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SHORT COMMUNICATION

In vivo growth inhibition of sarcoma 180 by *Kielmeyera rugosa* Choisy (Calophyllaceae)

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The plant *Kielmeyera rugosa* Choisy (family Calophyllaceae), popularly known as 'pau-santo', is traditionally used in Brazilian folk medicine. Recently, the dichloromethane extract–dichloromethane partition from stems of *K. rugosa* (KR) has shown positive results in our cytotoxic screening programme. Therefore, the aim of this study was to validate the antitumour activity of KR on sarcoma 180 tumour-bearing mice. KR showed antitumour activity with both administration routes: intraperitoneal (50 and 100 mg/kg/day) and oral (100 and 200 mg/kg/day). Tumour growth inhibition rates were 40.8–34.9% and 25.4–51.8% after intraperitoneal and oral administrations, respectively. Treatment with KR did not significantly affect body mass, macroscopy of the organs or blood leukocyte counts. In conclusion, KR exhibited an *in vivo* antitumour effect without substantial toxicity.

Keywords: *Kielmeyera rugosa*; Calophyllaceae; antitumour; sarcoma 180

1. Introduction

The influence of natural product structures on drug discovery and development is unquestionable. For example, in the anticancer area, about 74% of drugs are either natural products or derived from natural products (Tan et al. 2006).

The genus *Kielmeyera* (family Calophyllaceae) is native to South America with some species popularly known as 'pau-santo'. These species are traditionally used in Brazilian folk medicine to treat several diseases, including schistosomiasis, leishmaniasis, malaria, bacterial and fungal infections (Alves et al. 2000). In addition, several biological activities have been reported for the plants belonging to this genus, such as antibacterial (Pinheiro et al. 2003), antifungal (Silva et al. 2009), trypanocidal (Scio et al. 2003), anxiolytic (Biesdorf et al. 2012), antidepressant (Sela et al. 2010) and cytotoxic (Mesquita et al. 2009, 2011) activities.

The plant *Kielmeyera rugosa* Choisy is endemic to Brazil, but there are few scientific research reports to this regard (Andrade et al. 2007; Nogueira et al. 2009; Ribeiro et al. 2012). Recently, the dichloromethane extract–dichloromethane partition from stems of *K. rugosa* (KR) has shown positive results in a cytotoxic screening carried out by us (Ribeiro et al. 2012). Therefore, the aim of this study was to validate the antitumour activity of KR on tumour-bearing mice. In addition, toxicological evaluation was also carried out.

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2. Results and discussion

This work reports, for the first time, the antitumour activity of KR on mice implanted with sarcoma 180 tumour cells. Sarcoma 180 is an original mouse tumour and well-characterised experimental model used in the research of antitumour activity (Lee et al. 2003; Bezerra et al. 2008; Britto et al. 2012; He et al. 2012).

KR showed an antitumour effect with both administration routes: intraperitoneal (i.p.) and oral (p.o.), but it was more potent by i.p. administration. In i.p. administration, it showed an antitumour effect at 50 mg/kg/day, whereas in p.o. administration, the antitumour effect was observed only at 200 mg/kg/day. In fact, usually, the oral route is disadvantageous because of less absorption. The effects of KR on mice transplanted with sarcoma 180 tumour cells are presented in Table S1. On day 8, the average tumour weight of control mice was 1.55 ± 0.16 and 1.55 ± 0.09 g for i.p. and p.o. routes, respectively. In the presence of KR by i.p. (50 and 100 mg/kg/day), the average tumour weights were 0.92 ± 0.07 and 1.01 ± 0.15 g, respectively. In the presence of KR by p.o. (100 and 200 mg/kg/day), the average tumour weights were 1.16 ± 0.21 and 0.75 ± 0.12 g, respectively. Tumour growth inhibition rates were 40.8–34.9% and 25.4–51.8% after i.p. and p.o. administrations, respectively. 5-FU (25 mg/kg/day), used as the positive control, reduced tumour weight by 66.8%.

The chemical constituents of dichloromethane extract–dichloromethane partition from stems of KR, used in this work, include the coumarins 5-hydroxy-6-(3-methyl-1-oxobutyl)-4-phenyl-6′,6′-dimethylpyrano(2′,3′:7,8)-coumarin; 5-hydroxy-6-(3-methyl-1-oxobutyl)-4-n-propyl-6′,6′-dimethylpyrano(2′,3′:7,8)-coumarin; and 5-hydroxy-6-(4-cinnamoyl-3-methyl-1-oxobutyl)-4-phenyl-6′,6′-dimethylpyrano (2′,3′:7,8)-coumarin. Coumarins constitute one important group of plant secondary metabolites displaying several biological activities, including an anticancer property that is dependent on their substitution pattern (López-Pérez et al. 2005; Riveiro et al. 2010; Musa et al. 2011). In a previous work, we demonstrated that this last cited phenylcoumarin shows weak cytotoxicity (Ribeiro et al. 2012). Probably, it, or its association with other coumarins, is responsible for the antitumour activity of KR.

In the genus *Kielmeyera*, the anticancer potential of *K. coriacea* was also studied. The extract from *K. coriacea* showed significant cytotoxic activity on tumour cell lines (Mesquita et al. 2009). In addition, the hexane root bark extract of *K. coriacea* led to a mixture of δ-tocotrienol and its dimer, which induces tumour cell death by apoptosis and necrosis (Mesquita et al. 2011).

The toxicological aspects were also subject to investigation in this study. Tables S1 and S2 show body mass loss, organ weight alteration and leukogram from KR-treated animals. Treatment with KR did not significantly affect body mass, macroscopy of the organs (kidney and liver) or blood leukocyte counts ($p > 0.05$). Moreover, spleen weights were increased in animals treated with KR by i.p. at the dose of 50 mg/kg/day ($p < 0.05$), which might be related to an immunostimulatory action. In contrast, 5-FU reduced the body weights and the weight of the liver and spleen organs ($p < 0.05$). In the peripheral blood from mice transplanted with sarcoma 180 tumour, 5-FU induced a decrease in total leukocytes ($p < 0.05$). This unwanted myelosuppression is frequent and can potentially seriously complicate the administration of 5-FU with increased susceptibility to pathogens, such as bacteria and virus, and reduced anticancer immunity (Macdonald 1999).

3. Conclusions

In conclusion, KR inhibited *in vivo* growth of tumour cells without substantial toxicity. Therefore, further investigations are required to elucidate the mechanism(s) of the antitumour effect exhibited.

Supplementary material

Supplementary material relating to this article is available online, alongside Tables S1 and S2.

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