# The Dual Edema-Preventing Molecular Mechanism of the Crataegus Extract WS 1442 Can Be Assigned to Distinct Phytochemical Fractions

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The hawthorn (Crataegus spp.) extract WS 1442 is used against mild forms of chronic heart failure. This disease is associated with endothelial barrier dysfunction and edema formation. We have recently shown that WS 1442 protects against this dysfunction by a dual mechanism: it both promotes endothelial barrier integrity by activation of a barrier-enhancing pathway (cortactin activation) and inhibits endothelial hyperpermeability by blocking a barrier disruptive pathway (calcium signaling). In this study, we aimed to identify the bioactive compounds responsible for these actions by using a bioactivity-guided fractionation approach. From the four fractions generated from WS 1442 by successive elution with water, 95 % ethanol, methanol, and 70 % acetone, only the water fraction was inactive, whereas the other three triggered a reduction of endothelial hyperpermeability. Analyses of intracellular calcium levels and cortactin phosphorylation were used as readouts to estimate the bioactivity of subfractions and isolated compounds. Interestingly, only the ethanolic fraction interfered with the calcium signaling, whereas only the methanolic fraction led to an activation of cortactin. Thus, the dual mode of action of WS 1442 could be clearly assigned to two distinct fractions. Although the identification of the calcium-active substance(s) was not successful, we could exclude an involvement of phenolic compounds. Cortactin activation, however, could be clearly attributed to oligomeric procyanidins with a distinct degree of polymerization. Taken together, our study provides the first approach to identify the active constituents of WS 1442 that address different cellular pathways leading to the inhibition of endothelial barrier dysfunction.
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