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Invited Review

Plant constituents and thyroid: A revision of the main phytochemicals that interfere with thyroid function

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ABSTRACT

In the past few decades, there has been a lot of interest in plant constituents for their antioxidant, anti-inflammatory, anti-microbial and anti-proliferative properties. However, concerns have been raised on their potential toxic effects particularly when consumed at high dose. The anti-thyroid effects of some plant constituents have been known for some time. Indeed, epidemiological observations have shown the causal association between staple food based on brassicaceae or soybeans and the development of goiter and/or hypothyroidism. Herein, we review the main plant constituents that interfere with normal thyroid function such as cyanogenic glucosides, polyphenols, phenolic acids, and alkaloids. In detail, we summarize the *in vitro* and *in vivo* studies present in the literature, focusing on the compounds that are more abundant in foods or that are available as dietary supplements. We highlight the mechanism of action of these compounds on thyroid cells by giving a particular emphasis to the experimental studies that can be significant for human health. Furthermore, we reveal that the anti-thyroid effects of these plant constituents are clinically evident only when they are consumed in very large amounts or when their ingestion is associated with other conditions that impair thyroid function.

1. Introduction

Several plant constituents can interfere with the thyroid function posing the risk of goiter or functional abnormalities such as hypothyroidism. The goitrogenic effects of foodstuffs rich in cyanogenic glucosides or in flavonoids have been known for at least 60 years (Gaitan, 1990; Moudgal et al., 1958). Indeed, several plant constituents can interfere with thyroid function competing with the enzymes involved in thyroid hormonogenesis, such as thyroid peroxidase (TPO), or inhibiting the expression of the thyroid specific genes involved in the glandular function (Fig. 1A). The impairment of thyroid hormonogenesis causes a decreased production of the thyroid hormones T_3 and T_4 and consequently a rise of TSH secretion. The latter stimulates thyrocytes growth and function and may induce the thyroid enlargement (goiter), (Fig. 1B). This process is observed mainly when several goitrogenic factors are associated, i.e. when the ingestion of food rich in phytochemicals with anti-thyroid properties is associated with a low iodine intake. In severe case hypothyroidism may develop.

In the past few decades, several studies have identified the main plant constituents with anti-thyroid properties and their mechanisms of action. In this review we summarize the *in vitro* and *in vivo* studies present in the literature, focusing on the compounds that are more abundant in food or that are available as dietary supplements. We discuss the mechanism of action of these compounds on thyroid cells, focusing on the data that can be translated into clinical practice. Noteworthy, many plant constituents such as polyphenols and alkaloids not only can interfere with thyroid hormones production or metabolism, but also may have antiproliferative effects on thyroid cancer cells (Benvenga et al., 2020; Gonçalves et al., 2017; Montané et al., 2020; Sharifi-Rad et al., 2020). These observations are spurring studies for the use of these compounds as therapeutic agents in poor differentiated thyroid cancer. Furthermore, some of these compounds have also a potential role in the

Abbreviations: AP-1, activator protein 1; B.W., body weight; D1, type I 5′-deiodinase activity; D2, type II 5′-deiodinase activity; IC_{50}, half maximal inhibitory concentration; ip, intraperitoneal; NIS, sodium/iodide symporter; p.o, per os; s.c., subcutaneous; TG, thyroglobulin; TPO, thyroid peroxidase; TRβ, thyroid receptor β; TSHR, TSH receptor.

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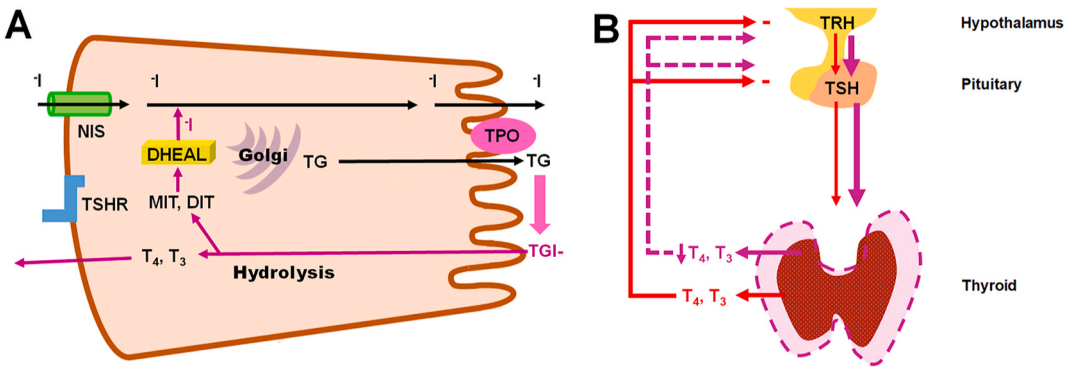

Fig. 1. A, schematic illustration of a thyrocytes showing the main steps of thyroid hormonogenesis. Iodide uptake is an active process performed by the sodium/iodide symporter (NIS) located in the basolateral membrane. Iodide is transported in the follicular lumen where it is oxidized and covalently bound to the thyroglobulin (TG) by the action of the enzyme thyroid peroxidase (TPO) located on the apical membrane. TG iodination (TGI) brings to the formation of the thyroid hormones molecules still covalently bound to the protein. TGI is reabsorbed by endocytosis and hydrolyzed with consequent release of the thyroid hormones (T_4 and T_3) into cytosol and thence to the capillaries. The hydrolytic process causes also the release of moniodo- and diiodothyrosine (MIT and DIT, respectively) that are further metabolized by iodothyrosines dhealogenases (DHEAL) to allow recycle of iodide. All these steps are under the control of the TSH through the TSH receptor (TSHR). B, schematic drawing of the hypothalamus-pituitary-thyroid axis. The physiologic negative feedback of thyroid hormones (T_4 and T_3) on the hypothalamus and pituitary function is depicted in red straight lines. Anti-thyroid compounds cause a decreased secretion of T_4 and T_3 that results in a reduction of the negative feedback (dashed purple lines) with an increased secretion of TRH and TSH (straight purple lines) that stimulates thyroid growth and function. In some cases, the enlargement of the thyroid gland can compensate the impaired function and the patient is euthyroid, in other cases the compensation is not sufficient and hypothyroidism will develop. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

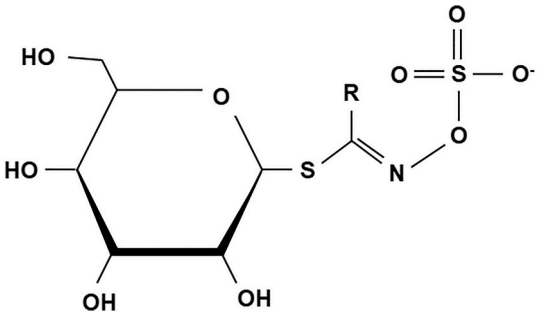

Fig. 2. General structure of the glucosinolates. R indicates the aglycone side chain.

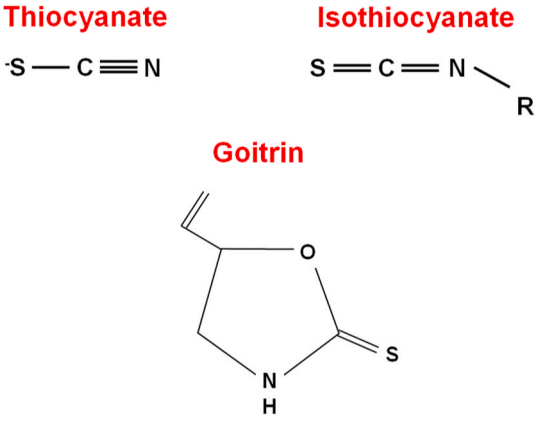

Fig. 3. Chemical structures of thiocyanate, isothiocianate and goitrin. R is an alkyl or aryl group.

treatment of thyroid autoimmunity (Caturegli et al., 2012; Hosseinzade et al., 2019; Khan et al., 2020; Schmeltz et al., 2014). However, these two issues are beyond the purpose of this review and will not be discussed below.

2. Search methods

Electronic databases such as PubMed, Web of Science and Scopus were screened for *in vivo* and *in vitro* animal or human studies which investigated the effects of various isolated plant constituents on the thyroid gland. The search keywords were: "thyroid" and "phytochemicals" or "glucosinolates" or "polyphenols" or "flavonoids" or "non-flavonoid phenolic compound" or "alkaloids" in the title and abstract. Only English language full-text papers were considered and included in this review. Irrelevant documents, incomplete articles, duplicates, and conference papers were excluded. Data collection was carried out between June 1, 2020 and September 1, 2020. A selection of relevant references related to the topic of interest was performed based first on title and abstract, and finally on the full text of the paper. Since this review focuses on the effects of the plant constituents on thyroid function, we did not consider the studies regarding their effects on thyroid cancer or thyroid autoimmunity. Furthermore, we focused on experimental data that assessed the effects of the specific single molecules and not of the whole plant extracts except for human studies where the effects of ingesting whole plants or mixtures of phytochemicals were also considered.

