 2020 yielded 1567 potentially eligible reports. Criteria were publication in English and participants aged 12 – 67 years. After excluding 716 duplicates, 571 were excluded based on title and abstract screening and 280 were further evaluated. Of these, 143 used supplements other than POM, 124 reported other outputs, and seven did not provide numerical results or did not use a control group. Six are included, reported between 2011 – 2020. Two include two separate RCTs for a total of eight RCTs. POMj was used in all selected RCTs, at 50 – 250 mL/d for two to 48 weeks. Of 296 participants, 165 were in POMj groups: 131 in placebo (PLA) groups. Bayesian MA was used, computing for each study and outcome the mean changes from baseline to study's end for POMj and PLA and the difference between these changes. $P < 0.05$ was considered statistically significant. Risk was assessed using the Cochrane quality assessment tool for RCTs as being low, high, or unclear for bias. A Bayesian sensitivity analysis using Dvina's statistic was conducted. Heterogeneity was assessed via the I^2 statistic.

In four RCTs from the same three articles, results showed no significant benefit for POMj vs. PLA in levels of ICAM-1 (with insignificant heterogeneity [$I^2 = 0.0\%$]; $P = 0.866$), VCAM-1 (significant heterogeneity [$I^2 = 0.86.8\%$]; $P = 0.001$), or E-selectin (significant heterogeneity [$I^2 = 86.0\%$]; $P = 0.000$). However, in seven RCTs from five reports, POMj significantly reduced IL-6 ($P < 0.001$), albeit with significant heterogeneity ($I^2 = 87.6\%$). Risk of publication risk using the Egger test were not significant for ICAM-1 or IL-6 results but were significant for VCAM-1 ($P = 0.013$) and E-selectin ($P = 0.043$). Some studies had directly conflicting results, such as two reporting a significant decrease in E-selected in the POMj group vs. one reporting a significant increase.

The authors write that ellagitannins, gallotannins, punicalagin, and punicalin are important POM tannins but do not elaborate. Phenolic anthocyanins, responsible for POM fruit's red color, include delphinidin and cyanidin glucosides, the latter was reported to reduce levels of nuclear factor-κB and sirtuin 1 (SIRT1). Some studies report higher SIRT1, with both pro- and anti-inflammatory effects. Ellagic acid and urolithin have also been cited as having a role in POMj's anti-inflammatory effects. POMj's antioxidant capacity is three times that of red wine from grapes (*Vitis vinifera*, Vitaceae). An in vitro study in human monocyte cell line THP-1 found that POM peel extract and punicalagin reduced release of ICAM-1 but not VCAM-1. However in vitro data supporting the effects of polyphenols are not always replicable in clinical studies, partly due to limited bioavailability. POM supplements of various kinds are available but apparently have not been evaluated for endothelial effects. The authors do not comment on any content analyses in RCTs included.

Limitations of this SR and MA include a small number of eligible RCTs, small population sizes, and short durations. Significant heterogeneity also demands caution in interpreting results. Future research should include stronger phytochemical analysis of the POM products used in clinical studies.

—*Mariann Garner-Wizard*

*Also known as CD62 antigen-like family member E, endothelial-leukocyte adhesion molecule-1, or leukocyte-endothelial cell adhesion molecule-2.