Review

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Review

What's New about Parsley, a Potential Source of Cardioprotective Therapeutic Substances?

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Abstract: *Petroselinum crispum* (Mill.) Fuss (Apiaceae), popularly known as parsley, is a ubiquitous aromatic herb used for culinary and medicinal purposes worldwide. Besides the richness in nutrients, several bioactive secondary metabolites, especially the flavone apigenin and its glycosides, have been described in the species. Parsley has already been shown to have several health-promoting activities, such as antithrombotic, antihypertensive, and hypolipidemic. The multiple studies conducted in animal models so far suggest the species is a potential source of cardioprotective agents. This review provides up to date information and perspectives on the potential of parsley and its bioactive compounds for the development of nutraceutical products and drugs for the promotion of cardiovascular health. It includes not only a discussion on reported bioactivities, but also the knowledge of supplements and food additives developed as innovative parsley-based products.

Keywords: *Petroselinum crispum*; culinary herbs; antithrombotic activity; antihypertensive activity; hypolipidemic activity; cardiovascular health; nutraceutical; phytotherapy; apigenin glycosides

1. Introduction

Cardiovascular diseases (CVD) are a group of disorders that impact the quality of life of millions of people around the world. Annually, CVD are responsible for 17.9 million deaths worldwide, constituting a major concern for global health. Several causes are related to death from CVD, with emphasis on ischemic heart disease, ischemic stroke, hemorrhagic stroke, hypertension and peripheral arterial disease [1–3].

Some aromatic herbs used as food flavoring in various regions of the world are also known for their beneficial health properties [4–7]. Among them, we highlight basil (*Ocimum basilicum* L.; Lamiaceae), coriander (*Coriandrum sativum* L.; Apiaceae), oregano (*Origanum vulgare* L.; Lamiaceae) and parsley (*Petroselinum crispum* (Mill.) Fuss; Apiaceae), which are also popularly used as medicine against symptoms related to cardiovascular diseases. The ethnopharmacological use of these spices has encouraged research groups to investigate their alleged beneficial properties [8–11].

P. crispum (syn. Apium crispum Mill., A. petroselinum L., Carum petroselinum (L.) Benth. & Hook. f., Petroselinum hortense var. crispum L.H. Bailey, P. vulgare Lag., Selinum petroselinum (L.) E.H.L. Krause, and Wydleria portoricensis DC.) is an annual or biennial plant native to Europe and the Mediterranean region, but widely spread in various regions of the world where it is cultivated for its aromatic edible leaves. The triangular leaves are dark green, divided into curly or flat leaflets, mainly known by three varieties: Italian or flat-leaved parsley (P. crispum var. neapolitanum), curly leaved parsley (P. crispum var. crispum), and Hamburg parsley (P. crispum var. tuberosum). The curly-leaf variety occurs more frequently. The inflorescences have umbels composed of greenishyellow flowers. The great morphological variation of parsley is reflected in the large number of cultivars [12–14].

Aerial parts, fresh or dried leaves are used in a wide variety of culinary specialties. Parsley is commonly used as a condiment in sauces, salads and as garnish. Its use in soups, in addition to enhancing the flavor, contributes to less need for added salt. Parsley cultivars are known for their high vitamins content such as pantothenic acid (B5), nicotinamide (B3), riboflavin (B2), ascorbic acid (C), thiamine (B1), pyridoxine (B6), beta-carotene (pro vitamin A), folic acid (B9), alpha-tocopherol (E), and minerals, essential oils, as well as various polyphenol compounds, mainly flavonoids [13,15]. Terpenes and phenylpropanoids are abundant in the oil extracted from parsley seeds, fruits, root and leaf. Myristicin and apiol, both belonging to phenylpropanoid class and showing antioxidant activity, are the main components of parsley essential oil [12]. Its chemical composition is very variable and depends on several factors, such as the influence of the growing conditions, different cultivars and chemotypes, geographic regions, and the plant organ [16]. Such variation accounts for the difference in the aroma of the various cultivars of curly parsley and Italian parsley. The curly variety is generally less aromatic [6].

The World Health Organization (WHO) guidelines recommend reducing the intake of salt (sodium) in the diet with the aim of contributing to better health. The excess of salt in the diet is associated with 1.89 million deaths each year [3]. A lesser amount of salt in food can be compensated by the addition of herbs and spices to provide greater flavor [5]. A greater awareness of the importance of diet in health should explain, at least in part, the greater consumption of herbs and spices and, consequently, the growth of the market. The global seasonings and spices market was valued in 2022 at US$37.26 billion. The annual growth forecast is 5.6% between 2023 and 2030. This expansion is due, in part, to the fact that the medicinal benefits of spices and herbs are finding more and more users among the world population, leading to greater consumption [17]. The parsley market will grow at a CAGR of 4.84% between 2022 and 2027; and the size of the market is forecast to increase by USD 1.19 billion [18].

Medicinal plants continue to be the first therapeutic resource in many regions of the world where access to basic health care is precarious [19]. Several reviews cite traditional uses of parsley in folk medicine in many countries. Leaves and stems are used to treat menstrual problems, bladder inflammation, renal dysfunctions, prostate inflammation, edema, arthritis and rheumatism, among other conditions [11,12,20]. Parsley is also used to combat diabetes and hypertension [21–23]. Scientific evidence confirms the popular use of parsley as a diuretic [24].

Recent review articles reveal an increase in number of studies on cardioprotective natural products, which partly reflects the interest in the search for more natural therapeutic agents, especially those present in plants used in food preparations or with long-standing ethnomedicinal support and with less likelihood of adverse effects [25–27]. In this context, the therapeutic potential of parsley, as well as its application in food products, has been revealed in the growing number of articles. It is important to highlight that in their vast majority, the variety of parsley used (curly leaf or flat leaf) is not specified by the authors. Given the importance of the knowledge on the chemical composition of parsley, its therapeutic profile for cardiovascular health as well as the potential of this herb for application in nutraceutical products, the lack of a review bringing together this accumulated information becomes an important topic for public health. Therefore, this review focuses on the state of the art of cardiovascular-related activities (antithrombotic, antihypertensive and lipid-lowering) demonstrated for parsley extracts, with the aim of discussing the potential use of this medicinal herb as a source of nutraceutical and/or food preservative products.

