Hesperidin: synthesis and characterization of bioflavonoid complex

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Abstract

Flavonoids are widely recognized for their beneficial effects in the cosmetic industry, possessing many biological activities, such as antioxidant, anti-inflammatory and antimicrobial properties. The study presented an efficient and simple solution to improve the preparations of antioxidant complexes based on hesperidin. Obtained products are characterized by thermogravimetric, spectrophotometric method, electron scanning microscopy, color analysis and zeta potential. Lightness value (L^*) of hesperidin-silica complexes was found to be inversely correlated with the antioxidant activity values.

Keywords Flavonoid · Antioxidant · Hesperidin · Spectrophotometric · Zeta potential

1 Introduction

Flavonoids are a class of compounds found in plant cells. These polyphenolic compounds are generally nontoxic and belong to the natural pigments family. In food, they are responsible for taste and color. Existing research confirms that a number of positive health effects of flavonoids primarily results from their antioxidant activity. Flavonoids are responsible: for transition metal chelating such as copper and iron, so that prevent free radicals, interrupting a series of reaction of free radical in enzymatic and non-enzymatic lipid peroxidation [1–4]. Among of this large class of interesting compounds, hesperidin is a bioflavonoid found in citrus fruits. Structurally, hesperidin is a β -7-rutinoside of hesperetin consists of an aglycone, hesperetin and a disaccharide, rutinose. Anticancer and cancer chemopreventive properties of hesperidin and hesperetin are reported in literature [5]. It was interesting that these results are confirmed by in vitro and in vivo experiments. Many papers described the beneficial effects of the supplementation with hesperidin and hesperetin on the cardiovascular system include antihypertensive, anticoagulant, cardioprotective effects against oxidative

stress [6]. Current strategies to improve these properties include formation of derivatives of natural products. It was also demonstrated that the silver nanoparticles synthesized using hesperidin showed antibacterial effects and cytotoxicity [7]. In literature, the binding properties of hesperetin and its copper complex with calf thymus DNA were investigated. Tan et al. found that complex of flavonoid with Cu(II) may be a potential metal-based anticancer drug [8]. Cao et al. described preparation and characterization of complex hesperidin and chitoooligosaccharide. They reported that obtained product has stronger antioxidant properties than hesperidin [9]. The antioxidant properties of the flavonoid rutin and two derivatives: rutin laurate and rutin palmitate were investigated showing decreased reducing power and metal chelating abilities as compared to rutin [10]. The use of the colloidal lipid formulae loaded with rutin as dermal care products was studied by Kamel and Mostafa [11]. The reported colloidal system of rutin was employed as a successful photoprotective product. Baldisserotto et al. present the synthesis, antimicrobial, antiproliferative and pro-apoptotic effect on human leukemic K562 cells of synthesized rutin derivatives [12]. The newly synthesized transglycosylated compound

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from flavonoid, rhoifolin was reported by Aoki [13]. The encapsulation of rutin [14–16] and quercetin [17] was proposed as a way to obtain a product with protective effects against oxidative stress. Silica-based materials are suitable for oral delivery of drugs [18–22]. The advantage of silica is the simplicity of chemical modification due the presence of hydroxyl on the inner and outer surface of the material. The complexes of hesperidin may improve its physico-chemical and pharmacological properties. Therefore, the objective of this work was to investigate the ability of hesperidin to form complexes with aminofunctionalized silica, characterized by thermogravimetric, spectrophotometric method, electron scanning microscopy and zeta potential. Herein, the derivatives of hesperidin were assessed for their antioxidant properties, and compared with their parent compound, hesperidin.

2 Experimental

2.1 Chemicals

Hesperidin (Hesperetin 7-rhamnoglucoside, Hesperitin-7-rutinoside, Empirical Formula $C_{28}H_{34}O_{15}$, Molecular Weight: 610.56) was purchased from Sigma-Aldrich Co. (USA) and used without further purification. Silica: Syloid®72 was obtained from Grace Davison (USA)—synthetic and amorphous silica with average particle size: 2.5–12 microns. Silica was dried in 100 °C overnight before modification. (3-aminopropyl)trimethoxysilane—APTMS was purchased from Degussa (Germany). Methanol (pure for analysis, POCH, Poland) was used in all experiments.

