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Interaction of wine anthocyanin derivatives with lipid bilayer membranes

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ABSTRACT

This work deals with the capacity of various anthocyanin derivatives to insert lipid bilayer membrane. Malvidin-3-*O*-glucoside was studied in its various charge forms (flavylium cation, neutral and anionic quinonoid bases) as well as its deglycosylated, hydrated and conjugated derivatives. Based on molecular dynamics (MD) and COSMOmic simulations, membrane partitioning and crossing were evaluated. The free MD simulations provided molecular description of all intermolecular interactions driving penetration and orientation of these polyphenols in a model of DOPC lipid bilayer. Most of the derivatives are theoretically predicted to insert rather deep in the membrane i.e., embedded in between lipid chains, therefore being prone to scavenge both the initiation and propagation stages of lipid peroxidation. Here we also stress again the importance of the method used to evaluate atomic charge distribution to allow a correct description of membrane penetration.

1. Introduction

The antioxidant properties related to wine are mainly attributed to the presence of polyphenols, particularly flavonoid derivatives. Anthocyanins are a subclass of flavonoid largely distributed in red wine. They are known to participate in red, purple, and blue colors of grapes and wine [1], but also various berries, other fruits, vegetables and flowers.

The general chemical structure of anthocyanins is formed of three cyclic carbon rings C6–C3–C6 denoted as A, B and C (Fig. 1). The structure is usually written as a flavylium cation, which bears a positive charge. Most of anthocyanins occur in nature as glycosides, mainly 3-*O*-glucosides. The structural diversity of anthocyanins stems from the number and position of hydroxyl and methoxy groups in the aglycone, as well as from the nature, size and position of the sugar moiety. Stability, reactivity and chemical activity of anthocyanins depend on all the aforementioned structural parameters [2].

Anthocyanins are very sensitive to pH, providing various chemical forms and colors in aqueous solution depending on pH values. The (red) flavylium cation (AH^+, Fig. 1) predominates at pH values ranging from 1 to 3. When the pH value increases deprotonation from C7, C4′ and C5 occurs successively to form three (purple) quinonoidal basic forms (A_7, $A_{4'}$, and A_5, respectively, Fig. 1). Increasing again the pH values above 7 allows a second deprotonation yielding (blue) quinonoidal anions (e.g., $A^-_{4',7}$, Fig. 1) [3,4]. Alternatively, above pH values of 2–3, hydration reactions produce (colorless) hemiketals, which tautomerises through ring opening into (yellow-ish) chalcones (Fig. 1). Anthocyanins also react with other phenolic compounds to produce various derivatives, for example pyranoanthocyanins that are produced during wine aging.

In vivo, anthocyanins are extensively degraded. They can be deglycosylated and transformed into phenolic acids, aldehydes and other phenolic derivatives [5]. In plants and beverages such as wine, they can combine with other phenolic compounds to form pyranoanthocyanins [6,7]. Although anthocyanins are usually unstable as isolated compounds in solution, they can be partially stabilized by intra and intermolecular non-covalent interactions either with cofactors such as other phenolic compounds (copigmentation) or with themselves (self-association). These interactions are favored by the capacity of polyphenols to interact by π–π stacking and van der Waals interactions [2,8,9].

Anthocyanins have been extensively studied in vitro and in vivo for their biological and pharmacological activities such as antioxidant activities [10–14] possibly related to their role in the prevention of cardiovascular disease [15,16]; anti-inflammatory;

