イチジク（*Ficus carica* L.）葉のフェニルプロパノイド組成

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Phenylpropanoid Composition in Fig (*Ficus carica* L.) Leaves

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The leaves of fig (*Ficus carica* L.) have been used for traditional and Chinese medicine. We determined the composition of phenylpropanoids (polyphenols and furanocoumarins) as a functional agent in the leaves of 37 cultivars of fig. The most abundant polyphenol was caffeoylmalic acid (12.0–26.6 mg/g dry weight), followed by rutin (4.7–14.6 mg/g dry weight) and isoschaftoside (2.5–6.4 mg/g dry weight). Psoralen (3.8–23.0 mg/g dry weight) was dominant in the furanocoumarins. In molar amounts, psoralic acid glucoside (PAG), a precursor of psoralen, was equivalent to psoralen. Furanocoumarins and PAG were not detected in the leaves of only one cultivar, Grise de Tarascon. Fig leaves are potentially an excellent source of polyphenols such as caffeoylmalic acid and rutin. From the result of cluster analysis, some cultivars that contained large amount of polyphenols, and a small amount (e.g., Grise de Saint Jean) or no (Grise de Tarascon) furanocoumarins, were found. These cultivars are considered suitable for functional foods or medicinal products.

Key words: fig leaf, polyphenol, caffeoylmalic acid, furanocoumarin, psoralen, psoralic acid glucoside

Introduction

Fig (*Ficus carica* L.) is a deciduous tree of the Moraceae family. Its fruit is usually eaten raw or is processed into food products, while its leaves are used in traditional and Chinese medicine[1-3]. Fig leaves have some medicinal properties, e.g., inhibition of postcibal increase in blood glucose in patients with type 1 diabetes mellitus[4], reduction of blood glucose and cholesterol levels in diabetic rats[5], reduction of blood triglyceride levels[6] and inhibition of inflammation[7] in rats.

Phenylpropanoids are secondary metabolites and include polyphenols, coumarins and lignans. Polyphenols in particular are regarded as pharmacological agents. However, furanocoumarins have been shown to cause photodermatitis. Therefore, it is important to elucidate the composition of phenylpropanoids in plants when used in food and medicine. We have previously identified some phenylpropanoids, i.e., caffeoylmalic acid (CMA), rutin and isoschaftoside (ISS) as major polyphnenols, psoralen and bergapten (5-methoxypsoralen) as major furanocoumarines, and psoralic acid glucoside (PAG) as a precursor of psoralen, in the leaves of five fig cultivars[8].

Some beneficial effects for health have been reported for major fig leaf polyphenols. A decrease of blood glucose level in type II diabetic rats[9], prevention of retinal damage in streptozotocin-induced diabetic rats[10], and palliation of cerebral ischemia disorder in rats[11] were reported for rutin. CMA and CMA-containing plant (*Corydalis lutea*) extract reduced acetylcholine-induced contraction of rat isolated ileum[12], and CMA may therefore have antispasmotic activity. Extracts from nettle (*Urtica dioica*), a CMA-rich plant[13], showed the possibility of antiurolithiatic activity in rats[14]. Inhibition of lung inflammation induced by lipopolysaccharide in mice is reported for ISS[15].

Photodermatitis have been reported from the fig tree, caused by contact of fig furanocoumarins with the skin[16, 17]. There is a report that oral administration of 15 mg per person (body weight 63–85 kg) of xanthotoxin (8–methoxypsoralen), an analog of psoralen and bergapten, induced photodermatitis[18]. Xanthotoxin is also administered orally in psoralen ultraviolet A therapy for psoriasis or vitiligo (the dose is 0.5–0.6 mg/kg body weight)[19, 20]. Therefore, ingestion of fig furanocoumarins has the potential to induce photodermatitis. On the other hand, psoralen and bergapten exhibit no inhibitory effect of cytochrome P450 3A, one of the important enzymes in intestinal drug

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metabolism[21]. Therefore, the possibility of interference with drug bioavailability by ingestion of fig furanocoumarins is estimated to be low.

As there are several hundred cultivars of figs[22], it is necessary to investigate a large number of cultivars to evaluate the characteristics of fig leaves. The objective of this study was to elucidate the varietal diversity of the phenylpropanoid composition of fig leaves in 37 cultivars, and to evaluate their potential as functional food or medicinal products.

