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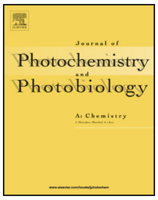

# Tunable optical properties of silymarin flavonolignans

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ABSTRACT

Exposure to UV radiation leads to several skin disorders. In particular, this can be attributed to an increase of the rate of DNA mutations, either due to direct absorption by proteins and DNA (mainly UVB), or due to ROS generation (mainly UVA). The plant extract silymarin is a promising sunscreen agent. It contains numerous flavonolignans and other polyphenol derivatives. In this joint experimental and theoretical study, we focus on silybin (SB), silychristin (SCH), silydianin (SD), and their 2,3-dehydroderivatives (DHSB, DHSCH, DHSD) and we describe their UV/Vis absorption properties, particularly the pH-dependence. Under acidic conditions, SB, SCH and SD exhibit a main and a minor absorption band in the UVB and UVA regions, respectively. The deprotonation in basic environment reverses this trend, making the UVA-absorption band predominant. The dehydrogenation of the C2-C3 bond (DHSB, DHSCH and DHSD) also shifts the main absorption band in the UVA region in acidic environment. In this case, basic environment causes further bathochromic shift, and the absorption band lies in the Vis region. A solvatochromic analysis revealed that, whereas the protonated forms are rather insensitive to other environmental factors, absorption properties of the deprotonated compounds strongly depend on intermolecular hydrogen bonding with solvent molecules. The time-dependent density functional theory (TD-DFT) calculations and molecular orbital analysis rationalized these effects.

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## 1. Introduction

The skin is the organ playing the role of barrier protecting the body from external effects including UV exposure. The exposure to UV radiation can lead to skin disorders such as immunosuppression, skin aging, inflammation, cancer and others [1,2]. UVB radiation (280–320 nm) is a minor but important component of sunlight as it is absorbed by DNA, but also by proteins, lipids or carbohydrates (in a decreasing order of importance). The toxic effect of UVB radiations are of particular concern in this context [3]. UVB exposure increases the rate of mutation, and subsequently, the risk of skin cancer when DNA repair systems are deficient. Tissue damage can also be caused indirectly; UVB, but also UVA (320–390 nm) from sunlight generate reactive oxygen species (ROS), which induce harmful oxidative processes on DNA, proteins or lipid membranes. The indirect effects associated with ROS production can lead to the initiation, promotion and progression of photocarcinogenesis and/or photoaging, by activating cellular signaling pathways [3–5].

Sunscreens contain agents that protect the skin by reflecting, scattering or absorbing UV radiation [6]. Silymarin is a promising sunscreen agent, which can reduce UV-induced skin damaging effects [7]. It is a plant extract obtained from the seeds of milk thistle [*Silybum marianum* (L.), Gaertn. (Asteraceae)] [8]. The flavonolignan silybin (SB) is the major component of silymarin, which also contains other polyphenols including silychristin (SCH), silydianin (SD), 2,3-dehydrosilybin (DHSB), flavonols (mainly taxifolin) and some other rare or unidentified (poly)phenolic compounds [9]. Silymarin possesses a number of biological activities including anti-inflammatory and antioxidant activity

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[10], which makes this extract active *in vitro* and *in vivo* as anticancer-, neuroprotective-, cardioprotective-, or hepatoprotective agents [4,11–14]. Silybin protects from UVB-caused DNA damages in skin epidermal cells. When applied topically prior to or immediately after UV exposure, it reduces thymine-dimer-positive cells in SKH-1 hairless mice [15]. Topical or dietary administrations of silymarin strongly inhibited UVB-induced tumor initiation and promotion in SKH-1 hairless mouse skin [16]. Silymarin was shown to prevent UVB-induced apoptosis and enhances DNA repair in UVB-exposed skin cells [17]. Svobodová et al. [1,2] showed that a post-treatment by flavonolignans dose-dependently reduced apoptosis in UVA-irradiated HaCaT cells, increasing cell viability. Additionally, SB and DHSB suppressed intracellular ATP and GSH depletion, ROS production, and peroxidation in lipid bilayer membranes [1,2].

A thorough characterization of UV absorption properties of (the topically applied) natural polyphenols is of major importance for their possible usage as skin protectors. Over the past decades, quantum-chemical calculations appeared increasingly adapted tools to comprehensively support spectroscopic experimental data [18,19]. Time dependent density functional theory (TD-DFT) is well adapted to provide accurate prediction of optical features for large series of natural compounds [20,21]. Within the TD-DFT formalism, a complete description of excited states can be obtained, supported by the description of electron transitions between molecular orbitals (MO).

Here we describe a joint experimental and theoretical study focused on pH-dependence of UV absorption properties of six major silymarin flavonolignans, namely SB, SCH, SD and their dehydro- derivatives (Fig. 1). The influence of solvents has also been under scrutiny. We have identified the major structural and environmental factors that can shift the absorption bands between UVB and UVA.

