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A perspective on phenolic compounds, their potential health benefits, and international regulations: The revised Brazilian normative on food supplements

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Abstract

Phenolic compounds possess a myriad of health benefits, thus making them potential ingredients for the procurement of food supplements. Anvisa, Brazil's national regulatory body, has recently revised the regulation on food supplements and only a few phenolic compounds (chlorogenic acid, rutin, proanthocyanidins, and α-tocopherol) have been mentioned. Despite several scientific evidences on the bioactivity of phenolics, especially concerning their antioxidant activity, Anvisa does not authorize any claims for supplements containing these compounds, except for α-tocopherol, which was mentioned as "vitamin E". The upper limit doses allowed for the phenolics appear to be lower than what the literature suggests as necessary to achieve potential health benefits and might be prohibitive for supplements available in the international market. Moreover, Brazilian sources of phenolic compounds are not listed in the Normative Instruction (NI) as authorized ingredients for supplements. The Brazilian NI on food supplements has moved forward, but it is still limited.

Keywords: Normative Instruction (NI) N° 28; Flavonoids; Tocopherols; Brazil; Phenolic acids.

1. Introduction

Brazil's National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*–Anvisa) is a regulatory body linked to the country's Ministry of Health. The agency is responsible for the supervision and approval of food, cosmetics, tobacco, pharmaceuticals, health services, medical devices, among others. In addition, food supplements, which are regulated by the Normative Instruction (NI) N° 28 from July 26th, 2018, fall under the Anvisa's scope. The normative establishes the list of components, limits of usage, claims, and labeling for food supplements (Agência Nacional de Vigilância Sanitária, 2019a). Recently, Anvisa updated the information contained in NI N° 28 and created a tool (Agência Nacional de Vigilância Sanitária, 2019c) that enables anyone to easily track each authorized ingredient for this type of product.

The tool created by Anvisa is a set of interactive tables separated by ingredient category (e.g., bioactive substances, protein, fibre, enzymes, among others). It provides details regarding the lower and upper limits for each nutrient/bioactive substance/enzyme according to age group and individual condition (e.g., pregnant and breastfeeding women). There are also tables specifying the authorized ingredients that can be used to provide the target compounds, as well as their function, specifications, allowed claims and requirements to produce them, requisites for complementary labels as well as other relevant information (Agência Nacional de Vigilância Sanitária, 2019c). The objective is to facilitate the access to information about food supplements to agencies connected to the National System of Health Surveillance, manufacturers, and

final consumers.

It is not uncommon to find supplements that are legally commercialized in other countries but do not fall under the revised Brazilian regulation. This may be explained by the different approaches regarding food regulation in each country. In the United States, for example, the manufacturer is entirely responsible for the safety of food supplements, their efficacy, and health claims. Regulatory agencies monitor the products in the market, interfering when the product's safety is not adequate. Food companies that put consumers' health at risk may suffer severe consequences. In Brazil, the approach is focused on the prevention of risk exposure. Therefore, a mandatory registration under Anvisa's rules is required before the product reaches the market. Usually, the incidents reported are associated with the commercialization of illicit products. If manufacturers intend to use an ingredient that is not specified in the NI, they should submit a petition to Anvisa to get the approval. Currently, depending on its complexity, Anvisa may take about 55 days to reach a decision on a petition (Agência de Vigilância Sanitária, 2019b).

2. Phenolics compounds as bioactive substances

Phenolic compounds are secondary metabolites, with one or more hydroxyl groups on the aromatic ring(s). They are widely studied due to their potential beneficial health effects, such as antioxidant, anti-inflammatory, anti-microbial, and cardioprotective properties (Shahidi et al., 2019). Therefore, as bioactive substances, they can be used in the formulation of food supplements. More than 8,000 phenolic compounds have been reported in the literature (de Camargo et al., 2018). However, as specified in the bioactive substances section (Table 1), Anvisa mentions the use of only some phenolics, namely chlorogenic acid, rutin, proanthocyanidins and α-tocopherol, this latter as "vitamin E". The list of approved ingredients that can be used as sources of such substances is shown in Table 2. Due to the importance of phenolic compounds for food supplements formulation, one should explore in more detail the aspects concerning the revised NI. Accordingly, the rationale behind the limits established, approved claims, as well as the scientific support about the potential health benefits associated with them will be discussed. A quick comparison with similar regulations from other countries will be addressed.