Results and Discussion

Polyphenol composition

The content of CMA, rutin and ISS are shown in **Table 1**. CMA content varied from 12.0–26.6 mg/g dry weight (DW) (18.2 mg/g DW on average), rutin content varied from 4.7–14.6 mg/g DW (9.6 mg/g DW on average), and ISS content varied from 2.5–6.4 mg/g DW (4.0 mg/g DW on average). The average content of CMA, rutin and ISS was 61.4, 15.8 and 7.1 μmol/g

Table 1. Content of phenylpropanoids (mg/g DW) in the leaves of 37 fig cultivars

Cultivar	CMA	Rutin	ISS	Psoralen	Bergapten	PAG
Group 1[a]						
Violette de Sollies	20.6 ± 0.6	11.4 ± 0.4	4.3 ± 0.1	23.0 ± 0.5	5.0 ± 0.1	42.2 ± 0.9
PR Bordeaux[b]	12.0 ± 0.6	9.1 ± 0.6	3.2 ± 0.1	19.9 ± 0.9	2.4 ± 0.1	38.7 ± 1.2
Short Bridge	18.2 ± 0.3	7.5 ± 0.2	3.8 ± 0.1	16.6 ± 0.3	1.6 ± 0.0	33.2 ± 0.4
Lisa	18.7 ± 0.2	10.7 ± 0.1	4.6 ± 0.0	17.4 ± 0.4	1.7 ± 0.0	32.5 ± 0.3
Dalmatie	15.5 ± 0.7	5.7 ± 0.3	2.5 ± 0.1	18.2 ± 0.9	2.0 ± 0.1	30.5 ± 2.0
Noire Sucre	21.7 ± 0.5	13.5 ± 0.3	4.7 ± 0.1	15.1 ± 0.3	3.3 ± 0.1	26.7 ± 0.6
Noire de Caromb	20.7 ± 0.4	13.4 ± 0.4	4.1 ± 0.1	15.7 ± 0.4	2.1 ± 0.1	30.2 ± 0.7
California Black	19.7 ± 0.5	7.6 ± 0.3	4.6 ± 0.1	13.2 ± 0.4	1.7 ± 0.0	28.8 ± 0.1
Group 2						
Grise de Tarascon	12.0 ± 0.1	10.5 ± 0.1	3.8 ± 0.0	ND[c]	ND	ND
Group 3						
White Genoa	19.0 ± 1.1	12.1 ± 0.9	4.4 ± 0.1	3.9 ± 0.1	0.4 ± 0.0	6.6 ± 0.3
Horaishi	17.6 ±0.3	11.3 ± 0.2	4.2 ± 0.1	3.8 ± 0.0	0.8 ± 0.0	6.7 ± 0.2
Grise de Saint Jean	23.2 ± 0.2	12.3 ± 0.1	3.6 ± 0.0	4.6 ± 0.1	0.6 ± 0.0	8.6 ± 0.3
Grise Bifere	26.6 ± 0.6	13.0 ± 0.4	4.4 ± 0.1	5.4 ± 0.1	0.6 ± 0.0	10.0 ± 0.0
Sugar	15.2 ± 0.5	5.8 ± 0.2	4.0 ± 0.0	6.5 ± 0.2	0.4 ± 0.0	13.0 ± 0.5
Goutte d'Or	17.7 ± 0.4	7.4 ± 0.1	3.0 ± 0.0	5.4 ± 0.1	1.0 ± 0.0	10.2 ± 0.3
Peau Dure	20.4 ± 0.2	10.2 ± 0.1	4.8 ± 0.1	6.7 ± 0.0	1.0 ± 0.0	12.3 ± 0.6
Daw Low	22.5 ± 0.5	13.7 ± 0.3	5.0 ± 0.1	7.1 ± 0.2	1.1 ± 0.0	12.8 ± 0.4
Kadota	18.7 ± 0.1	8.7 ± 0.1	3.8 ± 0.1	7.0 ± 0.1	1.1 ± 0.0	14.0 ± 0.6
Black Mission	18.2 ± 0.3	7.3 ± 0.1	3.3 ± 0.0	6.7 ± 0.1	0.9 ± 0.0	15.9 ± 0.4
Group 4						
Zebra Sweet	21.8 ± 0.6	12.1 ± 0.3	4.1 ± 0.1	11.0 ± 0.2	2.3 ± 0.1	19.1 ± 0.3
Bellone	20.8 ± 0.3	8.0 ± 0.2	3.9 ± 0.1	11.0 ± 0.2	2.2 ± 0.0	20.7 ± 0.7
Panachee	23.2 ± 0.5	11.9 ± 0.2	4.5 ± 0.1	9.7 ± 0.1	2.2 ± 0.0	15.7 ± 0.3
Negro Largo	22.0 ± 0.1	9.2 ± 0.0	4.3 ± 0.1	9.2 ± 0.0	2.1 ± 0.0	17.0 ± 0.6
Reculver	18.4 ± 0.6	9.8 ± 0.4	4.5 ± 0.1	12.4 ± 0.2	1.4 ± 0.0	22.5 ± 0.0
Bourjassotte Grise	18.6 ± 0.5	14.6 ± 0.5	4.5 ± 0.1	11.4 ± 0.3	1.4 ± 0.0	21.9 ± 0.6
White Ischia	16.5 ± 0.6	8.3 ± 0.3	4.7 ± 0.2	11.0 ± 0.5	0.6 ± 0.0	18.0 ± 0.8
Masui Dauphine	16.6 ± 0.6	9.7 ± 0.4	3.3 ± 0.1	10.2 ± 0.5	1.4 ± 0.1	18.0 ± 1.4
Brunswick	17.2 ± 0.4	8.0 ± 0.2	3.8 ± 0.1	9.9 ± 0.3	0.7 ± 0.0	18.7 ± 0.1
Brown Turkey	16.0 ± 0.0	8.1 ± 0.1	4.0 ± 0.0	9.3 ± 0.2	0.8 ± 0.0	17.8 ± 0.4
Pastiliere	19.0 ± 0.3	9.3 ± 0.1	3.8 ± 0.0	10.0 ± 0.4	1.9 ± 0.1	17.3 ± 0.6
Portogallo	15.7 ± 0.2	4.7 ± 0.2	3.6 ± 0.0	10.8 ± 0.1	0.6 ± 0.0	20.4 ± 0.3
White Adriatic	16.8 ± 0.2	9.2 ± 0.1	3.4 ± 0.0	8.0 ± 0.1	0.9 ± 0.0	17.8 ± 0.5
Wase Dauphine	15.1 ± 0.7	7.8 ± 0.4	2.9 ± 0.1	7.7 ± 0.4	1.2 ± 0.0	15.5 ± 0.4
Athene	16.3 ± 0.2	9.9 ± 0.2	3.6 ± 0.1	8.6 ± 0.1	1.3 ± 0.0	14.4 ± 0.4
Negronne	14.4 ± 0.7	7.2 ± 0.4	3.5 ± 0.1	9.2 ± 0.3	1.1 ± 0.0	15.4 ± 0.6
Mission	13.6 ± 0.2	5.3 ± 0.1	3.1 ± 0.0	8.6 ± 0.1	0.6 ± 0.0	15.8 ± 0.1
Celeste	13.2 ± 0.4	11.8 ± 0.3	6.4 ± 0.1	10.9 ± 0.1	1.3 ± 0.0	19.7 ± 0.4

