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SHORT COMMUNICATION

A High-Yield Process for Extraction of Hesperidin from Orange (*Citrus sinensis* L. *osbeck*) Peels Waste, and Its Transformation to Diosmetin, A Valuable and Bioactive Flavonoid

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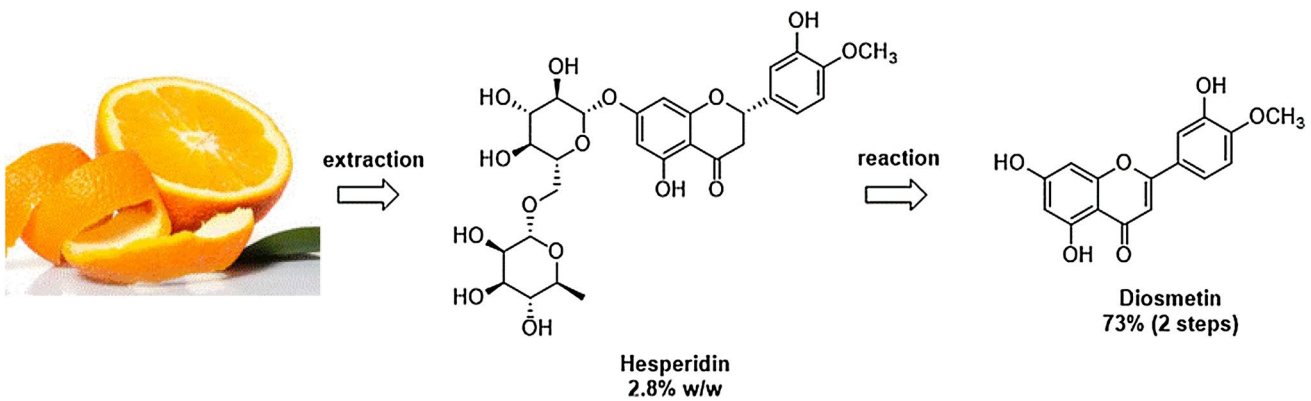
Abstract

An alternative and high-yield method to obtain hesperidin, a bitter flavored flavanone glucoside, from orange (*Citrus sinensis* L. *osbeck*) peels waste is described. The proposed process, which add high-value to this kind of residue from orange juice processing industry, was based on a successful modification applied to extraction of naringin from grapefruit. This method involves extraction with methanol and crystallization in water with addition of dichloromethane, requiring shorter times and reducing of volume of solvent employed. Changing to hot extraction with methanol of fresh orange albedo led to higher yields of extraction in half the time required due to the direct method, avoiding air-dried albedo step. Application of described method led to 2.8% yield (w/w dry albedo) of hesperidin extracted in 89.4% purity determined by HPLC analysis. To add high-value to the flavanone obtained, it was subject to chemical transformation (oxidation and hydrolysis, 83% and 88% yield, respectively) into the flavone diosmetin (73% yield for 2 steps), an expensive and naturally-occurring flavonoid in low yields which exhibits a wide range of pharmacological properties.

Graphic Abstract

This paper describes high-yield process for extraction of hesperidin from orange peels waste, and their use as feedstock in the production of diosmetin.



Keywords Orange waste · Hesperidin extraction · Flavonoid · Diosmetin · High-value by-product

Statement of Novelty

The novelty of this work lies on the valorization of waste of citrus processing from orange industry. Hesperedin and diosmetin exhibit biological properties as analgesic and

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anti-inflammatory, antihypercholesterolemic, antihypertensive and diuretic, neuroprotective, anticancer, antimicrobial and antioxidant, among others. In this context, the present study shows optimized methodology based on the information of previous studies of extraction of bioactive compounds. Three methodologies were applied on fresh albedo of orange waste, leading to 2.8% w/w yield of hesperedin, with shorter time and with better yields. The obtained natural product was transformed in two-steps sequence in diosmetin, a high-value product, with 73% yield. Due these results, the valorization of orange waste industry could be an attractive alternative, with value added insertion and good environmental management practices.

