



## Vasodilation and radical-scavenging activity of imperatorin and selected coumarinic and flavonoid compounds from genus *Casimiroa*



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### ABSTRACT

Hypertension is a very widespread condition which is not strictly considered as an illness but if not countered, progressively causes damage to all tissues and loss in their functionality. For this reason the find of new antihypertensive agents is prominent and medicinal plants and their derivatives are valuable for the purpose. The genus *Casimiroa* (Rutaceae) includes plants from Central America and Mexico; among these, *Casimiroa edulis* Llave et Lex. and *Casimiroa pubescens* Ramirez are the most relevant species, even for their medicinal uses. The decoction of leaves and seeds is traditionally taken as a tea mainly to lower blood pressure. The object of this research was the study of vascular activity of coumarinic and flavonoid compounds isolated from seeds of *Casimiroa* spp. in comparison with *Casimiroa edulis* and *Casimiroa pubescens* extracts. The phenolic compounds isolated from *Casimiroa* were herniarin (Her), imperatorin (Imp), 8-geranyloxypsoralen (GOP) and 5,6,2',3',4'-pentamethoxyflavone (PMF). All these compounds induced vasorelaxation on rat arterial tissues although with different effectiveness. To study the cellular mechanisms of the vasorelaxation exhibited by imperatorin, we used selective inhibitors of different receptors and enzymes, such as atropine, pyrilamine, nifedipine, L-NAME and DETC. In a further step of this research, we evaluated the radical-scavenging activity of *Casimiroa* extracts and isolated compounds by means of DPPH assay. In general, we observed that the scavenging activities increased in a concentration-dependent manner for all substances. The phenolic compounds highlight a synergism of vasodilation and antioxidant activity which may be very useful in the management of cardiovascular diseases. Among the evaluated compounds, imperatorin shows a significant vasorelaxant activity even higher than acetylcholine and similar to nitrite, and also useful antiradical capabilities. All these properties suggest its possible role against hypertension and vasculopathies, even if *in vivo* studies are needed to determine the actual applications.

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### Introduction

Hypertension is a global health issue that causes cardiovascular illnesses and disabilities in about 1 in 3 adults worldwide. Further, findings from serial surveys show an increasing prevalence of hypertension in developing countries, possibly caused by urbanization, population ageing, changes to dietary habits and social stress (Ibrahim and Damasceno, 2012). Although the benefits of treating hypertension have been known since the 1960s, inadequate control remains frequent in many countries. Overall, the antihypertensive treatments for preserving cardiovascular function are of high interest in medicine. Traditional medicines propose various plants linked to this specific area. In Traditional Mexican Medicine, the genus *Casimiroa* is used as anxiolytic and antihypertensive remedy (Randolph Major, 1958; Sarris et al., 2013). In Mexico and in

countries with subtropical climate *Casimiroa edulis* fruits are available in local markets for food use as a dessert, while leaf and seed extracts are readily available for traditional medicine. The use of *Casimiroa* is also described in the African continent, particularly as Egyptian folk medicine. In Europe and Italy the genus *Casimiroa* is little-known. However, the Italian Ministry of Health has included the seeds of *Casimiroa edulis* in the list of herbs not permitted in food supplements (G.U. n. 57 of 09/03/2007, Annex 1). Of course, the fruits are admitted.

In the present study, we compared the *in vitro* vasodilation and antioxidant activity of *Casimiroa edulis* (CE) and *Casimiroa pubescens* (CP) seed extracts with their isolated coumarin and flavone derivatives, as herniarin (Her), imperatorin (Imp), 8-geranyloxypsoralen (GOP), and 5,6,2',3',4'-pentamethoxyflavone (PMF) (Fig. 1). Further, the cellular mechanism of vasodilation was investigated by the use of standard compounds known for their vascular activity, such as acetylcholine and nitrite, an endothelium-dependent and endothelium-independent vasodilator, respectively (Joannides et al., 2006). Previous studies evidenced