2.2 Modification of silica and preparation of complex of modified silica with hesperidin

The modified silica was prepared by reaction of Syloid®72 with (3-aminopropyl)trimethoxysilane. Various quantities of (3-aminopropyl)trimethoxysilane (0.1, 0.2 and 0.3 ml) was added drop wise to suspension of 0.5 g of silica in 60 ml of dry toluene. Then, the mixture was heated under reflux for 8 h. The products were filtered and washed several times with toluene and methanol. Then, the samples labeled as AMS-1, AMS-2 and AMS-3 was dried in 100 °C overnight. The complex of aminofunctionalized silica and hesperidin was prepared using various hesperidin/silica ratios—1/1, 1/2 and 2/1. The calculated amount of hesperidin was dissolved in methanol and then the modified silica was added. The mixture was stirred on magnetic stirrer in room temperature for 24 h. Afterwards, the samples were filtered and washed with methanol. The samples labeled as: HESP-AMS-1, HESP-AMS-2 and HESP-AMS-3 were dried in 100 °C for 12 h. The percentage of hesperidin

linked with aminofunctionalized silica was calculated from spectrophotometric and thermogravimetric analysis.

2.3 The zeta potential

The zeta potential was determined with Metasizer 3000 (0.6–1000 nm) instrument (Malvern Instruments Ltd., UK) using the non-invasive dynamic light scattering method (DLS).

2.4 SEM images

The morphological characterization of products was performed by electron scanning microscopy (Zeiss EVO40, Germany). The samples were previously coated with gold.

2.5 FT-IR analysis

Chemical properties of samples were analyzed as KBr pellets using a Bruker IFS 66v/S instrument. Spectral scanning was taken in the wavelength region between 400 and 4000 cm^{-1} with a resolution of 2 cm^{-1} . 64 scans were taken with the average from each spectrum. The background of pure KBr spectrum was subtracted from the sample spectrum.

2.6 TG analysis

Thermal stability analysis of samples was performed by Setsys 1200 (Setaram, France) instrument. Obtained materials were analyzed under helium in the range of temperature between 16 and 1000 °C and 5 °C/min.

2.7 Total antioxidant scavenging activity

2,2-Diphenyl-2-picrylhydrazyl (DPPH) assay [23, 24] were chosen to investigate the free radical scavenging activity. The method is based on the observation of the changes in optical density of DPPH radicals. First, 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) was dissolved in methanol to obtain 5×10^{-5} M solution. Then, the stock solution was then diluted to obtain a final absorbance about 1.0. The solutions of pure hesperidin labeled as: HESP-1, HESP-2 and HESP-3 contain 1, 3 and 7 mg of free hesperidin, respectively. The samples of hesperidin complex were suspended in methanol. Then, the solution of DPPH was added and the samples were stored for 30 min at room temperature in the dark. The absorbance was measured at 516 nm using a UV–visible spectrophotometer and methanol was used as a blank. Values are expressed as mean of three measurements. The free radical scavenging activity are calculated as percentage of inhibition (IC%), according to formula: $\text{IC\%} = \frac{(\text{Abs}_{\text{DPPH}} - \text{Abs}_{\text{sample}})}{\text{Abs}_{\text{DPPH}}} \times 100\%$,

where: Abs_{DPPH} and Abs_{sample} correspond to the absorbance of DPPH solution and antioxidant sample, respectively [23, 24]. Trolox was used as a standard and results are expressed as mg trolox equivalents (T_{eq}).

2.8 Spectrophotometric measurements

The absorbance was determined from electronic spectra recorded in methanol on a Hewlett Packard Diode Array Spectrophotometer HP 8452 fitted with thermostated cell holder to keep the temperature constant within ± 0.1 °C. All measurements are performed in triplicate. Results are expressed as mean values with standard deviation.

2.9 Color analysis

The spectral reflectance and CIELab coordinates of the studied complexes were measured using UV–Vis spectrophotometer Jasco V-630 (Japan) equipped with illuminant D65 and observer placed at 2°. The spectral range of the apparatus was 300–1000 nm. Sample placed in a spherical cuvette (the 20 mm diameter) and a calibration with white standard—pure $BaSO_4$.

3 Results and discussion

The aim of this research was to characterize the complex formed by hesperidin and aminofunctionalized silica. The studied complexes are synthesized according method described in experimental section. The physical and chemical characterization was performed using different techniques. First of all, the efficiency of reaction between hesperidin and functionalized silica was confirmed by spectrophotometric and thermogravimetric method. The results collected in Table 1 indicate that the efficiency of hesperidin complexation increases with increasing hesperidin/silica ratio. However, the duplication of the amount of hesperidin does not significantly improve the obtained results. Thermogravimetric analysis showed the content of a small, 1.0–1.2% water content in the studied samples. The results indicate good compatibility of data

obtained with spectrophotometric and thermogravimetric analysis.