The searches were carried out in the PubMed database and Google Scholar, from 1946 to October, 2023, using the keywords "parsley" OR "Petroselinum crispum" combined with "cardiovascular", "anticoagulant", "antiplatelet", "antithrombotic", "antihypertensive" or "hypolipidemic". Research articles reporting antithrombotic, antihypertensive, and/or hypolipidemic activities of *Petroselinum crispum* were then selected for this review. In addition, to understand the currently or potential use of this species as nutraceutical, food additive, supplement and preservative, a search and a brief analysis of patents deposited around the world has been also

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conducted. The search was carried out employing the Derwent Innovation database, using the title, abstract and claims fields and "(Petroselinum or parsley) AND (nutraceutical* OR "food supplement*" OR "food additive*" OR preservative OR digestive)" as terms, combined also with the IPC code A23V, related to "Food compositions, function of food ingredients or processes for food or foodstuffs".

2. Chemical composition of parsley extracts

Aerial parts, leaves and seeds are the most used parts of parsley. These are also the most investigated in studies of biological activities. The majority of these studies were carried out with aqueous extracts, emulating the popular use of the plant, or extracts obtained with polar organic solvents (methanol and ethanol) [12]. This is also true for the studies related to the cardiovascular health, as discussed in the next topic.

The chemical composition of polar extracts of parsley leaves and aerial parts has been extensively investigated. Among the reported compounds, flavonoids stand out. A study conducted with a hydrolyzed methanolic extract of parsley aerial parts revealed that its major aglycone is apigenin [28]. Apigenin and its glycosides, especially apiin (apigenin-7-*O*-apioglucoside) and malonylapiin (Figure 1), where confirmed as major compounds in polar extracts from aerial parts or leaves of parsley by multiple studies [29–33], including those carried out by our group [34,35]. Bioavailability studies with human volunteers evidenced that apigenin can be detected in plasma and urine after parsley ingestion [36,37]. Thus, it is possible to presume that apiin and other apigenin glycosides present in the plant are metabolized into apigenin. This is indeed the fate of most glycosylated flavonoids after oral intake [38]. A recent study showed that the ingestion of a leaf parsley infusion or of parsley leaf powder mixed in yogurt resulted in the detection of apigenin metabolites (apigenin-4'-glucuronide and apigenin-7-sulfate) in plasma and urine of human volunteers. These metabolites probably are the outcome of apigenin release in the colon followed by phase II metabolism. The intake of pure apigenin mixed in hot water resulted in the same metabolites, however, its bioavailability was much lower in comparison with the flavone availability after parsley ingestion [39].

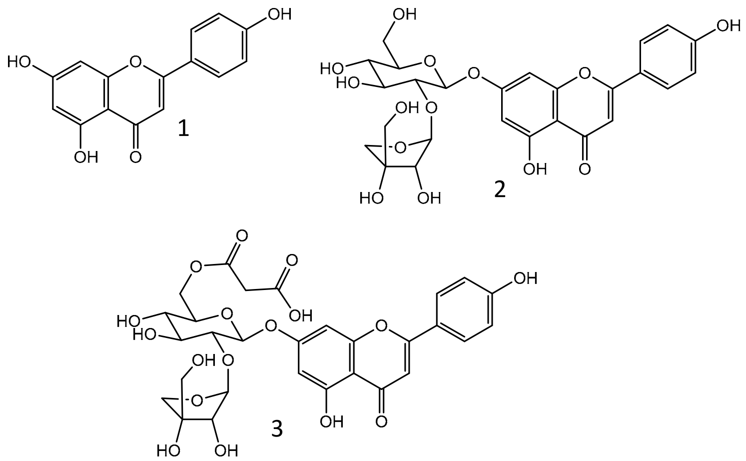

Figure 1. Chemical structure of apigenin (1) and its glycosides apiin (2) and 6''-*O*-malonylapiin (3).

Despite the predominance of apigenin derivatives, other flavonoids can be found in in polar extracts of parsley aerial parts and/or leaves, such as glycosides of luteolin, diosmetin, kaempferol, quercetin and isorhamnetin. Phenolic acids, coumarins and coumaric acid derivatives are also frequently reported [29–32,34,35,40]. Table 1 summarizes secondary metabolites identified in these extracts.

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Table 1. Secondary metabolites reported in polar extracts[1] of parsley aerial parts and/or leaves.[2.]

Chemical class	Compounds		Ref.
Coumarins	• Cnidilin • Isoimperatorin • Oxypeucedanin • Oxypeucedanin hydrate	• Pabulenol • Xantothoxin/bergapten* • Xantothoxol/bergaptol*	[34,41–43]
Flavonoids (*flavones*)	• Apigenin-7-*O*-apiosylglucoside (apiin) • Apigenin • Apigenin acetylapiosylglucoside • Apigenin acetylglycosides • apigenin-6,8-di-*C*-glucoside • Apigenin-7-*O*-glucoside (cosmosiin) • Apigenin *O*-glycosides • Apigenin *C*-glycosides • Apigenin-7-*O*-malonyl-apiosylglucoside (malonylapiin) • Apigenin malonylglycosides • Chrysoeriol-7-O-glucoside	• Chrysoeriol *O*-glycosides • Chrysoeriol-7-*O*-malonylapiosylglucoside • Chrysoeriol malonylglycosides • Diosmetin • Diosmetin 7-*O*-apiosylglucoside • Diosmetin-acetylapiosylglucoside • Disometin-7-*O*-glucoside • Luteolin • Luteolin-7-*O*-apiosyl-glucoside, • Luteolin-7-*O*-malonyl-apiosylglucoside	[29–32,34,35,40,42,44]
Flavonoids (*flavonols*)	• Isohramnetin-3-*O*-glucoside • Isorhamnetin 3-*O*-(6-*O*-malonyldiglucoside) • Isorhamnetin-dimalonyl-diglucoside • Isorhamnetin *O*-glycosides • Kaempferol • Kaempferol-3-*O*-[6´´- malonyl-apiosyl-(1→2)-glucoside]	• Kaempferol-3-*O*-glucoside • Kaempferol *O*-glycosides • Quercetin • Quercetin *O*-glycosides • Quercetin-*O*-malonylhexoside • Rutin	[29,32,40,42,44]
Phenolic acids and derivatives	• Caffeic acid • Chlorogenic acid • *p*-Coumaric acid • *p*-Coumaric acid 4-*O*-hexoside • *p*-coumaric acid derivatives	• Ferulic acid • Gallic acid • Syringic acid • Vanillic acid	[30,35,40,44]
Miscellaneous	• Apiole (phenylpropanoid) • Capsanthone (carotenoid) • Icariside F2 • Myristicin (phenylpropanoid)	• Petranol (monoterpene) • Petroselinic acid (Fatty acid) • Petroside (monoterpene glycoside) • Piperochromanoic acid (terpenoid)	[42,43]

[1] Extracts obtained with water, ethanol, methanol or hydroalcoholic mixtures; [2] Some compounds were not fully characterized and are thus referred as glycosides or derivatives. *Isomers were not differentiated, both are possible [43].

