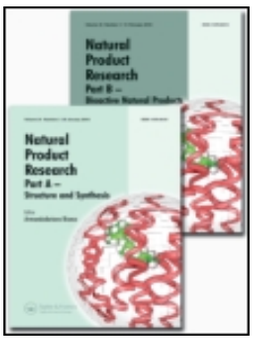

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Natural Product Research
Formerly Natural Product Letters

ISSN: 1478-6419 (Print) 1478-6427 (Online) Journal homepage: http://www.tandfonline.com/loi/gnpl20

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To cite this article: Samy Selim & Soad Al Jaouni (2016) Anti-inflammatory, antioxidant and antiangiogenic activities of diosgenin isolated from traditional medicinal plant, Costus speciosus (Koen ex.Retz.) Sm, Natural Product Research, 30:16, 1830-1833, DOI: 10.1080/14786419.2015.1065493

To link to this article: http://dx.doi.org/10.1080/14786419.2015.1065493

NATURAL PRODUCT RESEARCH, 2016
VOL. 30, NO. 16, 1830–1833
http://dx.doi.org/10.1080/14786419.2015.1065493

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SHORT COMMUNICATION

Anti-inflammatory, antioxidant and antiangiogenic activities of diosgenin isolated from traditional medicinal plant, *Costus speciosus* (Koen ex.Retz.) Sm

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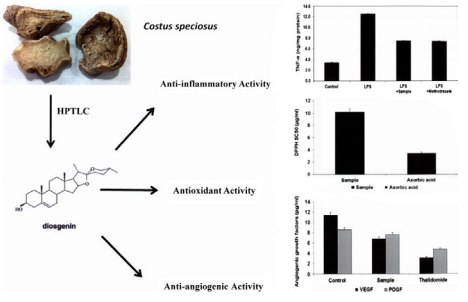
ABSTRACT

Costus speciosus is an important medicinal plant widely used in several indigenous medicinal formulations. The present study was conducted to evaluate the *in vitro* anti-inflammatory, antioxidant and antiangiogenic activities of diosgenin isolated from *C. speciosus*. The diosgenin was isolated from *C. speciosus* by HPTLC and its biological activities were studied by different protocols. The results demonstrated that LPS stimulated TNF-α generation in RAW 264.7 macrophage culture supernatant up to 3.7-fold of the control and that sample treatment (50 µg/mL) resulted in a highly significant inhibitory effect on LPS-stimulated TNF-α ($p < 0.01$) in a similar manner to methotrexate inhibitory effect. The tested sample possessed an effective antioxidant scavenging affinity against DPPH radicals as compared with the standard antioxidant activity of vitamin C. The results presented here may suggest that diosgenin isolated from *C. speciosus* possess anticancer, apoptotic and inhibitory effects on cell proliferation.

ARTICLE HISTORY
Received 18 May 2015
Accepted 14 June 2015

KEYWORDS
Anti-inflammatory; antioxidant; anti-angiogenic; diosgenin; *C. speciosus*

GRAPHICAL ABSTRACT



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Supplemental data for this article can be accessed at http://dx.doi.org/10.1080/14786419.2015.1065493.

1. Introduction

Costus speciosus is a perennial rhizomatous herb with erect or spreading stems commonly called as crepe ginger or spiral flag in English (Gupta 2010). *C. speciosus* is native to the Malay peninsula of the South-East Asia. The rhizomes are bitter and showed anthelmintic, astringent, depurative and expectorant properties, antioxidant, antifungal, antituberculosis and oestrogenic activities (Vijayalakshmi & Sarada 2008). The rhizome extract is used as tonic and useful in reliving burning sensation, constipation, asthma, bronchitis, leprosy, anaemia and other skin ailments. Pharmacological studies showed that the rhizomes of *C. speciosus* possess cardiotonic, hydrochloric, diuretic and CNS depressant activity (Jagtap & Satpute 2014). Diosgenin is a bioactive steroidal sapogenin belonging to the triterpene group and is of great interest to the pharmaceutical industry (Hirai et al. 2010; Jagadeesan et al. 2012). It serves as an important starting material for the production of corticosteroids, sexual hormones, oral contraceptives as well as other steroidal drugs via hemisynthesis (Liagre et al. 2004; Patel et al. 2012). In the present work, we evaluated the anti-inflammatory, antioxidant and antiangiogenic activities of diosgenin isolated from *C. speciosus*.

2. Results and discussion

Our study is the first to report the anti-inflammatory, antioxidant and antiangiogenic activities of diosgenin extracted from *C. speciosus.* Diosgenin isolated from the hexane extract of *C. speciosus* rhizome was studied for its biological activity. HPTLC mobile phase was optimised to toluene: ethyl acetate 7:3 v/v and diosgenin content was found to be 0.152% after extraction for 8 h in alcohol.