## 2. Material and methods

### 2.1. Theoretical calculations

The DFT-B3P86/6-31 + G(d,p) method was used, as it has repeatedly provided accurate evaluation of various properties of polyphenol including redox potentials and UV/Vis absorption wavelengths [22,23]. Geometry optimization was performed using DFT for all six chemical structures (Fig. 1). After a systematic evaluation of the conformational space, only the most stable conformer of each six derivative was used for TD-DFT calculations. For each compound, several conformers were actually obtained, which were within less than 2 kcal/mol in terms of Gibbs energies. The conformational flexibility mainly depends on the torsion angles between the rings C and B, and D and E (more details on relative stability and geometrical characteristics of the different conformers are given in Ref. [24]). Although the most stable conformer was considered, the others may exist in solution as relatively minor conformers. However, as checked on several conformers of SB and DHSB (data not shown), $\lambda_{MAX}$ values differed by less than 0.2 nm, and the MO distributions were very similar.

Standard Gibbs energies ($G^0$) were obtained at 298 K, 1 atm. Ground-state geometries were confirmed by a vibrational frequency analysis showing absence of any imaginary frequency. Concerning the UV/Vis absorption properties, TD-DFT calculations were performed with both B3P86 and CAM-B3LYP functionals with the 6-31 + G(d,p) basis set. After comparison to experimental data, B3P86 was confirmed to correctly describe the UV/Vis spectra for the neutral forms, as already described for polyphenol derivatives [20,25]. Concerning the deprotonated form, the global spectral feature is well described (description of all peaks), but the maximum absorption wavelength ($\lambda_{MAX}$) is underestimated by using B3P86 (shift in energy of 0.46 eV). It is also underestimated

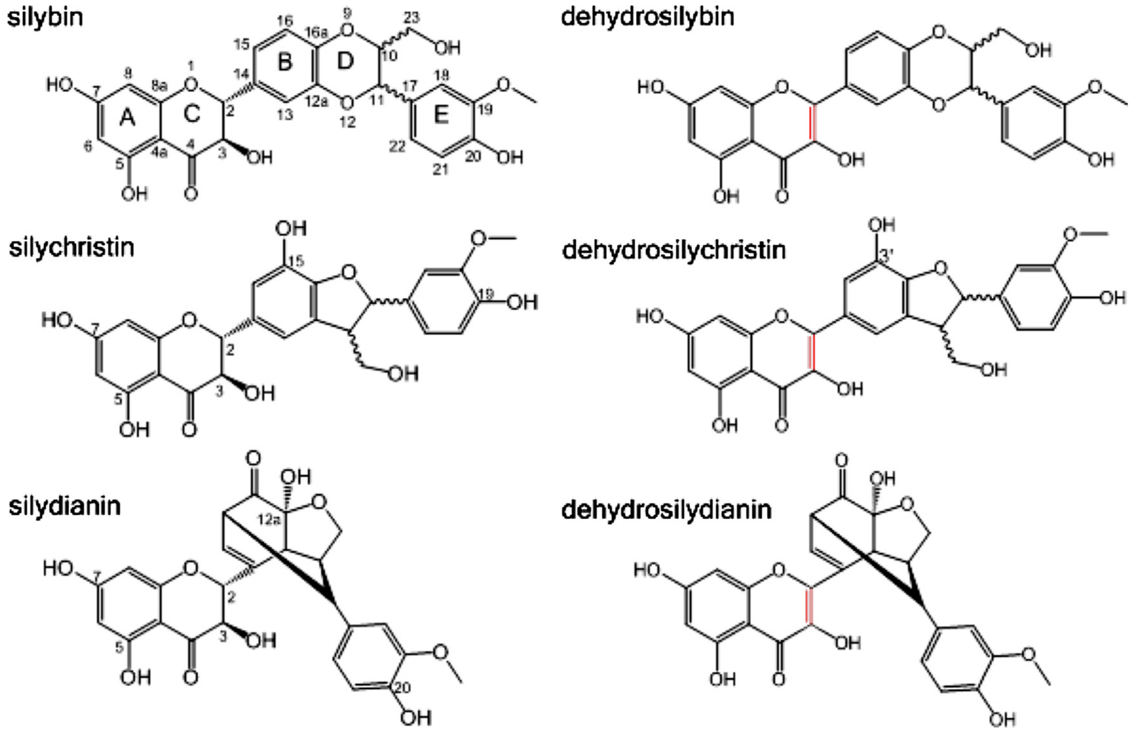

**Fig. 1.** Structures of the silybin (SB), silychristin (SCH), silydianin (SD) and their dehydro- derivatives (DHSB, DHSCH and DHSD, respectively). The 2,3-double bond in dehydro-derivatives is highlighted in red.

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