It is also noteworthy that most studies do not take into consideration the parsley variety investigated, hindering thus comparison among them. Interestingly, in a recent study, Liberal et al. (2020) [29] assessed the phenolic composition of hydroethanolic leaf extracts of different cultivars from three varieties of parsley (flat-leaved, curly-leaved and turnip-rooted). The HPLC-MS/MS

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analysis revealed seven flavonoids in all cultivars: three apigenin glycosides and four kaempferol glycosides. All of them, regardless of the variety, had apigenin-*O*-pentoside-*O*-hexoside, which probably corresponds to apiin, as the major detected phenolic. Moreover, great quantitative variability were detected among cultivars of each variety [29].

The chemical composition of aqueous and hydroalcoholic preparations of parsley seeds have been much less investigated, despite their ethnomedicinal use and the several pharmacological studies carried out with them. Early studies of parsley seeds revealed apiin as one of its constituents. The compound was extracted from defatted seeds with ethanol and then purified and crystalized [45]. Fixed and essential oils of parsley seeds have been thoroughly characterized. The last has shown a high content of apiole [46,47]. The components of these oils, however, are expected to represent only a minor fraction of polar extracts due to their limited solubility in water and hydroalcoholic mixtures.

3. Parsley and the cardiovascular health

Over the last twenty years, there has been a notable advance in knowledge of the beneficial properties of parsley for cardiovascular health. The studies began with the investigation of the *in vitro* protective effects of parsley on thrombosis. Later, *in vivo* studies have proven the antithrombotic activity of parsley extracts. The cardioprotective profile of parsley was strengthened with the proof of its antihypertensive effects *in vivo*. More recently, it was possible to show that parsley also contributes to improving lipid parameters, which are closely related to coronary heart disease and stroke. The studies reporting antithrombotic, antihypertensive, and hypolipidemic activities of parsley are summarized in Table 2. They were conducted with aerial parts, leaves and seeds from parsley and, in most of them, aqueous extracts were employed. Additionally, more than half of these studies were based on animal models. This provides more robust evidence for the possible effects of parsley in the cardiovascular system since *in vitro* activity does not always translate into *in vivo* effects. In the following subsections, these studies will be further discussed. Moreover, since apigenin and its derivatives seem to be major compounds in parsley, cardiovascular-related activities of this flavone will be discussed alongside the effects reported for parsley extracts.

Table 2. Cardiovascular health-related studies carried out with parsley extracts or fractions.

Activity	Plant part	Type of extract	Type of study	Main outcomes	Ref.
Antithrombotic	Aerial parts	Infusion (5.5 g in 100 mL); 30 min	*In vitro*	Inhibition of thrombin and ADP-induced platelet aggregation (IC_{50} 6.4 and 6.7 mg/mL, respect.)	[48]
	Leaves	Infusion (10% w/v); 30 min	*In vivo* and *ex vivo* (rats)	A 2-fold increase of bleeding time after a single oral dose (3 g/kg) increase of approx. 20% in thrombin, ADP and collagen-induced platelet aggregation in blood collected from treated rats.	[49]
	Leaves	Decoction (10% w/v); 10 min	*In vitro*	Inhibition of ADP-induced platelet aggregation (IC_{50} 1.81 mg/mL); apigenin and cosmosiin isolated from the extract also inhibited ADP-induced aggregation (IC_{50} 0.036 and 0.18 mg/mL, respect.)	[34]
	Leaves	Fraction enriched in aglicone flavonoids	*In vitro*	Inhibition of thrombin, ADP, and collagen-induced platelet aggregation (IC_{50} 0.16; 0.28 and 0.08, respect.)	[50]
	Aerial parts	Decoction (30% w/v); 10 min	*In vivo* and *ex vivo* (rats)	An oral dose (125 mg/kg), 60 min before venous induction inhibited thrombus formation by 76.2%. In arterial thrombosis model, the oral doses of 15 or 25 mg/kg, 60 min before induction, increased the carotid artery occlusion time by 150% and 240%, resp. Treatments produced antiplatelet (recalcification time *ex vivo* assay) but not anticoagulant activity (PT and aPTT *ex vivo* assays).	[35]
Antihypertensive	Seeds	Infusion (20% w/v); 5 min	*In vivo* (rats)	Treatment with 1 mL extract orally produced approx. 20% reduction in blood pressure after 90 min. Effect related to diuretic activity.	[51]
	Leaves	Decoction (1% w/v); 10 min	*In vivo* (rats)	A single oral dose (160 mg/kg) reduced systolic and diastolic pressure of hypertensive rats in approx. 20%, while daily treatment	[23]

				for seven days (160 mg/kg) resulted in a 30% decrease in the 7th day. Effects possibly related to vasodilatory activity.	
Hypolipidemic	Leaves	Decoction (10% w/v); 30 min	*In vivo* (rats)	Diabetic rats orally treated with a daily dose (2g/kg b.wt.) of extract for 45 days showed levels of TC, TG, LDL and HDL similar to untreated normal rats.	[52]
	Seeds	Methanol extract (20% w/v); 5 days in low temperature	*In vivo* (rats)	Oral administration of extract partially prevented the effects of hypercholesterolemic diet; Treated rats showed 20-30% lower levels of TC, TG, LDL, and VLDL and 20% higher HDL approx.*	[53]

* Acronyms: TC: total cholesterol, TG: triglycerides; LDL: low-density lipoprotein; VLDL: very-low-density lipoprotein; HDL: high-density lipoprotein.

3.1. Antithrombotic activity

Thrombosis consists in the formation of a blood clot within an arterial or venous vessel. The consequent limitation of blood flow can result in major life-threatening events such as myocardial infarction, ischemic stroke, and pulmonary embolism [54,55]. Free blood flow in vessels is maintained by a complex homeostasis in which many factors take part: platelets, endothelial cells, plasmatic proteins, coagulation factors, cytokines, among others. Imbalances in this physiologic processes result in a higher risk of thrombosis [54]. The widespread nature and the high mortality and morbidity of thrombosis-related events make prevention strategies for thrombosis a major goal to reduce its global burden [55]. Furthermore, the pharmacological management of arterial and venous thrombotic conditions, which rely mainly on antiplatelet and anticoagulant agents, can be limited by side effects, such as increased risk of bleeding [56,57]. Thus, the search for new therapeutic agents to prevent and/or treat thrombosis has attracted much attention recently.

