Phytochem Rev
https://doi.org/10.1007/s11101-023-09892-x

Edible fruits and berries as a source of functional polyphenols: current scene and future perspectives

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Received: 15 November 2022 / Accepted: 11 September 2023

Abstract In recent years, there is a growing interest in nutraceutical-rich functional foods for promoting human health. Wild fruits and berries are excellent sources of phytochemicals even though the most deeply studied are the polyphenolic compounds, among them, the major ones such as flavonoids, anthocyanins, or tannins. This review aimed to comprehensively analyze the currently available literature on wild edible fruits and berries, since these fruits are characterized for their high content of polyphenolic compounds. Moreover, both intrinsic (ripening and genetic variability) and extrinsic (environmental conditions: habitat, light, temperature) factors where considered since they affect the polyphenolic content in these fruits. Besides, the therapeutic potential of berries for treating human diseases was assessed through the revision of in vivo and in vitro assays and clinical studies, having in mind that most of these effects are exerted due to their antioxidant capacity. Furthermore, recent challenges and future trends on the research and utilization of wild fruits and berries were addressed to complete the overview of this sustainable source of natural

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ingredients. Finally, ScienceDirect, Scopus, and Google Scholar were the databases used for the compilation of the information present in this review, selecting the more recent studies and comparing from a critical point of view, the information found. Thus, this review compiled information of berries regarding their polyphenolic content and the variations this suffer depending on different variables; the potential use of the berries for a therapeutic application; and the trends and challenges that the use of berries faces after the research done.

Keywords Berries · Nutraceuticals · Antioxidant · Polyphenols · Clinical studies · Bioactivity

Introduction

The chemical composition of food presents a wide variety of bioactive compounds of significant importance for human nutrition and health. The deeper study of the biological properties of these biomolecules has prompted the development of innovative products in the food industry whose presence has become evident in the markets. In the last years, consumers have demanded healthy and sustainable products, therefore, to attend these claims the food industry has developed the concept of functional food products (Nicoletti 2012). Functional food is defined as processed food containing ingredients that boost beneficial cellular, tissular or body functions besides being nutritious. It is important to understand that functional foods do not include drugs, it just refers to foodstuffs whose daily consumption as part of a normal diet triggers positive and beneficial health effects. Another closely related term is nutraceuticals which are naturally occurring molecules in foods, which have been demonstrated to effectively prevent or treat one or more diseases or improve physiological performance, thereby improving human health (Jalili et al. 2000). Some kinds of food like berries symbolize the simplest, most common, and best-known examples of functional foods due to their rich content in bioactive compounds, especially polyphenols.

Berries destined to consumption belong to just various plant families (genus), among them: Arecaceae (*Euterpe*), Berberidaceae (*Berberis*), Elaeocarpaceae (*Aristotelia*), Ericaceae (*Arctostaphylos, Gaultheria, Gaylussacia,* and *Vaccinium*), Grossulariaceae (*Ribes*), Lauraceae (Cryptocarya), Malpighiaceae (*Malpighia*), Monimiaceae (*Peumus*), Moraceae (*Artocarpus, Ficus, Morus Prainea,* and *Treculia*), Myrtaceae (*Amomyrtus, Luma, Myrteola* and *Ugni*), Onagraceae (*Fuchsia*), Rosaceae (*Amelanchier, Fragaria,* and *Rubus*), and Solanaceae (*Physalis, Lycium*). Photographs of some representative fruits/berries are shown in Fig. 1. Worldwide berry crop production is constantly growing but nowadays it has been estimated to occupy more than 1.8 million acres and to produce 6.3 million tons (Mt) of fruit. Apart from grapes, the major berry crops are strawberries and red and black currants, followed by red raspberries, cranberries, blueberries, blackberries, gooseberries, or black raspberries (Table 1). Other minor berry crops with commercial relevance include hardy kiwifruit, chokeberries, elderberries, saskatoons, and lingonberries (Strik 2007).

The commercial relevance of berries is supported for their associated beneficial properties since they represent a natural source of important bioactive compounds that modulate metabolic processes and promote health. The most abundant bioactive compounds are polyphenols, a chemical family of compounds that comprises several subclasses: phenolic acids, stilbenes, tannins, coumarins, and flavonoids (Fig. 2).

To exemplify the aforementioned, some researchers have recently conducted a review in which they

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Fig. 1 Photographs of some commonly known wild edible berries and fruits

Table 1 Worldwide berries extension (acres) and annual production (tons) (Strik 2007)

Berry crops	Productive extension (acres)	Annual productivity (Tons)
Strawberry	609,633	3,871,869
Red and black currants	402,146	939,918
Blueberries-Highbush	107,289	194,830
Blueberries-Lowbush	280,129	295,580
Red raspberries	252,701	503,393
Gooseberries	96,576	150,897
Cranberries	74,679	417,534
Blackberries	49,499	154,578
Black raspberries	1,350	485

were capable of bringing to a successful conclusion that the intake of blueberries in a large number of in vivo assays led to the to ameliorate the impacts of obesity, T2D and chronic inflammation. Especially, blueberries belonging to the genus Vaccinium have been emphasized to be an important source of bioactive compounds that potentially aid in the upregulation of key pathways related to glucose, lipid metabolism and the amelioration of inflammation (Tikkanen 2015).

According to the bottom line of a trial in which the impact of blueberry on glucose metabolism and pancreatic β-cell proliferation was assayed in obese mice. Blueberry-supplemented diets were found to substantially increase insulin responsiveness and glucose tolerance, and to hinder the expansion of β-cells. On top of that, this study also demonstrated the