Introduction

Among processing fruits, the citrus industry plays an important role in the agro-industrial system. Brazil was responsible for 64% of world orange juice production in 2018/9 and 87% of its production was worldwide exported [1]. This industry generates significant amounts of discarded (peels, pulp and seeds) which brings a complex waste-disposal and economic burdens on production. Citruses (oranges, tangerines, mandarins, grapefruit, lemons and limes) are most abundant fruit crop worldwide with more than 100 million tons in 2018/9, of which about 30% was destined for industrial processing. After processing, the quantity of solid/semi-solid residue can reach 50–70% w/w of processed fruits, resulting in large amounts of biomass which has promising potential uses and developed novel strategies for extraction of bioactive compounds [2–6].

The citrus peel waste valorization without differentiating individual constituents is the most common way to process the biomass *Citrus* raw material. However, most profitable and environmentally friend employments for these wastes have been proposed recently, such as their utilization in biorefineries, energy production (bioethanol and biogas) and extraction procedures of added-value products [5]. The former compounds can be extracted from *Citrus* waste and be use as food additives, as pharmaceuticals and in cosmetic industry [4]. Due this, studies have been directed to these materials to isolate bioactive compounds of economic interest, besides their typical uses as raw material to agricultural uses or animal feedings [7].

Hesperidin (3′,5,7-trihydroxy-4′-methoxy-flavanone-7-rhamnoglucoside, Fig. 1) is the most abundant flavanone glycoside present in citrus peels, being a major component in rind tissues and it is characteristic of oranges. Its consumption may be associated with health benefits and in the prevention of many diseases. It exhibits biological properties as analgesic and anti-inflammatory [8], antihypercholesterolemic [9], antihypertensive and diuretic [10], neuroprotective [11, 12], cytotoxic against HEP-G2 cancer cells [13], among others.

Diosmetin (5,7,3′-trihydroxy-4′-methoxyflavone, Fig. 1) also known as methylluteolin is a bioflavonoid distributed in different plant species. This flavone exhibits different in vitro and in vivo bioactivities, including anticancer, antimicrobial, antioxidant, oestrogenic and anti-inflammatory activities, it also acts as a weak TrkB receptor agonist [14–16]. Today there is no natural source providing this compound with good yields, the latest API* average price for this compound is U$ 3,337/kg but the sales of this compound are no substantial due the prices. However, once orange peels are known to provide hesperidin, a flavanone glucoside, in good yields, it can be an important synthetic and inexpensive (API reference price U$ 3/kg) raw material inclusive for diosmetin synthesis.

Hesperidin is detected in sweet orange juice [17] and measured from edible part of different *Citrus* species [18], however peel (albedo plus flavedo) is richest source of the cited glycosylated flavonoid from sweet orange [19]. A subcritical water extraction of defatted orange peel reaches 2.0%, showing hesperidin yield 3.3-fold higher than that obtained by conventional extraction in Soxhlet apparatus. However, this method is not selective, due narirutin combined extraction [20]. Similarly, a citrus pulp of floater

