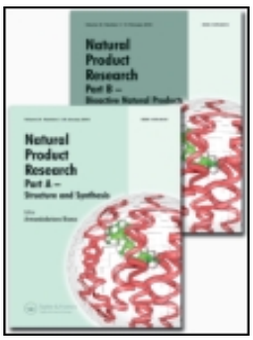

Natural Product Research
Formerly Natural Product Letters

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

# 6'-O-Caffeoylarbutin inhibits melanogenesis in zebrafish

**Min Xu, Qiao-Cong Lao, Ping Zhao, Xiao-Yu Zhu, Hong-Tao Zhu, Xu-Lu Luo, Chong-Ren Yang, Jian-Hui He, Chun-Qi Li & Ying-Jun Zhang**

**To cite this article:** Min Xu, Qiao-Cong Lao, Ping Zhao, Xiao-Yu Zhu, Hong-Tao Zhu, Xu-Lu Luo, Chong-Ren Yang, Jian-Hui He, Chun-Qi Li & Ying-Jun Zhang (2014) 6'-O-Caffeoylarbutin inhibits melanogenesis in zebrafish, Natural Product Research, 28:12, 932-934, DOI: 10.1080/14786419.2014.883395

**To link to this article:** http://dx.doi.org/10.1080/14786419.2014.883395

*Natural Product Research*, 2014
Vol. 28, No. 12, 932–934, http://dx.doi.org/10.1080/14786419.2014.883395





## SHORT COMMUNICATION

# 6′-*O*-Caffeoylarbutin inhibits melanogenesis in zebrafish

Min Xu[a], Qiao-Cong Lao[b], Ping Zhao[c]*, Xiao-Yu Zhu[b], Hong-Tao Zhu[a], Xu-Lu Luo[c], Chong-Ren Yang[a], Jian-Hui He[b], Chun-Qi Li[bd]* and Ying-Jun Zhang[a]*

[a]*State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, P.R. China;* [b]*Hunter Biotechnology, Inc., Transfarland, Xiaoshan Economic&Technology Development Zone, Hangzhou City 311231, P.R. China;* [c]*Key Laboratory for Forest Resources Conservation and Use in the Southwest Mountains of China, Ministry of Education, Southwest Forestry University, Kunming 650224, P.R. China;* [d]*Zhejiang Provincial Key Laboratory for Technology and Application of Model Organisms, Wenzhou Medical University, Wenzhou, Zhejiang Province 325035, P.R. China*

(*Received 24 November 2013; final version received 6 January 2014*)

6′-*O*-Caffeoylarbutin, an arbutin derivative, is a naturally occurring glucoside of hydroquinone from *Vaccinium dunalianum*. On anti-melanogenic effect assay, 6′-*O*-caffeoylarbutin expressed a stronger anti-melanin activity in a dose-dependent manner with about a two-fold more than that of arbutin, but with less toxicity about a two-fold lower than that of arbutin. In addition, melanin synthesis could be fully recovered after the removal of 6′-*O*-caffeoylarbutin. The result suggested that 6′-*O*-caffeoylarbutin could be a candidate natural product to serve as a skin-whitening ingredient with the merits of potent melanin inhibition, less toxicity and reversible melanin synthesis after stopping use.

**Keywords:** 6′-*O*-caffeoylarbutin; anti-melanogenic; *Vaccinium dunalianum*

## 1. Introduction

Melanin is the pigment responsible for skin colour. Epidermal hyperpigmentation, such as melasma, freckles and post-inflammatory hyperpigmentation, are closely associated with abnormal content and distribution of melanin (Huang et al. 2008). So far, several natural or synthetic substances have been utilised as de-pigmentation for both pharmaceutical and cosmetic purposes (Hu et al. 2009). However, due to the numerous safety concerns, only a few of them, such as arbutin and hydroquinone, have been employed as skin-whitening agents. Moreover, hydroquinone as a skin-whitening ingredient has been in use topically for more than 50 years (Hu et al. 2009); however, recently it has been found that it may induce tumours, such as thyroid follicular cell hyperplasias, anisokaryosis, mononuclear cell leukaemia, hepatocellular adenomas and renal tubule cell adenomas (Nordlund et al. 2006; Levitt 2007). Intense effort has been devoted in the recent years to the screening of natural, safe and effective skin-whitening agents for both pharmaceutical and cosmetic purposes (Huang et al. 2008; Lee et al. 2012).

6′-*O*-Caffeoylarbutin, an arbutin derivative, is a naturally occurring glucoside of hydroquinone from *Vaccinium dunalianum*, first isolated by one of our co-authors (Zhao et al. 2008). Herein, we report the effect of 6′-*O*-caffeoylarbutin on melanogenesis in *in vivo* zebrafish model.

*Corresponding authors. Email: hypzhao@yahoo.com; zhangyj@mail.kib.ac.cn; jackli@zhunter.com

## 2. Results and discussion

The inhibition of 6′-*O*-caffeoylarbutin (Figure 1) on melanogenesis was tested *in vivo* in a live zebrafish model. The result demonstrated that the inhibitory effect of melanin formation in zebrafish treated with 6′-*O*-caffeoylarbutin was much stronger than that in zebrafish treated with arbutin at the same concentration (Figure S1, Supplementary material). By quantitative assay of zebrafish melanin using an image-based morphometric analysis, 6′-*O*-caffeoylarbutin expressed inhibition activity on melanin production with an $IC_{20}$ (the concentration with an ability to inhibit 20% of the melanin production) value of 63.89 μM, which is stronger than arbutin with an $IC_{20}$ value of 244.6 μM (Figure S1, Supplementary material). The minimum concentration to inhibit melanin formation in zebrafish was 60 μM for 6′-*O*-caffeoylarbutin and 100 μM for arbutin. To verify whether melanin suppression could be reversible after removal of 6′-*O*-caffeoylarbutin, we removed 6′-*O*-caffeoylarbutin from zebrafish culture medium after a treatment period of 24 h. As indicated in Figure S2 (Supplementary material), we observed that the melanin in the zebrafish body was increased with time, and by 24 h after removing 6′-*O*-caffeoylarbutin, melanin content and distribution in zebrafish had no visually observable difference from untreated and vehicle control groups.