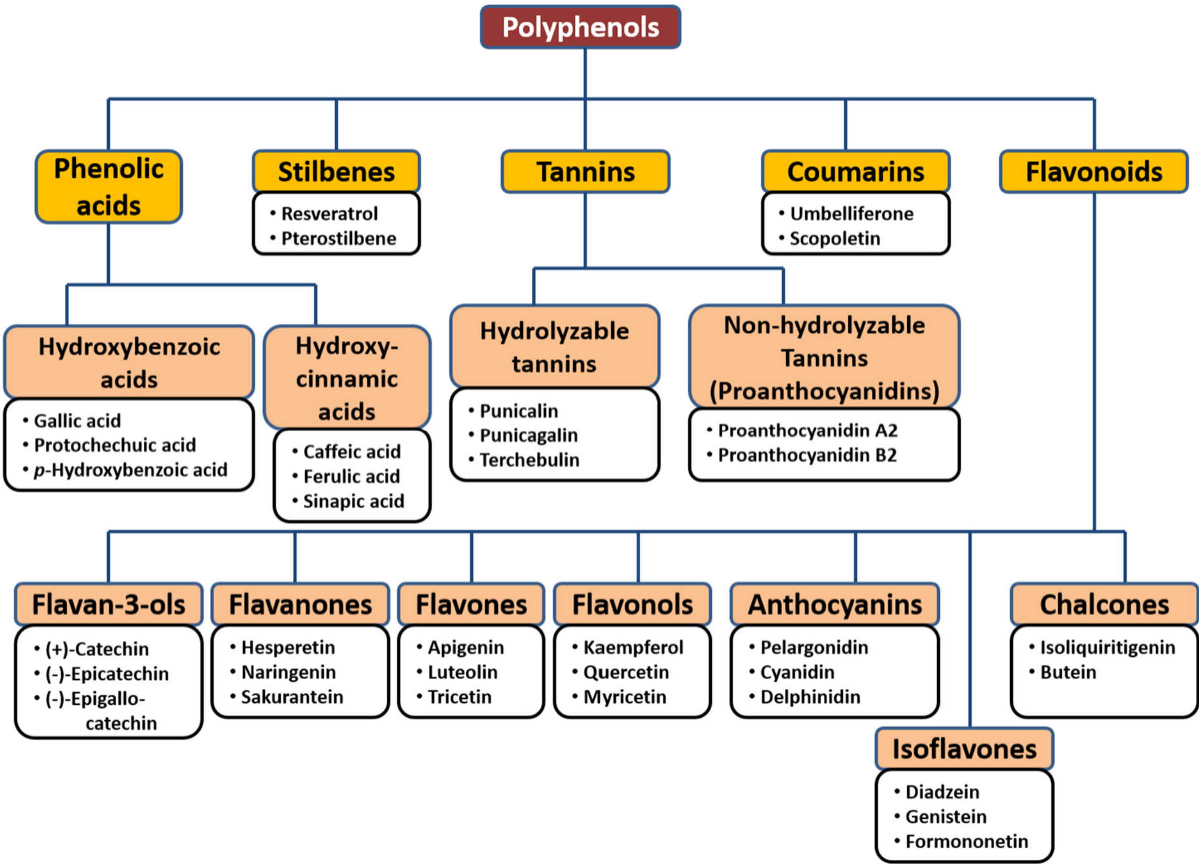
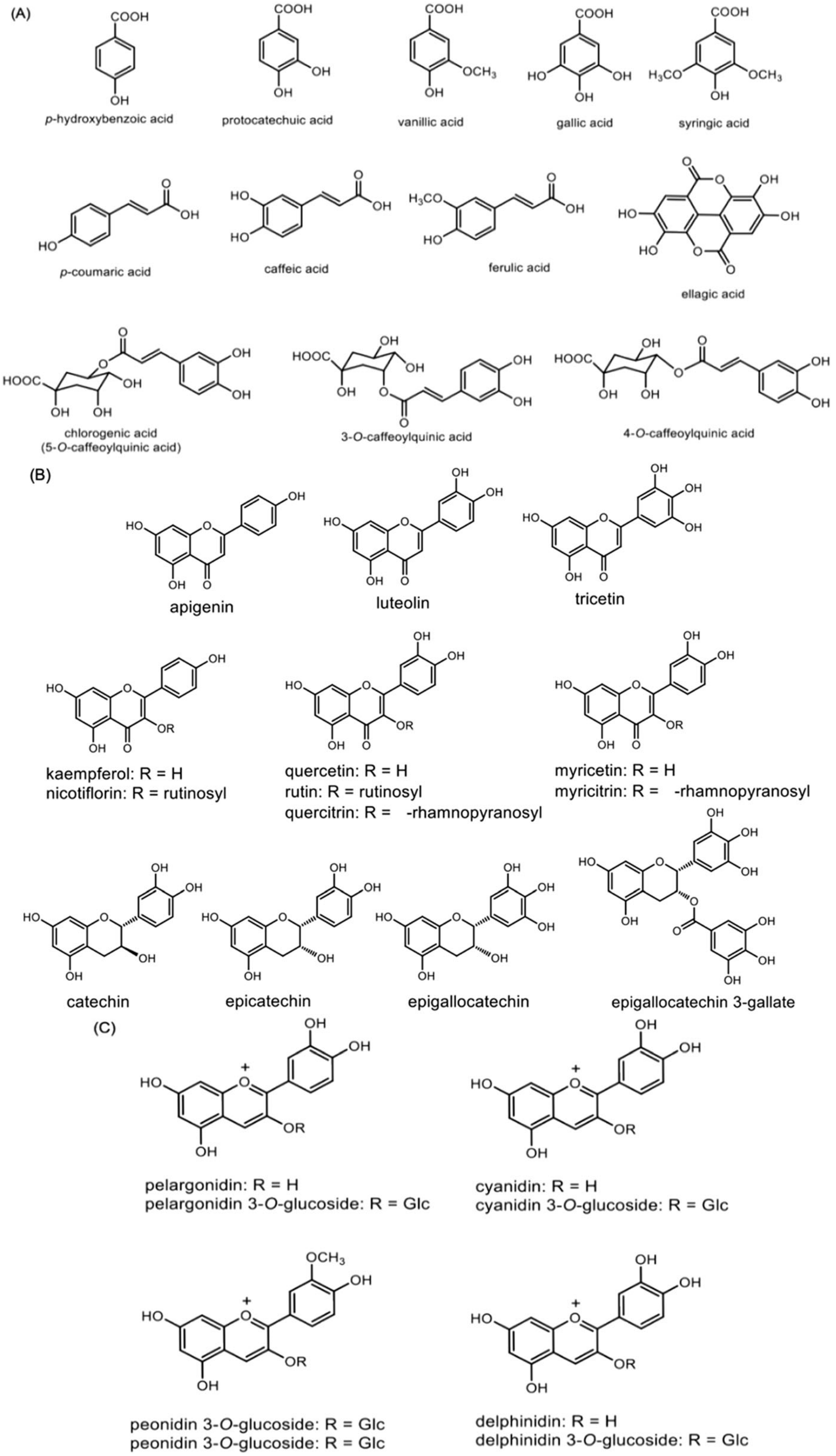


Fig. 2 Major classes of polyphenols found in fruits and berries and their common examples

possible role of blueberry in pancreatic β-cell regeneration (Liu et al. 2019). On the other hand, in a separate study, authors pointed out some of the beneficial vascular health effects of blueberry intake. For this purpose, they assessed if the effect of dietary blueberries on the diabetic vasculature of mice is dose- and time-dependent. Results proved that blueberries act as a prebiotic and supplementation with doses equivalent to ∼ 1.5 cups in normal human measurements might suppress monocyte binding to diabetic vasculature along with, mRNA expression of MCP1, IL8 and VCAM1. Consequently, dietary blueberries hold a potential approach to ameliorate diabetes-induced vascular disorders by regulating the intestinal gut microbiota (Satheesh Babu et al. 2023).