3. Glucosinolates and other cyanogenic glucosides

The glucosinolates are thioglucosides in which the glucose molecule is linked to an O-sulfated (Z)-thiohydroximate group (Fig. 2) (Blažević et al., 2020).

They are present in several plants of the Brassicaceae family (known also as Cruciferae). This family includes numerous components of the human diet such as broccoli, cabbage, sprouts Brussels, cauliflower, rape, mustard, turnip. The glucosinolates are the source of anti-thyroid compounds such cyanate, isothiocyanate and 5-vinyloxazolidine-2-thione (goitrin) (Barba et al., 2016; Gaitan, 1990; Melrose, 2019). Indeed, the glucosinolates are easily hydrolyzed by the enzyme mirosinase, a β-thioglucosidase which is present in the same plant (where it can be activated by cutting or chewing the plant) and in the intestinal lumen. After hydrolysis the aglycon group is further transformed in several breakdown products among which thiocyanate, isothiocyanate and goitrin (Fig. 3) (Barba et al., 2016; Gaitan, 1990; Melrose, 2019).

Thiocyanate is also the breakdown product of other cyanogenic glucosides contained in several staple food of developing countries such

as cassava, lima beans, bamboo shoots. For example cassava roots contain high levels of linamarin a glucoside which after ingestion is transformed first into cyanate and then into thiocyanate for about 25% (Carlsson et al., 1999). A diet rich in these foods has been associated with goiter endemia (Bourdoux et al., 1978; Chandra et al., 2013). The anti-thyroid effect of thiocyanate has been known for over 70 years since it was demonstrated its ability to inhibit iodide uptake in thyroid tissue (Wolff et al., 1946). Thiocyanate is a competitive inhibitor of iodide at the sodium/iodide symporter (NIS) with an affinity slightly lower than that of iodide (thiocyanate K_m = 30–100 μM vs iodide K_m = 10–30 μM) (Concilio et al., 2020; Portulano et al., 2014). For this reason, the anti-thyroid effect of thiocyanate is enhanced by iodine deficiency and a low iodide/thiocyanate ratio is related to the development of endemic goiter (Brauer et al., 2006; Gaitan, 1990). Since NIS is also involved in the iodide transport of the mammary gland and placenta, the effects of thiocyanate excess on these tissues have also been evaluated. Thiocyanate may decrease iodine concentration in the milk and this can contribute to neonatal goiter and/or hypothyroidism in iodine deficient regions (Laurberg et al., 2002, 2004). By contrary, the iodide placental transport is unaffected even by high concentrations of thiocyanate (Andersen et al., 2013). However, thiocyanate crosses the placenta and may directly affect the fetus thyroid function causing neonatal hypothyroidism (Moreno-Reyes et al., 1993). Besides its effects on thyroid iodide uptake, thiocyanate inhibits also TPO activity decreasing iodide organification and thyroid hormones synthesis (Willemin and Lumen, 2016, 2019). TPO is a key enzyme in thyroid hormonogenesis (Fig. 1A) since it catalyzes iodide oxidation and the binding of the oxidized iodine to the tyrosyl residues of thyroglobulin (TG), process defined as iodine organification. Furthermore, TPO catalyzes the coupling of iodotyrosines to generate the iodothyronines T_4 and T_3 (Colin et al., 2013). Thiocyanate is a competitive inhibitor of iodide oxidation and organification and this effect is independent of its effect on iodide uptake (Fukayama et al., 1992; Willemin and Lumen, 2019).

Regarding the isothiocyanates, their anti-thyroid effects are due both to their transformation in thiocyanate and in their ability to react with amino groups and form thiourea derivatives (Agerbirk et al., 2015), which are competitive inhibitors of the TPO activity (Cooper, 2005). Goitrin is also a potent inhibitor of the TPO activity (Langer, 1966).

The content of glucosinolates and other cyanogenic glucosides varies among the different plant. However, even in the case of the highest concentrations, a diet containing a normal serving size of brassicaceae (100–200 g of fresh weight) does not affect thyroid function (Felker et al., 2016). In a study performed in China, the administration to healthy volunteers for 84 days of a broccoli sprout beverage containing 600 μmol of the glucosinolate glucoraphanin showed no adverse effect on thyroid function (Chartoumpekis et al., 2019). It has to be noted that fresh broccoli contain an amount of glucoraphanin ranging from 11 to 296 μmol/100 g of fresh weight (Felker et al., 2016).

Moreover, the mean concentration of thiocyanate, the main end product of glucosinolates, in the plasma of subjects with a regular western diet is from 2.5 to 3.5 mg/L (~43 μM–60 μM) (Braverman et al., 2005; Lundquist et al., 1995). These values are not an issue for thyroid function in a population with an optimal iodine intake. On the other hand, a diet based on cassava causes an increase of plasma thiocyanate above 66–78 μM (Carlsson et al., 1999; Oluwole et al., 2002) and in tobacco smokers the thiocyanate plasma concentrations exceed 100–150 μM (Ockene et al., 1987), values associated with an increased risk of developing goiter (Brauer et al., 2006). However, since thiocyanate acts as a competitive inhibitor of thyroid iodide uptake and TPO activity, many experts consider the urinary iodide/thiocyanate ratio as a more accurate parameter than thiocyanate plasma concentration to assess the risk of anti-thyroid effects (Brauer et al., 2006; Erdogan, 2003).

In conclusion, the anti-thyroid effects of Brassicaceae is not an issue except in conditions of iodine deficiency or in the event of their excessive intake, as in a case of a severe hypothyroidism observed in an old woman who was eating up to 1–1.5 Kg of raw bok choy daily for several months (Chu and Seltzer, 2010).

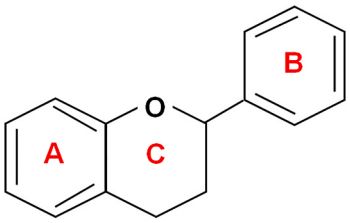

Fig. 4. General structures of flavonoids.

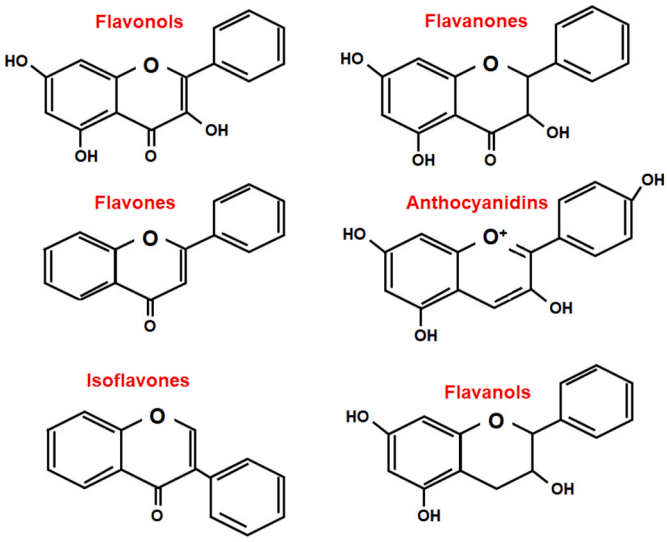

Fig. 5. General structures of the flavonoid subgroups.

4. Polyphenols

Polyphenols are plant secondary metabolites characterized by the presence of two or more phenolic groups. By definition these compounds are the products of two biochemical pathways, the shikimate and/or the polyketide pathway (Quideau et al., 2011). Therefore, compounds constituted by only one phenolic ring, even with two or more hydroxyl groups are more correctly defined as phenols instead that polyphenols (Quideau et al., 2011). Polyphenols have several functions in plants, mainly they act as phytoalexins providing defense against microbes and insects (Manach et al., 2004; Pecyna et al., 2020; Zaynab et al., 2018). They also give protection against solar UV-A and UV-B (Pecyna et al., 2020; Saric and Sivamani, 2016). Based on their chemical structure polyphenols are classified in flavonoids, stilbens, lignans, and curcuminoids (Montané et al., 2020; Quideau et al., 2011).