The physical stability is a required condition essential for the characterization of the obtained product, being quantified by the evaluation of the zeta potential, defined as a parameter that describes the electric charge on the particles surface [25–28]. In aqueous solution the zeta potential depends on the pH value. The Fig. 1 shows the changes of zeta potential as a function of pH. The results indicate that the unmodified silica has negative zeta potential through the pH range that was analyzed and is stable in the basic medium what is affected by presence of the deprotonated silanol groups. After modification process by aminosilan, the zeta potential increased significantly (Fig. 1). This effect is caused by the introduction of the amino groups on the silica surface. In the acidic medium, the amino groups are protonated which generated the positive charge and increase the zeta potential. The isoelectric point of unmodified silica is determined to be approximately 4.0 and differ considerably after silica modification.

The Fig. 1 show that the isoelectric point of modified silica is found at pH 9.68. The experimental pH range of stability shifts to the lower values of pH scale. The attaching a hesperidin to modified silica does not change significantly the stability of resulted molecules in comparison with functionalized silica. The isoelectric point was shifted after reaction of about one pH unit, from pH 9.68 to pH 8.55 and the values of zeta potential decreased slightly. This result is caused by a reduction of number of free amino groups after reaction and presence of hydroxyl groups of hesperidin. It is also annotate that at pH values higher than isoelectric point, the negative values of zeta potential were determined for AMS (around -4 mV at pH 10) and AMS–HESP (-26 mV), which results from the deprotonation of silanol groups of silica surface.

The characterization of described complex between hesperidin and aminofunctionalized silica has been based on the information obtained with different techniques. The thermogravimetric analysis provided information on the amount of hesperidin linked with silica as well as the thermal stability of obtained complex.

Table 1 The results of thermogravimetric and spectrophotometric analysis

Sample	HESP/AMS ratio	% hesperidin, TG	% hesperidin, UV–vis	% of adsorbed water
HESP–AMS-1	1/2	12.5 $\pm$ 0.3	15.0 $\pm$ 0.1	1.1 $\pm$ 0.1
HESP–AMS-2	1/1	15.0 $\pm$ 0.4	16.2 $\pm$ 0.2	1.2 $\pm$ 0.1
HESP–AMS-3	2/1	15.2 $\pm$ 0.3	16.1 $\pm$ 0.2	1.0 $\pm$ 0.2
AMS	–	–	–	1.1 $\pm$ 0.2

Fig. 1 Zeta potential of: (a) unmodified silica, (b) amino-functionalized silica and (c) complex of hesperidin with aminofunctionalized silica as a function of pH

The thermal decomposition profiles obtained for modified silica, hesperidin and hesperidin complex, acquired in the same experimental conditions are showed in Fig. 2. Comparison of TG curves for modified silica and complex with hesperidin shows the high thermal stability of the studied complex. The complexation reaction with hesperidin affects the thermal stability of modified silica. The results indicate that in a first part of TG curves of AMS and AMS–HESP complex a 1–1.2% weight loss was observed what is associated with the loss of surface water. In the next step, the thermal decomposition of samples is observed. Between 100 and 250 °C, the curves are almost flat suggesting high stability of material in

this temperature range. The decomposition of AMS and AMS–HESP complex occurs above 300 °C. The Fig. 2 shows also the thermal stability of obtained AMS–HESP complex with a 12.5–15.2% loss of weight (Table 1). However, the pure hesperidin has low thermal stability, reported previously by Cao et al. They described the loss of weight about 60% between 266 and 500 °C [9]. The results obtained for pure hesperidin are similar to those in literature (Fig. 2).