Phenolic acids, one of the most widely studied compounds in wild fruits and berries, can be divided into two groups, i.e., benzoic acid derivatives and hydroxycinnamic acid derivatives. Some of the most-reported phenolic acids in berries/fruits include gallic, protocatechuic, caffeic, coumaric, chlorogenic, and ellagic acids (Fig. 3A). These compounds have been quantified at higher concentrations in the epidermis than in the central part of the fruits. Another well-known group of polyphenols present in berries is the family of flavonoids whose backbone consists of two aromatic rings connected by a three-carbon bridge. Flavonoids comprise six subclasses: flavonols, flavones, flavanones, flavan-3-ols, isoflavones, and anthocyanidins (representative flavonoids are presented in Fig. 3B).

Flavonoids are one of the most common and prominent sources of polyphenols in the human diet (Valant-Vetschera and Brem 2006). Among them, the sub-class of anthocyanins is remarkable since they are responsible for the colorful appearance of fruits and vegetables. They may confer a wide range of colors like bright red, blue and purple. Besides, anthocyanins have many associated bioactivities proved in numerous preclinical and clinical studies, as we will discuss


(A)
COOH
OH
p-hydroxybenzoic acid
protocatechuic acid
OCH3
vanillic acid
HO
gallic acid
H3CO
syringic acid
p-coumaric acid
caffeic acid
ferulic acid
ellagic acid
HOOC
chlorogenic acid
(5-O-caffeoylquinic acid)
3-O-caffeoylquinic acid
4-O-caffeoylquinic acid
(B)
apigenin
luteolin
tricetin
OR
kaempferol: R = H
nicotiflorin: R = rutinosyl
quercetin: R = H
rutin: R = rutinosyl
quercitrin: R = -rhamnopyranosyl
myricetin: R = H
myricitrin: R = -rhamnopyranosyl
catechin
epicatechin
epigallocatechin
epigallocatechin 3-gallate
(C)
+
pelargonidin: R = H
pelargonidin 3-O-glucoside: R = Glc
cyanidin: R = H
cyanidin 3-O-glucoside: R = Glc
peonidin 3-O-glucoside: R = Glc
peonidin 3-O-glucoside: R = Glc
delphinidin: R = H
delphinidin 3-O-glucoside: R = Glc

◀**Fig. 3** Structures of some common phenolic compounds (**A**), flavonoids (**B**), and anthocyanins (**C**) reported from wild edible berries and fruits

later. The last polyphenolic group, tannins, are mainly classified into two categories: hydrolysable (*e.g*., glycoside esters of gallic acid) and condensed ones (catechin dimers, *e.g*., procyanidins). Tannins play an essential role in the sensory properties of fruits, being responsible for the color changes and tart taste. They have been described as anti-nutrients because of their effect as enzyme inhibitors which can induce a decrease in the nutritional value of some plant-based products. However, they can create chemical associations with other compounds to stabilize them, for example, in fruits rich in anthocyanins, tannins have been described to bound and stabilize them by forming copolymers (Shahidi and Ambigaipalan 2015).

Besides these bioactive compounds, berries also contain micro- and macronutrients, recognized as potentially essential constituents for maintaining physiological functions and human health. Therefore, the functional properties of nutraceuticals derived from wild berries and fruits are of high importance for the development of dietary supplements and functional foods with health-promoting activities, as some reviews published in recent years has supported (Del Bo' et al. 2015; Luís et al. 2018). This review is meant to update and underline the importance of wild edible berries as functional nutraceuticals based on their high content on bioactive compounds, including polyphenols. Therefore, this work will critically examine the polyphenolic content present in wild berries, factors affecting their synthesis and concentration, their pharmacology, and related clinical studies. Moreover, this review will assess the functional properties of wild berries for their optimal utilization as a functional food.

Polyphenolic content in wild berries and fruits: modulating factors

Berries and wild fruits are a very well-known source of nutrients and bioactive polyphenolic compounds however their content can be drastically different depending on several intrinsic and extrinsic factors. The accumulation of polyphenolic compounds is highly dependent on their geographical distribution (altitude/latitude) which directly affects to the environmental factors (such as temperature and light exposition) and so to the modulation of ripening stages. Besides, the genetic features of each strain and species have been demonstrated to be involved in the regulation of the content of polyphenols. Therefore, all these factors are further discussed along this section in relation with their capacity to modulate the concentration of polyphenols in wild fruits and berries.

Altitude and latitude

One unique specie may be adaptable to different habitats located at different latitudes or altitudes. On each geographical position, plant will have to adapt itself to diverse climatic and edaphic conditions which will induce modifications in the plant physiology and thus in the accumulation of bioactive components. Even though very few studies were conducted with respect to changes in polyphenolic contents along altitude/latitude among wild edible fruits/berries, this review has compiled some of them to deeper analyze the influence of these factors. In fact, the importance of the variations in the polyphenolic content in berries lays in the high value of these compounds in the market, since several products can be developed (*e.g.,* nutraceuticals and fortified food products). Thus, knowing which latitudes and altitudes lead to berries with higher polyphenolic content could be key information for the farmers.

Sea buckthorn, *Hippophaë rhamnoides* L. (Elaeagnaceae) is well recognized for its nutritional and medicinal properties, however its quality depends on its content in biomolecules like vitamin C, carotenoids, and phenolic compounds (Ma et al. 2016). In 2016, a study demonstrated significant differences in the proanthocyanidins content of berries cultured in different geographical areas. The variety Tytti (*H. rhamnoides* ssp. *rhamnoides*) growth in Finland displayed the highest concentration 19.4 mg/g of DW whereas the variety Prozcharachnaya (*H. rhamnoides* ssp. *mongolica*) grown in Canada showed the lowest value, 3.9 mg/g of DW. These differences are probably due not just to the different geographical distribution but also to the variable content and composition of proanthocyanidins found between subspecies: ssp. *rhamnoides* presented 12.0 ± 5.4 mg/g of DW, ssp.

sinensis 8.3 ± 2.9 mg/g of DW and ssp. *mongolica* 6.4 ± 1.7 mg/g of DW. This study concluded that sea buckthorn berry quality differs according to subspecies, cultivar, growth site, and harvesting time (Yang et al. 2016). In another later study, same authors, analyzed the variation of content and composition of proanthocyanidins of the same three sub-species of sea buckthorn but according to different latitudinal points located within Finland. They considered berries growth at 60–61°N represented southern Finland while those cultured at 67–68°N represented northern. Berries growth in the north part of the country contained higher content of proanthocyanidins accounting for 6.1–9.7 mg/g DW than those cultures at the south with a range of values of 3.4–4.5 mg/g DW. In this case, no significant differences in the total content of proanthocyanidins were observed among the three analyzed sub-species. Besides, this study found a negative correlation between the length, temperature and radiation of the growth season and the total content of proanthocyanidins. Therefore, in this case, latitude seems to be involved in the final concentration of proanthocyanidins detected in sea buckthorn (Yang et al. 2017). Similar results were observed in a previously published work for the sub-species *mongolica* and relative to the content of total acids (mainly malic and quinic acids) and sugar (mostly glucose and fructose) where more significant concentrations were found in sea buckthorn berries of ssp. *mongolica* grown in northern latitudes than in the south (Zheng et al. 2012). Another work that analyzed the content of flavonol glycosides pointed in the same direction. This study also underlined that latitude was negatively correlated with the content of flavonol glycosides, however the altitude increment was positively correlated (Ma et al. 2016). These results seemed to indicate that the high latitude in the north region produced abiotic stress and promote a higher synthesis of fruit acids and polyphenolic compounds as a mechanism of defense (Ma et al. 2016; Zheng et al. 2012).