2.1. Chlorogenic acid (CGA)

The term CGA corresponds to a wide range of compounds generated via condensation of the carboxy group of *trans*-caffeic acid with the 3-hydroxy group of quinic acid. Figure 1 shows the basic chemical structure of CGA and other phenolic compounds addressed in NI N° 28. CGA exhibits antioxidant activity due to the presence of vicinal hydroxyl groups on the aromatic ring, allowing the donation of hydrogen atoms to reduce free radicals. Each chlorogenic acid subgroup possesses several isomers (Celli and de Camargo, 2019). In green coffee beans, for example, the predominant isomer (3-(3,4-dihydroxycinnamoyl)quinic acid) accounts for 76-84% of the total CGA content (Liang and Kitts, 2016). Coffee is the primary source of chlorogenic acid in nature, with green coffee beans presenting around 5-12 g CGA/100 g on a dry weight basis (DW) while a cup of 200 mL of standard brewed coffee has 0.07-0.35 g (Farah et al., 2008).

Coffee and coffee-based products are subjects of a fair number of studies associating the intake of CGA with health-promoting

Table 1. List of phenolic compounds for food supplements authorized by Anvisa's Normative Instruction (NI N° 28) from July 26th, 2018

Phenolic compound	0-6 months	7-11 months	1-3 years old	4-8 years old	9-18 years old	+19 years old	Breastfeeding women	Pregnant women	Observations
Chlorogenic acid	Not allowed	Not allowed	Not allowed	Not allowed	Not allowed	Min: Not established Max: 0.12 mg	Not allowed	Not allowed	–
Rutin	Not allowed	Not allowed	Not allowed	Not allowed	Not allowed	Min: Not established Max: 0.6 mg	Not allowed	Not allowed	–
Proanthocyanidins	Not allowed	Not allowed	Not allowed	Not allowed	Not allowed	Min: Not established Max: 7.5 mg	Not allowed	Not allowed	–
Vitamin E	Not allowed	Not allowed	Min: 0.9 mg Max: 200 mg	Min: 1.05 mg Max: 300 mg	Min: 2.25 mg Max: 600 mg	Min: 2.25 mg Max: 1,000 mg	Min: 2.85 mg Max: 800 mg	Min: 2.25 mg Max: 800 mg	As α-tocopherol. α-Tocopherol includes RRR-α-tocopherol, the only α-tocopherol form that naturally occurs in food., and the 2R-stereoisomers of α-tocopherol (RRR-, RSR-, RRS-, and RSS-α-tocopherol) that occur in fortified foods and supplements. Considering the commercially available synthetic form (rac-α-tocoferyl) with an activity of 0.67 x RRR-α-tocopherol, considering 1 IU of vitamin E as 1 mg of acetate of rac-α-tocoferyl.

Source: Adapted from Agência Nacional de Vigilância Sanitária (2019c).

Table 2. List of source ingredients of bioactive compounds for food supplements authorized by Anvisa's Normative Instruction (NI N° 28) from July 26th, 2018

Authorized Component	CAS	Specifications	Function	Authorized claims and requirements to make them	Requirements for Complementary Labelling and other	Other information
Tomato hydrosoluble concentrate (*Lycopersicon esculentum*)		For this component, the approved specifications belong to the following manufacturers: C.A.S. S.p.A – Verona – Italy; Hans Zipperle AG/S.p.A – Merano – Italy; Indena S.A.S. – Tours – France	Source of chlorogenic acid	No claims	The warning "This product should not be consumed by pregnant and breastfeeding women and children" must be written on the label.	–
Tomato hydrosoluble concentrate (*Lycopersicon esculentum*)		For this component, the approved specifications belong to the following manufacturers: C.A.S. S.p.A – Verona – Italy; Hans Zipperle AG/S.p.A – Merano – Italy; Indena S.A.S. – Tours – France	Source of rutin	No claims	The warning "This product should not be consumed by pregnant and breastfeeding women and children" must be written on the label.	–
Powdered cranberry (*Vaccinium macrocarpon*)		For this component, the approved specifications belong to the following manufacturer: Naturex – DBS LLC – Sagamore – Massachusetts – USA	Source of proanthocyanidins	No claims	The warning "This product should not be consumed by pregnant and breastfeeding women and children" must be written on the label.	–
Propolis extract		Normative Instruction N° 3, DE from January 19th, 2001	Source of phenolic compounds	No claims	The warning "This product should not be consumed by pregnant and breastfeeding women and children" must be written on the label.	–
Powdered guarana (*Paulinia cupana*)		These components must follow the specifications evaluated and approved by ANVISA.	Source of caffeine	1) Claim: Caffeine enables an elevated state of alert and improves the concentration. Requirements: this claim is exclusive for the dietary supplements in which the caffeine content meets the minimum amount established by IN 28/2018–Appendix III. 2) Claim: Caffeine improves endurance and performance during endurance physical activities. Requirements: this claim is exclusive to the dietary supplements in which the caffeine content is 200 mg, consumed 1 h prior to the physical activity.	The warning "This product should not be consumed by pregnant and breastfeeding women and children" must be written on the label.	–
Dextroalphatocopherol acetate/D-alpha-tocopherol acetate	58-95-7	FCC 6 FCC 10 ADOPTED: February 10th, 2016 PUBLISHED: March 2nd, 2016 doi: 10.2903/j.efsa.2016.4412	Source of Vitamin E	1) Claim: Vitamin E is an antioxidant that helps protect against the damages caused by free radicals. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III 2) Claim: Source of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III.	No additional requirements.	–

