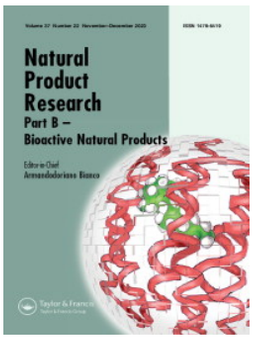

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Vascular effects of *Fragaria vesca* L. in human arteries

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ABSTRACT

Fragaria vesca L. (wild strawberry) is traditionally used for its anti-inflammatory activity and for gastrointestinal, cardiovascular and urinary disorders. A previous study with the rat aorta showed that its leaves extract elicits endothelium-dependent vasorelaxation. Our aim was to investigate the clinical application of *Fragaria vesca* in vascular disease, by assessing the vascular effects of an infusion and hydroalcoholic extract in internal thoracic arteries from patients with coronary artery disease. The extracts elicited no effects on basal vascular tone and did not induce any vasorelaxation. At low concentration (0.02 mg/mL), the infusion potentiated the noradrenaline-induced contraction, while the other concentrations did not elicit significant changes in efficacy or potency. Differences between our findings and the previous report on rat aorta may result from methodological differences, e.g. vascular bed, method of extraction and extract composition. The clinical applicability of extracts of *Fragaria vesca* in patients with cardiovascular disease remains to be fully validated.

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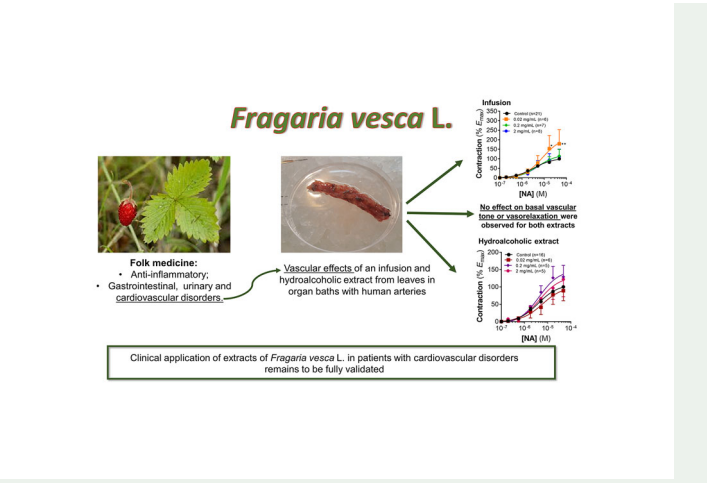

Abbreviations: HPLC-PDA: high-performance liquid chromatography with photodiode array detector; ANOVA: analysis of variance; CCRCs: cumulative concentration-response curves; ITA: human internal thoracic artery.

1. Introduction

Fragaria vesca L. (*F. vesca*), commonly known as wild strawberry, belongs to the Rosaceae family and has been used in folk medicine for its anti-inflammatory activity and for gastrointestinal diseases, cardiovascular and urinary disorders (Liberal et al. 2014). In terms of bioactivity, this extract has also been shown to exhibit anti-diabetic, antioxidant, and anti-apoptotic activity (Ibrahim and Abd El-Maksoud 2015). Furthermore, the anti-*Helicobacter pylori* activity of the leaf extract (Cardoso et al. 2018) and the potential use of the ethanolic extract in the treatment of gastrointestinal inflammatory diseases, such as Crohn's disease, have also been suggested (Kanodia et al. 2011). Regarding cardiovascular disorders, *F. vesca* has been reported for lowering blood pressure and heart rate (Camejo-Rodrigues et al. 2003; Manolova 2003; Liberal et al. 2014).

To the best of our knowledge, the only report that assays the vasodilator properties of extracts of *F. vesca* used the rat aorta and showed that the leaves infusion had an endothelium-dependent vasodilator effect, which was mediated by nitric oxide and cyclooxygenase products (Mudnic et al. 2009).

Considering the previously published data and the ethnomedicinal use in cardiovascular disorders, our aim was to assess the vascular effects of leaves extracts of *F. vesca* (an infusion and a hydroalcoholic extract) in human internal thoracic arteries (ITAs), in order to investigate the clinical application of extracts of this plant species in patients with underlying cardiovascular disease.

2. Results and discussion

2.1. Phytochemical profile

The phenolic profile of the infusion and hydroalcoholic of *F. vesca* was carried out by HPLC coupled with PDA detector (Figure S1A and B, respectively). An

analysis of the phytochemical profile of both extracts is presented in Supplementary material.