Furthermore, safety of 6′-*O*-caffeoylarbutin and arbutin were parallelly compared in zebrafish treated with gradient concentrations: 10 μM, 100 μM, 1 mM, 2 mM and 3 mM. Mortality rate of zebrafish was used as a toxic indicator. The results revealed that at the highest dose tested (3 mM), no mortality was recorded at 52 hours post-fertilisation (hpf) for both the compounds. However, showing no mortality at 96 hpf, the concentrations of 6′-*O*-caffeoylarbutin and arbutin were 2 and 1 mM, respectively. This indicated that the biosafety of 6′-*O*-caffeoylarbutin is better than that of arbutin.

In this study, 6′-*O*-caffeoylarbutin expressed a stronger anti-melanin activity in a dose-dependent manner with about a two-fold more than that of arbutin, but with less toxicity about a two-fold lower than that of arbutin. In addition, melanin synthesis could be fully restored after removal of 6′-*O*-caffeoylarbutin. Our discovery reported in the article may mean that 6′-*O*-caffeoylarbutin could be a novel, safer and more potent skin-whitening natural product. From the perspective of the tertiary structure, the de-pigmentation mechanism of 6′-*O*-caffeoylarbutin could be the competitive inhibition, similar to that of the monophenol chemicals such as hydroquinone and arbutin, since they share structural homologies with the substrate tyrosine (Boissy et al. 2005; Hamed et al. 2006). Furthermore, the polar caffeoyl moiety in 6′-*O*-caffeoylarbutin increases its hydrophilic property and should be consistent with its promising effects on melanogenesis.

## 3. Conclusion

6′-*O*-Caffeoylarbutin could be a candidate natural product to serve as a skin-whitening ingredient with the merits of potent melanin inhibition, less toxicity and reversible melanin synthesis after stopping use. In our opinion, new advances in understanding the molecular

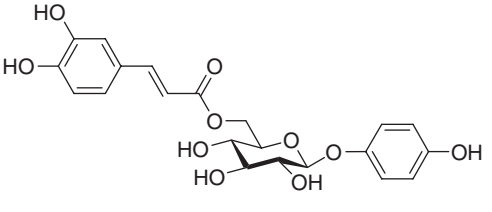


Figure 1. The structure of 6′-*O*-caffeoylarbutin.

mechanisms of 6′-*O*-caffeoylarbutin will be useful in the future to develop new skin-whitening agents by molecular modifications towards the parent chemical hydroquinone via the addition of hydrophilic moieties, especially caffeoyl derivatives moiety.

## Supplementary material

Experimental details relating to this article are available online.

## Acknowledgements

We are grateful to the members of the analytical group of our institute for the measurement of spectroscopic data. This work was supported by the NSFC 21062018, the 973 Program of Science and Technology of the People's Republic of China (2011CB915503), the Fourteenth Batch Candidates of the Young Academic Leaders of Yunnan Province (Min XU, 2011CI044) and by West Light Foundation of the Chinese Academy of Sciences, and the Scientific Research Foundation (SRF) for the Returned Overseas Chinese Scholars (ROCS), State Education Ministry (SEM).



## References

Boissy RE, Visscher M, DeLong MA. 2005. Deoxyarbutin: a novel reversible tyrosinase inhibitor with effective *in vivo* skin lightening potency. Exp Dermatol. 14:601–608.

Hamed SH, Sriwiriyanont P, deLong MA, Visscher MO, Wickett RR, Boissy RE. 2006. Comparative efficacy and safety of deoxyarbutin, a new tyrosinase-inhibiting agent. J Cosmet Sci. 57:291–308.

Hu ZM, Zhou Q, Lei TC, Ding SF, Xu SZ. 2009. Effects of hydroquinone and its glucoside derivatives on melanogenesis and antioxidation: biosafety as skin whitening agents. J Dermatol Sci. 55:179–184.

Huang YH, Lee TH, Chan KJ, Hsu FL, Wu YC, Lee MH. 2008. Anemonin is a natural bioactive compound that can regulate tyrosinase-related proteins and mRNA in human melanocytes. J Dermatol Sci. 49:115–123.

Lee JS, Kim WS, Kim JJ, Chin YW, Jeong HC, Choi JS, Min HG, Cha HJ. 2012. Identification of anti-melanogenic natural compounds from *Galega officinalis* and further drug repositioning. J Dermatol Sci. 67:61–63.

Levitt J. 2007. The safety of hydroquinone: a dermatologist's response to the 2006 Federal Register. J Am Acad Dermatol. 57:854–872.

Nordlund J, Grimes P, Ortonne JP. 2006. The safety of hydroquinone. J Cosmet Dermatol. 5:168–169.

Zhao P, Tanaka T, Hirabayashi K, Zhang YJ, Yang CR, Kouno I. 2008. Caffeoyl arbutin and related compounds from the buds of *Vaccinium dunalianum*. Phytochemistry. 69:3087–3094.