Table 2. List of source ingredients of bioactive compounds for food supplements authorized by Anvisa's Normative Instruction (NI N° 28) from July 26th, 2018 - *(continued)*

Authorized Component	CAS	Specifications	Function	Authorized claims and requirements to make them	Requirements for Complementary Labelling and other	Other information
				3) Claim: Rich in/High content of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content corresponds to the double of the minimum amount established in IN 28/2018–Appendix III, since it does not surpass the maximum amount established in the Appendix IV.		
DL-alpha-tocopherol acetate/rac-alpha-tocopherol acetate/DL-alpha-tocopheryl acetate	7695-91-2	ADOPTED: February 10th, 2016 PUBLISHED: March 2nd, 2016 doi: 10.2903/j.efsa.2016.4412 European pharmacopoeia 9.0	Source of Vitamin E	1) Claim: Vitamin E is an antioxidant that helps protect against the damages caused by free radicals. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III 2) Claim: Source of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III. 3) Claim: Rich in/High content of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content corresponds to the double of the minimum amount established in IN 28/2018–Appendix III, since it does not surpass the maximum amount established in the Appendix IV.	No additional requirements.	–
Dextro-alpha-tocopherol/D-alpha-tocopherol	59-02-9	European pharmacopoeia 9.0 FCC 6 Prepared at the 55th JECFA (2000) and published in FNP 52 Add 8 (2000), superseding tentative specifications prepared at the 30th JECFA (1986) and published in FNP 37 (1986) and in FNP 52 (1992). A group ADI of 0.15-2 mg/kg bw for dl-alpha-tocopherol and d-alpha-tocopherol, concentrate, singly or in combination, was established at the 30th JECFA (1986).	Source of Vitamin E	1) Claim: Vitamin E is an antioxidant that helps protect against the damages caused by free radicals. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III 2) Claim: Source of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III. 3) Claim: Rich in/High content of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content corresponds to the double of the minimum amount established in IN 28/2018–Appendix III, since it does not surpass the maximum amount established in the Appendix IV.	No additional requirements.	–

Table 2. List of source ingredients of bioactive compounds for food supplements authorized by Anvisa's Normative Instruction (NI N° 28) from July 26th, 2018 - *(continued)*