4.1. Flavonoids

Flavonoids are an important group of polyphenols comprising more than 6000 molecules (Montané et al., 2020). Their general structure (Fig. 4) is constituted by two benzene rings (named A and B) linked by a heterocyclic pyran ring (named C) (Montané et al., 2020; Santhakumar et al., 2018). This structure is also indicated as C_6–C_3–C_6.

Flavonoids are widely distributed in plants including fruits and vegetables and they are the main constituents of several medical plants. Based on their chemical structure flavonoids are further classified in six subgroups: flavonols, flavones, isoflavones, flavanones, anthocyanidins and flavanols (Fig. 5) (Montané et al., 2020; Santhakumar et al., 2018).

The goitrogenic effects of some flavonoids have been observed in

Table 1
Effects of the main flavonoids on thyroid growth and function and on thyroid hormones metabolism from studies performed *in vitro*.

Class	Compound	Experimental model	Dose	Effects	Reference
Flavonols	Quercetin	TPO purified from porcine thyroid glands	2.4 ± 0.6 μM	- Inhibition of tyrosine iodination	Divi and Doerge (1996)
			199 ± 8 μM	- Inhibition of TPO activity	Habza-Kowalska et al. (2019b)
		Rat thyroid microsome fractions	13.2 ± 1.5 μM	- Inhibition of thyroid D1 activity	Ferreira et al. (2002)
		Cell culture: RMS-13 cells	20 μmol/l	- Stimulation of D2 activity	da-Silva et al. (2007)
		Cell culture: FRTL-5 cells	1–10 μM	- Inhibition of cell growth	Giuliani et al. (2008)
				- Down-regulation of TSH-increased NIS gene expression through inhibition of the PLA2 pathway	
				- Decrease of thyroid-specific genes expression (NIS, TSHR, TPO and TG)	Giuliani et al. (2014b)
				- Activation of AP-1	Giuliani (2019)
	Kaempferol	TPO purified from porcine thyroid glands	1.2 ± 0.5 μM	- Inhibition of tyrosine iodination	Divi and Doerge (1996)
			61.7 ± 3.1 μg/ml	- Inhibition of TPO activity	Habza-Kowalska et al. (2019a)
		Rat thyroid microsome fractions	71.8 ± 12.8 μM	- Inhibition of thyroid D1 activity	Ferreira et al. (2002)
		Cell culture: GH4C1, HSM myoblasts, MSTO-211H and RMS-13 cells	20 μmol/l	- Stimulation of D2 activity	da-Silva et al. (2007)
		Cell culture: GH4C1 cells	20 μmol/l	- Inhibition of D1 activity	
	Myricetin	TPO purified from porcine thyroid glands	0.6 ± 0.2 μM	- Inhibition of tyrosine iodination	Divi and Doerge (1996)
		TPO purified from human thyroid glands	2.9 μM	- Inhibition of TPO activity	Ferreira et al. (2006)
	Mearnsitrin	TPO purified from human thyroid glands	1.97 μM	- Inhibition of TPO activity	Ferreira et al. (2006)
	Morin	TPO purified from porcine thyroid glands	2.1 ± 0.8 μM	- Inhibition of tyrosine iodination	Divi and Doerge (1996)
		Rat thyroid microsome fractions	55.1 ± 0.1 μM	- Inhibition of thyroid D1 activity	Ferreira et al. (2002)
	Fisetin	TPO purified from porcine thyroid glands	6.3 ± 0.6 μM	- Inhibition of tyrosine iodination	Divi and Doerge (1996)
		Rat thyroid microsome fractions	70.4 ± 2.6 μM	- Inhibition of thyroid D1 activity	Ferreira et al. (2002)
		Cell culture: RMS-13 cells	20 μmol/l	- Stimulation of D2 activity	da-Silva et al. (2007)
	Rutin	TPO purified from porcine thyroid glands	40.6 ± 3.9 μM	- Inhibition of tyrosine iodination	Divi and Doerge (1996)
			122 ± 4 μM	- Inhibition of TPO activity	Habza-Kowalska et al. (2019b)
		D1 activity measured in rat thyroid microsome fractions	68 ± 1.0 μM	- Inhibition of thyroid D1 activity	Ferreira et al. (2002)
		TPO purified from rat thyroid glands	3.4 μM	- Inhibition of TPO activity	Gonçalves et al. (2013)
		Cell culture: PCCL3 cells	25 μM	- Increase of iodide uptake and reduction of iodide efflux	Gonçalves et al. (2018)
				- Increase of NIS expression.	
Flavones	Apigenin	Cell culture: pig thyrocytes	1–100 μM	- Inhibition of thyroid hormones synthesis	Sartelet et al. (1996)
		Cell culture: PCCL3 cells	20 μM	- Increase of TSH-induced iodide uptake in combination with inhibitors of Akt	Lakshmanan et al. (2014)
		TPO purified from porcine thyroid glands	116.3 ± 5.4 μg/ml	- Inhibition of TPO activity	Habza-Kowalska et al. (2019a)
	Baicalein	Rat thyroid microsome fractions	10.6 μM	- Inhibition of thyroid D1 activity	Ferreira et al. (2002)
	Luteolin	Cell culture: pig thyrocytes	1–100 μM	- Inhibition of thyroid hormones synthesis	Sartelet et al. (1996)
Isoflavones	Biochanin A	TPO purified from porcine thyroid glands	6.2 ± 0.8 μM	- Alternate substrate inhibition of iodination	Divi and Doerge (1996)
		Rat thyroid microsome fractions	77.0 ± 1.0 μM	– Inhibition of thyroid D1 activity	Ferreira et al. (2002)
	Genistein	TPO purified from porcine thyroid glands	3.2 μM	– Inhibition of tyrosine iodination and iodotyronine formation	Divi et al. (1997)
		Human serum	10 μmol/l	– Inhibition of thyroid hormones binding to Transthyretin	Radović et al. (2006)
		Culture cell: HEK293 cells	3 μM	- Inhibition of thyroid D1 activity	Renko et al. (2015)
	Daidzein	TPO purified from porcine thyroid glands	7.6 μM	- Inhibition of tyrosine iodination	Divi et al. (1997)
Flavanones	Naringenin	TPO purified from porcine thyroid glands	2.7 ± 1 μM	- Inhibition of tyrosine iodination	Divi and Doerge (1996)
	Naringin	TPO purified from porcine thyroid glands	12.6 ± 1.6 μM	- Inhibition of tyrosine iodination	Divi and Doerge (1996)
Flavanols	Catechin	TPO purified from porcine thyroid glands	36.4 ± 3.9 μM	- Inhibition of tyrosine iodination	Divi and Doerge (1996)
			29.8 ± 2.1 μg/mL	- Inhibition of TPO activity	Habza-Kowalska et al. (2019a)
		Rat thyroid microsome fractions	17.5 ± 6.4 μM	- Inhibition of thyroid D1 activity	Ferreira et al. (2002)

experimental studies about sixty years ago (Moudgal et al., 1958). Later Gaitan and coworkers showed that the goiter endemia induced in a population of the West Africa by a diet rich in millet was due to the high content of glycosilflavones present in this food (Gaitan et al., 1989, 1995). The increased interest on the therapeutic properties of flavonoids as antioxidants, antimicrobial, anti-inflammatory and antitumor, led to several studies on their effects on thyroid growth and function in the last 25 years (Benvenga et al., 2020; de Souza Dos Santos et al., 2011; Gonçalves et al., 2017; Pistollato et al., 2019). The seminal work of Gaitan and coworkers showed that the anti-thyroid effect of millet glycosilflavones was due to the inhibition of the TPO activity (Gaitan et al., 1989). Subsequent studies performed *in vitro* showed that several flavonoids share this mechanism of action, some with a competitive mechanism and other with a non-competitive mechanism, and interfere with other functions of thyroid cells, Table 1. Beside their effects on thyroid cells, flavonoids also interfere with thyroid hormone metabolism and action, Table 1.

Most of these data observed *in vitro* were also confirmed *in vivo*

Table 2
Effects of the main flavonoids on thyroid growth and function from experimental study performed *in vivo*.