The first evidence we retrieved of the activity of parsley in the hemostatic system comes from an *in vitro* study (Table 2). Mekhfi *et al*. (2004) [48] demonstrated that an infusion from aerial parts of parsley is able to inhibit thrombin and ADP-induced platelet aggregation (IC_{50} 6.4 and 6.7 mg/mL, respectively). Later, interdisciplinary studies developed by the teams of Sônia S. Costa and Russolina B. Zingali showed the *in vitro* antiplatelet activity of a parsley (flat leaves variety) leaf decoction and two of its flavonoids: apigenin and comosiin (apigenin-7-*O*-glucoside), which had IC_{50} values of 1.8, 0.04 and 0.2 mg/mL, respectively, in ADP-induced aggregation assay. The extract and flavonoids showed no anticoagulant effect, on the other hand, having not prolonged the clotting time in PT and aPTT assays, used to assess coagulation pathways [34]. In addition, a study showed that a fraction of aglicone flavonoids from parsley, among which apigenin and kaempferol were identified, evidenced *in vitro* inhibition of thrombin, ADP, and collagen-induced-platelet aggregation, with IC_{50} values ranging from 0.28 to 0.08 mg/mL [50]. Therefore, flavonoids, especially apigenin, seem to have an important contribution to parsley *in vitro* antiaggregant effects.

The antiplatelet activity of parsley was later confirmed by *in vivo* studies. Gadi *et al*. (2009) [49] showed that a parsley leaf decoction orally administered to rats (3 g/kg) was able to reduce in around 20% thrombin, ADP, and collagen-induced-platelet aggregation 2 hours after administration, while rats treated with aspirin showed approximately 40% reduction in this parameters. The treatment with parsley also doubled the bleeding time, an effect attributed by the authors to the antiplatelet activity. The phytochemical composition of the extracts employed in this study was, however, not assessed.

Recently, the antithrombotic activity of a decoction from aerial parts of the flat-leaved variety of parsley in rats in the laboratories of Russolina B. Zingali and Sônia S. Costa [35]. This extract (PC) was chemically characterized by HPLC-DAD-MS/MS, having apiin (major phenolic substance) and coumaric acid derivatives as the main identified compounds. In a model of arterial thrombosis, oral administration of PC at 15 and 25 mg/kg, 60 minutes before thrombosis induction, resulted in an increase of artery occlusion time by 150% and 240%, respectively. The assays conducted with the blood collected from animals similarly treated (same doses, administration routes and time before collection) revealed that PC was able to increase recalcification time of platelet-rich plasma (58.2% increase), but not of platelet poor plasma, thus corroborating previous findings of antiplatelet effects of parsley extracts. It is noteworthy that these effects were obtained with a much lower dose than those used in the study of Gadi et al. [49]. This can be attributed to differences in the chemical composition of the extracts, resulting from distinct extraction processes (infusion vs decoction) and/or variation in the chemical composition of the plant itself. However, this earlier study provides no information on the parsley variety evaluated nor on the chemical composition of the extract, which hinder comparison.

The effect of parsley in the venous thrombosis model was also evaluated in the same study. The intravenous administration of PC to rats at 25 mg/kg, 5 min before thrombosis induction, reduced thrombi formation in 98.2%, while the oral administration at 125 mg/kg, 60 minutes before induction, produced a reduction of 76.2%. Since coagulation plays a major role in venous thrombosis, the anticoagulant activity of PC was also evaluated in blood collected from experimental animals similarly treated, by means of PT and aPTT assays. No anticoagulant activity was observed, confirming previous *in vitro* results [35]. It is noticeable that the effects of PC on venous thrombosis were obtained with a 5 times higher oral dose than that in which arterial thrombi formation was prevented. In summary, this study evidenced the *in vivo* antithrombotic activity of parsley in both arterial and venous models, however, only antiplatelet activity was observed, with no alteration in the coagulation process. Platelets are known to have a prominent role in arterial thrombosis, but are also recognized to take part in venous thrombosis [54,58]. Therefore, the antiplatelet activity of parsley extracts may contribute to prevention of both types of thrombosis.

As suggested by some of the studies above discussed, apigenin and its derivatives, which are likely metabolized into apigenin, seem to be in some measure responsible for the antithrombotic activity of parsley. The effects of apigenin in platelet aggregation have been investigated *in vitro*. The antiplatelet activity of the flavone seems to be related to its capacity to block thromboxane A2 (TxA2) receptors [59,60] and to interfere with thrombin intracellular signaling without interacting with thrombin receptors [61]. Interestingly, it also showed the ability to potentiate the antiaggregant effects of aspirin, as assessed in platelets *in vivo* exposed to aspirin and *in vitro* incubated with apigenin [59]. In a recent study, an apigenin-based formulation, containing the flavone esterified with docosahexaenoic acid (4'-DHA-apigenin) in olive oil evidenced a more potent *in vitro* antiaggregant activity and a better bioavailability than pure apigenin [62]. It would be interesting to prepare and evaluate the effects of apigenin-rich parsley-based formulations in future studies, as they may also present improved properties in comparison with the isolated flavone and the extracts not incorporated in a formulation.

3.2. Antihypertensive activity

Hypertension, defined as arterial blood pressure values of 140/90 mmHg or higher, is the most common risk factor for cardiovascular diseases (e.g.: stroke and heart failure) and also the one with the strongest evidence for causality [63–65]. According to WHO estimates, approximately 1.3 billion people between 30 and 79 years of age have hypertension, among which less than half are aware of the condition and receive proper treatment [64]. Many antihypertensive drugs are available, such as angiotensin-converting enzyme inhibitors, diuretics, and calcium channel blockers [66]. Nevertheless, lifestyle interventions, particularly in the nutritional level, play a prominent role in prevention and management of hypertension [65].

The effects of parsley in arterial blood pressure were assessed in two *in vivo* studies (Table 2). Campos *et al*. (2009) [51] evaluated the outcomes of an oral single dose (1 mL) of a parsley seed infusion in rats. The extract had a hypotensive effect (arterial pressure values around 20% lower than the control group) and also increased the urinary flow and the sodium and potassium excretion. Hypertension is related to the retention of sodium and consequently water and, therefore, diuretic drugs are used to its management [67]. Seeds and leaves of parsley have evidenced diuretic activity in previous studies as well [24,68]. Probably, this activity is at least partially related to the hypotensive effect of the plant.