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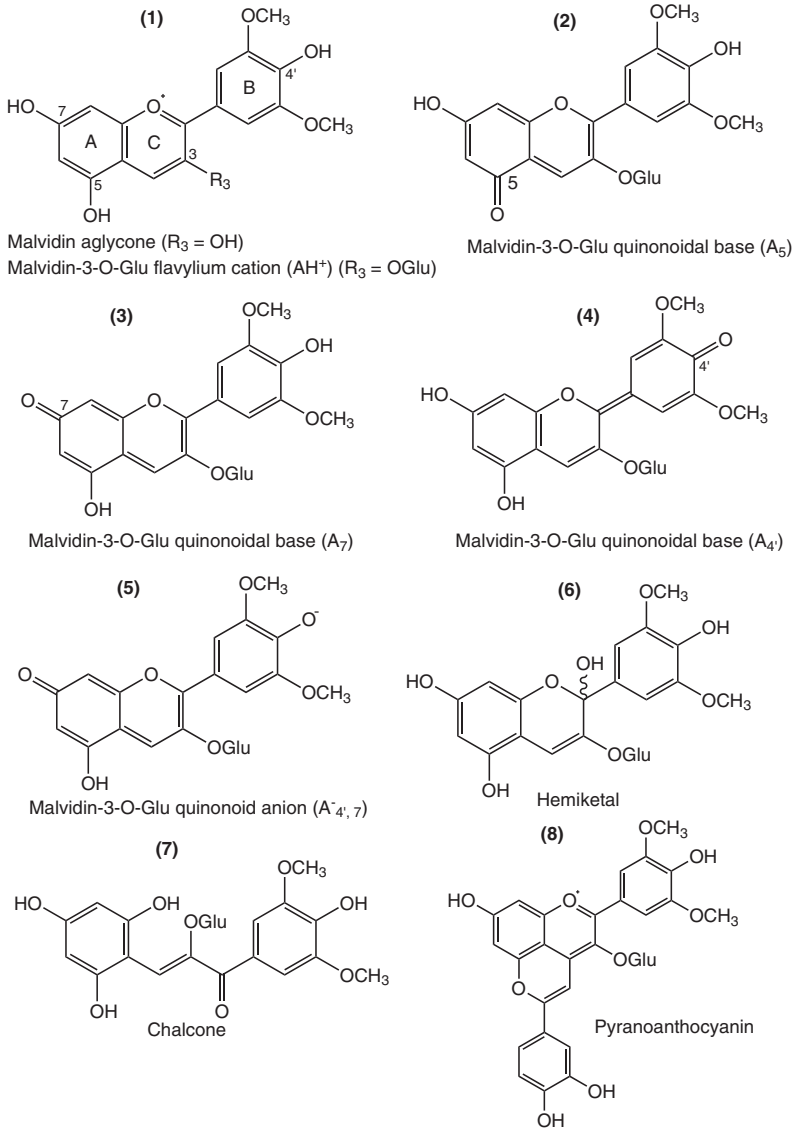

Fig. 1. Chemical structures of a series of anthocyanin derivatives, based on the malvidin moiety.

anti-tumor [17]; anti-diabetic [18]; and their capacity to control oxidative stress during pregnancies [19]. Here, we focused on the antioxidant activities of certain wine anthocyanin derivatives. As antioxidants and scavengers of reactive oxygen species (ROS), phenolic compounds are efficient electron and hydrogen atom donor from their OH groups towards free radicals [20,21]. This capacity is largely attributed to their capacity to delocalize spin in the rather extended π-conjugated system. As antioxidants, they have also been shown to inhibit lipid peroxidation in biological membranes [10,14,22,23]. It should be noted that several polyphenols having structures similar to anthocyanins exhibited the capacity to partition into the lipophilic core of membrane, even affecting membrane fluidity [24,25]. However, there is a lack of information about the molecular mechanisms of this inhibition; mainly because the incorporation of anthocyanins in lipid bilayers and their capacity to cross cell membrane is not fully elucidated at the molecular level. This work presents a theoretical evaluation of interactions between anthocyanins derivatives and lipid bilayer membranes. A series of representative wine anthocyanin derivatives have been selected for this study, based on the malvidin structure, the major anthocyanin structure found in wine. To cover a wide range of physical–chemical properties, molecular dynamics (MD) simulation were carried out for (i) the different charge forms of malvidin-3-*O*-glucoside (AH^+, A_7, $A_{4'}$, A_5 and $A^-_{4',7}$); the aglycone form, malvidin; and the corresponding chalcone, hemiketal and pyranoanthocyanin.

2. Material and methods

2.1. Free MD simulations

MD simulations were carried out using a bilayer constituted of 128 molecules of DOPC (1,2-dioleoyl-*sn*-glycero-3-phosphocholine). An explicit SPC (single point charge) water model was used to model the water molecules surrounding the membrane. Ions (Na^+ and Cl^-) were added at physiological ionic concentration (0.9%). An 8 nm thick box was used with periodic boundary conditions in all dimensions. The *z*-axis was defined as the vector normal to membrane surface. The lipid model was minimized without flavonoid presence during 100 ns. All MD simulations were performed with the GROMACS package version 5.0.4 [26].

Conformations were optimized using density functional theory (DFT) at the B3LYP/6-31+G(d,p) level. The topology was built using the online server PRODRG [27]. Partial atomic charges of molecules