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Quantitative studies on structure–ORAC relationships of anthocyanins from eggplant and radish using 3D-QSAR

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ABSTRACT

The 3-dimensional quantitative structure activity relationship (3D-QSAR) models were established from 21 anthocyanins based on their oxygen radical absorbing capacity (ORAC) and were applied to predict anthocyanins in eggplant and radish for their ORAC values. The cross-validated q^2 = 0.857/0.729, non-cross-validated r^2 = 0.958/0.856, standard error of estimate = 0.153/0.134, and F = 73.267/19.247 were for the best QSAR (CoMFA/CoMSIA) models, where the correlation coefficient r^2_{pred} = 0.998/0.997 (>0.6) indicated a high predictive ability for each. Additionally, the contour map results suggested that structural characteristics of anthocyanins favourable for the high ORAC. Four anthocyanins from eggplant and radish have been screened based on the QSAR models. Pelargonidin-3-[(6″-*p*-coumaroyl)-glucosyl(2→1)glucoside]-5-(6″-malonyl)-glucoside, delphinidin-3-rutinoside-5-glucoside, and delphinidin-3-[(4″-*p*-coumaroyl)-rhamnosyl(1→6)glucoside]-5-glucoside potential with high ORAC based the QSAR models were isolated and also confirmed for their relative high antioxidant ability, which might attribute to the bulky and/or electron-donating substituent at the 3-position in the C ring or/and hydrogen bond donor group/electron donating group on the R_1 position in the B ring.

1. Introduction

Anthocyanins belong to the widespread class of flavonoid compounds and are considered as natural, water-soluble, nontoxic pigments (Kong, Chia, Goh, Chia, & Brouillard, 2003). Researches on anthocyanins were carried out because of their biological and pharmacological properties, especially antioxidant activity (Kahkonen & Heinonen, 2003).

The relationship between anthocyanin structure and antioxidant capacity has been studied. The number and position of hydroxylation and methoxylation in the B ring is commonly regarded as important for the radical scavenging activities of anthocyanins (Kahkonen & Heinonen, 2003; Noda, Kneyuki, Igarashi, Mori, & Packer, 2000; Wang, Cao, & Prior, 1997). Delphinidin containing three hydroxylation in the B ring showed a higher antioxidant activity among the six common anthocyanidins (Kahkonen & Heinonen, 2003; Noda et al., 2000) whereas the pelargonin had the lowest antioxidant activity (Wang et al., 1997). Anthocyanin glycosylation patterns affected the total antioxidant capacity (Azuma et al., 2008; Bao, Cai, Sun, Wang, & Corke, 2005; Rahman, Ichiyanagi, Komiyama, Hatano, & Konishi, 2006; Rice-Evans, Miller, & Paganga, 1996; Seeram & Nair, 2002; Wang et al., 1997, 1999; Yoshiki, Okubo, & Igarashi, 1995). A general trend of decreasing TEAC by glycosylation was observed (Rice-Evans et al., 1996). However, glucosylation at C-3 and C-5 of the anthocyanin skeleton have shown an enhancing effect in the chemiluminescence intensity (lipid peroxidation) (Yoshiki et al., 1995). Different sugars may have different effects on the antioxidant activity of an anthocyanin (Wang et al., 1997). Depending on anthocyanidins, different glycosylation patterns either enhanced or reduced the antioxidant power (Kahkonen & Heinonen, 2003). Additional hydroxylation in delphinidin did not increase the Trolox equivalent antioxidant capacity in ORAC assay (Wang et al., 1997) but increased the chemiluminescence intensity in the chemiluminescence assay (Yoshiki et al., 1995) compared to cyanidin. Delphinidin derivatives acyled with caffic acid showed a higher antioxidant activity than the deacyled corresponding (Azuma et al., 2008).

More recently quantitative structure activity relationship (QSAR) studies have served as an efficient tool to elucidate the structure–activity relationships of antioxidants (Jing et al., 2012;

Abbreviations: 3D-QSAR, 3-dimensional quantitative structure activity relationship; ORAC, oxygen radical absorbing capacity; CoMFA, comparative molecular field analysis; CoMSIA, molecular similarity indices analysis; LOO, Leave-One-Out; TEAC, trolox equivalent antioxidant capacity.

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Vajragupta, Boonchoong, & Wongkrajang, 2000; Yamagami, Akamatsu, Motohashi, Hamada, & Tanahashi, 2005). This study aimed to build the QSAR models of the anthocyanins using the comparative molecular field analysis (CoMFA) and the comparative molecular similarity indices analysis (CoMSIA) methods to predict eggplant/radish anthocyanins potential with high oxygen radical absorbance capacity and also understand their quantitative structure–activity relationships. The study should provide an efficient tool to screen anthocyanins from natural sources for a high bioactivity. Then target anthocyanins could be directly isolated for further experiment evaluation. Additionally structure criteria of anthocyanins for a high ORAC were also explored.