The total content of phenolic compounds was also investigated in different cultivars of currants (*Ribes* spp.) showed different values among them but also for each cultivar depending on the growth site latitude. Green currant 'Vertti' presented the highest amount of hydroxycinnamic acid conjugates (11.3 ± 2.2 g/100 mg of fresh weight FW) and flavonol glycosides (8.9 ± 1.9 g/100 mg of FW) than those in white currant 'White Dutch' (1.3 ± 0.3 and 1.4 ± 0.5 g/100 mg of FW, respectively) and red currant 'Red Dutch' (0.23 ± 0.04 and 2.4 ± 1.2 g/100 mg of FW, respectively). Regarding the effect of the latitude, the total content of phenolic compounds displayed higher values when cultured at the north, with differences quantified in a range of 10 to 19%, than when growth at the south. Specifically, respective results obtained for cultivars growth in the south and the north were: for green currant18.9 ± 3.3 and 21.4 ± 2.5, for white currant 2.4 ± 0.9 and 2.9 ± 0.4, and for red currant 28.2 ± 5.3 and 30.9 ± 4.4 g/100 mg of FW. Similarly, data obtained for anthocyanins of red currant showed a 12% higher content in berries from the north (values for south 25.4 ± 4.7 and north 28.5 ± 4.1 g/100 mg of FW). Results regarding the total content of hydroxycinnamic acid conjugates in green and white currants were 30% higher when growth at north (Yang et al. 2013).

Considering the results of these studies, it seems that latitude is a key factor involved in the concentration of different biomolecules. In fact, berries cultured at north latitudes were described to content higher amounts of polyphenols than those growth at south latitudes. This information could be interesting from a market point of view, since polyphenolic compounds are valuable products for the food industry.

Effect of temperature

Low temperatures can induce high photosynthetic rates, so plants tend to produce more secondary metabolites as a defense mechanism. Flavonoids, the very highly diverse group of polyphenolic compounds, are affected by temperature and radiation during biosynthesis in plants (Jaakola and Hohtola 2010). Indeed, low temperature stimulates flavonoid biosynthesis in many plants through direct transcriptomic modifications of the biosynthesis pathway (Albert et al. 2009; Crifò et al. 2011). For instance, in pomegranate fruits, low temperature resulted in a higher accumulation of anthocyanins (Borochov-Neori et al. 2011). Similar results were obtained for proanthocyanidins in sea buckthorn, which concentration was positively correlated with low temperatures and radiation but directly related to other variables like precipitation and humidity. At the same time, berries cultured at the north of Finland under high radiation, low precipitation, and low humidity produced higher ratios of proanthocyanidins oligomers. On the other hand, berries growth in the south, before ripening, showed higher contents of proanthocyanidins that were correlated to a combination of different climatic conditions: low temperature, radiation, humidity, and high precipitation (Yang et al. 2017). Similarly, the concentration of anthocyanins at 25 °C was higher than at 30 °C but was lower at lower temperatures in high bush blueberries (Zoratti et al. 2015). Similarly, another study performed with bilberry fruits reported that the concentration of flavonols and hydroxycinnamic acids was higher at 12 °C than at 18 °C (Uleberg et al. 2012). In the same line, black currant cultivar (*Ribes nigrum* L.) was demonstrated to reduce its ascorbic acid concentration when increasing the temperature from 12 to 24 °C, while the total anthocyanin and total phenolic content showed maximal contents at 18 °C even though higher temperatures had a negative effect on the quality of black currant fruits due to the suppression of anthocyanins biosynthesis (Woznicki et al. 2015). In another work, it was evaluated the effect of temperature on cloudberry fruits (*Rubus chamaemorus* L). The berry size and anthocyanins levels were higher at 9 and 12 °C compared to higher temperatures (15 and 18 °C), while the temperature did not affect the total phenolic content (Martinussen et al. 2010). Finally, the fruit color intensity of strawberries (*Fragaria vesca* L.) cultivated in different regions of Italy were compared and related with the differences in environmental temperature. Strawberries cultured in Cireglio (Tuscany, north region of Italy) presented a brighter red skin color than those grown in Sicily (south region of Italy). This difference was attributed to the lower temperatures registered in the northern regions, compared to those of the south, which may have increased the anthocyanin expression in the skin of strawberries.

Contrarily, another work performed with *Vitis vinifera* L. cv. Carignan and Grenache demonstrated the implication of two factors, UV light and high permanence of elevated temperatures, in the increment of the anthocyanin acylation degree. Among these two factors, authors underlined that that the main responsible of the increment of anthocyanin derivatives was the constancy of the high temperatures induced by the action of the solar radiation. Indeed, the higher accumulation of delphinidin and petunidin derivatives (acetyl- and coumaroylglucosides) was observed under higher temperatures (Fernandes de Oliveira et al. 2015).

Hence, most of these studies, performed using different species from different geographical locations, seem to confirm that berries cultured under lower environmental temperatures are capable of synthesizing and storing higher concentrations of polyphenols than those submitted to higher temperatures. Nevertheless, each class of polyphenols may present different chemical and biosynthetic behaviors in relation to the temperature, and plant species may respond in a different manner to temperature changes.

Effect of light

Light plays an essential role in the biosynthesis of polyphenolics by inducing or inhibiting the expression of several associated genes and stress conditions.

Proanthocyanidins and flavonols showed variable biosynthesis regulation induced by different light exposures in young berry skins of wine grape (*Vitis vinifera* L. cv. Cabernet Sauvignon). Visible light (wavelength between 380 and 750 nm) mainly boosted the biosynthesis of proanthocyanidins and promoted the hydroxylation of B-rings and increased the degree of polymerization, two mechanisms suggested to have photoprotection roles. Whereas ultraviolet (UV) radiation (wavelength 100–400 nm) triggered the flavonol biosynthesis and its exposure exclusion strongly induced its fast and complete decrease of the biosynthetic pathway (Koyama et al. 2012). Another work performed with grapes (*Vitis vinifera* L.) of the varieties Carignan and Grenache demonstrated the impact that two factors, UV light and high permanence of elevated temperatures, have in the increment of the anthocyanin acylation degree. However, authors pointed out that the high temperature (drove by the solar radiation impact) was the main responsible of the modulation of anthocyanin (Fernandes de Oliveira et al. 2015).