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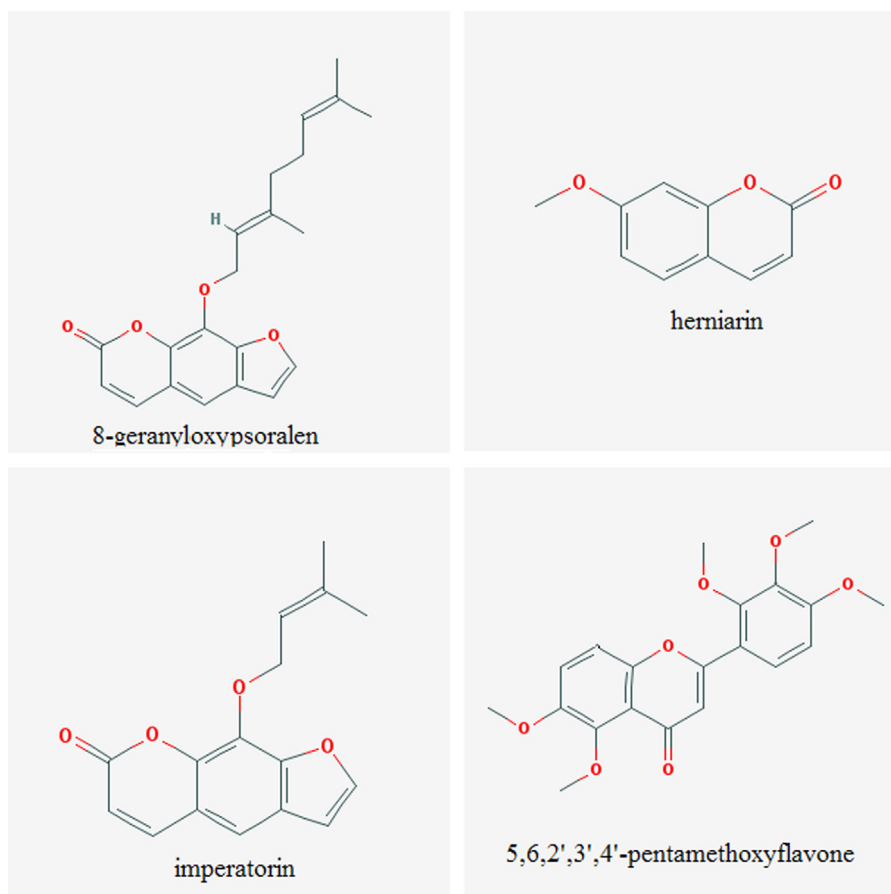


Fig. 1. Chemical structures of Phenolic derivatives isolated from *Casimiroa edulis* (CE) and *Casimiroa pubescens* (CP).

that *Casimiroa* spp. extracts cause relaxant effects on rat aorta and caudal arteries mainly by activation of M<sub>3</sub>-muscarinic receptor through the cGMP-dependent NO pathway (Froldi et al., 2011). Taking into account this knowledge, we determined the influence of selective inhibitors such as atropine, pyrilamine, nifedipine, L-N<sup>G</sup>-nitro-arginine methyl ester (L-NAME), and diethyldithiocarbamate (DETC) on the *in vitro* dilation of imperatorin, as a reference compound isolated from *Casimiroa* seeds. In addition to the vascular dilation activity, we also studied the scavenging activity of CE, CP and single isolated compounds. For this, we also determined the Total Phenolic Content (TPC), the Total Flavonoid Content (TFC) for both extracts, and carried out for all substances the 1, 1-diphenyl-2-picrylhydrazyl (DPPH) scavenging assay.

## Materials and methods

### *Casimiroa* samples

Seeds of *Casimiroa edulis* and *Casimiroa pubescens* were collected in the wild and their voucher specimens were deposited at the Herbarium of Facultad de Ciencias UNAM. *Casimiroa pubescens* was collected between Vithe and Cardonalito Towns in Ixmiquilpan County, Hidalgo (voucher number FCME-84835-2). *Casimiroa edulis* was collected in the surroundings of Comala County, Colima (voucher number FCME-84837-2).

### Preparation of the *Casimiroa* extracts

Dried and milled seeds of each selected species were extracted with methanol for 24 h (3 times). The three extracts were

gathered and, after evaporation of the solvent at low pressure, the total dry weight was recorded: the yields for *Casimiroa edulis* (CE) and *Casimiroa pubescens* (CP) were  $4.1 \pm 2.3\%$  and  $8.1 \pm 2.1\%$  w/w, respectively. For each extract the furocoumarin imperatorin was quantitatively characterized by HPLC-DAD (Fig. 3). Previously, imperatorin has been identified in *Casimiroa edulis* leaf extract (Awaad et al., 2012). Imperatorin in CE and CP was  $0.39 \pm 0.05\%$  and  $0.73 \pm 0.09\%$  w/w, respectively.

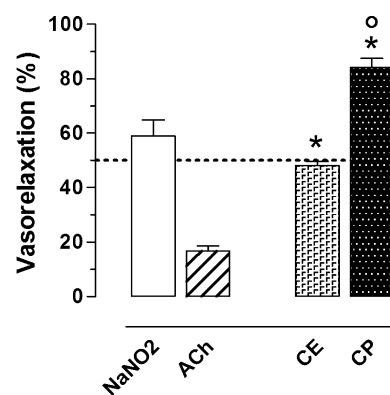


Fig. 2. Vasorelaxant effects induced by methanolic seed extracts of *Casimiroa edulis* (CE) and *Casimiroa pubescens* (CP) in comparison with NaNO<sub>2</sub> and acetylcholine (ACh), endothelium-independent and endothelium-dependent agents, respectively (positive controls), in rat caudal arteries. Values are mean  $\pm$  S.E.M. of 6–8 experiments. \*:  $p < 0.05$  vs. ACh relaxation; ○:  $p < 0.05$  vs. NaNO<sub>2</sub> relaxation.

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