A more recent study evaluated the effects of a parsley leaf decoction orally administered to normotensive and L-NAME-induced hypertensive rats in a single dose or once daily during seven days (subchronic test) [23]. In normotensive rats, a single dose (160 mg/kg) had no significant effects in blood pressure. Hypertensive rats, on the other hand, showed an important reduction in both systolic and diastolic pressure, resulting in values similar to those of normotensive rats, an effect comparable to the positive control drug (Lasilix®). The repeated oral administration of parsley extract (160 mg/kg) showed similar results in hypertensive rats. In this case, however, a reduction of around 15 - 20% was also observed in the blood pressure of normotensive animals. The study also reported the *in vitro* effects of the extract in rat aortic rings, having observed a vasorelaxant activity through blockage of calcium channels. The authors state that this mechanism leads to the hypotensive effects revealed, however, this was not confirmed *in vivo*. The possible contribution of diuretic activity, as previously mentioned, can also play a role for the hypotensive effects of parsley leaves and should be considered for further investigation as well.

Since aqueous extracts from parsley leaves and seeds presented hypotensive activity, it is possible to infer they share the same bioactive substances. Indeed, apiin was shown to be present in both leaves and seeds from parsley (see Section 2). However, it is not impossible that different bioactive substances respond for these effects. The correlation between the chemical composition and the hypotensive activity of extracts from different plant parts should be object of future studies to clarify this issue.

Apigenin may also play a role in the antihypertensive activity of parsley. The flavone showed *in vitro* vasorelaxant activity in rat aortic rings [69]. An *in vivo* study with a renovascular hypertension mouse model showed that the treatment with apigenin (50-100 mg/kg; *p.o.*) for 4-weeks resulted in a reduction of blood pressure and an improvement in cardiac hypertrophy and abnormal glucolipid metabolism, which are consequences of the adaptative response to heart pressure overload. The mechanism of these effects seems to be related with the downregulation of HIF-1α expression. This hypoxia inducible factor is overexpressed in the cardiac hypertrophy process, which in its turn alters the expression of peroxisome proliferator-activated receptors (PPARα and PPARγ). The expression levels of the later were also regulated by apigenin treatment [70].

In another *in vivo* study, the effects of a much lower apigenin dose (1.44 mg/kg; *p.o.*; 6 weeks) was evaluated in L-NAME-induced hypertensive rats. In this model, also used to evaluate the effects of parsley [23], hypertension is induced by nitric oxide (NO) deficiency, an event that is observed in endothelial dysfunction [71]. Animals that received apigenin showed lower blood pressure, better vasodilatory response, lower sodium retention and less renal and cardiac damages than the control group, an effect probably related to an increased production of NO [72]. The same researchers carried out a similar study with a different hypertension model (spontaneous hypertensive rats) and obtained markedly different results. In this model, in which hypertension is a result of elevated peripheral vascular resistance and not NO deficiency, apigenin (1.44 mg/kg; p.o.; 6 weeks) produced no significant reduction in blood pressure. It presented, however, moderate benefits, such as improving aortic vascular relaxation and reducing vascular abnormalities. This contrasting results evidence that the effects of apigenin in attenuating hypertension and improving vascular function are more efficient in cases of NO deficiency, since this flavone seems to induce NO production [73]. It would be interesting to evaluate the effects of parsley extracts in this hypertension model as well. If apigenin and its derivatives are the main responsible for parsley bioactivity, similar results can be expected. On the other hand, since other phenolic can take part in the activity, their possible role could also be assessed in the case of divergent results.

3.3. Hypolipidemic activity

Dyslipidemias consist in a range of lipid abnormalities: high plasmatic concentrations of total cholesterol, LDL-cholesterol and/or triglycerides, as well as low HDL-cholesterol levels [74,75]. They represent a major risk factor for coronary heart disease and stroke. In 2019, it is estimated that 44% of global deaths caused by ischemic heart disease were related to high LDL-cholesterol levels [74]. Management of dyslipidemias include lifestyle modifications and often lipid-lowering drugs, mainly statins [74,75]. Nutraceuticals such as plant sterols and soluble fibers can also improve lipid profiles, representing an additional tool in management and prevention of dyslipidemias [76].

Two *in vivo* studies have evidenced the hypolipidemic potential of parsley extracts (Table 2). A dry methanolic seed extract resuspended in water and Tween 80 orally administered for 8 weeks to

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rats with a hypercholesterolemic diet had remarkable effects in their lipid levels. As expected, the cholesterol-enriched diet induced an increase in total cholesterol, triglycerides, LDL and VLDL-cholesterol, as well as a reduction in HDL-cholesterol. The deterioration of the lipid profile was, nevertheless, partially prevented by the treatment with parsley seed extract. Treated animals also exhibited an improvement in liver function, resulting in less damage and inflammation in hepatic tissues histologically evaluated, as well as lower activity of liver enzymes – alanine transaminase (ALT), aspartate aminotransferase (ASP), and alkaline phosphatase (ALP) - which were also affected by the hypercholesterolemic diet. An additional effect of the parsley seed extract was cardioprotection: treated animals showed lower levels of lactate dehydrogenase, an enzyme related to myocardial damage, and less detrimental effects to heart tissue in comparison with the control group, whose myocardial muscles showed marked degeneration [53].

