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Antihypertensive and vasorelaxant effect of leucodin and achillin isolated from *Achillea millefolium* through calcium channel blockade and NO production: *In vivo*, functional *ex vivo* and *in silico* studies

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Abstract

Ethnopharmacological relevance

Achillea millefolium L. (Asteraceae), known as yarrow (milenrama), is a plant used in Mexican traditional medicine for the treatment of hypertension, diabetes, and related diseases.

Aim

To determine the vasorelaxant and antihypertensive effect of *A. millefollium* and to isolate the main bioactive antihypertensive agents.

Materials and methods

Organic (hexane, dichloromethane and methanol) and hydro-alcohol (Ethanol-H_2O: 70:30) extracts obtained from flowers, leaves and stems were evaluated on isolated aorta rat rings with and without endothelium to determine their vasorelaxant effect. Hexane extract from flowers (HEAmF) was studied to evaluate its antihypertensive effect on spontaneously hypertensive rats (SHR). From HEAmF, bioactive compounds were obtained by bio-guided phytochemical separation through chromatography.

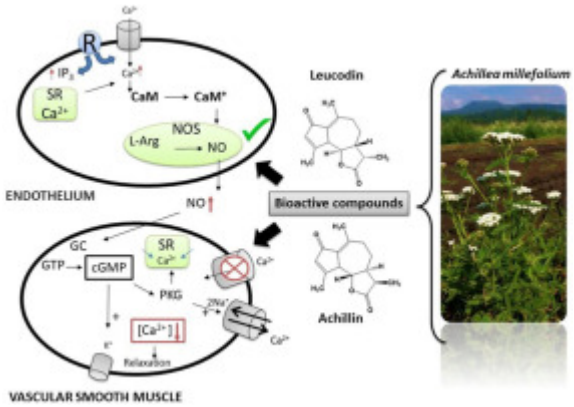
Results

Organic extracts showed the best vasorelaxant activity. Hexane extract from flowers was the most potent and efficient *ex vivo* vasorelaxant agent, showing significant decrease of systolic and diastolic blood pressure in SHR ($p < 0.05$). Phytochemical separation of HEAmF yielded two epimeric sesquiterpene lactones: leucodin (**1**) and achillin (**2**), the major components of the extract. Both **1** and **2** showed similar vasorelaxant action *ex vivo* ($p < 0.05$), and their effects where modified by L-NAME (10 μM, nitric oxide synthase inhibitor), by ODQ (1 μM, soluble guanylyl cyclase inhibitor), and also relaxed the contraction induced by KCl (80 mM). Finally, **1** and **2** intragastric administration (50 mg/kg) decreased systolic and diastolic blood pressure in SHR.

Conclusions

Achillea millefolium showed antihypertensive and vasorelaxant effects, due mainly to leucodin and achillin (epimers). Both compounds showed antihypertensive activity by vasorelaxation putatively by endothelium-dependent NO release and cGMP increase, as well as by calcium channels blockade.

Graphical abstract



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Introduction

Systemic arterial hypertension is characterized by a constant high blood pressure (BP). BP is expressed as the systolic pressure (pressure exerted by the blood on the arterial walls when the heart contracts), and diastolic pressure (when the heart relaxes) ratio. It is the main risk factor for myocardial infarct, endothelial dysfunction, metabolic syndrome, kidney dysfunction, congestive heart failure, among others (Oparil et al., 2018; Ogihara et al., 2005). Currently, efficient medications to control blood pressure are known; however, developing drugs with new mechanisms of action on a specific target, or on more than one of them (multitarget drugs) are needed. In this context, traditional herbal medicine is a major treatment alternative

for the most common diseases, including hypertension. In addition, medicinal plants are a pillar for obtaining new and/or known chemical entities with novel pharmacological effects.

Achillea millefolium L. (Asteraceae) is a very important medicinal plant of traditional medicine to treat headaches, hepatobiliary disorder, gastrointestinal complaints and inflammations, wounds, cuts, abrasions, cardiovascular diseases and diabetes (Cavalcanti et al., 2006; Benedek and Kopp, 2007; Chávez-Silva et al., 2018; Ali et al., 2017; Monroy-Ortiz and Castillo-España, 2007). It is important to mention that the Pharmacopoeia of the Russian Federation refers to the infusion of aerial parts of *A. millefollium* (15 g in 200 mL), 2–3 times a day as a hemostatic, anti-inflammatory and sedative (Shikov et al., 2017, 2021). Also, several active compounds derived from *A. millefolium* show hypotensive, vasodilator, bronchodilator, antiproliferative, antispasmodic, antioxidant, etc., actions observed *in-vitro* and *in-vivo* (De Souza et al., 2011; Csupor-Löffler et al., 2009; Lemmens-Gruber et al., 2006; Khan and Gilani, 2011; Arias-Durán et al., 2020). Therefore, seeing the importance of *A. millefollium* to treat several diseases, current work investigates the efficacy of yarrow as antihypertensive on *in vivo* and *ex vivo* murine models, and *in silico* approach to characterize bioactive compounds responsible for its actions.

Section snippets

Chemicals and drugs

Noradrenaline hydrochloride (NA) ≥98%, Carbamoylcholine chloride (carbachol) ≥98%, Theophylline, *N*-nitro-L-arginine methyl ester hydrochloride (L-NAME) ≥98%, 1-*H*-[1,2,4]-oxadiazolo-[4,3a]-quinoxalin-1-one (ODQ), dimethylsulphoxide (DMSO), and Nifedipine were purchased from Sigma–Aldrich Co. (St. Louis, MO, USA). All other reagents were analytical grade from local sources....

Plant material, preparation of the extract and isolation

Achillea millefolium plant material was collected in September 2018 by Luis Arias-Durán and identified by Dra. Irene...

Results and discussion

In order to give pharmacological support to the ethnomedical uses attributed to the medicinal plant *A. millefolium* for treatment of hypertension and due to the lack of studies on cardiovascular diseases, organic and aqueous-ethanolic extracts from aerial parts, leucodin (**1**) and achillin (**2**) were investigated to establish their ability to modify blood pressure on SHR rats. Furthermore, the collected plant material was cleaned and separated into the different organs (flowers, leaves and stems)...

Conclusions

Achillea millefolium showed significant antihypertensive and vasorelaxant effects mainly due to the presence of leucodin and achillin (epimeric compounds). Both compounds showed significant antihypertensive activity consequence of vasorelaxation mediated, in part by endothelium involving NO release and cGMP increase, and by membrane calcium channels blockade....

CRediT author statement

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Declaration of competing interest

The authors declare no conflict of interest. Author contributions to the paper were as follows: Extracts preparation, and leucodin and achillin isolation: L. A-D., M. H-M, S. E-S. Structural elucidation: G. N–V., L. A-D. M. H.-M. Pharmacological evaluation: R. V-M., M. I–B., L. A-D., S. E-S, J. A.-P. Identification and recollection of plant material: L. A-D. J. A.-P. Docking studies: C. M.-P., L. A.-D. Study design: J. A.-P., S. E-S. Manuscript preparation: all authors....

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[1] Taken from the PhD thesis of L. Arias-Durán.

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