Content was determined by High-Performance Liquid Chromatography with Diode-Array Defection. Values are mean ± standard deviation (n = 3)
DW dry wight

[a] Groups and the order of cultivar name by cluster analysis shown in Fig. 2

[b] Precoce Ronde de Bordeaux

[c] ND Not detected

DW, respectively. The CMA content was approximately 4- and 8.6-fold greater than rutin and ISS, respectively.

The CMA content has been measured in other plant leaves, and was found to be 1.4–2.4 mg/g fresh weight (FW) in red clover (*Trifolium pretense*)[23] and 1.4–3.3 mg/g FW in nettle[13]. In our results, the CMA content of fig leaves was equivalent to 2.4–5.3 mg/g in fresh weight. Thus, fig leaves are likely to contain more CMA than nettle or red clover. Buckwheat is known to be a rutin-rich edible plant. Previous reports demonstrated that the rutin content of common buckwheat (*Fagopyrum esculentum*) was 13.7–35.9 mg/g DW in the seeds, and 1.9–3.6 mg/g DW in the leaves of 27 cultivars[24]. From our results, the rutin content of fig leaves seems to be higher than the buckwheat leaves, and to be comparable to the buckwheat seeds. The content of ISS and its isomer schaftoside was reported to be 0.013 and 0.68 (mg/g DW), respectively, in the root of *Arisaema erubescens*[25]. The ISS content in the peel of banana passion fruit (*Passiflora tripartite*) was reported to be 0.63 (mg/g DW)[26]. Compared with these reports, the ISS content of fig leaves was observed to be higher. The above results show that fig leaves are potentially an excellent source of polyphenols such as CMA and rutin.