Authorized Component	CAS	Specifications	Function	Authorized claims and requirements to make them	Requirements for Complementary Labelling and other	Other information
DL-alpha-tocopherol	10191-41-0	Prepared at the 30th JECFA (1986), published in FNP 37 (1986) and in FNP 52 (1992). Metals and arsenic specifications revised at the 61st JECFA (2003). A group ADI of 0.15-2 mg/kg bw for dl-alpha-tocopherol and d-alpha-tocopherol, concentrate, singly or in combination, was established at the 30th JECFA (1986). European pharmacopoeia 9.0 FCC 10	Source of Vitamin E	1) Claim: Vitamin E is an antioxidant that helps protect against the damages caused by free radicals. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III 2) Claim: Source of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III. 3) Claim: Rich in/High content of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content corresponds to the double of the minimum amount established in IN 28/2018–Appendix III, since it does not surpass the maximum amount established in the Appendix IV.	No additional requirements.	–
Mixture of tocopherols		FCC10 Prepared at the 30th JECFA (1986), published in FNP 37 (1986) and in FNP 52 (1992). Metals and arsenic specifications revised at the 61st JECFA (2003). A group ADI of 0.15-2 mg/kg bw for dl-alpha-tocopherol and d-alpha-tocopherol, concentrate, singly or in combination, was established at the 30th JECFA (1986).	Source of Vitamin E	1) Claim: Vitamin E is an antioxidant that helps protect against the damages caused by free radicals. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III 2) Claim: Source of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III. 3) Claim: Rich in/High content of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content corresponds to the double of the minimum amount established in IN 28/2018–Appendix III, since it does not surpass the maximum amount established in the Appendix IV.	No additional requirements.	–
Acidic succinate of D-alpha-tocopheryl	893081	European pharmacopoeia 9.0 FCC 10	Source of Vitamin E	1) Claim: Vitamin E is an antioxidant that helps protect against the damages caused by free radicals. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III 2) Claim: Source of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III. 3) Claim: Rich in/High content of vitamin E.	No additional requirements.	–

Table 2. List of source ingredients of bioactive compounds for food supplements authorized by Anvisa's Normative Instruction (NI N° 28) from July 26th, 2018 - *(continued)*

Authorized Component	CAS	Specifications	Function	Authorized claims and requirements to make them	Requirements for Complementary Labelling and other	Other information
				Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content corresponds to the double of the minimum amount established in IN 28/2018–Appendix III, since it does not surpass the maximum amount established in the Appendix IV.		
Acidic succinate of DL-alpha-tocopheryl	17407-37-3	European pharmacopoeia 9.0	Source of Vitamin E	1) Claim: Vitamin E is an antioxidant that helps protect against the damages caused by free radicals. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III 2) Claim: Source of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III. 3) Claim: Rich in/High content of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content corresponds to the double of the minimum amount established in IN 28/2018–Appendix III, since it does not surpass the maximum amount established in the Appendix IV.	No additional requirements.	–
Acidic succinate of D-alpha-tocopheryl-polyethylene glycol-1000		USP NF 34	Source of Vitamin E	1) Claim: Vitamin E is an antioxidant that helps protect against the damages caused by free radicals. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III 2) Claim: Source of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content meets the minimum amount established in IN 28/2018–Appendix III. 3) Claim: Rich in/High content of vitamin E. Requirements: this claim is exclusive to the dietary supplements in which the vitamin E content corresponds to the double of the minimum amount established in IN 28/2018–Appendix III, since it does not surpass the maximum amount established in the Appendix IV.	No additional requirements.	–

Source: Adapted from Agência Nacional de Vigilância Sanitária (2019c).

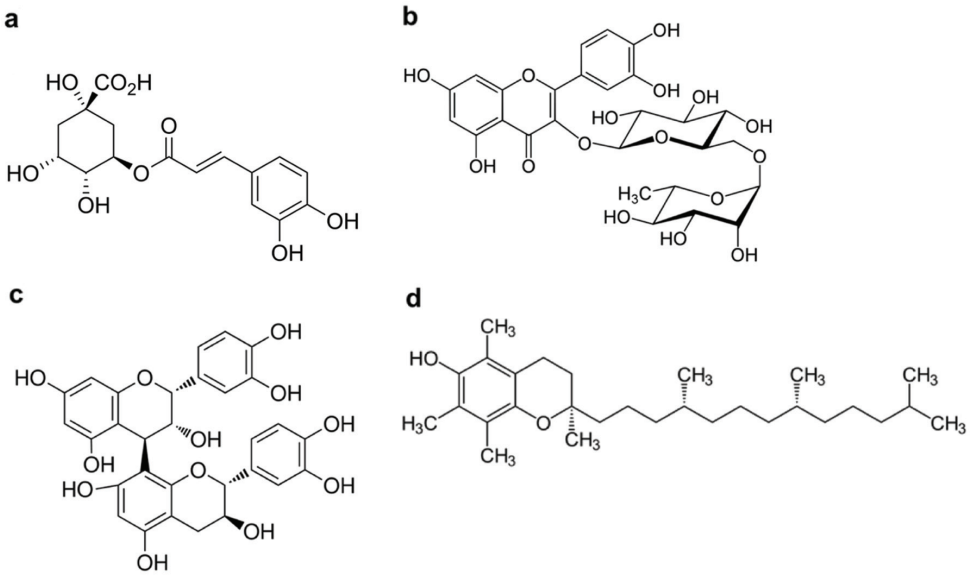

Figure 1. Chemical structures of phenolic compounds mentioned in the Brazilian Normative Instruction N° 28. (a) chlorogenic acid, (b) rutin, (c) procyanidin B2, and (d) α-tocopherol.