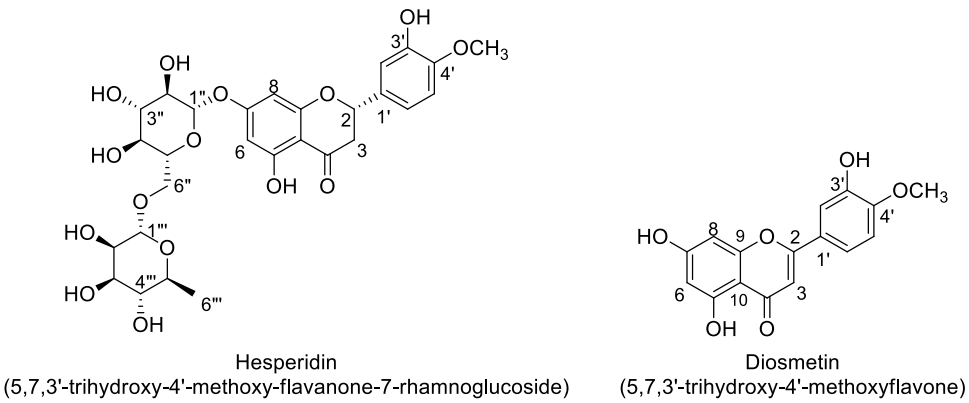

Fig. 1 Structures of hesperidin and diosmetin

(CFP), a solid residue obtained after fresh fruit squeezing, was employed as biomass resource to hesperidin mining. Soxhlet extraction with methanol followed recrystallization from DMSO/water resulting in 1.2% yield [21]. Treatment of orange peels with calcium hydroxide solution followed by microwave extraction furnished crude hesperidin, which requires purification to yielding 2.8% of pure compound [13]. Methanol extraction after petroleum ether refluxing within orange peels followed by purification led to 2.4% yield of hesperidin [22].

Recently was established that modification of known processes [23] to extract naringin from pomelo (*Citrus grandis*) allowed enhancement of extraction of same flavonoid from grapefruit (*Citrus x paradisi*) [24]. It was found by former authors that dichloromethane added during water crystallization step was crucial for efficient purification during naringin crystallization, but for the method to be efficient the albedo needed to be air dried for 3 days, followed by oven drying overnight, totaling 4 days of substrate preparation only in this step. Extraction and crystallization steps requiring more 6–7 days, leading to long time for whole process. Our group confirmed that use of fresh albedo and hot extraction with methanol reduced the time (from 10 to 3–4 days) and upgraded yields (from 2.2 to 4.1%) in the extraction method. Due these better results, we decided to employ a same successful strategy for the isolation and purification of hesperidin from wastes of sweet orange dry peels. Besides, in this work we also would like to display the transformation in good yields from hesperidin into diosmetin, a low abundance and high market value natural product.

Materials and Methods

Chemicals and Instruments

Methanol, ethanol, dichloromethane (all solvents from Hexis, Brazil), sulfuric acid (Aldrich Co., USA), and iodide (Merck, Germany) were commercially available and were used without further purification. Pyridine (Aldrich Co., USA) were treated with calcium hydride (Aldrich Co., USA), distilled and stored over 4 Å molecular sieves (Aldrich Co., USA). The reactions involving anhydrous solvents were carried out under argon atmosphere. Reactions were monitored by Silica TLC plates (Macherey–Nagel, Germany) through UV lamp viewing and/or developed with $KMnO_4$ solution on heating. ^1H NMR spectra were recorded at 400.15 MHz and ^{13}C NMR spectra at 100.04 MHz on a Bruker equipment mod. Avance DRX. Chemical shifts, given on the δ (ppm), were referenced to the residual, non-deuterated solvent. Liquid chromatograms were performed in a HPLC–UV system (Shimadzu©, Kyoto, Japan) with DAD scan range from 200 to 400 nm employing commercial octadecyl group (C18) column (Shim-pack PREP-ODS (H) KIT; 250.0 × 4.6 mm ID, 5 µm, Shimadzu). Infrared spectra were recorded as KBr discs on a Shimadzu FTIR spectrophotometer model IRAffinity-1S. Melting points were determined on a Microquímica MQAPF 301 hot plate apparatus and are uncorrected.

Oranges

Fresh oranges (*Citrus sinensis* L. *osbeck*) were purchased from a local market in Salvador (Bahia), Brazil, and they are originated from northeast Brazilian region.

Oranges Peels

The peel of oranges was hand-sliced, and pulp was discarded and, sequentially, the albedo (white spongy interior) was separated from flavedo (orange exterior). To perform dried experiments albedo was cut in small pieces (less than 1 cm) and air-dried for 2–3 days over an aluminum-foil in the laboratory, and then placed in an oven at 40 ºC overnight until constant weight. To not-dry extractions, fresh albedo was cut in small pieces (less than 1 cm) immediately after separation from flavedo and put it into methanol.