The results indicated that bacterial lipopolysaccharide (LPS) significantly induced nitric oxide (NO) production in RAW 264.7 macrophages up to 38-fold of the control as concluded from the nitrite concentration in cell culture supernatant and that the tested sample (50 µg/mL) possessed a remarkable significant inhibitory effect on NO ($p < 0.01$), which is close to the NO inhibitory activity of methotrexate as shown in Supplementary Figure S1. The treatment with the tested sample led to 38.1% inhibition in the LPS-stimulated nitrite level. The results demonstrated that LPS stimulated TNF-α generation in RAW 264.7 macrophage culture supernatant up to 3.7-fold of the control and that sample treatment (50 µg/mL) resulted in a highly significant inhibitory effect on LPS-stimulated TNF-α ($p < 0.01$) in a similar manner to methotrexate inhibitory effect, as shown in Supplementary Figure S2. The treatment with the tested sample led to 41.1% inhibition in the LPS-stimulated TNF-α level. The results indicated that LPS induced COX-2 production in RAW 264.7 macrophage lysate up to 3.03-fold of the control and that samples (50 µg/mL) possessed a significantly high inhibitory activity for COX-2 ($p < 0.01$) to the extent nearly to methotrexate, as shown in Supplementary Figure S3. The treatment with the tested sample led to 43.6% inhibition in the LPS-stimulated COX-2 level. Our findings revealed that LPS induced 5-LO level in RAW 264.7 macrophage lysate up to 3.4-fold of the control and that the tested sample (50 µg/mL) showed no inhibitory effect on 5-LO as well as methotrexate, which exhibited a non-significant inhibition ($p > 0.05$), as shown in Supplementary Figure S4. Inflammation is known to be associated with the induction of COX-1 and COX-2, activation of inducible NO synthase, translocation/activation of lipoxygenases and induction of expression of pro-inflammatory cytokines such as TNF-α. TNF-α is implicated in inflammation-associated cancers, which

induces other inflammatory mediators that orchestrate inflammatory responses. TNF-α is known to modulate angiogenesis, and tumorigenesis, including cellular transformation, promotion, proliferation, invasion, angiogenesis and metastasis (Murakawa et al. 2006).

To control and neutralise the free radicals in the cellular environment, cells maintain a defence system based on different endogenous antioxidant enzymes such as catalase, superoxide dismutase and glutathione peroxidase and thiol proteins like glutathione. The tested sample possessed an effective antioxidant scavenging affinity against DPPH radicals, concluded from its low SC_{50} value 10.18 µg/mL, 7.21 µg/mL, as compared with the standard antioxidant activity of vitamin C (ascorbic acid) (SC_{50} 3.47 µg/mL), as shown in Supplementary Figure S5. Using 30% of the IC_{50} of the tested sample in the treatment of HepG2 cells resulted in a significantly high induction in glutathione ($p < 0.05$) to the extent nearly to N-acetylcyctein (NAC, a known antioxidant), as shown in Supplementary Figure S6. The treatment with the tested sample resulted in 52% induction in glutathione concentration. Using 30% of the IC_{50} of the tested sample to treat of HepG2 cells induced the activity of superoxide dismutase enzyme ($p < 0.05$) to the extent higher than NAC-induced activity, as shown in Supplementary Figure S7. The treatment with the tested sample resulted in 148% induction in SOD activity. Using 30% of the IC_{50} of the tested sample to treat of HepG2 cells resulted in a non-significant induction in the catalase enzyme activity ($p > 0.05$) compared to the significant NAC-induced activity ($p < 0.05$), as shown in Supplementary Figure S8. Using 30% of the IC_{50} of the tested sample to treat of HepG2 cells resulted in a non-significant induction in the glutathione peroxidase enzyme activity ($p > 0.05$) compared to the significant NAC-induced activity ($p < 0.05$), as shown in Supplementary Figure S9.

The formation of new blood vessels (angiogenesis) is critical for cancer progression since the growth potential of cells is limited by the availability of the nutrients. Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) are the most potent identified tumour pro-angiogenic factor (Mackenzie et al. 2011). Using 30% of the IC_{50} of the tested sample to treat of Mcf-7 cells resulted in a significant inhibition in the VEGF concentration ($p < 0.05$) and a non-significant reduction in PDGF concentration compared to the significant inhibition to both of VEGF and PDGF by thalidomide, a known antiangiogenic drug ($p < 0.01$), as shown in Supplementary Figure S10. In conclusion, our current study is the first to identify the remarkable anticancer activity of apoptotic and inhibitory effects on cell proliferation of diosgenin isolated from *C. speciosus*.

Supplementary materials

Experimental details relating to this article are available online, alongside Figures S1–S10.

Acknowledgements

The authors, therefore acknowledge with thanks Y.A. Jameel Scientific Chair of Prophetic Medical Applications technical and financial support. The authors are grateful to Prof. Amira M. Gamal-Eldeen, Cancer Biology Lab., Center of Excellence for Advanced Sciences, Biochemistry Department, Genetic Engineering and Biotechnology division, National Research Center, Dokki, Cairo, Egypt, for excellent assistance during this study.

Disclosure statement

No potential conflict of interest was reported by the authors.

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