effects (Naveed et al., 2018). Johnston et al. (2003) observed anti-obesity and anti-diabetic properties promoted by CGA when administering coffee (caffeinated and decaffeinated, 0.88 g CGA/L) to nine healthy volunteers. According to these authors, this was due to the fact that CGA inhibits the activity of hepatic glucose-6-phosphatase, reducing glucose release, as well as diminishing the glucose absorption in the small intestine via inhibition of glucose-6-phosphate translocase 1. The reduced amount of glucose in the blood circulation decreased insulin activity, which led to burning excessive adipose tissue.

The antioxidant and anti-inflammatory properties of CGA have also been investigated. A study by Zhao et al. (2008) using Caco-2 cell line model verified that this phenolic acid was capable of inhibiting oxidative stress-induced secretion of interleukin-8 (IL-8), a chemokine associated with the initiation of pro-inflammatory responses, in human intestinal epithelial cells *in vitro*. A dose-dependent response was observed, and the highest bioefficacy was found in cells exposed to 0.7 g/L. Kozuma et al. (2005) also verified a dose-dependent relationship between the administration of CGA-rich green coffee bean extracts and antihypertensive effects. In a human trial involving 117 male volunteers, the administration of 93 and 185 mg of extract (50.22 and 100 mg of CGA, respectively) was capable of reducing both systolic and diastolic blood pressures. Furthermore, adverse effects on hematological parameters and/or blood chemistry were not observed.

Judging by the studies presented, chlorogenic acid seems to be responsible for a myriad of health benefits. Therefore, it is indeed an unusual choice that the revised regulation does not mention any claims associated with the intake of chlorogenic acid (Table 2), not even its well-reported antioxidant properties (Celli and de Camargo, 2019; Kamiyama et al., 2015; Yao et al., 2019). In addition, Table 2 only suggests tomato hydrosoluble concentrate as an approved source ingredient for the manufacture of CGA-based supplements. Tomato is indeed a rich source of CGA, showing concentrations ranging from 14.31 to 32.84 mg/kg on a fresh weight (FW) basis (Martínez-Valverde et al., 2002). However, coffee remains the major source of this phenolic compound. Furthermore, Brazil is among the most important suppliers of coffee. Therefore, due to its potential as a source of CGA and economic importance, coffee would be the most reasonable choice as a source ingredient in the development of CGA-based supplements.

Furthermore, the outcome of studies (Johnston et al., 2003; Zhao et al., 2008) investigating the health benefits of CGA suggest that in order to efficiently act as an antioxidant, anti-inflammatory, anti-obesity, and anti-diabetic factor, the dosage of CGA needs to be around 700-880 mg/L of coffee/coffee extract, much higher than the upper limit established by the regulation (0.12 mg). This raises the question if the approved maximum CGA dosage (Table 1) would be sufficient to promote the full range of health benefits.

In comparison with regulations from other countries, the Brazilian one is stricter regarding the limit of usage, and it lacks detailed information. The European Food Safety Authority (EFSA) released in 2011 a scientific opinion on the use of coffee and coffee extracts as a source ingredient in CGA-based supplements. It was suggested that coffee extract should be limited to a maximum of 400 mg/day, containing 45% CGA (180 mg/day). According to EFSA (2011a), the proposed claims "chlorogenic acids from coffee extract contributes to keeping normal blood glucose levels" and "chlorogenic acids from coffee extract have a beneficial effect on glucose/insulin metabolism" are allowed.

Coffee extract (as a source of CGA) is also included in the U.S. Department of Health and Human Services list as an approved ingredient for the manufacture of food supplements aiming weight loss and/or weight management. However, the agency states that clinical trials on the efficacy of CGA for weight reduction are limited and of poor methodological quality. Additionally, some safety concerns have been reported in a few studies when the coffee extract dosage was above 200 mg/day (U.S. Department of Health and Human Services, 2019).