Class	Compound	Experimental model	Dose	Effects	Reference
Flavonols	Quercetin	Sprague–Dawley rats (M, 8 weeks old)	50 mg/kg/day i.p. for 14 days	– Decrease of iodide uptake	Giuliani et al. (2014b)
		Swiss albino mice (F, adult)	10 mg/kg/day p.o. for 10 days	– Decrease of thyroid hormones serum concentrations and liver D1 activity in euthyroid animals.	Panda and Kar (2007b)
		C57BL/6J mice (F, 3 weeks old) fed with HFD	1 g/100 g of HFD for 26 weeks p.o.	– Restoration of changes induced by HFD on the expression of thyroid hormone receptor α1 and D1 in the heart. – Amelioration of the decreased T_3 levels induced by HFD	Cheserek et al. (2016)
	Myricetin	C57BL/6J mice (M, 4 weeks old) fed with HFD	100 mg/kg of BW by oral gavage for 16 weeks	– Restoration of changes induced by HFD on serum TSH, thyroid hormones levels, and liver D1	Xia et al. (2019)
	Rutin	Wistar rats (M, 12 weeks old)	20 mg/kg of BW s.c. for 5 days	– Increase of iodide uptake and NIS expression – Reduction of serum T_4 and T_3 – Decrease of liver D1 activity and increase of D2 activity	Gonçalves et al. (2013)
		Albino Wistar rats (sex and age N.A.) rendered thyrotoxic by T4 administration	50 mg/kg of BW p.o. for 14 days	– Improvement of thyrotoxicosis (decrease of serum T_4 and T_3) – Decrease of liver D1 activity	Panda and Kar (2014)
Flavones	Apigenin	Swiss albino mice (M, adult)	0.78 mg/kg, s.c. for 10 days	– Decrease of serum T_4 and T_3	Panda and Kar (2007c)
Isoflavones	Genistein	Sprague–Dawley rats (M and F, pups)	genistein-fortified diet (5–500 ppm) for 20 weeks	– Inhibition of TPO activity	Chang and Doerge (2000)
		Wistar rats (M, 15–16 months old) orchidectomized	10 mg/kg of BW s.c. for 3 weeks	– Increase of serum TSH levels with decrease of T_4 and T_3 – Induction of microfollicular changes in thyroid tissue – Decrease of TG and TPO expression and increase of liver D1	Sosic-Jurjevic et al. (2010, 2014)
		Wistar rats (M, 15–16 months old) orchidectomized	30 mg/kg of BW s.c. for 3 weeks	– Decrease of serum T_4 and T_3 – Induction of microfollicular changes in thyroid tissue	Filipović et al. (2018)
	Daidzein	Wistar rats (M, 15–16 months old) orchidectomized	10 mg/kg of BW s.c. for 3 weeks	– Increase of serum TSH levels with decrease of T_4 and T_3 – Induction of microfollicular changes in thyroid tissue – Decrease of TG and TPO expression and increase of liver D1	Sosić-Jurjević et al. (2010) (Šošić-Jurjević et al., 2014)
Flavanones	Hesperitin	Albino Wistar rats (sex and age N.A.) rendered thyrotoxic by T4 administration	50 mg/kg of BW p.o. for 14 days	– Improvement of thyrotoxicosis (decrease of serum T_4 and T_3) – Decrease of liver D1 activity	Panda and Kar (2014)
		Wistar rats (M, 24 months old)	15 mg/kg of BW p.o. for 4 weeks	– Induction of thyroid morphological changes	Miler et al. (2017)
	Naringenin	Wistar rats (M, 24 months old)	15 mg/kg of BW p.o. for 4 weeks	– Induction of thyroid morphological changes and increase of serum TSH levels	Miler et al. (2017)
	Naringin	Albino Wistar rats (sex and age N.A.) rendered thyrotoxic by T4 administration	50 mg/kg of BW p.o. for 14 days	– Improvement of thyrotoxicosis (decrease of serum T_4 and T_3) – Decrease of liver D1 activity	Panda and Kar (2014)
Flavanols	Catechin	Albino Sprague–Dawley rats (M, 3 months old)	30 mg/kg of BW i.p. for 15 days	– Induction of goiter, increase of TSH, decrease of thyroid hormones, inhibition of TPO activity and liver and kidney D1	Chandra and De (2013)

BW: body weight; F: female; HFD: high fat diet; i.p.: intraperitoneal; M: male; N.A.: not available; p.o.: per os; ppm: parts per million; s.c.: subcutaneous.

(Table 2), although results may vary based on dose, route of administration and animal models used.

The effects of flavonoids on thyroid function depends on the amount ingested and, as discussed for the glucosinolates, on their association with other anti-thyroid conditions such as iodine deficiency.

The daily intake of flavonoids varies widely depending on eating habits: in the Western world the daily average intake is between 20 and 35 mg and can reach 500 mg in subjects who have a diet rich in fruits and vegetables (Manach et al., 2004; Pérez-Jiménez et al., 2011). In people who take dietary supplements containing flavonoids, the daily intake can be up to 2 g (Andres et al., 2018; Manach et al., 2005). The intestinal absorption of the flavonoids ingested vary from 10 to 60% and is influenced by several factors such as the processing and preparation of foods, the molecular structure of the flavonoid (glycoside or aglycone) and the intestinal and liver metabolism (Gonçalves et al., 2017; Manach et al., 2004, 2005). Therefore, there is a high interindividual variability in the human plasma concentrations of flavonoids after food ingestion, which vary between 0.1 and 5 μM (Erlund et al., 2006; Larson et al., 2012; Williamson and Manach, 2005).

These data must be kept in mind when evaluating the anti-thyroid effects of the flavonoids reported in the experimental studies. Indeed, the effects observed *in vitro* with concentrations above 20 μM are hardly applicable to the intake of flavonoids in human through diet or dietary supplements. Higher concentrations are only observed when an abnormal amount of flavonoids is taken for therapeutic use, e.g. the administration of 945 mg/m^2 of quercetin intravenously in cancer patients has resulted in a plasma concentration greater than 200 μM.

Although the flavonoids that possess an effect on thyroid function are numerous, as reported in Tables 1 and 2, we will discuss in detail the compounds that are most abundant in the diet and/or are available as dietary supplements.

Quercetin is the most abundant flavonoid present in fruit and vegetables and its plasma concentration can reach 0.7–2.5 μM in subjects eating high quantities of vegetables such as onions or taking dietary

supplements.

Quercetin is the most abundant flavonoid present in fruit and vegetables and its plasma concentration can reach 0.7–2.5 μM in subjects eating high quantities of vegetables such as onions or taking dietary supplements containing 500 mg of quercetin per tablet (Bondonno et al., 2016; Erlund et al., 2006; Henning et al., 2020; Larson et al., 2012; Williamson and Manach, 2005). Indeed, the administration of 1095 mg of quercetin results in a plasma concentration of 2.3 ± 1.8 μM (Larson et al., 2012). It is noteworthy that some of the anti-thyroid effect of quercetin are observed *in vitro* at a concentration of 1–2.5 μM. Indeed, quercetin decreases NIS mRNA expression in thyroid cells at 1 μM (Giuliani et al., 2008) and inhibits TPO activity with a IC_{50} of 2.4 μM (Divi and Doerge, 1996). The inhibition of the thyroid iodide uptake as well as that of the expression of the thyroid-specific genes TG, TPO, TSHR is observed at 5 μM with a maximum effect at 10 μM (Giuliani et al., 2008, 2014b). Of relevance is the observation that the anti-thyroid effects of quercetin were also confirmed *in vivo*. Indeed, treatment of Sprague-Dawley rat with 50 mg/kg of quercetin by intraperitoneal (i.p.) injection for 14 days resulted in a significant decrease of the radioiodide uptake (Giuliani et al., 2014b). This treatment was chosen since a previous study demonstrated that it is able to give a quercetin plasma concentration in Sprague-Dawley rats that can peak 2.6 μM (Piantelli et al., 2006). Of note, the dose of quercetin administered to the animals is equivalent to a dose of about 8 mg/kg in human according to dose translation from animal to human (Nair and Jacob, 2016). Furthermore, the administration of quercetin 10 mg/kg/day p.o. to Swiss albino mice reduced the serum concentrations of thyroid hormones and the enzymatic activity of the type I 5′-deiodinase (D1) in euthyroid animals (Panda and Kar, 2007c). These effects were observed also in mice rendered thyrotoxic by the administration of L-T_4, suggesting a potential use of quercetin in hyperthyroidism (Panda and Kar, 2007c).

The data reported above indicate that the anti-thyroid effects of quercetin are relevant only when high amount of the compound is ingested. Therefore, there is no reason to concern about the intake of vegetables and fruits rich in quercetin. Instead, caution should be used in the administration of high amount of quercetin until human information is available, particularly in subjects with thyroid impairment.