2. Materials and methods

2.1. Chemicals

Cyanidin, delphinidin, pelargonidin 3-glucoside, cyanidin 3-glucoside, cyanidin 3-galactoside, cyanidin 3-rutinoside, cyanidin 3-sophoroside, cyanidin 3,5-diglucoside, delphinidin 3,5-diglucoside, pelargonidin 3,5-diglucoside and cyanidin 3-O-β-(6″-*p*-coumaroyl-sambubioside)-5-glucoside were purchased from Polyphenols (Sandnes, Norway). Dephinidin3-sambubioside, delphinidin3-rutinoside, delphinidin3-glucoside, cyanidin3-arabinoside were purchased from Phytolab (Vestenbergsgreuth, German). Pelargonidin was purchased from Chromadex (Santa Ana, CA, USA). All other chemicals were purchased from Sigma–Aldrich (Shanghai, China).

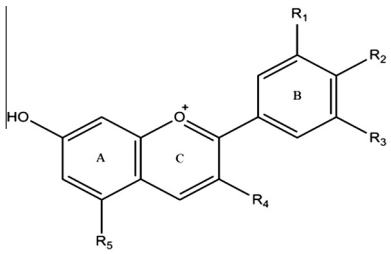
2.2. Experimental design

Common anthocyanins were randomly selected for the study. The 3D-QSAR models were established from the data set of 21 anthocyanins (Table 1). The experimental biological activity values were measures of Trolox equivalent antioxidant capacity (TEAC) for ORAC. The QSAR models were established by comparative field analysis (CoMFA, SYBYL-X 1.2) and comparative molecular similarity index analysis (CoMSIA, SYBYL-X 1.2). The critical structural characteristics of anthocyanins associated with free oxygen radical scavenging activities were analysed. Four anthocyanins in eggplant and radish were randomly chosen for their ORAC calculation in established QSAR models. Three among them were isolated from eggplant and radish and evaluated experimentally at 20 μmol/L were prepared for the antioxidant capacity.

2.3. Oxygen radical absorbance capacity (ORAC) assay

The determination of oxygen radical absorbing capacity of the studied compounds was performed according to the previously reported procedure (Moore et al., 2005) in a Synergy 2 Multi-Mode Microplate Reader (BioTek, Winooski, VT, USA). Samples and Trolox standards were prepared with 50% acetone. All other reagents were prepared in 75 mmol/L phosphate buffer (pH 7.4). Briefly, each well in 96-well plate contained 30 μL of 20 μmol/L sample or 50% acetone for blank and 225 μL fluorescein (81.63 nmol/L). The plate with cover was incubated for 20 min in 37 °C, and then 25 μL AAPH (0.36 mol/L) were added to each well to start reaction,

Table 1
Chemical structure and oxygen radical absorbance capacity of anthocyanins.



Compounds	R_1	R_2	R_3	R_4	R_5	Experimental TEAC	Predicted TEAC	
							CoMFA	CoMSIA
1	OH	OH	H	OH	OH	6.764	5.978	6.372
2	H	OH	H	OH	OH	5.801	6.068	5.276
3	OH	OH	OH	OH	OH	3.084	2.689	2.725
4	OH	OH	H	O-glc	OH	4.723	5.347	6.454
5	H	OH	H	O-glc	OH	6.309	6.721	6.754
6	OH	OH	OH	O-glc	OH	5.137	4.420	4.435
7[a]	OH	OH	H	O-gal	OH	9.608	9.375	8.595
8	OH	OH	H	O-ara	OH	1.286	1.768	2.696
9	OH	OH	H	O-rut	OH	5.940	5.954	5.108
10	OH	OH	H	O-sop	OH	5.809	6.291	5.725
11	OH	OH	OH	O-rut	OH	4.098	3.673	4.141
12	OH	OH	OH	O-sam	OH	5.101	4.707	4.957
13	OH	OH	H	O-glc	O-glc	4.468	4.225	4.991
14	H	OH	H	O-glc	O-glc	5.808	5.608	5.901
15	OH	OH	OH	O-glc	O-glc	3.223	3.496	3.574
16	OH	OH	H	O-cou-sam	O-glc	8.620	8.193	8.597
17	OCH_3	OH	H	O-glc	OH	5.178	5.116	5.084
18	OCH_3	OH	H	O-gal	OH	2.615	2.980	2.490
19	OCH_3	OH	OCH_3	O-glc	OH	2.916	2.718	2.295
20	OCH_3	OH	H	O-ara	OH	4.070	4.134	3.844
21	OCH_3	OH	OCH_3	O-glc	O-glc	4.099	3.895	3.897

glc, glucoside; gal, galactose; ara, arabinose; gut, rutinose; sop, sophoroside; sam, sambubioside; cou-sam, sambubioside acyled with *p*-coumaric acid; cou-rut, rutinose acyled with *p*-coumaric acid; cou-sop, sophoroside acyled with *p*-coumaric acid; mal-glc, glycoside acyled with malonic acid.

[a] Compound for the template alignment.