Furanocoumarin composition

The content of psoralen, bergapten and PAG are shown in **Table 1**. These three compounds were not detected in the leaves of the cultivar Grise de Tarascon. Therefore, in the following results, we only describe 36 cultivars, excluding Grise de Tarascon. Psoralen content ranged from 3.8–23.0 mg/g DW (10.4 mg/g DW on average), bergapten content ranged from 0.4–5.0 mg/g DW (1.4 mg/g DW on average), and PAG content ranged from 6.6–42.2 mg/g DW (19.4 mg/g DW on average). Psoralen was the most abundant furanocoumarin in the fig leaves. Moreover, in molar amounts, the content of psoralen (molecular weight 186.17) was equivalent to PAG (molecular weight 366.30) content (**Fig. 1**).

The furanocoumarin content of other plants used for foods or medicines has been measured. For example, celery (*Apium graveolens*) is known to contain 0.001–3.9 μg/g FW of psoralen, 0.002–28 μg/g FW of bergapten and 0.02–17.9 μg/g FW of xanthotoxin[27–29]. Examples of herbal medicines include the root of Japanese angelica (*Angelica acutiloba*) which was shown to contain 0.001–0.2 mg/g DW of psoralen, 0.004–0.15 mg/g DW of bergapten, and 0.007–1.2 mg/g DW of xanthotoxin[30]; the root of *Glehnia littoralis* which was shown to contain 0.4–0.8 mg/g DW furanocoumarin (sum of 7 furanocoumarins including psoralen, bergapten and xanthotoxin)[31]; and the fruit of *Angelica archangelica* which was shown to contain 14.0–31.6 mg/g DW furanocoumarin (sum of 8 furanocoumarins including bergapten and xanthotoxin)[32]. The furanocoumarin content of the fig leaves is quite high compared to celery, so fig leaves should not be ingested as much as vegetables like celery. Compared to herbal medicines, the furanocoumarin content of the fig leaves is not significantly high. However, it is safer to select cultivars with a low as possible furanocoumarin content for food or medicinal use.

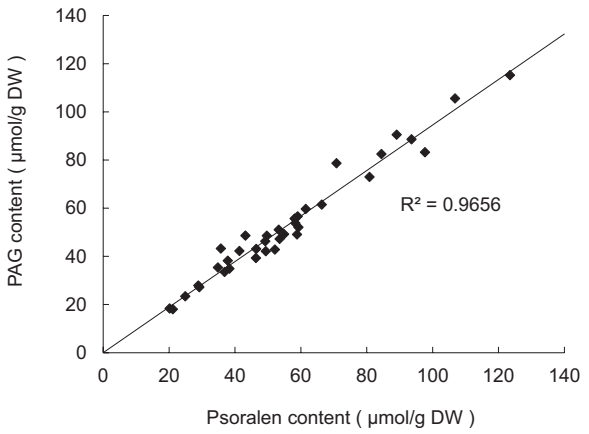

Fig. 1 Relationship between psoralen and PAG content in the leaves of 36 fig cultivars (Grise de Tarascon was excluded). The content is expressed in molar amount

The PAG content of some edible or medicinal plants has also been studied. The dried fruit of *Psoralea corylifolia*, an ingredient of the Chinese medicine 'Buguzhi', contained 3–30 mg/g DW within 23 commodities[33]. The PAG content in fig leaves appears to be equal to or greater than the fruit of *P. corylifolia*. The furanocoumarin and PAG content of fig leaves was higher than many edible plants. Moreover, the psoralen content of fig leaves can be potentially doubled by hydrolysis of PAG. Therefore, it is important to note that fig leaves have a high furanocoumarin content when used for edible or medicinal use.

Grise de Tarascon did not contain psoralen, bergapten or PAG. Only Grise de Tarascon is San Pedro-type of fig (pollination is required for development of the second crop fruit) while the other 36 cultivars are the common type of fig (pollination is not necessary). This trait may be associated with the furanocoumarin composition; however, additional investigation is required to understand the lack of furanocoumarins in the Grise de Tarascon cultivar.

