

Bioavailability, antioxidant and biological properties of the natural free-radical scavengers cyanidin and related glycosides

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Summary. Cyanidin and its glycosides (Cy and Cyg) have been indicated as promising candidates as dietary compounds with a potential role in human health. They are the largest class of water-soluble compounds in plants, where they are responsible for the brilliant color (red, orange, blue) of fruits and flowers. As natural compounds of several foods such as vegetables, fruits and red wines, they are estimated to be widely ingested by humans. This paper, basing on the data previously reviewed in 2002, focuses on the findings regarding human and animal studies on Cy and Cyg absorption and metabolism, antioxidant activity and biological properties, with particular attention to anti-carcinogenic activity, vasoprotective, anti-inflammatory, anti-obesity and anti-diabetes effects. It is concluded that although Cy and Cyg bioavailability is low, further investigations are necessary because some important metabolites may still not have been identified. Literature data on antioxidant activity and biological properties, however, widely confirm Cy and Cyg as dietary compounds with a potential beneficial role in human health.

Key words: cyanidin, cyanidin glycosides, biological properties, antioxidant activity.

Riassunto (*Biodisponibilità e proprietà biologiche dell'antiossidante naturale cianidina e dei suoi derivati glicosidici*). Il ruolo potenzialmente benefico per la salute umana espresso dalla cianidina e dai suoi derivati glicosidici (Cy e Cyg) è confermato da un crescente numero di dati in letteratura. Queste molecole rappresentano la più larga classe dei composti idrosolubili nelle piante, nelle quali sono responsabili del colore brillante (rosso, arancione, blu) dei frutti e dei fiori. Essendo contenuti in diversi alimenti come vegetali, frutti e vini rossi, si stima che siano ampiamente assunti con la dieta umana. Il presente articolo, partendo dai dati precedentemente raccolti nel 2002, focalizza la propria attenzione sulle scoperte riguardanti studi su uomini ed animali inerenti l'assorbimento e il metabolismo di Cy e Cyg, la loro attività antiossidante e le proprietà biologiche, con particolare attenzione alla attività anticarcinogenica, vasoprotettiva, antinfiammatoria, anti obesità ed anti diabetica. Dai risultati analizzati si evince che non è ancora possibile trarre conclusioni definitive sulla biodisponibilità delle cianidine in quanto alcuni importanti metaboliti potrebbero non essere ancora stati identificati. I dati relativi all'attività antiossidante e alle proprietà biologiche, tuttavia, confermano ampiamente il ruolo della cianidina e dai suoi derivati glicosidici come composti dietetici con un ruolo potenzialmente benefico per la salute umana.

Parole chiave: cianidina, glicosidi della cianidina, proprietà biologiche, attività antiossidante.

INTRODUCTION

The anthocyanins (Greek *antos*, flower and *kyanos*, blue) are part of the very large and widespread group of plant constituents known collectively as flavonoids. They are water-soluble glycosides of polyhydroxy and polymethoxy derivatives of 2-phenylbenzopyrylium or flavylium salts. In fruits and vegetables there are six basic anthocyanin compounds.

The differences between individual anthocyanins are the number of hydroxyl groups in the molecule; the degree of methylation of these hydroxyl groups, the nature, number, and location of sugars attached to the molecule; and the number and the nature of aliphatic or aromatic acids attached to the sugars in the molecule [1-3]. All these variables account for the large number of compounds belonging to the