In line with these findings, a study developed with *Ribes nigrum* L., found lower concentrations of flavonoids in berries matured in phytotron than those matured outdoor. Authors suggested that the glass cover of the phytotron may have created an screening of UV-B (280–315 nm) radiation that has inhibited their biosynthesis and accumulation. On the other hand, this effect was not observed for the accumulation of the hydroxycinnamic acids, so it was hypothesized to be due to the strong UV-B up-regulation of the chalcone synthase gene which directly acts on the flavonoid biosynthesis pathway downstream of the phenylpropanoid (Woznicki et al. 2016).

Contrarily, in different cultivars of currants (*Ribes* sp.) from Finland both variables, radiation, and temperature, seemed to impact negatively in the total content of hydroxycinnamic acid conjugates in green and white currants and in the final concentration of the major anthocyanin, cyanidin-3-O-sambubioside, in red currant. Regarding the anthocyanin results of this work, they were discordant with other studies that associated their higher production with low temperatures and high radiation exposure. This contradictory data was suggested to be due to the concurrent changes in temperature and radiation may have altered these results (Yang et al. 2013). On the other hand, this correlation was previously suggested in other works where they pointed to a higher production of flavonoids and phenolics under reduced photoinhibition at low light levels through the up-regulation of carbon-based secondary metabolites which ultimately was induced by the high activity of the phenylalanine ammonialyase, the key enzyme for flavonoids biosynthesis (Ibrahim and Jaafar 2012; Yang et al. 2013). This condition may have been unique from this study performed in very north latitudes, in Finland, where solar declination is low and day length is longer (Yang et al. 2013). Similar results were obtained for the concentration of proanthocyanidins in sea buckthorn that displayed positive correlation with low temperatures and radiation and other variables like precipitation and humidity (Yang et al. 2017).

The effect of this combination of factors on the modulation of the synthesis and accumulation bioactive molecules was further analyzed by other studies. For instance, Alonso et al. (2016) studied the impact of high-altitude solar UV-B, moderate water deficit, and the plant growth regulator abscisic acid (ABA) applications on *Vitis vinifera* cv. Malbec berries concerning their sugar content, fruit yield, and phenolic compounds profile. Low UV-B radiation and a moderate water deficit treatment reduced berry growth and sugar accumulation. These two conditions combined with spraying the aerial parts at version with 1 mM ABA also decreased fruit yield. This work also proved that ambient UV-B increased the antioxidant potential of these berries with an increment of 16% of the oxygen radical absorbance capacity (ORAC) assay and the total amount of low molecular weight phenols by 32%. Specifically, the UV-B treatment increased the yield of the dihydroflavonol astilbin, quercetin, quercetin-3-glucoside, and kaempferol-3-glucoside, by 39, 47, 124, and 116%, respectively. ABA (1 mM) treatment also increased gallic acid and gallocatechin (GC) by 15 and 25%, respectively, while a moderate water deficit treatment decreased picatechin-3-gallate (ECG), quercetin, and quercetin-3-glucoside content by 19, 12, and 25%, respectively. The combination of ABA (1 mM) with ambient UV treatments increased the ORAC of berries while ABA (1 mM) combined with a well-watered treatment increased astilbin and the total amount of low molecular weight phenols. On the other hand, neither of these treatments affected syringic acid, catechin, epicatechin (EC), gallocatechin gallate (GCG), caffeic acid, and ferulic acid. Spraying with ABA (1 mM) induced an increment of 15% of the total anthocyanins, including dihydroxylated, trihydroxylated, and nonacylated anthocyanins, besides it incremented in 34% the dihydroxylation of peonidin compared to 0.1% v/v of Triton X-100 solution. ABA did not affect the major anthocyanidin, malvidin, and acetylated or *p*-coumarylated derivatives, but reduced relative abundances of trihydroxylated and methoxylated anthocyanins. Meanwhile, methoxylated anthocyanins were the only type affected by water treatment with a moderate water deficit causing‘ 1% increase in their content, while UV-B did not affect anthocyanins (Alonso et al. 2016).

Studies on other berries showed positive effects of light on flavonoid biosynthesis. However, this is not the case in all fruit species. For instance, anthocyanins were better accumulated in bilberry fruits under shaded growth habitats (Jaakola et al. 2004). Furthermore, in grapevines, light stimulated biosynthesis of flavonoids in a cultivar-dependent manner (Matus et al. 2009), while this was not the case in some white berry cultivars, where the flavonoid pathway was genetically modified. These types of mutations were observed in strawberry (Salvatierra et al. 2010), bilberry (Zheng et al. 2012), grape berries (Walker et al. 2007), and Chinese bayberry (Zoratti et al. 2014). Both, the light amount and quality affect the final quality of berries. For instance, intense white light stimulated the gene expression of carotenoid synthesis in bilberries un-ripened fruits, while in the mature fruits, both carotenoid biosynthetic and cleavage gene expression were stimulated by red/far-red light wavelengths (Karppinen et al. 2016). In addition, anthocyanins in bilberries were affected by irradiation type. In fact, during the ripening process of bilberries, the total anthocyanin content, and especially the delphinidin glycosides, was significantly increased upon exposure to blue, red, and far-red light compared to white light exposure or darkness (Zoratti et al. 2014). Similarly, the concentration of total monomeric anthocyanin and polyphenols of fruits of *Berberis microphylla* under high light intensity conditions was thrice higher than under medium light intensity (Arena et al. 2017). However, in the case of the total phenolic content no significant differences were found between high- and medium-light intensities.

Therefore, the effect of the light has been proved to be variable when combined with other atmospheric conditions and depending on the berry and the polyphenolic family assessed.

Ripening stages

Berries undergo various developmental steps along the process of ripening that have associated changes in the bioactive content and the physical appearance. From a commercial point of view, it is essential to assess these changes and select the optimum berry/fruit development stage for its maximum utilization as a functional food. As such, maqui (*Aristotelia chilensis*) fruits were investigated to figure out the effect of successive years on their polyphenolic content along six different ripening stages. Within 2 years, the polyphenolic concentrations significantly increased, however, it got stabilized the following growing seasons. Regarding, the anthocyanin concentration, it showed an increasing trend directly related with the evolution of the ripening that gets dramatically decreased in over-ripened fruits (González et al. 2015). Similarly, the total proanthocyanidins content was demonstrated to significantly decrease in over-ripened berries of sea buckthorn compared to ripened samples of the varieties 'Terhi' and 'Tytti' (Yang et al. 2017).