2.2. Rutin

Rutin is a glycoside form of quercetin (Ganeshpurkar and Saluja, 2017). Its chemical structure is shown in Figure 1. Some issues concerning other phenolic compounds, such as rutin, are

also noticeable when one analyzes the revised Anvisa regulation. Some of the primary sources of this phenolic include capers (332 mg/100 g FW), black olive (45.36 mg/100 g FW), and buckwheat (36.14 mg/100 g FW) (Inocencio et al., 2000; Romani et al., 1999; Vlahov, 1992; Oomah and Mazza, 1996; Holasova et al., 2002; Steadman et al., 2001; Dietrych-Szostak and Oleszek, 1999). Nevertheless, neither of these sources are listed by Anvisa amongst the approved ingredients (as rutin sources) for the development of rutin-based supplements. Furthermore, rutin has been found in fruits, including orange peels (Gosslau et al., 2019; Omoba et al., 2015). Therefore, as an important orange producer, the Brazilian industry would benefit if orange peel extract could be included as a natural source of rutin.

Similar to what was addressed for chlorogenic acid, tomato hydrosoluble concentrate appears as the only authorized source ingredient for rutin (Table 2). This phenolic compound has been shown to possess *in vivo* antioxidant activity in a 6-week clinical trial (Boyle et al., 2000) with 18 female volunteers. The administration of a supplement containing 500 mg of rutin was able to elevate plasma flavonoids and decrease endogenous oxidation of pyrimidines. Rutin has also been associated with antidiabetic and antihypertensive effects. In another clinical trial (Sattanathan et al., 2011), 40 patients with type 2 diabetes mellitus (40-60 years old) received tablets with 500 mg of rutin daily over 120 days. By the end of the trial, the subjects presented lower blood sugar levels and reduced systolic and diastolic blood pressures.

Once again, the maximum dose established by Anvisa appears to be an issue that needs to be addressed. The regulation limits rutin to 0.6 mg, much lower than the dose administered in the clinical trials that presented favorable outcomes. A scientific opinion released by EFSA in 2010, recommends the use of rutin as an antioxidant compound, allowing a daily dosage of up to 300 mg, which is 50 times higher than the value indicated by Anvisa. The same document also acknowledges that, given the available scientific data, rutin may have beneficial physiological effects by counteracting protein-induced, lipid-induced, and DNA-induced oxidative damage. The agency allows the claims "a strong antioxidant that protects the body's cells from the harmful effects of free radicals" and "improves the immune system" to be used in the label of rutin-based supplements (European Food Safety Authority, 2010a). In contrast, the revised version of Anvisa's regulation does not cite any approved claim for this substance.

2.3. Proanthocyanidins (PACs)

PACs are also present in the revised regulation. This phenolic class of compounds, also known as condensed tannins, includes dimeric, polymeric or oligomeric flavonoids. Procyanidins are composed of catechin and epicatechin, while prodelphinidins contain (epi) gallocatechin in their structures (de Camargo et al., 2015). Cocoa is a rich source of proanthocyanidins (119.78 mg catequin eviquivalent (CE)/100 g of cocoa powder), with procyanidin B2 (Figure 1) as the major compound (Tomas-Barberán et al., 2007). Peanuts are sources of proanthocyanidin A while grape is a rich source of proanthocyanidin B (de Camargo et al., 2017; Ma et al., 2014; de Camargo et al., 2014; de Camargo et al., 2015; de Camargo et al., 2016). Therefore, PACs type B are amongst the major polyphenols in red wine, grape juice, and other grape-based products and by-products (de Oliveira et al., 2017; Toscano et al., 2017; da Silva et al., 2015).

According to the literature (de Camargo et al., 2014), grape by-products from juice and winemaking are sources of different forms of PACs, namely free (26.6–68.1 mg CE)/g and 20.2–23 mg CE g, respectively), esterified (7.22–17.1 mg CE/g and 25–45.6 mg CE/g, respectively), and insoluble-bound (91.3–142 mg CE/g and 85.7–145 mg CE/g, respectively), depending on the grape variety. Furthermore, PAC-rich extracts (also composed of other phenolics) were able to inhibit copper-induced LDL-cholesterol (LDL-c) oxidation *in vitro* (de Camargo et al., 2014). The presence of oxidized LDL-c has been accepted as a biomarker that indicates a risk factor for the development of cardiovascular diseases (Amarowicz, 2016), while DNA-damage signaling and repair are crucial pathways to the etiology of most, if not all, human cancers (Khanna and Jackson, 2001). The same study (de Camargo et al., 2014), reported the protection of DNA against oxidation induced by peroxyl radicals. Both *in vitro* biological assays correlated with total phenolics and proanthocyanidin contents of the test sample, which suggests a dose-dependent relationship between PACs and specific health-promoting effects.

