Garcinielliptone FC, a polyisoprenylated benzophenone from Platonia insignis Mart., promotes vasorelaxant effect on rat mesenteric artery

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SHORT COMMUNICATION

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Polyisoprenylated benzophenones represent a group of chemical compounds commonly identified in Clusiaceae species and are responsible for a large amount of biological activities. In this work, the vasorelaxant effect induced by garcinielliptone FC (GFC) isolated from *Platonia insignis* Mart. (Clusiaceae), a monotype species from *Platonia* genus, was investigated. GFC promoted an endothelium-independent vasorelaxation on phenylephrine (PHE, 10⁻⁵ mol L⁻¹)-induced vasoconstriction, but not on KCl (80 mmol L⁻¹)-induced vasoconstriction, on rat superior mesenteric artery rings. In addition, a concentration-dependent decrease of PHE- or serotonin-induced cumulative concentration–response curves was observed for GFC, and a slight decrease of pD₂ value on CaCl₂-induced vasoconstriction. In a Ca²⁺-free medium, GFC interfered in calcium mobilisation from PHE (10⁻⁵ mol L⁻¹)-sensitive intracellular stores. GFC-induced vasorelaxant effect is probably mediated by a dual effect on mobilisation of calcium intracellular stores and attenuation of transmembrane calcium influx.

Keywords: benzophenone; calcium; Clusiaceae; garcinielliptone; *Platonia*; vasorelaxant

1. Introduction

The Clusiaceae family has been demonstrated to be a rich source of secondary metabolites, including the polyisoprenylated benzophenones, a chemical group with a bicycle-[3,3,1]-nonane-2,4,9-trione core structure rarely found outside this family and usually found in *Garcinia* genus. Besides, it represents the major intermediate of the xanthone biosynthesis, another important chemical group found in Clusiaceae species (Acuña et al. 2009). Similarly, this class of compounds has been systematically studied for its several biological activities and represents an important source of bioactive compounds with several therapeutic applications, including cytotoxic, antimicrobial, leishmanicidal, antioxidant and anti-inflammatory activities (Kumar et al. 2013).

Garcinielliptone FC (GFC; Figure 1A), a tautomeric pair of polycyclic polyprenylated benzophenones with antioxidant activity, was isolated from dried seeds of *Platonia insignis* Mart.
Mart. (Clusiaceae), a monotype species from *Platonia* genus as well as a native species from the Brazilian Amazon commonly known as ‘bacuri’ (Costa-Júnior et al. 2011). Several biological properties have been reported for GFC, such as *in vitro* (Costa-Júnior et al. 2011) and *in vivo* (Costa-Júnior et al. 2012) antioxidant, cytotoxic and leishmanicidal (Costa-Júnior et al. 2013) and anti-inflammatory (Weng et al. 2004).

Interestingly, the benzophenones represent a class of compounds that possess vasorelaxant property (Luna-Vásquez et al. 2013). Accordingly, the 7-epiclusianone, a prenylated benzophenone from *Rheedia gardneriana* (Clusiaceae), has been reported for its vasorelaxant effect and underlying mechanisms (Cruz et al. 2006). Thus, considering the promising biological potential of GFC, the GFC-induced vasorelaxant effect was investigated in this study.

### 2. Results and discussion

GFC promoted a concentration-dependent vasorelaxation on phenylephrine (PHE, $10^{-5}$ mol L$^{-1}$)-induced vasoconstriction on rat superior mesenteric artery rings, and the endothelium removal did not decrease this response, suggesting an endothelium-independent
effect and probably a direct action on vascular smooth muscle (Figure 1B). Then, the GFC probably act in some stage of the vascular smooth muscle contractile machinery, since \( \alpha_1 \)-adrenergic receptors activation until the increase of extracellular Ca\(^{2+} \) influx through receptor-operated Ca\(^{2+} \) channels (Karaki & Weiss 1998). Therefore, the modulation probably induced by GFC on each one of these steps was investigated.

The participation of extracellular Ca\(^{2+} \) influx in GFC-induced vasorelaxant response was assessed on KCl (80 mmol L\(^{-1} \))-induced depolarisation which promotes vasoconstriction by an electromechanical coupling, allowing the influx of extracellular Ca\(^{2+} \) through voltage-operated calcium channels (Gurney 1994), while the PHE-induced vasoconstriction is the result of both electromechanical and pharmacomechanical coupling (Leung et al. 2008). The results revealed that GFC induced a minor vasorelaxant response by 15.0% decrease in \( E_{\text{max}} \) only at the highest concentration (Figure 1C), different from that observed in PHE-induced pre-contractions.

Figure 2. Effect of GFC on CaCl\(_2\)-induced (A), PHE-induced (B) or 5-HT-induced (C) concentration–response curves (B) and on PHE-sensitive calcium mobilisation from intracellular stores (D). Data are expressed as mean ± SEM (\( n = 5 \)). * \( p < 0.05 \), ** \( p < 0.01 \) and *** \( p < 0.001 \) versus control.
Similarly, GFC did not inhibit CaCl$_2$-induced cumulative concentration–response contractions, but promoted a slight attenuation observed by a rightward-shifted curve with a decrease in pD$_2$ value of 15.0% (Figure 2A). Thereby, these results indicate that GFC probably promotes vasorelaxant response on vasoconstriction induced by a pharmacomechanical coupling with a slight participation of transmembrane calcium channel activation on endothelium-denuded preparations.

On the other hand, GFC attenuates PHE-induced concentration–response vasoconstriction in endothelium-denuded preparations (Figure 2B). This response was attenuated on vasoconstriction induced by concentration–response cumulative addition of serotonin (5-HT $10^{-5}$ mol L$^{-1}$) (Figure 2C). After binding their respective receptors, PHE or 5-HT stimulates the formation of inositol-1,4,5-triphosphate (IP$_3$), which binds to and activates the specific IP$_3$ receptor (IP$_3$R) in sarcoplasmic reticulum membrane (Erlich & Watras 1998), inducing the release of internal Ca$^{2+}$ from sarcoplasmic reticulum and causes a transient contraction of the mesenteric artery.

Considering this response, the effect of GFC on mobilisation of PHE-sensitive Ca$^{2+}$ intracellular stores was assessed, and GFC significantly attenuates the transient contraction induced by PHE in a concentration-dependent manner (Figure 2D), demonstrating that it can attenuate the vasoconstriction induced by IP$_3$R-mediated intracellular Ca$^{2+}$ release.

3. Conclusions
This work demonstrated that GFC-induced vasorelaxant effect is probably mediated by a dual effect on mobilisation of calcium intracellular stores and attenuation of transmembrane calcium influx. Further experiments are necessary in order to identify additional mechanisms involved as well as what steps in cell signalling pathways are responsible for these effects.

Supplementary material
Experimental details relating to this article are available online.

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