Another study compared the changes in anthocyanin and soluble sugar levels between two grape varieties, 'Fengzao' (early ripening) and 'Kyoho' (middle-late ripening), during berry development to check if the anthocyanin and antioxidant activities were related to berry ripening. Seven developmental stages of the grape berry were checked during this study: (1) pea-size berries, (2) berries touching, (3) hard and green berries, (4) berries starting to soften, (5) berries starting to veraison (color change), (6) berries involving sugar and anthocyanins accumulation, and (7) ripening berries. Both varieties, 'Fengzao' and 'Kyoho', increased their size before berries started to veraison, being the growth rate of 'Fengzao' faster and showing significant differences in the size from the third to the sixth ripening stages. In both cultivars, the soluble sugar content displayed no significant changes before the fourth ripening stage neither at the seventh. In general terms, 'Kyoho' reached higher sizes and accumulated more soluble sugars in intermediary stages. Regarding the anthocyanin amount present in the berries notable differences were found from the third to the final ripening stage. Although the final concentration was higher in the last stages of ripening of 'Fengzao', 'Kyoho' showed higher anthocyanin content until the fifth stage. Thus, it was concluded that the soluble sugar content and anthocyanins concentrations increased during ripening, but most of them decreased in over-ripened fruits (Xi et al. 2017).

In the same zone, the ripening effect on hydroxycinnamic acid derivatives levels in calafate (*Berberis microphylla* G. Forst) fruits were studied over three months (from December to February). During this period, fruits maintained their hydroxycinnamic acid profiles. However, the total concentration of hydroxycinnamic acids decreased along the one-moth ripening process from 11.5 (immature fruits) to 4.5 µmol/g (ripe fruit: optimal palatability). In contrast, the anthocyanin concentration in the berries increased during the ripening, according to the same process described for other berries (Ruiz et al. 2013).

Fruits from both botanical forms, *Fragaria chiloensis* ssp. chiloensis *F. chiloensis* (native white strawberry) and *F. patagonica* (native red strawberry) collected in Chile were analyzed through 4 ripeing stages. They showed a differential expression of genes involved in the biosynthesis of anthocyanins that was related to increments in the cyanidin 3- and peonidin 3-glucoside along the fruit development for both botanical forms. Cyanidin 3-glucoside was detected along all ripening stages of both forms, with a maximum level at the third stage specially for the form patagonica (11.8 μg/g). In this later form, pelargonidin 3-glucoside also showed its highest level at the last (fourth) stage (12.5 μg/g), while for the chiloensis from it just reached its maximum at 4.0 μg/g (Salvatierra et al. 2010).(Panico et al. 2009).

In the fruit of *Vaccinium corymbosum* L., anthocyanins of all varieties increased during successive harvest stages. Meanwhile, flavonols and hydroxycinnamic acids decreased from unripe green to ripe blue stage of berry ripening. Also, the antioxidant activity and total phenolic content tended to reduce during ripening (Castrejón et al. 2008). On the other hand, the anthocyanins of *Luma apiculata* fruits displayed higher levels of antioxidant capacity and phenolic contents during the last stages of development (Fuentes et al. 2016). Similarly, in another work it was analyzed the effect of ripening on the polyphenol contents of five wild fruits from the Indian Himalayan region, such as *Berberis asiatica, Pyracantha crenulata, Morus alba, Rubus ellipticus,* and *Myrica esculenta*. The contents of various phenolic compounds, including chlorogenic acid, *m*-coumaric acid, *p*-coumaric acid, gallic acid, and vanillic acid were compared at different ripening stages. In general terms, the contents of simple phenolic compounds generally decreased during ripening, as well as the antioxidant activity (Belwal et al. 2019). Moreover, in a study in which strawberry crops were studied in three maturation stages, it was observed that the phenolic profile is similar. However, the amount found within the harvest and the degree of maturity vary significantly, especially for glycosylated compounds (flavonols and anthocyanins) (Panico et al. 2009).

Hence, as for other factors, ripening, which is depending on other intrinsic and extrinsic conditions, has different effects on the concentration of each polyphenol group evaluated. Therefore, each chemical group and species must be considered to establish its optimal concentration along the ripening stages.

Genetics

The genetic is a primary factor affecting the content of bioactive compounds of fruits and so to its nutritional value, as demonstrated along several studies (Capocasa et al. 2008; Pantelidis et al. 2007; Scalzo et al. 2005b). *In* this sense, cultivated and wild species have been demonstrated to present different features not just regarding the phenotype but the genotype, hence this diversity also affects to their chemical composition and organoleptic properties.

Taking strawberry fruits as a representative example, cultured species (*F. x ananassa*) had a lower antioxidant capacity, total phenolic and organic acids content than wild ones (*F. vesca*) which possess inferior organoleptic properties, such as fruit size and firmness. For instance, total sugars and organic acids in the cultured strawberry (325 mmol/kg) and wild (267 mmol/kg) strawberries was higher, whereas the total content of organic acids and phenolic compounds was lower in *F. x ananassa* (57 mmol/kg and 863 mg of gallic acid equivalents/kg, respectively) than in *F. vesca* (77 mmol/kg and 4347 mg of gallic acid equivalents/kg, respectively) (Mikulic-Petkovsek et al. 2012).

Another work was performed with two pairs of wild strawberry varieties grown in the same region and agricultural practices. This study evidenced the effect that genotype exerts on the synthesis of different biocompounds. Differences between varieties reached limits within the range of 10–30% for the total content of polyphenols. Genotype had no effect on the sugar concentration, but it affected to the total ascorbic acid equivalents which was variable. Some with varieties presented a mixture of ascorbic acid (major one) and dehydroascorbic acid while other varieties only presented the dehydroascorbic acid. This distinction among the content of these two metabolites may be crucial about their nutritional value since ascorbic gets metabolized into dehydroascorbic acid in humans. The genotype (Valitutto variety) involved in favoring higher concentrations of this metabolite seemed to present a lower expression of the dehydroascorbate reductase which may result of interest for further back crossings. Regarding the effect of the genotype in the concentration of short chain organic acids, citric acid, the major one, displayed differences between varieties however no variability was found for malic acid content. Finally, the antiradical activity of berry extracts was related with the content of polyphenols and citric acid, and so it also varied among the varieties. In general terms, it was observed that wild strawberries possess inferior organoleptic properties, such as fruit size and firmness but, have stronger antioxidant capacity than the cultured ones but they strawberries. Authors reported that observed differences can be mainly attributed to the effects of the

Table 2 Traditional uses of wild berries

Berries	Areas of use	Traditional use	References
Açaí	Brazil	Treatment against fever, pain, and flu	Matheus et al. (2006)
Maqui	Chile	Treatment against diarrhea, fever, hemorrhoids, inflammation, kidney pains, migraines, sore throat, ulcers, lesions, and scars	Schreckinger et al. (2010)
Blueberry, huckleberry, whortleberry bilberry, cranberry	Asia, Europe, North America	Act as digestive, antidiabetic, antidiarrheal antipyretic, diuretic, and urinary antiseptic	Abreu et al. (2014)
Wild gooseberry	Brazil	Treatment of asthma, dermatitis, hepatitis, malaria, and rheumatism Act as anticoagulant, antimutagenic, anti-leukemia, and antispasmodic	Ojeda et al. (2002)
Goji berries	China	Mild tonic for liver and kidneys, lung moistener, abdominal pain, blurry and diminished vision, dry cough, infertility, fatigue, headache, etc	Deng (1999)
Mulberry	China	Treatment of diabetes, dizziness, hypertension, insomnia, anemia, neurasthenia, premature hair loss, tinnitus, constipation, urinary incontinence and as blood tonifier	Chan et al. (2016)
Mulberry syrup and juice	India	Treatment against fever, cough, sore throat, dry throat and thirst. Expectorant agent	Singhal et al. (2010)

anthropic pressure exerted on *F. x ananassa*. In the case of the analyzed wild berries, the study concluded that altitude is related with the modification of the synthesis of primary metabolites while genotype mainly affected to the expression of secondary metabolites (Doumett et al. 2011).