Table 1 | Human studies of cyanidins bioavailability

Source	Cy and Cyg	Ingested amount (mg)	Plasma C _{max} (nmol/L)	Plasma T _{max} (h)	Urinary excretion (% of intake)	Urine T _{max} (h)	Duration of urinary collection (h)	References
Elderberry extract	Cy 3-samb, Cy 3-glc	720			0.077		4	[15]
Blackcurrant juice	Cy 3-rut,	716-1239		~ 0.75	0.048-0.072		4	[7]
Blackcurrant concentrate	Cy 3-rut, Cy 3-glc	188			0.064	≈ 2	7	[6]
Boysenberry concentrate	Cy 3-glc, Cy 3-soph	344			0.029	≈ 2	7	[6]
Elderberry juice concentrate	Cy 3-samb, Cy 3-glc	3570			0.053	≈ 1	5	[8]
Elberberry extract	Cy 3-samb, Cy 3-glc	147	~ 27	1.5	0.37	1.5	7	[25]
Blackcurrant juice	Cy 3-rut	145	~ 5.7	1	0.04	1.5	7	[25]
Purple sweet potato beverage	Acylyated Cy	311	~ 2.3	~1.5	0.01-0.03 ^a		24	[9]
Purple carrots	Acylyated Cy glycosides	416	5.8	~ 2	0.030	≈ 4	24	[12]
Blackberries	Cy 3-glc	418			0.16	2-4	24	[18]
<i>Hibiscus sabdariffa</i> extract	Cy 3-samb	147	~ 5.6	1.5	0.018	1.5	7	[5]
Freeze-dried black raspberries	Cy 3-rut, Cy 3-ylrut	1440	~ 56	1-2.5	0.032-0.045 ^a	0-4	12	[14]
Chokeberry extract	Cy 3-gal, Cy -3-ara	721	96	2-4	0.15	3-4	24	[19]
Elderberry juice	Cy 3-samb, Cy 3-glc	361-722	~ 95	~ 1	0.033-0.040 ^a	0.5-1.5	7	[13]
Concentrated elderberry juice	Cy 3-samb, Cy 3-glc	3570			0.06	0.50	24	[11]

Cy: cyanidin. a: depending on the cyanidin considered in the mixture.

anthocyanin family and allow the researchers to study fingerprints of many different vegetables species, just on the basis of their anthocyanin composition. They are of great nutritional interest because of the marked daily intake (180 to 215 mg/day in the United States) [2], which is much higher than the intake (23 mg/day) estimated for other flavonoids, including quercetin, kaempferol, myricetin, apigenin, and luteolin [2]. They have been reported to have positive effects in the treatment of various diseases [3] and are prescribed as medicines in any countries. The anthocyanin-health properties are due to their peculiar chemical structure, as they are very reactive towards reactive oxygen species (ROS) because of their electron deficiency. In the last years, great attention was given to the possible protection exerted by natural antioxidants present in dietary plants, particularly flavonoids and polyphenols, towards tissue injury mediated by ROS. Anthocyanins are included in the list of natural compounds known to work as powerful antioxidants. Since cyanidin and its glycosides (collectively: Cy and Cyg) represent one of the major groups of naturally occurring anthocyanins their antioxidant and biological properties have been deeply investigated [4] and recent findings, indicating the possibility that anthocyanins are absorbed as glycosides, have renewed the interest for the studies on their bioavailability, including their absorption, metabolic fate and excretion. Cy are considered the widest spread anthocyanin in the plant kingdom. They are largely distributed in the human diet through crops, beans, fruits, veg-

etables and red wines, suggesting that we daily ingest significant amounts of these compounds from plant-based diets. Various authors, using different analytical methods, have reported the presence of Cy in many fruits and vegetables. However, almost the totality of the studies does not report quantitative estimation of Cy and Cyg [4].

BIOAVAILABILITY

Human studies

Basing on the data review by Galvano *et al.* [4], the results of a literature survey since 2002 on Cy and Cyg bioavailability in humans are presented in Table 1. In the studies here reported, single doses of 188-3570 mg total Cyg were given to the volunteers, most often in the form of berries, berry extracts, or juices. After such intakes, maximal plasma anthocyanin concentrations were very low, on the order of 2.3-96 nmol/L. The mean time to reach these concentrations was around 1.5 hour. Most studies reported very low relative anthocyanin urinary excretions, ranging from 0.018 to 0.37%. Maximal urinary Cy excretion is usually achieved in less than 4 h. The most striking features of these surveys are thus that Cyg are very quickly absorbed and urinary excreted and that the fraction of orally administered Cy excreted in urine is very low.

Many studies have only detected unchanged anthocyanin glycosides in both plasma and urine [5-14]. However, these last years, methylated derivatives, anthocyanidin glucuronide conjugates as well as an-