Hesperidin Extraction

Hesperidin isolation from dry and fresh albedos were carried out according method described in the literature [24] and already successfully used to improved naringin extraction from grapefruits, by methanol extraction followed by crystallization in water/dichloromethane. Methanol extractions were performed at room temperature and under heating. Each experiment was repeated at least three times. Hesperidin was characterized by physical and spectrometric data and comparison with the reported data in the literature.

Method A: Dry Albedo/Room Temperature Methanol Extraction

To 30.0 g of dry albedo in an Erlenmeyer flask were added 190 mL of methanol. After 3 days, the slurry was filtered, and the methanol was distilled off in a rotary evaporator under reduced pressure at 45 ºC. Water (20 mL) was added to methanolic extract obtained and sequentially the mixture was stirred at 60–70 ºC for 30 min before being transferred into a separating funnel. Dichloromethane (3 mL) was added and the mixture was transferred to a stoppered flask and left for 4 days at room temperature. The organic layer was removed off and the hesperidin crystals (298 mg, 1.0% yield) were collected by filtration through filter paper and dried in vacuum desiccator.

Method B: Dry Albedo/Hot Methanol Extraction

To 13.4 g of dry albedo in an Erlenmeyer flask were added 60 mL of methanol. The mixture was heated at 55 ºC for 3 h, the organic solvent was decanted and more 60 mL of methanol were added and new hot extraction during 30 min was carried out. The combined organic phases were combined, and methanol was distilled off in a rotary evaporator under reduced pressure at 45 ºC. Treatment of methanolic extract with water/dichloromethane and collection of another crop of hesperidin crystals (337 mg, 2.5% yield) were performed as described above.

Method C: Wet Albedo/Hot Methanol Extraction

To 55.0 g of fresh albedo in an Erlenmeyer flask were added 330 mL of methanol. The mixture was heated at 55 ºC for 3 h, the organic solvent was removed and more 100 mL of methanol were added, and new hot extraction was carried out. The combined organic phases were dried in a rotary evaporator under reduced pressure at 45 ºC. Treatment of methanolic extract with water/dichloromethane and collection of another crop of naringin crystals (518 mg, 2.8% based on estimated 18.2 g of dry albedo by 33.1 w/w %, see Table 1) were performed as described above.

Analytical Data for Hesperidin [22]

(Supplementary material, Figs. S1–S3): white solid, mp 250–254 °C [lit. 250–253 °C]; purity was determined to be 89.4% by HPLC analysis; IR (KBr disc, cm^{-1}): 3545, 3475, 2978, 2935, 2916, 1647, 1608, 1519, 1467, 1442, 1300, 1276, 1242, 1203, 1184, 1157, 1134, 1095, 1068, 1033; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 12.02 (*s*, 1H, OH-5), 9.08 (br. *s*., 1H, OH-3′), 6.94–6.89 (*m*, 3H, H-2′, H-5′and H-6′), 6.14 (*d*, *J* = 6.4 Hz, 2H, H-8 and H-6), 5.50 (*dd*, *J* = 12.2, 2.6 Hz, 1H, H-2), 5.17 (*t*, *J* = 5.5 Hz, 1H, H-1‴), 4.98 (*d*, *J* = 7.3 Hz, 1H, H-1″), 4.67 (*d*, *J* = 5.5 Hz, 1H, H-2‴), 4.59 (*d*, *J* = 3.5 Hz, 1H, H-6″), 4.53 (*s*, 1H, H-1), 4.46 (*d*, *J* = 5.5 Hz, 1H, H-4‴), 4.05–4.14 (m, 1H, H-3″ or 6″), 3.82 (br. s., 1H, H-4″), 3.78 (*s*, 3H, MeO-4′), 3.09–3.20 (*m,* 3H, H-3a), 2.78 (*dd*, *J* = 17.0, 2.6 Hz, 1H, H-3b), 1.09 (*d*, *J* = 6.1 Hz, 3H, H-6‴); ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 197.0 (C-4), 165.2 (C-7), 163.2 (C-5), 162.5 (C-10),