It is important to remark that the translation of the data obtained from animal studies to human requires caution. In fact, some studies have reported a discrepancy between the effects caused by quercetin and those caused by rutin, a glycoside of quercetin where the latter is linked to the disaccharide rutinose (Dihal et al., 2006; Gonçalves et al., 2013; Hsieh et al., 2013). Regarding the effects on thyroid, the treatment of Wistar rats with rutin 20 mg/kg of body weight (B.W.) s.c. for 5 days caused an increase of iodide uptake and NIS expression contrary to what was observed in Sprague-Dawley rats treated with quercetin 50 mg/kg/day i.p. for 14 days (Giuliani et al., 2014b). This discrepancy may be related to the different route of administration that can affect the metabolism of the compounds. Of note, despite the effect on NIS expression and iodide uptake the treatment with rutin resulted in a decrease of the serum T_3 and T_4 concentrations, presumably for the inhibition of TPO activity (Gonçalves et al., 2013).

Other subgroups of flavonoids that are important for their impact on thyroid function are flavones and isoflavones. Indeed, as already mentioned, the ingestion of food rich in flavones in West Africa has been associated with the development of goiter (Gaitan et al., 1989; Konde et al., 1994). A seminal work performed by Sartelet et al. showed that the flavones luteolin and apigenin are the main constituents of the fonio millet, a staple food in West Africa, and that they decreased the secretion of thyroid hormones in a culture of pig thyroid cells at a concentration of 10 μM (Sartelet et al., 1996). Further, the decrease of thyroid hormones production was observed in healthy Swiss albino mice treated with apigenin 0.8 mg/kg (Panda and Kar, 2007c).

The occurrence of goiter was also described in people eating food rich in isoflavones such as infants fed with soy formula (Hydovitz, 1960) and in healthy volunteers after the administration of 30 g of soybeans every day for 3 months (Ishizuki et al., 1991).

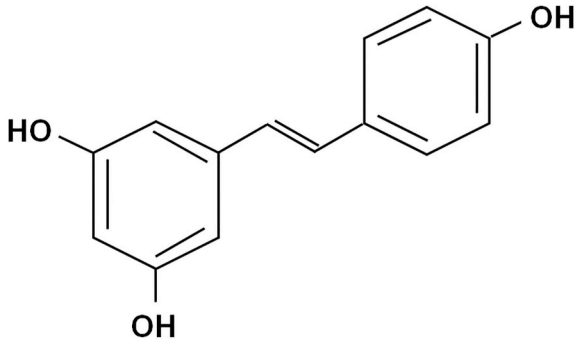

Fig. 6. Chemical structures of trans-resveratrol.

Soybean contains high amount of the isoflavones genistein and daidzein that are able to inhibit TPO activity at 1 μM (Divi et al., 1997), a concentration close to that detected in the serum of humans eating soy derivatives or taking isoflavones supplements (Hüser et al., 2018). Genistein is also an inhibitor of thyroid D1 with an IC_{50} of 3 μM (Renko et al., 2015).

A study performed in Sprague-Dawley rats fed with a diet fortified with genistein confirmed the inhibition of TPO activity observed previously *in vitro* (Chang and Doerge, 2000). The anti-thyroid effects of genistein and daidzein were further observed in middle-aged Wistar rats orchidectomized to minimize the effects of endogenous sex steroids on the pituitary (Filipović et al., 2018; Sosić-Jurjević et al., 2010; Šošić-Jurjević et al., 2014). In these studies, the treatment with genistein or daidzein increased the number of the pituitary thyrotrophs and the serum concentrations of TSH; it also decreased serum concentrations of T_3 and T_4. The effects of these compounds on thyrotrophs are not only a consequence of the decrease in the negative feedback of thyroid hormones on the pituitary, in fact daidzein has a greater effect on the thyrotrophs than genistein despite the same reduction of serum T_3 and T_4. This result has been explained by the greater estrogenic activity of daidzein, since estrogens stimulate thyrotrophs (Asa and Ezzat, 1999). Moreover, the treatment with genistein and daidzein decreased the expression of the thyroid genes TPO and TG (Šošić-Jurjević et al., 2014) and induced morphological changes in the thyroid histological architecture: small size follicles poor in colloid lined by cuboid or columnar epithelium (Filipović et al., 2018; Sosić-Jurjević et al., 2010).

The inhibitory effects of a diet rich in isoflavones on TPO activity was also confirmed in study performed in humans reviewed by Hüser et al. (2018). An interesting study performed in human volunteers showed that the administration of 16 mg of an isoflavones preparation, made by 54% genistein, 35% daidzein and 12% glycitein, induced the progression from a condition of subclinical hypothyroidism to an overt hypothyroidism in 16 female patients (Sathyapalan et al., 2011).

It is important to remark that the anti-thyroid effects of isoflavones in humans have been observed when their ingestion was associated with a condition of iodine deficiency in the population (Gaitan et al., 1989; Konde et al., 1994), or when large quantities (30 g/day) were administered in healthy volunteers (Ishizuki et al., 1991). An intake of isoflavones even up to 1 g/day, did not significantly affect thyroid function in euthyroid individuals (Messina and Redmond, 2006).

4.2. Stilbenoids or stilbenes

Stilbenoids are characterized by two phenyl groups linked by a transethane bond. Resveratrol (3,4',5-trihydroxystilbene) (Fig. 6) is the most well-known stilbenoid and it is found in grapes, berries, peanuts, and other several plants (Pecyna et al., 2020).

Resveratrol has many therapeutic properties, such as antioxidant, anti-inflammatory, antiaging, antidiabetic, neuroprotective, cardioprotective, and antiproliferative activities. The latter has also been

Table 3
Effects of non-flavonoids polyphenols on thyroid growth and function and on thyroid hormones action *in vitro* and *in vivo*.

Class	Compound	Experimental model	Dose	Effects	Reference
Stilbenoids	Resveratrol	FRTL-5 cells	10–100 μM	– Transient increase of iodide trapping, iodide influx and NIS expression after short-term treatment (6–12 h)	Sebai et al. (2010)
			10 μM	– Decrease of iodide uptake and expression of NIS, TG, TPO, TSHR, Nkx2-1, Foxe1 and Pax8 after long-term treatment (48–72 h)	(Giuliani et al., 2014a, 2017)
		Rat hepatocytes and HepG2 cells	20 μM	– Increase the T_3 induction of genes related to fatty acid oxidation and gluconeogenesis in the liver	Thakran et al. (2013)
		Sprague-Dawley rats (F, adult) ovariectomized	0.084 g–0.84 g per kg food for 3 months p.o.	– Increase of serum T_3 with slight decrease of serum TSH	Böttner et al. (2006)
		Sprague-Dawley rats (M, 8 weeks old)	50 mg/kg of BW i.p. for 14 days	– Down-regulation of NIS expression and iodide uptake	Giuliani et al. (2014a)
			25 mg/kg of BW i.p. for 2 months	– Increase of thyroid size – Induction of thyroid hypertrophy and hyperplasia – Decrease of thyroid TG – Increase of serum TSH	(Giuliani et al., 2017)
		Wistar rats fluoride-exposed (M, adult)	20 mg/kg of BW i.p. for 14 days	– Amelioration of the fluoride metabolic toxicity – Restoration of the fluoride-induced changes in serum T_3 and T_4, in thyroid TPO activity, and in thyroid histology	Sarkar and Pal (2014)
		Sprague-Dawley rats (M, 2 months old) with surgical-induced subclinical hypothyroidism	15 mg/kg of BW by oral gavage for 16 days	– Decrease of TRH and TSH secretion and improvement of animal behavior	(Ge et al., 2015, 2016)
Lignans	Arctigenin	cell-based hTRβ reporter assay	3.8 μM	– Antagonist of TRβ	Ogungbe et al. (2014)
	Pinoresinol	cell-based hTRβ reporter assay	8.2 μM	– Antagonist of TRβ	Ogungbe et al. (2014)
Curcuminoids	Curcumin	Wistar rats (M, 3 months old)	100 mg/kg of BW by gavage for 30 days	– Increase of serum FT_3 and FT_4	Papiez et al. (2008)
		Wistar rats (M, 18 months old)	100 mg/kg of BW by gavage for 30 days	– Decrease of serum FT_3	Papiez et al. (2008)
		Sprague-Dawley rats (M, 6–8 weeks old) fluoride-exposed	100 mg/kg of BW by gavage for 21 days	– Prevention of the fluoride-induced changes in serum TSH, T_3, T_4 concentrations and in thyroid morphology	Abdelaleem et al. (2018)
		Wistar rats (M, 5 months old) rendered thyrotoxic by L-T4 administration	30 mg/kg of BW per os for 30 days	– Amelioration of hepatic changes induced by thyrotoxicosis	Subudhi et al. (2008)
		Wistar rats (M, adults) rendered hypothyroid by PTU administration	30 mg/kg of BW by gavage for 30 days	– Up-regulation of superoxide dismutase (SOD1) and glutathione peroxidase (GPx1) – No changes in serum T_3, T_4 and TSH levels – Restoration of hepatic cell population and histoarchitecture	Subudhi and Chainy (2012) (Bunker et al., 2019)