In another study, an aqueous extract of parsley leaves had its effects evaluated in normal and streptozotocin-induced diabetic rats [52]. Diabetes is often associated with dyslipidemias, which increase the risk of atherosclerotic cardiovascular disease among diabetic patients [77]. In the above-mentioned study, diabetic rats presented higher levels of total cholesterol, triglycerides and LDL-cholesterol, as well as lower levels of HDL-cholesterol in comparison with non-diabetic rats. Normal rats treated with parsley leaf extract (2g/kg) for 45 days presented a slight reduction in total cholesterol and triglycerides, while the effects on diabetic rats were outstanding: their lipid levels were normalized by parsley treatment and the results were more pronounced than those obtained with gliclazide, an antidiabetic drug used as positive control [52]. As the authors did not assess the glycemic levels of treated animals, we cannot know if the effects of parley in lipid levels were associated with a reduction of glycemia, as it probably occurred in the group treated with gliclazide. Therefore, it is not possible to infer if the observed effects were secondary to a better glycemic control, resulting in an improvement of the metabolic imbalances that typically result from uncontrolled diabetes or if the parsley leaf extract acted in lipid levels by direct mechanisms. It is actually possible that both options take place: parley is known to possess antihyperglycemic activity, as previously mentioned, and as evidenced by the study above discussed, parsley seed extract can also improve lipid profiles in a non-diabetes model. If confirmed, a dual antihyperglycemic and hypolipidemic action would be particularly interesting for type 2 diabetic subjects, as most of them have lipid abnormalities, despite a good glycemic control [78]. However, the studies reported so far were conducted with different plant parts (leaves and seeds) and different solvents for extraction. Thus, the differences in the chemical composition of the evaluated extracts, even though some common substances may occur (section 2), do not allow further assumptions to be made. This issue should be clarified by more studies of the effects of chemically characterized parsley extracts in diabetic and non-diabetic animal models.

The hypolipidemic effects of parsley might also be partially attributed to apigenin and its derivatives. This flavone has evidenced similar effects in animal models with diet-induced metabolic disorders. High-fat diet-induced obese mice whose food was supplemented with 0.005% w/w apigenin for 16 weeks showed lower plasmatic levels of total cholesterol, free fatty acids, and apolipoprotein B (a component of lipoprotein particles) in comparison with the control group. Apigenin also improved glucose tolerance and hepatic function in treated animals [79]. Similarly, rats with high-fructose diet induced metabolic syndrome fed with apigenin (2.6 mmol/kg diet) for 13 weeks showed marked lower levels of total cholesterol, LDL-cholesterol, and free fatty acids, as well as higher levels of HDL-cholesterol and improved glucose metabolism [80]. Moreover, a study carried out with hamsters kept in a high cholesterol-diet showed the treatment with apigenin for nine weeks (60 and 300 ppm of diet) resulted not only in lower non-HDL-cholesterol levels but also a 30% reduction in aorta plaque formation in comparison with the control group [81].

An additional study conducted experiments differently: instead of apigenin administration simultaneously with high-fat or high-fructose diet, the authors treated rats already submitted to a 12-week high-fat diet with different doses of apigenin (20, 40 and 80 mg/kg) for six weeks. The flavone produced a dose-dependent reduction in the plasmatic levels of total cholesterol, triglycerides, and LDL-cholesterol, as well as an increase in HDL-cholesterol. The effects produced by the highest dose

(80 mg/kg) were comparable to those exerted by the positive control drug (simvastatin). These results evidence that apigenin could both prevent and treat hyperlipidemia.

4. New parsley-based nutraceuticals and food products: cultivation conditions, applications, patents, and technological aspects

The health-promoting action of parsley extracts and its constituents in different cardiovascular conditions, combined with the fact that it is a culinary herb, has prompted studies aimed at the potential application of parsley in the development of dietary supplements and fortified food products in the recent years. In addition, several patents focused on the use of this herb, alone or in combination with other herbs as food supplements, preservatives, or related products, have been deposited around the world.

Conventionally, parsley is used as a fresh culinary herb, being produced under environmental or in greenhouse conditions and, more recently, also hydroponically [82]. Due to the commercial importance of this herb, the producers urge the development of "improved production recipes" that take several environmental parameters into account, in order to produce better quality herbs, also enriched with bioactive molecules. In this sense, the recent modulation of light conditions can be cited [82]. For example, evaluating the effect of different light qualities in parsley microgreens, Samuolienė et al. [83] observed that the application of red light at 665 and 638 nm during the cultivation improved the β-carotene content and DPPH antioxidant activity of this herb [84]. In another study, a treatment with blue light (16%) increased the total tocoferol content of parsley microgreens, while higher percentage of blue light (33%) resulted in higher content of chlorophylls a and b, carotenoids, α- and β-carotenes, lutein, violaxanthin and zeathin [83]. Also working on parsley microgreens, Carillo et al.[85] showed that the mixture of red, green, yellow and blue light resulted in higher amounts of secondary metabolites, especially the total polyphenol content and the amounts of apigenin derivatives. Not only the light, but the application of other conditions has been also described as tools for improving the nutraceutical value of parsley leaves. The application of *Streptomyces fulvissimus* (strain AtB-42) and *Trichoderma harzianum* (strain T22) microorganisms in consortium under field conditions increased the content of some metabolites, including the carotenoid capsanthone [43].

Parsley is often freshly applied to food products, in certain cases to limit cholesterol oxidation caused by the cooking process, due to the high content of phenolic compounds and great antioxidant activity of parsley leaves. In this sense, the addition of fresh parsley (4% w/w) in grilled sardines effectively reduced cholesterol oxides formation in the final product [86]. A similar result was observed for omelets, for which the potential application of fresh parsley (at 0.75% w/w) as a natural inhibitor of cholesterol and lipid oxidation was described [87]. The authors observed the thermo-degradation of parsley phenolic compounds after cooking, with the preparation using air-frying conditions being the best one for preserving these metabolites.

Powdered parsley leaves have been proposed as a functional ingredient for fortification of wheat-based products as well [88–90]. Despite their important role as an energy source in human nutrition, these products are poor in bioactive compounds, and their fortification, especially with phenolic-rich ingredients, is therefore envisaged [88,89]. As an example of this application, Sęczyk et al. [88] evaluated the effects of dried-parsley supplementation on the nutraceutical and nutritional properties of wheat pasta. The parsley leaves employed were rich in apigenin, diosmetin and isorhamnetin derivatives, as wells as catechin, and most of them remained bioaccessible after simulated digestion. Pasta fortified with 4% of parsley leaf powder, after simulated digestion, was characterized by 67% more phenolics and a significantly higher antioxidant activity, as evidenced by a 146% increase in antiradical activity (ABTS assay) and a 220% increase in reducing power (FRAP assay). The supplementation did not affect starch digestibility but reduced protein digestibility, probably due to the interaction of phenolic compounds with proteins, including digestive enzymes [88].

In a similar study, the supplementation of wheat pasta with parsley leaf powder (2.5 – 10%) resulted in a concentration-dependent increase in its phenolic content and antioxidant activity. The authors also investigated the impact of the supplementation on the cooking quality and texture of the

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pasta. It resulted in color alteration, a reduction of its cooking time and hardness, as well as an increase in its adhesiveness and water absorption capacity. Most of these effects may be associated with changes in pasta composition and microstructure, such as an increased fiber content and reduced gluten proportion. Despite these differences, when evaluated for organoleptic properties, all the supplemented pasta were considered overall acceptable by evaluators. The pasta fortified with 5% parsley was considered the best compromise between nutraceutical quality and physical/organoleptic characteristics [90].