PACs were also found in high amounts in peanut skin (free soluble = 20.33–36.25 mg CE/g, esterified = 0.91–4.34 mg CE/g, and insoluble-bound = 1.33–3.03 mg CE/g) (de Camargo, et al., 2015) and guarana seeds extract (free soluble = 13.1-60.5 mg/g, depending on the extraction solvent) (Majhenič et al., 2007). Powdered guarana has been approved by Anvisa as a source of caffeine. However, guarana possesses many other bioactive compounds, including PACs, that exhibit *in vitro* and *in vivo* health-promoting effects. In fact, their potential anticancer, antioxidant, antihyperglycemic and anti-obesity effects have recently been reported (da Silva et al., 2019).

Like coffee, which has not been mentioned as a source of CGA, and despite of their well-documented potential as sources of PACs, grapes, peanuts, cocoa, guarana, and their processing by-products are not mentioned in the new version of the Brazilian regulation (Agência Nacional de Vigilância Sanitária, 2019c) as approved sources of PACs. Instead, cranberry powder is the mentioned ingredient for this purpose (Table 2). Cranberries are indeed rich sources of PACs, with 4.18 mg CE/g of fruit DW (Kruger et al., 2014). Therefore, establishing them as the source ingredient for PACs is coherent in countries (e.g., USA, Canada, and Chile) with a considerable production of this feedstock (FAOSTAT, 2017). However, Brazil is not known as a producer of cranberries. Therefore, indicating national sources of PACs would be expected.

EFSA also recognizes grape seeds extract as a source of PACs. A scientific opinion from 2010 recommends a dose of 25–50 mg PAC/day and proposes a variety of claims, such as "helps improve the general aging process, protecting skin from environmental stress" and "scientifically proven mix of naturally occurring antioxidants that work in synergy helping protect cells from free radical damage" (European Food Safety Authority, 2010b). The Brazilian regulation does not bring any authorized claim for PACs-based supplements, as it is the case for other phenolic compounds (Table 2).

2.4. Tocopherols and tocotrienols

The only phenolic class addressed in the revised version of the regulation comprises tocopherols, generically called vitamin E in the normative. This group consists of eight fat-soluble monophenols. They are composed of a chromanol ring carrying a hydroxyl group. The chromanol ring is bound to a hydrophobic side chain, responsible for differentiating between tocopherols and tocotrienols (Figure 1). In tocopherols, the side chain is completely saturated, whereas, in tocotrienols, there are three double bonds at carbons 3′, 7′, and 11′. Tocopherols and tocotrienols each have four possible homologs (α, β, γ, δ), determined by the number and

Table 3. α-Tocopherol content of common and specialty oils

Oil	Concentration (mg/100 g of oil)
Almonds	nd–34.9
Barley	14.2–20.1
Brazil nuts	nd–2.2
Camelina	2.81–3.80
Cashew	nd–7.84
Coconut	0.20–1.82
Corn	18.0–25.7
Cottonseed	30.5–57.3
Grape	11.8–18.8
Hazelnut	15.7–42.1
Linseed	0.54–1.20
Macadamia	0.08–0.11
Olive	11.0–17.0
Palm	6.05–42.0
Peanut	8.86–30.4
Pecan	nd–1.82
Pine	2.2–16.6
Pistachios	nd–32.8
Rapeseed	18.9–24.0
Rice bran	0.73–15.9
Safflower	36.7–47.7
Sesame	0.24–36.0
Soybean	9.53–12.0
Sunflower	32.7–59.0
Walnut	nd–3.80
Wheat germ	151–192

Source: Adapted from Shahidi and de Camargo (2016) and de Camargo et al. (2019). nd, non-detected.

position of methyl groups on the chromanol ring (Shahidi and de Camargo, 2016). This phenolic class is well-known for its capacity to donate a hydrogen atom to stabilize free radicals (Kamal-Eldin and Appelqvist, 1996). Thus, they are widely used to protect oils and lipid-rich foods against oxidation (Shahidi and de Camargo, 2016; Kamal-Eldin and Appelqvist, 1996). The homologs have different levels of vitamin E activity. α-Tocopherol has the highest vitamin E activity due to the presence of α-tocopherol transfer protein (α-TTP) in the liver, which facilitates the absorption of this specific form (Kamal-Eldin and Appelqvist, 1996).