Table 1 Orange composition data and albedo weight loss on drying

Fruit	Fresh albedo		Dry albedo[a]		Flavedo		Pulp	
Grams	Grams	%[b]	Grams	%[a,b]	Grams	%[b]	Grams	%[b]
182.89	23.58	12.9	9.18	38.9	16.32	8.9	142.99	78.2
192.69	15.74	8.2	6.71	42.6	14.20	7.4	161.18	83.6
185.69	19.56	10.5	8.37	42.8	15.66	8.4	149.17	80.3
220.52	15.35	7.0	7.54	49.1	15.51	7.0	189.66	86.0
183.35	37.98	20.7	13.18	34.7	17.00	9.3	127.39	69.5
246.05	30.31	12.3	9.99	33.0	38.56	15.7	173.17	70.4
247.36	20.00	8.1	5.94	29.7	40.05	16.2	182.27	73.7
257.69	19.85	7.7	5.65	28.5	41.30	16.0	194.36	75.4
239.92	29.27	12.2	7.59	25.9	36.46	15.2	170.79	71.2
114.48	19.39	16.9	5.37	27.7	9.04	7.9	84.21	73.6
141.72	14.91	10.5	4.61	30.9	12.07	8.5	113.43	80.0
124.83	14.44	11.6	4.21	29.2	10.03	8.0	98.88	79.2
115.08	12.32	10.7	3.43	27.9	10.64	9.2	90.84	78.9
145.64	10.31	7.1	3.21	31.1	11.13	7.6	122.80	84.3
127.30	16.45	12.9	5.13	31.2	10.22	8.0	99.20	77.9
116.35	11.07	9.5	3.71	33.5	9.67	8.3	94.69	81.4
116.96	11.93	10.2	3.36	28.2	10.30	8.8	93.56	80.0
115.04	15.85	13.8	4.29	27.1	10.00	8.7	84.87	73.8
181.26	27.21	15.0	8.26	30.3	20.33	11.2	132.72	73.2
199.11	22.74	11.4	10.17	44.7	16.42	8.2	157.66	79.2
208.58	29.80	14.3	9.69	32.5	21.11	10.1	155.80	74.7
169.69	21.80	12.8	6.05	27.8	23.14	13.6	124.23	73.2
174.19c	**19.99c**	**11.5c**	**6.62c**	**33.1a,b,c**	**18.60c**	**10.7c**	**133.81c**	**76.8c**

[a]Related to fresh albedo after 2–3 days air dried follow by oven overnight

[b]w/w

[c]Average

148.0 (C-4′), 146.5 (C-3′), 130.9 (C-1′), 118.0 (C-6′), 114.2 (C-2′), 112.1 (C-5′), 103.3 (C-9), 100.6 (C-1‴), 99.5 (C-1″), 96.4 (C-6), 95.6 (C-8), 78.4 (C-2), 76.3 (C-5″), 75.6(C-3″), 73.0 (C-4‴), 72.1 (C-2″), 70.7 (C-4″), 70.3 (C-3‴), 69.6 (C-2‴), 68.3 (C-5‴), 66.1 (C-6″), 55.7 (MeO-4′), 42.1 (C-3), 17.9 (C-6‴).