When regarding wheat-derived products, parsley powdered leaves were evaluated as an additive for bread. Breads prepared with flour containing 1-5% parsley were investigated for chemical composition, physical and sensorial properties [89]. Parsley-supplemented breads had a higher mineral and fiber amount but were similar to control bread in fat and protein content. The supplementation resulted in a decrease in the bread volume and an increase in the crumb moisture. Similar to what was observed for parsley-fortified pasta, these differences are probably associated with gluten dilution and an increased fiber content, which, in this particular case, would cause a reduction in dough capacity to retain carbon dioxide and an increased ability to retain water, respectively. The greenness and redness of the crumb were also altered by parsley supplementation due to the influence of plant pigments, however, no significant changes in crumb texture were observed. When evaluated for sensory properties, bread with up to 3% parsley were considered overall acceptable, while higher parsley proportions resulted in lower scores particularly for their smell and taste. Furthermore, the supplementation resulted in breads with a higher phenolic content and antioxidant activity. Particularly, the bread with 3% parsley had around two times more phenolic compounds [89].

All these studies evidence that parsley can be an interesting supplement for pasta and bread, as it is a source of bioaccessible phenolics and result in products that, regardless of some property changes, have adequate sensory acceptability. However, although the interest and potential of application of *P. crispum* leaves for the supplementation of food products [88–90], more research as well as the development of commercial food supplements using this herb is needed, being a niche to be explored.

In fact, conventional spice powders may impose issues that hinder their utilization, what could explain the low currently use of parsley as food supplements and similar products. One of the issues that can be mentioned is the drying process, a key step for food products preservation and applications [91]. The drying process, however, can cause loss of volatiles and pigment degradation, thus impairing color and flavor. Moreover, endogenous enzymes are only partially inactivated and may recover activity once the product is rehydrated. Considering this, some studies are proposing better techniques to dry parsley material, or alternatives for its use in food products.

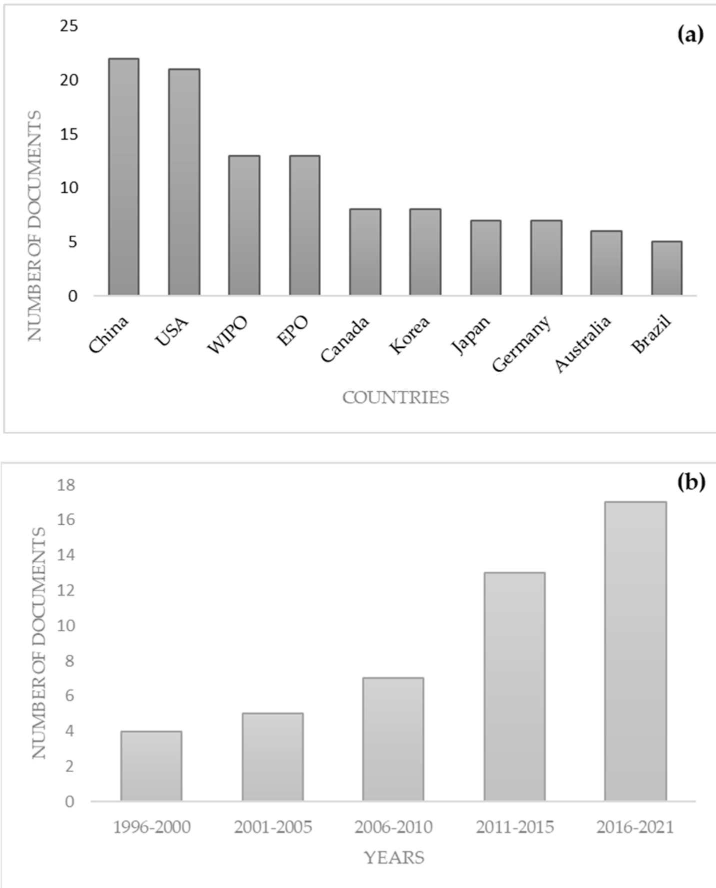
Regarding to the drying process, Mouhoubi and co-workers [92] recently showed that the use of microwave at 100W is the best way for drying parsley leaves without substantial modifications in polyphenol content and in antioxidant activity, when compared with ventilated oven under three temperatures (40, 80 and 120 °C) and the microwave at 500 or 1000W conditions. In fact, the use of microwave in parsley dryness has been already evaluated in a previous study [93].

Some other food products containing parsley leaves have been also investigated. Kaiser et al. [94] proposed paste-like parsley products as an alternative to powdered parsley. The authors evaluated different production processes: mincing fresh parsley followed by a heating step (80-100 °C), and steam or water-blanching (80-100 °C) of the plant material followed by mincing. The water bleaching process was considered the most suitable, since the resulting paste-like product had a brighter color and a higher pigment retention. At 90 and 100°C (but not 80 °C), a complete inactivation of peroxidase and polyphenol oxidase was observed. This process also enhanced the antioxidant activity of the samples, in spite of a decrease in the phenolic content [94]. The chemical composition of paste-like products obtained with bleaching processes were further evaluated by the authors. They observed that short-time (1 min) steam-and water bleaching had minimal effect on the phenolic composition, except for apiin, whose content is reduced. Thus, they recommend blanching for the production of parsley paste-like products [30]. These paste-like products may indeed confer advantages for the industrial application of parsley in the production of food and nutraceutical products, providing more chemical stability and microbiological safety for the raw plant material. However, the effects of the production process in the phenolic composition of the plant should be further evaluated regarding their possible impact on its biological activities.

It is important to mention that the application of new technologies and formulations can also be an alternative to be explored. Herbal supplements can be formulated into different delivery systems, which are able to enhance the stability, solubility and bioavailability of their active compounds [95]. Helmy et al. [96] evaluated the properties of silver nanoparticles synthetized with parsley extract. Silver nanoparticles are known to exert multiple biological activities and can be applied in the preparation of food, drugs as well as cosmetics [96,97]. In this study, silver nanoparticles prepared with a parsley aqueous extract in combination with corn silk and gum arabic extracts showed greater antioxidant, antimicrobial and anti-inflammatory activity than any of the plants crude extracts alone or combined [96]. Thus, silver nanoparticles can be considered a potentially useful system for parsley-based nutraceutical formulations.