In this sense, wild germplasm represents a genetic source for fruit nutritional quality improvement and could be used for variety development (Diamanti et al. 2014). *F. virginiana glauca,* also considered wild strawberries species and a reliable source of bio-compounds, was used for cross combination. Its genetic base was shown to be key for improving the nutritional and sensorial quality of commercial strawberries but also its own properties after just two subsequent inter-species back-crossing. Conversely, in raspberry (*R. parvifolius*), back-crossing with the wild germplasm did not improve the fruit nutritional value (Diamanti et al. 2012; Scalzo et al. 2005a).In another study, the potential to commercialize the *Vaccinium elliottii* germplasm was assessed, showing the potential applicability of the segregating population generated (Cabezas et al. 2021). But germplasm has being studied in other matrices. In fact, a novel tomato (*Solanum lycopersicum*) germplasm was created, achieving horticulturally desirable traits and abiotic stress tolerance (Li et al. 2023). Thus, at the light of these results. efforts should be placed for best matching of the germplasm and further overall superior quality of production.

Therapeutic effects of berries polyphenolic compounds and extract

Bioactive compounds present in plants offer plenty of health benefits that can be used in the treatment of several life-threatening diseases and lifestyles disorders (Shanmugam et al. 2022) The compounds present in fruits, such as vitamins, phenolic compounds and other phytochemicals, are linked to the enhancement of the human's immune system by supporting the proliferation of lymphocytes, reducing oxidative stress, or supporting the platelet's aggregation (Maheshwari et al. 2022). Wild berries have been traditionally applied for the treatment of different affections which have been collected through several ethnobotanical and ethnopharmaceutical reports (Table 2). Nowadays those recorded uses serve as basis for the development of research works which explore their chemical profile and biological activities and suggest their potential application in different industries. For instance, in food industry, berries are widely used either raw or in processed forms and include food products such as jams, jellies, juices, confectionery ingredients, bakery products, etc. Besides, they are also consumed as dietary supplements and nutraceutical products in tablets, capsules, syrups, extracts, etc. For example, food supplements based on Vaccinium fruits were demonstrated to possess high levels of anthocyanins (Lee 2016). Another food supplement product that contained a mixture of fruits and berries such as acerola, açaí, blueberry, etc. was demonstrated to possess a huge content of polyphenols which provided remarkable antioxidant activity (Wasek et al. 2015). However, their uses in other industrial sectors have been further explored due to advances developed in biomolecular/bioanalytical tools.

Due to their vast potential, different polyphenolic compounds or extracts obtained from berries have been tested widely in in vitro and in vivo models against various disease conditions (Table 3). Most of berry formulations assessed in in vivo studies were demonstrated to be mainly rich in polyphenols and so their protective effect was related with to their capacity to reduce the oxidative stress.

In vivo pharmacological activities of wild berries and fruits

As previously exposed, most of the pharmacological activities related to berry compounds have been related to their variable and high content in antioxidant molecules. For instance, the protective effect of *Vaccinium vitis-idaea* was associated to the presence of some flavanol oligomers, identified as procyanidins B1, B2, and A2. The in vivo assays revealed that lignoberry extract supplementation significantly declined the total oxidant status, affecting favorably the antioxidant defense enzymes in liver and red blood cells (Mane et al. 2011). Similarly, aqueous-ethanolic phenolics-containing extracts from the Tunisian *Ficus carica* showed significant antioxidant capacity in obesity-induced rats displaying special relevance in liver, heart, and kidney. Besides, these extracts also possessed hypocholesterolemic activities since they reduced the level of the total cholesterol, triglyceride, and low-density lipoprotein cholesterol and simultaneously increased the amount of high-density lipoprotein cholesterol (Belguith-Hadriche et al. 2016). In the same line of research, blackcurrant extracts were assessed in obesity-induced mice along different studies. One study showed the capacity of blackcurrant extracts to suppress M1-type macrophages which presence is associated to obesity inflammation and to the development of proinflammatory processes which were also decreased after the blackcurrant treatment. The anti-inflammatory effect was not directly mediated by alterations in macrophage phenotypes but by constraining obesity-associated inflammatory factors (Lee and Lee 2019). In the other work, blackcurrant extracts were again reported to be capable of preventing obesity-induced steatosis, liver fibrosis, and inflammation. Indeed, circulating and hepatic microRNA-122-5p and microRNA-192-5p, two non-alcoholic fatty liver disease (NAFLD) markers were reduced with the blackcurrant treatment which possibly contributed to the inhibitory effect on non-alcoholic steatohepatitis development (Lee et al. 2019). In another study, freeze-dried black raspberries were administrated to Apc$^{Min/+}$ mice, showing that a dietary supplementation with this fruits may potentially prolong the lifespan and increasing the survival of collateral cancer patients (Dong et al. 2021).

Among the multiple published pharmacological actions in terms of anti-inflammatory activity of berries few of them can be mentioned. For instance, the reduction in a rat paw edema model exerted by methanolic and aqueous extracts of *H. rhamnoidis* fruits, possibly due to the membrane stabilization induced by the inhibition of mast cells degranulation (Rédei et al. 2018). In an inflammatory bowel disease model, specifically an induced ulcerative colitis, the polyphenol-rich extract of *Aristotelia chilensis* was revealed to regulate gut microbiota and reduce immune stress, and thus therapeutic efficacy against ulcerative colitis (Zhou et al. 2019). In the same way, another study induced colitis ulcerative in mice and saw the effects of the supplementation with different fractions of *Aronia mitschurinii* 'Viking', that included a non-purified extract, neutral phenols, and microbial polyphenol catabolites. The results revealed the inhibitory effect of all these fractions on the production of TNF-α in T cells but also their anti-colitis effect (Martin et al. 2018).