High-Performance Liquid Chromatography (HPLC) Analysis for Hesperidin

(Supplementary material, Figs. S7, S8, Tables S1, S2): the purity of hesperidin was determined using a HPLC–UV system (Shimadzu©, Kyoto, Japan) equipped with binary pump LC-20AD XR, autosampler SIL 20A, column oven CTO-20A, DGU-20A3R degasser, controller system CBM-20A and a diode array detector (DAD) SPD-M20A. Was used for the separation commercial octadecyl group (C18) column (Shim-pack PREP-ODS (H) KIT; 250.0×4.6 mm ID, 5 µm, Shimadzu) and was processed collection data using the software LabSolutions 5.57 SP1. The mobile phase was a gradient elution system of A (HCOOH:H_2O = 0.1:100) and B (CH_3OH): 60% A, 40% B in the beginning for 20 min, linear gradient to 10% A, 90% B over 7 min and finally back to the initial conditions (equilibrating time was 10 min for each analysis). The injection volume for all samples was 5 µL (concentration 200 µg/mL). Flavonoids were monitored at 270 nm at a flow rate of 0.25 mL min^{-1} and the column temperature was 40 °C.

Synthesis of Diosmetin

The iodine (0.039 g, 0.15 mmol) was added to a solution of extracted hesperidin (0.100 g, 1.6 mmol) in dry pyridine (0.6 mL). The mixture was heated for 15 h at 95 °C, cooled to room temperature, and poured into ice. The resulting light-yellow solid was filtered, washed with saturated solution of sodium thiosulfate and water, respectively, and dried in a vacuum to afford 0.083 g of diosmin in 83% yield.

The hydrolysis was performed as described in the literature (Shan et al. 2008) [32]. The diosmin (0.052 g 0.08 mmol) was dissolved in ethylene glycol (1.22 mL) and concentrated H_2SO_4 (1 drop) was added. The mixture was heated in oil bath at 99 °C for 3 h and then cooled to room temperature. Next, 2 mL of crushed ice was added, and the crude product was filtered and purified by chromatography using ethyl acetate as solvent. It was obtained 0.022 g of diosmetin as a yellow solid in 88% yield, (73% overall yield).

Analytical Data for Diosmetin [25]

(Supplementary material, Figs. S4–S6): light yellow solid, mp 246–248 °C [Lit. 253–254 °C]; IR (KBr disc, cm^{-1}): 3417, 2919, 1667, 1610, 1566, 1421, 1261; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.58 (*dd*, *J* = 8.5, 1.7 Hz, 1H, H-6′), 7.47 (*d*, *J* = 1.7 Hz, 1H, H-2′), 7.12 (*d*, *J* = 8.5 Hz, 1H, H-5′), 6.78 (*s*, 1H, H-3), 6.51 (*d*, *J* = 1.5 Hz, 2H, H-8), 6.25 (*d*, *J* = 1.5 Hz, 2H, H-6), 3.91 (*s*, 3H, OMe-4′); ^{13}C NMR (DMSO-d_6,100 MHz): δ (ppm) 181.7 (C-4), 164.2 (C-7), 163.5 (C-2), 161.5 (C-5), 157.3 (C-9), 151.1 (C-4′), 146.8 (C-3′), 123.0 (C-6′), 118.7 (C-1′), 112.9 (C-2′), 112.1(C-5′), 103.7 (C-10), 103.5 (C-3), 98.9 (C-6), 93.9 (C-8), 55.7 (OMe-4′).

Results and Discussion

Orange (*Citrus sinensis* L. *osbeck*) is the most popular and consumed citrus around the world. Peel or rind is the exterior, being the flavedo the exterior orange/yellow part, and the albedo the white spongy constituent, and pulp or rag the edible part. As orange is the most widely-cultivated citrus worldwide, high variability of sizes/weight and composition is expected from different areas of production. Although albedo, flavedo and pulp are described as 17%, 10% and 73% of orange weight [4, 26, 27], in first approach we decided to separate the fruit in its constituents and took advantage to determine their percentage (Table 1). As expected, high variability of constituents was found. We also determine the average of weight loss in albedo drying, finding the value of 33.1% after 2–3 days air-drying follow by an oven-dry overnight.