Regarding the technological development of products based on parsley, the search for patents resulted in 186 documents containing the terms of interest. However, after reading the abstracts and specific claims of the patents, only 46 documents were selected. These documents consisted of food supplements, nutraceuticals, additives, and receipts adding parsley.

Most of these 46 documents were deposited in China, followed by the United States, the World Intellectual Property Organization (WIPO) and European Patent Office (EPO) offices (Figure 2a). In fact, most of the patents were from China, following a global tendency for many other areas [98]. These documents were related to the use of parsley in several food preparations, including pasta, fish, shrimp, among others. The documents' publication date indicates a trend toward more patent deposits in the previous ten to fifteen years (Figure 2b), with firms and natural persons making up most of the assignees (Figure 2c).



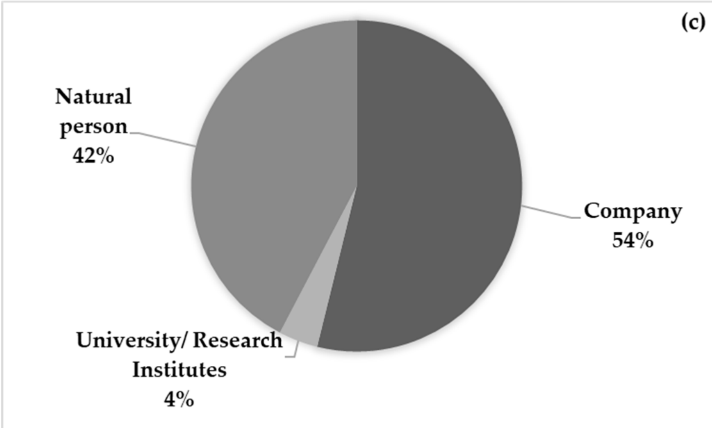


Figure 2. Details of the 46 patents searched in Derwent Innovation database, using the title, abstract and claims fields and the following strategy: (Petroselinum OR parsley) AND (nutraceutical* OR "food supplement*" OR "food additive*" OR preservative)" and the IPC code A23V. (a) Countries of deposit; (b) publication date; (c) assignees details.

After carefully checking all 46 documents, it was observed that 13 patents (Table 3) adequately described and focused on compositions using parsley as an ingredient for application as food supplements, dietary supplements, nutraceutical products, functional foods, or food additives.

Table 3. Details of the selected patents using parsley in food supplements, additives, or nutraceutical compositions.

Patent number	Year	Status	Type of product	Application	Plant use	Plant part
WO22079063	2020	Not granted	Extract	Food emulsifiers	Extract	Leaves
WO18172998	2017	Granted/ Not granted	Composition	Dietary supplement	Extract	Plant
WO18083115	2016	Granted/ Not granted	Herbal composition	Food supplement, nutraceutical	Dry plant	Fruits
CN105942235	2016	Refused	Composition	Appetite promoting	1-2 parts of plant	Leaves
KR20180067916	2016	Not granted	Herbal composition	Functional food	Fresh plant	Leaves
US2016242440	2015	Cancelled	Food additive composition	Food enhancer	5-15% of plant	Not described
US2016166602	2014	Cancelled	Composition	Dietary supplement	0.1-0.8% of plant	Not described
US2016015763	2011	Cancelled	Nutraceutical formula	Nutraceutical	Extract	Root
US2008219964	2006	Dead, suspended	Ingestible product	Nutraceutical	Fresh plant	Leaves
EP1616489	2004	Cancelled	Composition	Food supplement/additive	Extract	Not described
EP1602364	2004	Cancelled	Microcapsules	Food supplement	Extract	Not described
WO9850054	1997	Expired, dead	Nutritional composition	Nutraceutical	Extract	Plant
EP0799579	1996	Expired	Composition	Food supplement	Extract	Not described

In most of these documents, generally deposited by companies, parsley is used in association with other herbs. Only two documents include the possibility of using parsley as the only herb (EP1616489 and EP1602364). Few documents are currently alive, with most of them dead, suspended, cancelled, refused, or expired. Moreover, few are under evaluation (not granted). Regarding the type of products developed, most of the technologies described are for compositions, but extracts and microcapsules also appears as formulations. These different compositions have application as several food products, especially as food or dietary supplements (6) and functional food or nutraceutical (4), but other applications in food sector were also described, for example as food emulsifiers or additives (Table 3).

Several documents do not mention the part of parsley used in the composition, while those documents which detail this aspect mostly employ leaves (Table 3). It is interesting to observe that some other plant parts are also considered, such as fruits and roots, as well as the entire plant. Although leaves, fruits, roots, or the entire plant can be used as fresh or dry materials, most of the documents are focused on the plant extracts. This could be explained by the fact that extracts are better suited for use in plant-based formulations. Using plant extracts provides for greater quality control, larger-scale and regulated production, better transportation and storage, and the avoidance of mold and other microbial contamination [99].

Among the 46 documents analyzed, we found a recent patent (WO22103901) describing the use of apigenin isolated from parsley, an important bioactive compound, as a constituent of a nutritional supplement with nutraceutical application for support and protection of the immune system. In fact, there is a product related to this patent being sailed online with the commercial name STEMRCM®, produced by the company STEMSATION, the assignee of the patent [100].

The results of the patent analysis show that since 1996 there is an increased interest in the use of parsley in food products, some of them generically addressed to health improvement. The innovation in the use of parsley in food stuff are increasing throughout the years, but most of the patents in the area are specially focused on the application of this plant species in food preparations (such as dishes), much more than in finished goods (for instance nutraceutical formulations). Considering the whole importance of parsley, especially in cardiovascular conditions, the development of parsley-based food products is a market niche to be explored and developed by the food industry.

6. Conclusion

The role of parsley - aerial parts, leaves, and seeds - in diseases directly linked to cardiovascular problems is undeniable. The pharmacological data available today encourage a deeper study of the effect of parsley formulations with a view to the global assessment of parameters such as glycemia, lipidemia, hemostasis and hypertension. The efforts that have been made aiming the production of parsley-based food supplements show the potential of this herb in the development of formulations that contribute to the preservation of health. Despite the existence of several patents focused on parsley, few of them describe the use of the plant in formulations, and none of those are applied for the prevention of cardiovascular conditions. In this current state of knowledge, parsley can be considered a strong candidate for the development of an herbal formulation for the cardiovascular health promotion.

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