Tocopherols and tocotrienols (tocols) are mainly found in vegetable oils (Table 3). Wheat germ oil is the most abundant source of α-tocopherol (151–192 mg/100 g of oil) and β-tocopherol (31.2–65 mg/100 g of oil). Sunflower oil is also rich in α-tocopherol (32.7–59 mg/100 g of oil), while palm and soybean oil, the most produced vegetable oils worldwide, have significant amounts of γ-tocotrienol (11.3–36 mg/100 g of oil) and γ-tocopherol (61–69.9 mg/100 g of oil), respectively (Shahidi and de Camargo, 2016).

The different forms of vitamin E are associated with a variety of health-promoting effects. A supplementation with α-tocopherol at doses ranging from 400 to 800 IU/day showed a 20% decrease of fatal myocardial infarction, as evidenced by a meta-analysis that evaluated randomized clinical trials (Loffredo et al., 2015). γ-Tocopherol (300 mg) also had a positive impact on cardiovascular diseases (Christen et al., 1997). Tocotrienol homologs have displayed anticarcinogenic effects in breast cancer cell lines, while anti-diabetes and anti-obesity effects have also been widely observed both for tocopherol and tocotrienol homologs (Shahidi and De Camargo, 2016). However, tocotrienols are not mentioned in the revised version of the normative instruction, even though γ-tocotrienol is abundant in soybean (61.0-69.0 mg/100 g of oil) (de Camargo et al., 2019), one of the major commodities produced in Brazil.

EFSA acknowledges the scientific evidence on these benefits and proposes an array of claims that range from "helps memory and perception retention, especially in the elderly" to "due to vitamin E favorable effects on free radicals it could support reducing the age-related cognitive decline." These claims, however, can never suggest that such supplements are able to prevent or cure diseases (European Food Safety Authority, 2010b). A similar approach is taken by Health Canada, which states that selling vitamin E with the purpose of preventing diseases, including cardiovascular ailments and cancer, is not permitted. The agency considers 40 IU a normal dose of vitamin E while 400 IU is considered a "high dose" or "megadose" and explains that 15 mg of α-tocopherol/day corresponds to 22 IU (from natural sources) or 33 IU (from synthetic sources). Canadian regulation establishes a maximum daily intake of 1,000 mg for any form of vitamin E (Health Canada, 2019). This is also the upper limit for individuals over 19 years old in Brazilian law (Table 1). However, no claims related to health benefits, other than antioxidant activity, are allowed (Table 2).

In other countries in South America, such as Chile and Argentina, vitamin E is included in the list of approved compounds for food supplements. The Chilean regulation does not specify what form of vitamin E should be used and limits its dose to a maximum of 500 mg (Ministerio de salud, 2002). On the other hand, the Argentinian regulation allows up to 1,000 mg of vitamin E in food supplements, expressed as α-tocopherol equivalent (Conal, 2014). However, neither of them mentions other phenolics compounds nor brings a list of authorized health claims (Ministerio de salud, 2002; Conal 2014).

The knowledge about bioactive substances, especially phenolic compounds, has been continuously evolving. Some aspects regarding the bioavailability and bioaccessibility of many phenolics still are not completely elucidated, and that makes it hard to reach a consensus in order to establish lower and upper dose limits (Shahidi and Peng, 2018). The approach required for Anvisa to authorize an ingredient as part of food supplements requires that industry be capable of gathering as much scientific evidence as possible to petition for approval. However, changing the regulation in relation to phenolic compounds should be a collective effort involving food legislators, academia, and manufacturers of supplement ingredients.

3. Conclusion

In summary, the inclusion of phenolic compounds in the revised version of the normative NI N° 28 demonstrates a natural evolution. However, the number of approved compounds is still limited, and for the majority of them, the established upper limit doses may be prohibitive for products available in the international market.

The antioxidant action of polyphenols is well documented. Nevertheless, more clinical trials are needed in order to study aspects related do the bioavailability and bioactivity of different groups of polyphenols, which would help advance the current level of health claims approved in the regulation. Additionally, claims related to the antioxidant action and/or free radical scavenging activity of monophenols (e.g. tocopherols) should be extended to compounds such as chlorogenic acid, rutin, and proanthocyanidins. Finally, Brazilian sources of these compounds should be included.

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