With percentual of constituents assigned, we applied to isolation of hesperidin from orange same procedure previously employed for naringin extraction from grapefruit [24]. Accordingly, preliminary experiments were performed with room temperature extraction of dry albedo with methanol for 3 days, followed of isolation by filtration of the methanolic extract and solvent was distilled off under reduced pressure at 45 ºC in rotary evaporator. To the dry extract water was added and the mixture was heated at 70 ºC for 30 min before being transferred into an Erlenmeyer flask. Dichloromethane was added, and the mixture was swirled and left until crystallization of hesperidin (2–4 days). The organic layer was pulled off and crystals were collected by filtration and dried in desiccator on vacuum. This method allowed to obtain 1.0% of hesperidin extracted (see Table 2, Method A). Working on same direction of extraction of naringin from grapefruits, to reach higher yields and shorter times, we proposed a methanol extraction of dried-albedo at 55 ºC for 3 h, followed by separation of solvent from biomass and a new extraction with methanol. Despite the use of an extra amount of solvent, as it is recovered by distillation, there is no considerable increase in the costs of obtaining hesperidin. Solvent evaporation of combined organic phases followed by crystallization were completed in similar procedure as those described for method A. In addition to the decreasing in

Table 2 Yields of hesperidin extraction by different methods

Method A			Method B			Method C		
Dry albedo (g)	Hesper. (g)	Yield (%)	Dry Albedo (g)	Hesper. (g)	Yield (%)	Dry albedo (g)[a]	Hesper. (g)	Yield (%)
30.0248	0.3179	1.1	13.9647	0.3570	2.6	19.4393	0.5628	2.9
30.0194	0.3134	1.0	11.2240	0.2724	2.4	20.0355	0.7084	3.5
30.0029	0.2627	0.9	15.0010	0.3826	2.6	16.8523	0.3318	2.0
						16.5623	0.4707	2.8
30.0157b	**0.2980b**	**1.0b**	**13.3966b**	**0.3373b**	**2.5b**	**18.2224b**	**0.5184b**	**2.8b**

[a]Based on dry albedo and estimated from fresh albedo weighted by 33.1% w/w

[b]Average

extraction times, which resulted in a 3-days shorter process, higher mass content of hesperidin was observed, resulting in 2.5% yield (Method B, Table 2). More effectiveness of modification from room temperature to hot extraction was detected in hesperidin isolation from oranges when compared to naringin from grapefruits (1.0–2.5%, and 2.2–2.6%, respectively). Encouraged by higher enhancement in mass extraction of hesperidin and focused in the reduction of time and costs of whole process, we decided to accomplish the extraction of natural product on fresh albedo, avoiding the 3 days-drying steps, which was successfully applied with on the time and on yield of isolated naringin. However, in the situation of extraction of hesperidin from fresh albedo of oranges only a slightly higher yield was found (from 2.5 to 2.8% yield, based on 33.1% w/w loss of mass from fresh to dry albedo). It denotes a reduced gain on yields, but a shorter time-process was saved (Method C, Table 2). Finally, Method C means an enhancement of about 180% yield of hesperidin extracted compared to the Method A, besides shorter times of whole process (only 3–4 days for crystallization). Hesperidin was obtained with 89.4% purity by HPLC analysis. Considering the methodologies applied, statistical analysis of variance (ANOVA) was employed to determine the influence of the three extraction methods in the total content of hesperidin and the F-test was used to evaluate them. The calculated F values of 17.96 is much larger than the observed F critic (4.74). This showed differences between the methods and this statement can be confirmed by the $P < 0.05$ (see Supplementary Material).