observed in thyroid cancer cells (Rauf et al., 2018). In an experimental model of subclinical hypothyroidism, the treatment with resveratrol had beneficial effects on the animal behavior and decreased the secretion of TRH and TSH acting directly on the hypothalamus-pituitary axis, i.e. without increasing the plasma concentrations of thyroid hormones (Ge et al., 2015, 2016). An amelioration of serum T_3 and TSH has also been observed in female rats ovariectomized (Böttner et al., 2006), Table 3. However, high dose and/or long-term intake of resveratrol can cause harmful effects (Shaito et al., 2020). In particular, resveratrol can act as a thyroid function disruptor and a goitrogen, Table 3. Experiments performed *in vitro* in the FRTL-5 rat thyroid cells, showed that resveratrol 10 μM down-regulates the expression of the thyroid-specific genes NIS, TSHR, TG, TPO, Nkx2-1, Foxe1 and Pax8, furthermore it inhibits iodide uptake (Giuliani et al., 2014a, 2017). These anti-thyroid effects of resveratrol were also confirmed *in vivo* in male Sprague-Dawley rats. A short-term treatment with resveratrol 50 mg/kg/day i.p for 14 days resulted in an inhibition of iodide uptake with a decreased expression of the NIS protein on the thyroid (Giuliani et al., 2014a). A longer-treatment, with resveratrol 25 mg/kg/day i.p for 60 days, showed, in addition to the decreased expression of the NIS protein, also a reduction of the thyroid TG with a significant increase of the thyroid size. The thyroid gland was hyperplastic with irregularly shaped follicles, occasionally devoid of colloid. Furthermore, the hormonal evaluation showed an increase of the serum TSH in the rat treated with resveratrol (Giuliani et al., 2017). Noteworthy, the dose of resveratrol used in the rat experiments is equivalent to a dose of about 4 mg/kg/day in human (Nair and Jacob, 2016). This dose is not reached with a regular diet even if rich in vegetables and fruits; however, it can be reached or even overcome in individuals taking supplements (Giuliani et al., 2017).

4.3. Lignans

Lignans are a large class of naturally occurring secondary plant metabolites characterized by a phenylpropanoid core (Fig. 7). Lignans are found in a wide variety of plant-based foods, including seeds, whole grains, legumes, fruit, and vegetables (Rodríguez-García et al., 2019). These compounds possess several beneficial properties, such as anticancer, antioxidant, estrogenic, and antiestrogenic activities (Durazzo et al., 2018). Epidemiological data have suggested that lignans intake may be associated with a reduced risk of thyroid cancer due to their influence on estrogen metabolism, resulting in a milieu less favorable to cancer development (Horn-Ross et al., 2002). However, no data are available on their role on normal thyroid growth and function, except for the ability of (−) arctigenin and (+) pinoresinol, to act as antagonists of the human thyroid hormone receptor β (hTRβ) in a cell-based reporter bioassay (Table 3). The study showed that (−) arctigenin and (+) pinoresinol had an IC_{50} of 3.8 and 8.2 μM respectively for hTRβ (Ogungbe et al., 2014). However, it is doubtful whether this effect is of clinical relevance since the T_3 EC_{50} is in the nanomolar range (Cheng et al., 2010).

4.4. Curcuminoids

Curcuminoids extracted from the rhizomes of Curcuma longa

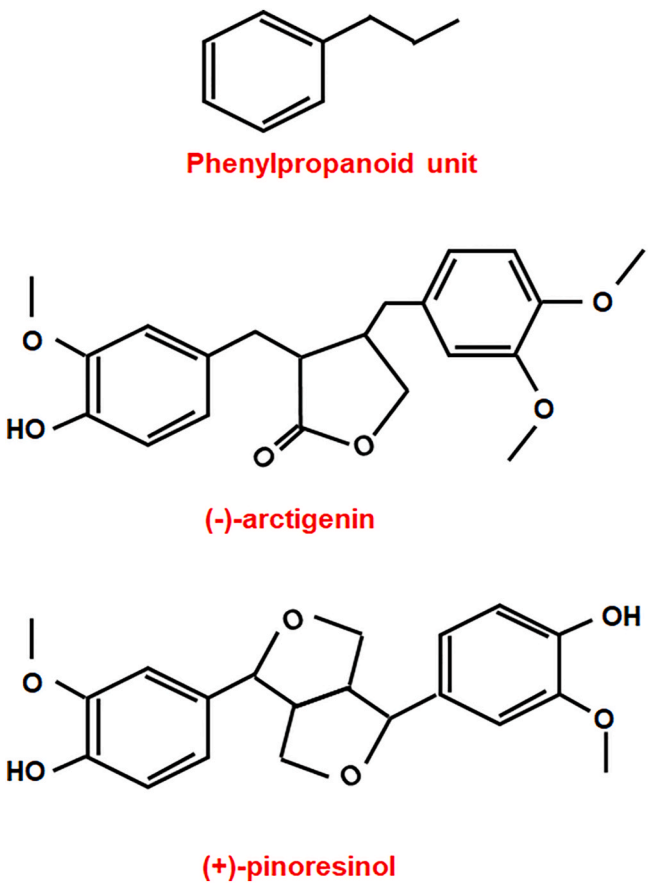

Fig. 7. Chemical structures of the phenylpropanoid unit and of the lignans (−) arctigenin and (+) pinoresinol.

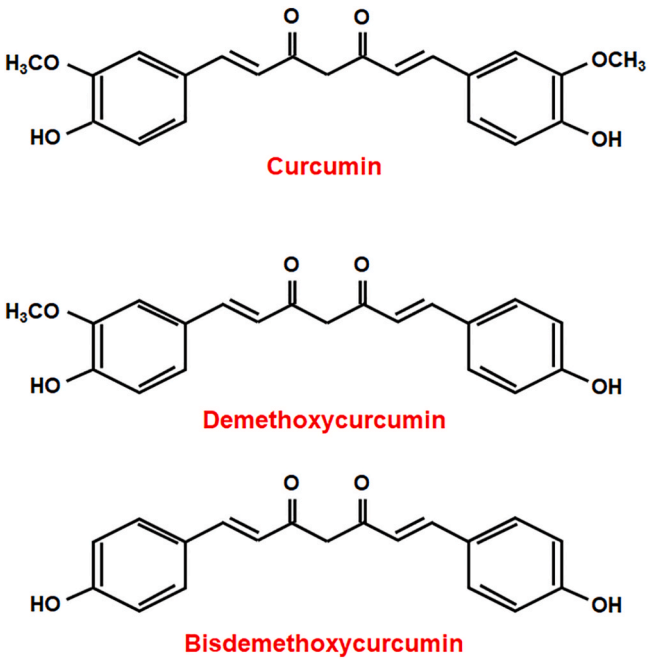

Fig. 8. Chemical structures of curcumin and its derivative demethoxycurcumin and bisdemethoxycurcumin.

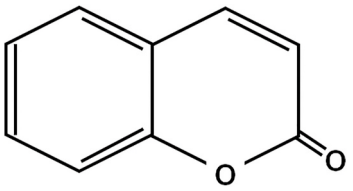

Fig. 9. Chemical structure of coumarin.