The obtained samples were also characterized morphologically by electron scanning microscopy. The selected SEM images are presented in Fig. 3. The unmodified silica and the modified silica form undefined, irregular flake-shaped particles. For comparison, the crystals of free

Fig. 2 Thermogravimetric analysis of amino modified silica, hesperidin and complex of hesperidin with aminofunctionalized silica

Fig. 3 Scanning electron microscopy images: **a** unmodified silica, **b** aminofunctionalized silica, **c** hesperidin, **d** hesperidin-modified silica complex

hesperidin and its complex with amino modified silica are showed. The morphology of functionalized silica is no different from the starting material. The association of amino functionalized silica with hesperidin also does not change significantly the shape of obtained particles. The reaction products appeared in the form of irregular particles. Besides the color, the hesperidin complex does not differ in its appearance from the starting silica. The results of the studies described in the paper confirm that the reaction took place and the expected product was obtained. The color of the samples, whitish for silica and yellow for the hesperidin complex is a clear difference in appearance. The color analysis presented later in this paper confirm these results.

FT-IR spectra of the hesperidin complex and pure substance were compared. The effect of silica modification is confirmed by the differences in FT-IR spectra. The intensity of the band at $3200\text{--}3600\text{ cm}^{-1}$, assigned for the OH stretching vibrations of silanol groups decreases

in comparison with the band in the spectrum of the unmodified silica. Next, the intensity of the band at $3005\text{--}2930\text{ cm}^{-1}$ assigned to C–H increases after amino modification, which is connected with presence of alkyl groups. The intensity of this band increases significantly after modification of silica and shifted from 2987 to 2949 cm^{-1} . The band at 1560 cm^{-1} corresponds to the N–H stretching vibration confirmed the amino modification of silica. Moreover, the changes are also observed at region $800\text{--}1000\text{ cm}^{-1}$ assigned to Si–OH vibration. The intensity of the band visible at 988 cm^{-1} decreases after modification of silica. Furthermore, in spectra of unmodified and modified silica, the characteristic broad and intense band is observed at around 1100 cm^{-1} due to Si–O–Si vibrations coming from silica matrix. The bands corresponding to the Si–O vibrations appear at 801 and 475 cm^{-1} .

The changes in the characteristic bands of pure hesperidin and modified silica confirm the formation of the reaction product. In the spectrum of free hesperidin

(Fig. 4), characteristic large absorption bands assigned to OH stretching vibrations at 3448 and 3552 cm^{-1} were present. The other band at 2940 cm^{-1} of CH and CH_2 aliphatic groups is observed. The next sharp bands at 1650 and 1638 cm^{-1} are specific for the carbonyl group and aromatic C=C vibration in benzene ring. After the reaction between free hesperidin and aminofunctionalized silica a complex is formed as showed in the FT-IR spectrum. The intensity of the bands for OH vibrations, aliphatic and carbonyl groups are visibly decreased suggesting the interaction between the hesperidin molecule and surface of the amino modified silica.

In order to investigate or the antioxidant properties of hesperidin will also be observed in prepared complexes, antioxidant tests for the complex and pure hesperidin were performed. For the DPPH free radical scavenging assay at different concentrations of hesperidin and complexes were used. The experimental method is based on the reduction of DPPH radical by hesperidin which contains hydroxyl groups.

Table 2 and Fig. 5 show the free radical scavenging activity determined for studied complex with aminofunctionalized silica. For comparison, an analogous experiment with free hesperidin was carried out. Results show that complex of hesperidin with modified silica exhibits antioxidant properties, slightly higher than in the case of the parent compound. The next stage of the research was to check the dependence of the obtained result on the hesperidin amount (1, 3 and 7 mg of hesperidin). For this purpose, absorbance measurements for three solutions of free hesperidin as well as studied complexes were taken. An increase in scavenger capacity with increasing concentration of free hesperidin was observed (Fig. 5).

Table 2 The total scavenging activity of hesperidin-silica complexes in comparison with pure hesperidin: a percentage of inhibition (IC) and trolox equivalent antioxidant capacity (T_{eq})

Sample	$\Delta\text{Abs} \pm \text{SD}$	IC (%)	T_{eq} (μM)
Functionalized silica, AMS			
	0.024 ± 0.001	2.3 ± 0.1	0.7 ± 0.1
Free hesperidin			
HESP-1	0.513 ± 0.001	50.8 ± 0.1	13.2 ± 0.1
HESP-2	0.656 ± 0.001	60.3 ± 0.2	15.5 ± 0.1
HESP-3	0.763 ± 0.001	75.5 ± 0.2	17.8 ± 0.1
Hesperidin-AMS complex			
HESP-AMS-1	0.603 ± 0.001	59.7 ± 0.1	14.8 ± 0.1
HESP-AMS-2	0.784 ± 0.001	60.3 ± 0.1	15.4 ± 0.1
HESP-AMS-3	0.908 ± 0.002	75.5 ± 0.2	16.5 ± 0.1

$\Delta\text{Abs} = A_0 - A$, where A_0 —initial absorbance at 516 nm , A —absorbance at 516 nm after reaction

Further, it was found that the antioxidant capacity change with increasing concentration of hesperidin in complex. For comparison, the value of percentage of inhibition for modified silica is shown, indicating weak antioxidant properties (Table 2, Fig. 5).