To add value to the hesperidin obtained, its transformation into diosmetin was accomplished. This flavonoid is a natural polyphenol with several biological properties

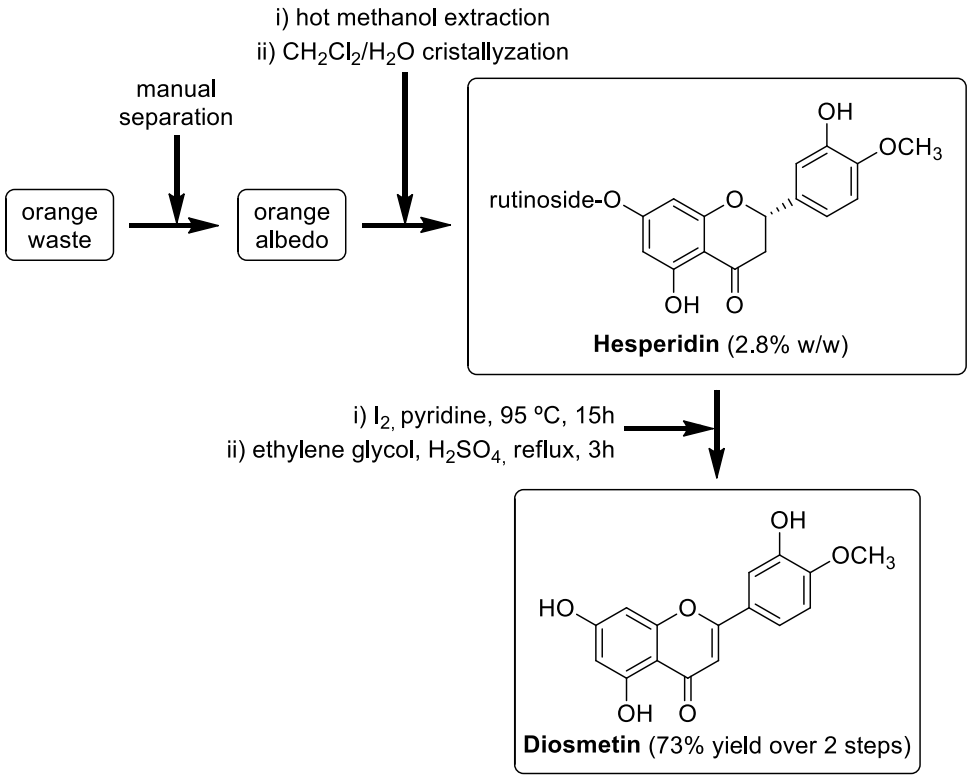

Fig. 2 Scheme of diosmetin synthesis from isolated hesperidin in 2 steps and 73% yield

and higher economic value (Fig. 2). A semisynthesis from a flavanone glycosylated natural product to its C2–C3 oxidized aglycone is found in the literature [25, 28–32]. While DDQ in refluxing 1,4-dioxane was employed in naringin oxidation [33], dehydrogenation of hesperidin is only performed with I_2/pyridine. Thus, oxidation of natural extracted hesperidin with iodide in pyridine at 95 ºC for 15 h furnished intermediary diosmetin in 83% yield. A second step of acid hydrolysis of rutinoside-glycoside moiety in hot ethylene glycol allowed diosmetin synthesis in 88% yield (73% yield in 2 steps).

Conclusion

In this communication, an alternative and efficient method to isolate hesperidin from orange waste (fresh albedo) was described, adding high-value to an underutilized biomass residue. The application of already developed methodology to extraction of naringenin from grapefruits, which involves extraction with methanol and crystallization in water with addition of dichloromethane, allowed furnishing of hesperidin in shorter times (3–4 days) and higher yields (2.8% yields, 89.4% purity by HPLC) through direct hot extraction with methanol of fresh albedo. To add value to the flavanone obtained, it was transformed into diosmetin by known methodology. Thus, this method proved to be robust, economical and reproducible, and can be used industrially for the extraction of hesperidin and its transformation into diosmetin. Besides, considering the Brazilian orange production used for processing (around 14.7 million tons in 2018/19) and its waste biomass, 15,700 tons of hesperidin or 5600 tons of diosmetin could be produced. That would have potential value of U$ 47.0 million in hesperidin or U$ 18 billion in diosmetin, allowing a green method of economic exploring of the orange wastes and also producing of natural bioactive compounds with high-economic value.

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