(known also as turmeric), are naturally occurring polyphenols responsible for the yellow color of the plant. They consist of a mixture of curcumin and its derivatives demethoxycurcumin and bisdemethoxycurcumin (Amalraj et al., 2017), (Fig. 8). Curcuminoids, used generally as spices or colorants, have gained interest in medicine for their antioxidant, anti-inflammatory, and anti-cancer properties (Gupta et al., 2013; Panda et al., 2017). Few studies are available on the effects of curcumin on thyroid function or thyroid hormones action (Table 3). A study performed on healthy rats treated with curcumin 100 mg/kg of B.W. by gavage revealed different effects depending on the age of the rats. In younger rats (3 months old) curcumin stimulated the secretory function of the thyroid gland as demonstrated by a weak increase of FT_3 and FT_4 serum concentrations, whereas in older rats (18 months old) curcumin induced a decrease of FT_3 concentrations associated with morphological changes of thyroid histology similar to that induced by anti-thyroid drugs (Papiez et al., 2008). However, this study has important weaknesses that make its evaluation difficult. Indeed, the authors did not report the serum TSH and total thyroid hormones concentrations, but they evaluated only the free thyroid hormones concentrations using a radioimmunoassay method. These data should be interpreted with caution since the measurement of free thyroid hormones by methods other than equilibrium dialysis can be erroneous (Bianco et al., 2014). A more recent study performed in Sprague-Dawley rats exposed to sodium fluoride showed that curcumin 100 mg/kg of B.W. by gavage prevented the fluoride-induced anti-thyroid effect on serum concentrations of thyroid hormones and on glandular morphology (Abdelaleem et al., 2018). However, the effect of curcumin on normal control rats was not evaluated. Some studies have evaluated the anti-oxidants effects of curcumin on thyrotoxic or hypothyroid rats (Bunker et al., 2019; Subudhi and Chainy, 2012; Subudhi et al., 2008). In rats rendered thyrotoxic by L-T_4 administration curcumin significantly improved the hepatic dysfunction and the oxidative stress induced by thyrotoxicosis (Subudhi et al., 2008). A beneficial effect of curcumin was also observed in rats rendered hypothyroid by propylthiouracile. In this model curcumin restored the glutathione redox status altered by the hypothyroidism, and modulated the activities of the genes involved in the antioxidant activity. In detail, the treatment with curcumin normalized the increased activities of superoxide dismutase (SOD) 1, SOD 2, glutathione peroxidase (GPx1) and glutathione reductase (GR), and the decreased activity of catalase (CAT) caused by hypothyroidism (Bunker et al., 2019; Subudhi and Chainy, 2012). However, in all these studies curcumin was unable to restore the altered concentrations of serum TSH, T_3 and T_4 and therefore its beneficial effects seem linked to the antioxidant properties and not to a direct action on thyroid function (Bunker et al., 2019; Subudhi and Chainy, 2012).

5. Coumarins and phenolic acids

Coumarins are plant secondary metabolites composed of a benzene ring linked to a pyrone ring. They comprise several compounds that have antimicrobial, antithrombotic, anti-inflammatory, and vasodilatory activities (Stringlis et al., 2019). Of these compounds only coumarin (Fig. 9) has been shown to affect thyroid function (Table 4). Indeed, administration of coumarin in female rats made thyrotoxic with L-T_4 reversed the increased thyroid hormones serum concentrations and the liver D1 activity (Panda and Kar, 2007a). Of note, this study

Table 4
Effects of other phenolic compounds on thyroid growth and function *in vitro* and *in vivo*.

Class	Compound	Experimental model	Dose	Effects	Reference
Coumarins	Coumarin	Wister Albino rats (F, adult)	10 mg/kg of BW for 15 days p.o.	– Decrease of serum T_3 and T_4, decrease of liver D1 activity in normal rats and in rats rendered thyrotoxic by administration of L-T_4	Panda and Kar (2007a)
Phenolic acids	Coumaric acid	Wister Albino rats (M, adults)	0.25 μmol/kg of BW for 3 weeks by gastric tube	– Induction of thyroid hypertrophy and hyperplasia – Decrease of serum T_3 and T_4 levels and increase of serum TSH	Khelifi-Touhami et al. (2003)
	Ferulic acid	Wister Albino rats (M, adults)	0.25 μmol/kg of BW for 3 weeks by gastric tube	– Induction of slight thyroid hypertrophy	Khelifi-Touhami et al. (2003)
	Caffeic acid	Wister Albino rats (M, adults)	0.25 μmol/kg of BW for 3 weeks by gastric tube	- Induction of slight thyroid hypertrophy	Khelifi-Touhami et al. (2003)
	Sinapic acid	TPO extracted from porcine thyroid glands	25.4 ± 1.1 μg/mL	– Inhibition of tyrosine iodination by TPO	Habza-Kowalska et al. (2019a)
	Chlorogenic acid	Human thyroid glands	80 μg/ml	– Inhibition of TSH binding to thyroid plasma membranes	Auf'mkolk et al. (1985)
		TPO extracted from porcine thyroid glands	1439 ± 40 μM	– Inhibition of tyrosine iodination by TPO	Habza-Kowalska et al. (2019b)
	Rosmarinic acid	Human thyroid glands	70 μg/mL	– Inhibition of TSH binding to thyroid plasma membranes	Auf'mkolk et al. (1985)
		TPO extracted from porcine thyroid glands	4 ± 0.1 μM	– Inhibition of tyrosine iodination by TPO	Habza-Kowalska et al. (2019b)
	Gallic acid	*In vitro* peroxidase assay	150 ± 23 μM	– Inhibition of peroxidase activity	Benarous et al. (2020)
	Ellagic acid	Human thyroid glands	20 μg/ml	– Inhibition of TSH binding to thyroid plasma membranes	Auf'mkolk et al. (1985)
		GH3-TRE-Luc cells	37.5 μM	– Antagonist activity on thyroid hormone receptor	Gramec Skledar et al. (2019)

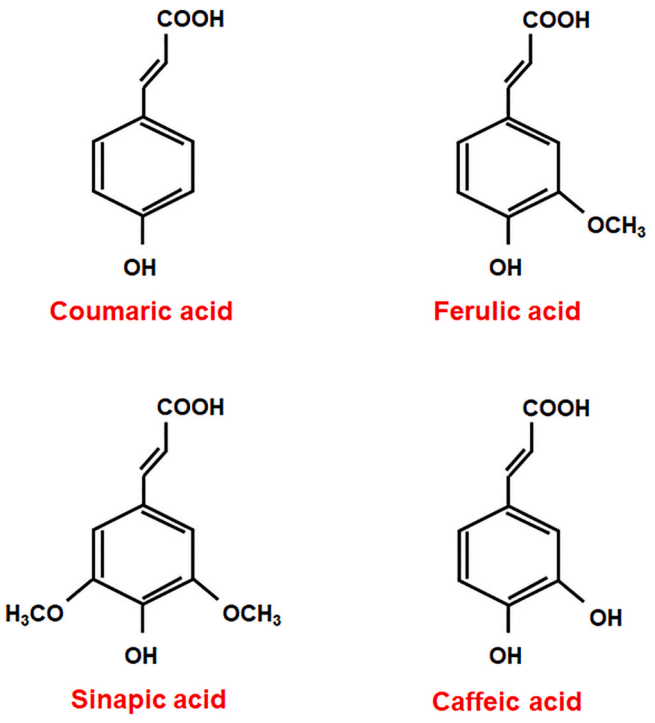

Fig. 10. Chemical structure of main hydroxycinnamic acids.

demonstrated that coumarin also had an inhibitory effect on the thyroid function of control euthyroid rats where the administration of the compound reduced serum thyroid hormone concentrations and D1 activity by about half (Panda and Kar, 2007a).

However, these data have little clinical impact as the maximum amount of coumarin ingested by humans is estimated to be approximately 0.06 mg/kg/day (Lončar et al., 2020).

Phenolic acids are aromatic secondary metabolites with a phenolic ring having at least one carboxylic acid group.

They are widely distributed in the plant kingdom and found in a variety of nuts and fruits, such as raspberries, grapes, strawberries, walnuts, cranberries, and black currants. They are divided into two subgroups: hydroxycinnamic and hydroxybenzoic acids (Kumar and Goel, 2019). The most common hydroxycinnamic acids include coumaric, ferulic, sinapic, and caffeic acids (Fig. 10).

They are found in fruits, vegetables, and beverages, such as coffee, tea, and wine (Coman and Vodnar, 2020). Studies performed *in vitro*, summarized in Table 4, have shown the abilities of several hydroxycinnammic compounds to inhibit TPO activity or the binding of TSH on thyroid plasma membrane (Auf'mkolk et al., 1985; Habza-Kowalska et al., 2019a; Habza-Kowalska et al., 2019b). However, in these studies the concentrations used are much higher than that observed in human plasma that are below 100 nM (Grabska-Kobylecka et al., 2020; Lee et al., 2016) Coumaric acid has been shown to exert a goitrogen activity in rats (Khelifi-Touhami et al., 2003). Indeed, the administration of coumaric acid (0.25 μmol/kg/day for 3 weeks by gastric tube) caused hypertrophy and hyperplasia of the thyroid follicles, a decrease of serum

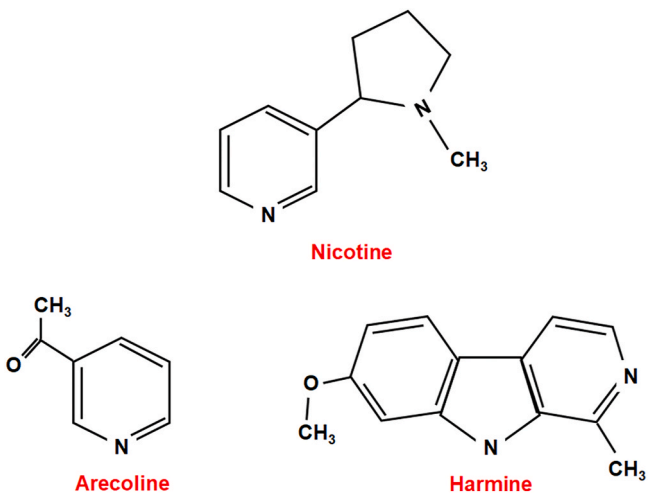

Fig. 11. Chemical structure of the main alkaloids that affect thyroid function.