Cluster analysis

Hierarchical cluster analysis was carried out on the phenylpropanoid composition of fig leaves as μmol/g DW, converted from the weights shown in Table 1 (**Fig. 2**). PAG was treated as furanocoumarin in the cluster analysis. Thirty seven cultivars were divided into 2 clusters by similarity (correlation coefficient) 0.000. Eight cultivars were included in Group 1, which contained a higher amount of furanocoumarins than polyphenols. The other cultivars were divided into two clusters with similarity 0.064. Group 2 consisted of only Grise de

Tarascon and was characterized by the lack of furanocoumarins. The characteristics of the 10 cultivars in Group 3 was that the content of polyphenols was the same or larger than the content of furanocoumarins. Four cultivars (Grise Bifere, Grise de Saint Jean, Horaishi, and White Genoa), were further divided by similarity 0.635 in Group 3, and contained polyphenols at twice the amount of furanocoumarins. Eighteen cultivars were included in Group 4; this group contained furanocoumarins at the same or larger amount as polyphenols. This characteristic was similar to Group 1, but contained less phenylpropanoids than Group 1.

Among the examined cultivars in this study, those in Group 3 and 2 can be considered suitable for use as a functional food or medicinal product due to their higher content of polyphenols and lower or no furanocoumarin content compared to the other groups. The average content of psoralen and bergapten in Group 3 cultivars was 5.7 mg/g DW and 0.8 mg/g DW, respectively. From the above-mentioned references[18-20], the oral intake dose of xanthotoxin is 0.2–0.6 mg/kg body weight (BW) per day to induce photodermatitis. Assuming that psoralen and bergapten causes photodermatitis at the same dose as xanthotoxin, the allowable oral intake amount for the leaves of Group 3 cultivars is estimated to be < 0.03–0.09 g DW/kg BW per day. Moreover, fig leaves contain PAG, a precursor of psoralen. In order to decide the allowable amount accurately, it is necessary to investigate PAG metabolism. On the other hand, Grise de Tarascon has a low CMA content, but has no risk of furanocoumarins, so more can be ingested than Group 3 cultivars.

Experimental

Plant material

Thirty-seven cultivars of fig cultivated in our orchard (Kawanishi, Hyogo, Japan) were used in this study. From mid-June to early July, the leaves at the nodes from the tip of the shoot to the fifth node were obtained. After washing with water,