Figure 6 shows the reflectance spectrum of the hesperidin-silica complexes for the spectral range of $300\text{--}1000\text{ nm}$. It can be seen that the reflectance spectrum increases gradually from 450 nm . The reflectance of complexes changes with different amounts of hesperidin. Low content of hesperidin results in higher reflectance and vice versa. For comparison, the reflectance spectrum for modified silica (AMS) is given.

CIELab values of studied complexes are given in Table 3. It can be seen that the amount of hesperidin has an

Fig. 4 FT-IR spectra of unmodified silica, modified silica, free hesperidin and hesperidin complex

Fig. 5 Percentage reductions in the absorbance of 2,2-diphenyl-2-picrylhydrazyl solution (% IC) in the presence of different amounts of free hesperidin and hesperidin complex. For comparison, % IC is given for the modified silica

Fig. 6 Reflectance spectra for hesperidin complexes (HESP-1, HESP-2, HESP-3) and modified silica (AMS)

Table 3 Color analysis of unmodified, modified (AMS) silica free hesperidin (HESP) and hesperidin complexes (HESP-1, HESP-2, HESP-3)

Sample	L*	a*	b*	Chroma	Hue (°)
Unmodified silica	87.9±0.2	−0.6±0.1	−0.3±0.2	1.2±0.1	−3.0±0.2
AMS	85.9±0.2	−0.5±0.1	−4.2±0.2	4.5±0.2	−2.6±0.2
HESP	72.4±0.1	−1.1±0.1	17.3±0.1	17.3±0.1	−86.3±0.2
HESP-1	68.5±0.2	3.4±0.1	33.4±0.1	33.5±0.2	81.2±0.2
HESP-2	63.5±0.3	3.6±0.1	32.6±0.1	31.8±0.1	83.6±0.2
HESP-3	59.7±0.3	3.8±0.2	29.5±0.1	29.8±0.2	83.8±0.1

$$\text{Chroma} = [(a^*)^2 + (b^*)^2]^{1/2}, \text{ Hue angle} = \tan^{-1} (b^*/a^*)$$

important effect on colorimetric properties. It is known that L^* indicates the specific brightness of the pigment from 0 (black) to 100 (white). Values of b^* greater than 0

represent yellow color. With these values, the values of hue angle (Hue°) and Chroma or saturation of the pigment were calculated. Hue angle value denotes 0 for redness, 90

for yellowness, 180 for greenness, and 270 for blueness. The Chroma of hesperidin-silica complexes was from 29.8 to 33.5 and the Hue angle from 81.2 to 83.6, which represents colors in the yellow region. It is consistent with the literature data. In the study evaluating the color of yellow pigments, an Hue angle of 84.37 was obtained, similar to that observed in this work [29]. Other investigation described by Venil et al. [30] show that the Hue angle for yellow pigment isolated from *Chryseobacterium* was 77.39. Lightness value (L^*) of hesperidin-silica complexes was found to be inversely correlated with the antioxidant activity values with the correlation coefficient of 0.994. This value could be a good indicator for the estimate of these products.

4 Conclusion

In this study, the method for preparation of complex between hesperidin and functionalized silica was developed. Presented investigations could play an important role to improvement the reported properties of hesperidin. The obtained material has been characterized and the antioxidant scavenging activity was evaluated. The analytical methods used, such as TG, UV-vis, FT-IR and potential zeta, show that the reaction took place and the expected product was obtained, although there are no noticeable morphological differences in the appearance of these samples. The color of the samples, whitish for silica and yellow for the hesperidin complex is a clear difference in appearance. The results of the CIELab color analysis and the reflectance spectra confirm these differences. The presented results lead to the following conclusions:

- The proposed method has facility to design the simple production of material with preferred properties
- The hesperidin complex has good stability as it appears from the zeta potential measurements
- The antioxidant properties of obtained complex has enhanced in comparison with free hesperidin

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest in this work.

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