2.2. Vascular effects

The ITAs were harvested from patients undergoing cardiac surgery, and *n* indicates the number of patients (2–4 arterial rings were obtained per segment). The infusion extract of *F. vesca* did not induce a significant effect on basal vessel tone (E_{max}=0.19 ± 0.11 mN, $n = 3$). As seen in Figure S2A, a significant potentiation of the maximal effect of the noradrenaline-induced contraction (about 78.64%, $n = 6$, $p < 0.01$ vs control) was observed for the lowest concentration of extract, i.e. 0.02 mg/mL. In higher concentrations, no significant effect on noradrenaline-induced contraction was detected. After precontraction with 20 μM noradrenaline, the infusion did not elicit vasorelaxation (R_{max}=-6.62 ± 16.52%, $n = 9$). Overall, the infusion displayed a mixed effect on noradrenaline-induced contraction, by eliciting a potentiation of the maximal effect only in the lower dose, with no changes in intermediate and higher doses. This may result from the fact that plant extracts are mixtures of compounds, some of which may evidence their properties more clearly in lower extract concentrations. Furthermore, no effects on basal vessel tone and vasorelaxation were observed, thus suggesting an absence of clinically-relevant effect in our arterial model.

Similarly, the hydroalcoholic extract of *F. vesca* did not elicit significant changes in basal vessel tone (E_{max}=0.62 ± 0.48 mN, $n = 3$). As can be seen in Figure S2B, no significant differences were observed between the control curve to noradrenaline and in the presence of different concentrations of the hydroalcoholic extract of *F. vesca*. Furthermore, no significant changes were observed in the potency of the response (Table S1). Concerning the vasorelaxant properties, the hydroalcoholic extract of *F. vesca* did not show a vasorelaxant effect (R_{max}=0.01 ± 17.87%, $n = 5$).

Our findings differ from the previous study by Mudnic et al. (2009) who showed an endothelium-dependent vasorelaxation mediated by nitric oxide and cyclooxygenase products in the rat aorta with a leaves infusion. A methodological difference should be highlighted compared to our study, i.e. a markedly lower amount of plant material was used in the preparation of our extract (4 g/150 mL) compared with the study by Mudnic et al. (2009), who used 15 g/150 mL. This difference can directly affect the concentration of bioactive compounds. Moreover, Mudnic et al. (2009) assayed two higher concentrations in their study (6 and 60 mg/mL), also these two concentrations were responsible for the statistically significant effect observed by Mudnic et al. (2009).

In regard to the *F. vesca* extracts assayed in this study, a phytochemical analysis of the hydroalcoholic and the infusion evidenced the presence of phenolic acids, flavonols and ellagic acid and its derivatives (Liberal et al. 2014; Couto et al. 2020). Interestingly, Mudnic et al. (2009) reports the presence of other constituents that could be responsible for the vasodilation that was observed by this author, such as epicatechin and procyanidin B2. In fact, previous studies by A. Novakovic with the ITA have shown the involvement of the vascular smooth muscle in the vasorelaxation elicited by both (-)-epicatechin (Novakovic et al. 2015) and the involvement of the vascular endothelium in the vasorelaxation to procyanidin B2 (Novakovic et al. 2017).

Overall, the differences between our findings and the results from previous studies could also be attributed to the vascular bed that was used. In fact, patients who undergo coronary revascularization commonly present several risk factors that could interfere with several pathways of regulation of vascular function, e.g. endothelial function, particularly the nitric oxide pathway. Therefore, a higher variability in results inherent to the use of human vascular tissue could mask the vascular effects that may be obtained with these extracts (Fonseca et al. 2014; Simões et al. 2020). However, this may also be an advantage from a translational point of view, as it gives a better perspective of the human vascular system, compared to animal-derived tissue. Furthermore, the ITA is a vascular bed with special characteristics as previously reviewed, namely atherosclerosis resistance (Fonseca et al. 2014; 2017). In terms of histomorphology, it has been recognized as a transitional-type artery due to its varying content in elastic and muscular elements, with a muscular pattern being more predominant in the distal end (Borović et al. 2010). Further, its distal portion exhibits a higher pharmacological reactivity (He 2015), which was used in our study, thus making it an interesting model for the investigation of the effects of natural extracts and compounds on blood pressure regulation.

In a clinical scenario, the administration of the *F. vesca* leaves infusion to patients with vascular disorders, who typically exhibit reduced endothelial nitric oxide production, could be debatable, as the main mechanism of action would be compromised, thus limiting the potential benefit of its consumption. However, the available evidence on this topic is scarse. Therefore, we would suggest pursuing further experimental studies with animal models of cardiovascular disease, specifically of atherosclerosis (e.g. ApoE-deficient mice) and hypertension (e.g. spontaneously hypertensive rats). Such studies would allow a clarification of the true cardiovascular benefit of extracts from leaves of *F. vesca*.

3. Conclusions

In our study, *F. vesca* extracts did not elicit vasorelaxant effects of human arteries harvested from patients with underlying coronary artery disease. In fact, the leaves extract elicited a significant potentiation on the noradrenaline contractile response. Differences between our findings and previous studies could be due to differences in extract preparation and composition and in vascular bed. Further studies should be carried out to fully understand the clinical applicability of *F. vesca* extracts in cardiovascular disorders.

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Authors' contributions

MDC, AF and DAF designed the study. PEA collected human arterial samples. JM and DMS performed the experiments. JM, DMS and DAF analyzed the results. JM wrote the manuscript. DAF, MDC and AF reviewed the manuscript.

Disclosure statement

The authors report there are no competing interests to declare.

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