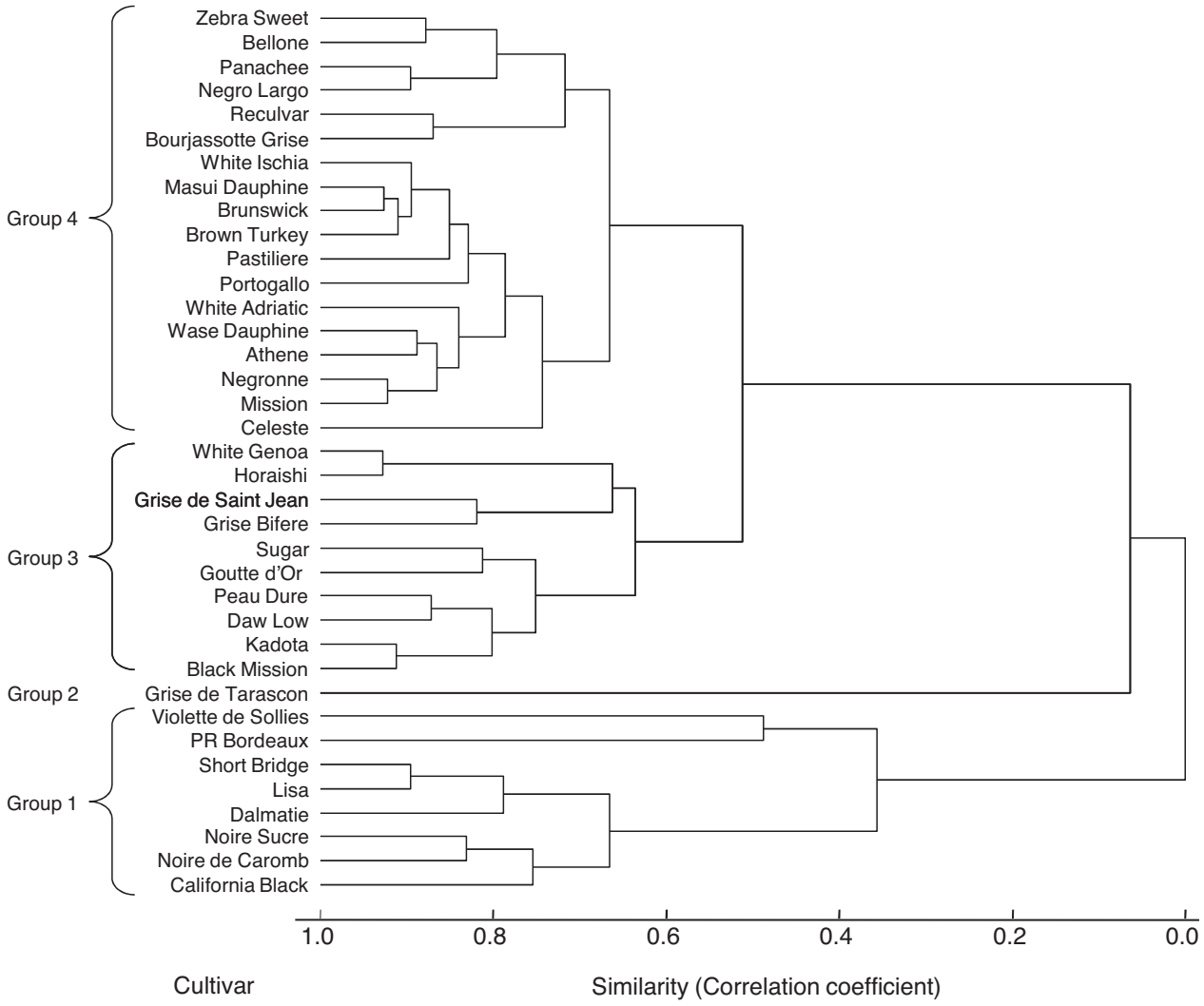

Fig. 2 Dendrogram of cluster analysis of 37 fig cultivars by leaf phenylpropanoid composition. Cluster analysis was carried out by Pirouette (Infometrix, Bothell, WA, USA). Distance metric: Euclidean distance. Linkage method: group average method

the leaves were cut with a ceramic kitchen knife into 1.5– cm squares. The leaves were packaged in a polyethylene bag with nitrogen gas and stored at −80 ºC until use.

Preparation of leaf extract

Fig leaf extracts were prepared as previously described[8]. In brief, the frozen leaves were freeze-dried and pulverized to powder. Leaf powder (0.2 g) and 30 mL of extractant, mixture of water/methanol/acetone (1/1/1, v/v) for polyphenols and furanocoumarins, or methanol for PAG, were placed in an Erlenmeyer flask and shaken in a circular motion for 3 h at room temperature. After centrifugation, the supernatant was collected. The residue was resuspended in 10 mL of extractant and centrifuged again under the same conditions. This process was repeated and the collected supernatant was combined. The volume of extract was adjusted to be 50 mL with extractant.

Quantification of individual phenylpropanoids

The phenylpropanoid content was measured according to our previous report[8]. In brief, a model 1100 High-performance Liquid Chromatography–Diode Array Detector system (Agilent Technologies, Santa Clara, CA, USA) and a Synergi™ Hydro-RP column (100 × 3 mm, 2.5 µm particle size; Phenomenex, Torrance, CA, USA) were used for separation. Mobile phase A was water/acetic acid (98:2, v/v) and B was acetonitrile/water/acetic acid (50/49.75/0.25, v/v). The gradient began with 10% B, increasing to 24% B at 8 min, 30% B at 16 min, 55% B at 24 min, 100% B at 30 min, 100% isocratic B from 30–33.2 min, 10% B at 34 min and 10% isocratic B to 36 min. The flow rate of the mobile phase was 0.4 mL/min. The temperature of the column oven was 40 °C. CMA and ISS were detected at an absorbance of 320 nm. Rutin, psoralen, bergapten and PAG were detected at an absorbance of 250 nm. The content was expressed per dry weight. On the other hand, the moisture content of the leaves of five cultivars (Dalmatie, Masui Dauphine, Negronne, Panachee, Precoce Ronde de Bordeaux) preliminarily measured was approximately 80% on average. In comparison with other plants, this value was extrapolated to calculate the content per fresh weight (1 g of DW is equivalent to 5 g of FW).

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