Table 5
Effects of alkaloids on thyroid growth and function *in vitro* and *in vivo*.

Class	Compound	Experimental model	Dose	Effects	Reference
Pyridines	Nicotine	Wistar rats (F and M, lactating pups from dams treated with nicotine during lactation)	6 mg/kg of BW for 14 days by s.c. minipump	– Decrease of serum FT_3 and FT_4 levels and of liver D1 activity – Transient increase with subsequent decrease of serum TSH levels – Decrease of thyroid iodide uptake	(Lisboa et al., 2015; Oliveira et al., 2009) (de Oliveira et al., 2011)
		Porcine thyroid follicles	0–200 μmol/L	– No effect on thyroid hormone synthesis – No effect on iodide efflux	Fukayama et al. (1992)
		Sprague Dawley rats (adults)	2 mg/kg of BW for 7 days by s.c. minipump	– No effect on serum T_4 and T_3 – No effect on D1 activity	Colzani et al. (1998)
		C57BL/6 mice	24 mg/kg of BW for 12 days by s.c. minipump	– Decrease of serum T_4 concentration and increase of T_3/T_4 ratio after 24 h of nicotine withdrawal	Leach et al. (2015)
	Arecoline	Albino mice (M, adults)	10 mg/kg of BW i.p. for 15 days	– Acute effect: increase of serum T_3 and T_4 levels and decrease of serum TSH levels – Chronic effect: increase of serum TSH concentrations and decrease of serum T_3 and T_4 levels with degenerations of thyrocytes	Dasgupta et al. (2017)
Isoquinoline purines	Harmine	*In vitro* peroxidase assay	141 ± 4.0 μM	– Inhibition of peroxidase activity	Benarous et al. (2020)
Piperidines	Piperine	Swiss albino mice (M, adults)	2.5 mg/kg of BW for 15 days p.o.	– Decrease of serum T_3 and T_4 levels and inhibition of liver D1 activity	Panda and Kar (2003)

T_3 and T_4 concentrations, with a parallel increase of serum TSH concentrations. In the same study, caffeic acid and ferulic acid caused only a slight increase in thyroid volume without increasing cell proliferation and without affecting the serum concentrations of TSH and thyroid hormones (Khelifi-Touhami et al., 2003). However, also in this study high concentrations of compounds were used in comparison with that detected in human plasma. Of note, no data are available on hydroxycinnamic acids consumption and risk of thyroid dysfunction in humans.

Hydroxybenzoic acids in plant foods include p-hydroxybenzoic, gallic, syringic, protocatechuic, and vanilic acids (Valanciene et al., 2020). There are no data regarding their effects on thyroid function *in vivo,* some studies have shown that gallic acid and its dimeric derivative, the ellagic acid, inhibit *in vitro* the TPO activity and the TSH binding to thyroid plasma membranes (Auf`mkolk et al., 1985; Benarous et al., 2020; Gramec Skledar et al., 2019) (Table 4). However, even in these studies the concentrations used are much higher than that detected in human plasma (Fan et al., 2020; Long et al., 2019).

6. Alkaloids

Alkaloids are secondary plant metabolites containing cyclic structures with at least one basic nitrogen atom being incorporated within (Fig. 11). These compounds have a wide distribution in the plant kingdom and are important for plants defense against herbivores and pathogenic organisms (Zaynab et al., 2018).

Alkaloids can be classified, based on their heterocyclic ring system and biosynthetic precursor, into several groups, including: tropanes, pyrrolidines, isoquinoline purines, imidazoles, quinolizidines, indoles, piperidines and pyrrolizidines (Thawabteh et al., 2019). Alkaloids have been extensively investigated because of their biological activity and therapeutic potential. They are endowed, indeed, with several biological activities, including anti-inflammatory, anti-oxidant, anti-microbial, anti-cancer (Mondal et al., 2019), immunomodulatory (Khan et al., 2020), anticholinergic, analgesic, and antiangiogenic properties (Alasvand et al., 2019). However, many alkaloids are well known poisons and are toxic to both humans and animals (Matsuura and Fett-Neto, 2015). They can also interfere with many enzymatic systems, including those involved in thyroid hormone status. The main alkaloids that interfere with thyroid function are reported in Table 5.

Nicotine is one of the best-known alkaloids being a main constituent of tobacco. In addition to smoking, nicotine can be ingested by chewing tobacco leaves or taking tablets. Several studies have shown that nicotine can affect thyroid function particularly in the early stages of life. In studies performed in lactating rats, treatment of dams with nicotine caused a central hypothyroidism in the lactating pups (de Oliveira et al., 2011; Lisboa et al., 2015; Oliveira et al., 2009). Of note, plasma nicotine concentration in these studies was similar to that observed in heavy smokers. However, no effect of nicotine was observed on thyroid hormone synthesis and metabolism both *in vivo* in adult rats (Colzani et al., 1998) and *in vitro* in cultured porcine thyroid follicles (Fukayama et al., 1992).

Other alkaloids that interfere with thyroid function are harmine, piperine, arecoline and mitragynine.

Harmine, present in several medical plants, is an inhibitor of the horseradish peroxidase activity with an IC_{50} of 141.4 μM. Molecular modelling showed that this data can also apply to TPO, suggesting a potential use of this compound as anti-thyroid drug (Benarous et al., 2020).

Piperine, the major alkaloid contained in Piper nigrum (black pepper), significantly lowered serum T_3 and T_4 concentrations, and liver D1 activity in Swiss albino mice (Panda and Kar, 2003). These results were observed treating the mice with 2.5 mg/kg/day. A lower dose, 0.25 mg/kg/day, decreased only liver D1 activity and serum T_3 concentrations. However, these doses are far from those reached in human nutrition since black pepper contains approximately 5–9% piperine (Dudhatra et al., 2012). Arecoline is a naturally occurring psychoactive alkaloid from the betel nut of the Areca catechu, a plant that growth in Southeast Asia, East African and Western Pacific seaboards. The nuts are chewed by millions of people to increase capacity to work and reduce stress. Arecoline is a partial agonist of nicotinic and muscarinic acetylcholine receptors and exhibits several pharmacological activities including endocrine and metabolic effects (Volgin et al., 2019). Arecoline showed dual actions on mouse thyroid gland, it stimulates thyroid function initially with a subsequent inhibition of thyroid activity, probably due to the cytotoxic effect of this compound as demonstrated by the ultrastructural changes observed in thyrocytes (Dasgupta et al., 2010). Indeed, acute exposure to arecoline caused an increase of serum T_3 and T_4 levels associated with a decrease of serum TSH concentrations in adult male mice within 40 min from i.p. injection. Instead, a long-term treatment (10 mg/kg B.W. daily for 15 days) induced ultrastructural degeneration of thyroid follicular cells with reduction of serum T_3 and T_4 levels followed by an elevation of TSH. Furthermore, arecoline treatment has been shown to aggravate hypothyroidism in mice under metabolic stress (Dasgupta et al., 2017) and to ameliorate hyperthyroid condition in cold-stressed mice (Dasgupta et al., 2018).

Mitragynine, an indole alkaloid, is the main component of the

psychoactive plant Mitragyna speciosa (commonly known as Kratom). A case of severe primary hypothyroidism in a 44-year-old man has been reported following the chronic use (4 months) of high dose of kratom for abdominal pain (Sheleg and Collins, 2011). However, no experimental data are available on the effects of this alkaloid on thyroid function. Therefore, further experimental investigations are necessary to establish an anti-thyroid effect of mitragynine.

7. Conclusions

In this review we have discussed the main plant constituents that have anti-thyroid effects. We have described the several groups of phytochemicals based on their chemical classification and we have reported their known mechanisms of action on thyroid cells and/or thyroid hormones metabolism mainly in tabular forms. Furthermore, we have discussed more extensively the compounds that are most abundant in food or dietary supplements, indicating the concentrations at which they are active and highlightening the data available on humans. We believe this information is important to evaluate the real impact of phytochemicals in the clinical practice.

CRediT authorship contribution statement

Giulia Di Dalmazi: Writing – original draft. **Cesidio Giuliani:** Conceptualization, Methodology, Writing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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