Dietary phytoconstituents, polyphenolic rich components, are also well known for their cytotoxicity on cancer cells. Among the well described signaling pathways involved in human malignancies, the ones triggered by Met, a receptor tyrosine kinase that binds

Table 3 In vivo and in vitro activities of various berries polyphenolic compounds/extract

Berries/fruits	Composition/extract	In vivo and in vitro activities	References
Neurological and behavior effects			
Aronia melanocarpa	Berry juice	Antianxiety and antidepressant	Tomic et al. (2016)
Aristotelia chilensis	Anthocyanins	Antidepressant, antioxidant, and antidiabetic	Rojo et al. (2012)
Vaccinium virgatum	H_2O-EtOH extract of fruits	Antiamnesic, antidepressant, anti-cancer against glioma	Jeong et al. (2013), Vega Custódio et al. (2021)
Crataegus pinnatifida	Chlorogenic, isoquercitrin, hyperoside, triterpene acids	Antidepressant and anxiolytic	Nitzan et al. (2022)
V. angustifolium and *V. vitis-idaea*	Leaves and fruits extract	Neuroprotective effect against glutamate-mediated excitotoxicity	Vyas et al. (2013)
V. ashei	Polyphenol rich diet	Revert capacity and prevention of age-related memory decline	Malin et al. (2011)
Billberry	Mashed fresh fruits	Neuroprotective effects on hippocampal neurons of diabetic individuals	Matysek et al. (2017)
Anticancer effects			
V. corymbosum	Juice of fresh fruits	Inhibition of growth and metastatic potential of breast cancer cells (MDA-MB-231)	Adams et al. (2010)
Rubus chamaemorus	Ellagitannin-rich extract	Reduction of tumor growth and cancer cell motility. Inhibition of cancer progression and metastasis	Pajari et al. (2016)
R. fairholmianus	MeOH subfraction: α-tocopherol, flavonol glycoside and apigenin	Reduction of tumor volume, weight and increment of life span	George et al. (2017)
Fragaria x ananassa, Rubus idaeus, Ribes nigrum	Digested and fermented phenolic-rich extracts	Anti-genotoxic, anti-mutagenic and anti-invasive activity on colon cancer cells	Brown et al. (2012)
Diabetes, metabolic syndrome, and cardiovascular effects			
Hippophae rhamnoides	Rich-fruit extract in palmitoleic & palmitic acids	Lowered blood glucose, improved insulin indices and glucose uptake in insulin resistance cells. Promotion of PI3K and GS expression and inhibition of GSK-3β	Gao et al. (2017)
F. x *ananassa*	H_2O and MeOH fruit extracts	Biochemical profile reversed to normal levels, restoration of body weight, hypoglycemic activity	Abdulazeez and Ponnusamy (2016)
Ficus carica	H_2O-EtOH extract	Antihyperlipidemic and antioxidant	Belguith-Hadriche et al. (2016)
V. floribundum	Phenolic extract	Inhibition of adipogenesis and inflammation	Schreckinger et al. (2010)
Lonicera caerulea	Chlorogenic acid, cyanidin-3-glucoside, and catechin	Reduction of total cholesterol, triglycerides, and LDL-C. Increment of HDL-C	Liu et al. (2018)
Vitis vinifera	Grape-seed polyphenols	In vivo reduction of abdominal aortic aneurysm incidence, aorta dilatation, elastin degradation, macrophage infiltration, activation and expression of MMP − 2 and 9	Wang et al. (2017)

Table 3 continued

Berries/fruits	Composition/extract	In vivo and in vitro activities	References
V. meridionale	Freeze dried fruit extract rich in cyanidins and other polyphenols	Increment of scavenging activity of serum in patients with metabolic syndrome. Antioxidant capacity	Quintero-Quiroz et al. (2019)
Panax quinquefolius L	Fruit pulp extract	Myocardial infarction and oxidative stress	Parikh et al. (2019)
Anti-inflammatory effects			
Ribes nigrum	Blackcurrant extract	Reduction of pro-inflammatory genes expression in macrophages. Inhibition of obesity-associated inflammatory factors	Lee et al. (2019)
Lycium barbarum, V. macrocarpon and *V. myrtillus*	MeOH extract: quercetin, rutin, among other phenolic compounds	Anti-inflammatory effect in paw edema	Nardi et al. (2016)
Hippophae rhamnoides	H_2O-70% MeOH extract: ursolic and oleanolic acids	Anti-inflammatory effect in paw edema through membrane stabilization caused by the inhibition of degranulation of mast cells	Rédei et al. (2018)
Ribes nigrum	Buds and leaves extracts: flavonoid glycosides, quercetin, kaempferol, and prodelphinidins derivatives	Anti-inflammatory activity. Inhibition of activity of MPO and ROS production by endothelial cells and polymorphonuclear neutrophils	Tabart et al. (2012)
Antioxidant effects			
Fragaria x *ananassa*	Flavonols, anthocyanins, and ellagitannins	In vitro antioxidant capacity	Diamanti et al. (2014)
Rhodomyrtus tomentosa	Flavonoids rich extract: vitexin, myricetin, quercetin and derivatives, kaempferol	In vitro superoxide anion and hydroxyl radical scavenging activities, reducing power and inhibition of lipid peroxidation. In vivo increment of SOD and GSH-Px activities and reduction of MDA content in serum	Wu et al. (2015)
Aronia melanocarpa, Ribes nigrum, Sambucus nigra, V. corymbosum, V. myrtillus	Rich-flavonoid berry juice: hydroxycinnamic acids, flavonols and anthocyanins	In vitro and in vivo antioxidant capacity	Slatnar et al. (2012)
Ribes nigrum	Buds and leaves extracts: flavonoid glycosides, quercetin, kaempferol, and prodelphinidins derivatives	Antioxidant activity. Inhibition of activity of myeloperoxidase and ROS production by endothelial cells and polymorphonuclear neutrophils	Tabart et al. 2012)
V. vitis-idaea	Polyphenol fractions: procyanidins B1, B2, and A2 and other flavonol oligomers	Protection against oxidative stress: prevention of decrease of glutathione levels in serum, maintenance of low levels of uric acid. Reduction of oxidant status and improvement of antioxidant defense enzymes in red blood cells and liver	Mane et al. (2011)
Crataegus sp.	Leaf and flower infusion, berry decoction & tinctures	Preserved antioxidant capacity of leaf and flower infusions after simulated gastrointestinal digestion	Keating et al. (2014)
Gastrointestinal tract related effects			
Aronia mitschurinii	Lyophilized berries: neutral phenols, proanthocyanidins, anthocyanins & catabolites	Inhibition of TNF-α production in T cells in colitis-induced models. Anti-colitis activity	Martin et al. (2018)

Table 3 continued

Berries/fruits	Composition/extract	In vivo and in vitro activities	References
Ribes nigrum	Anthocyanins: delphinidin- and cyanidin-3-rutinoside and -glucosides	Suppression of M1-type macrophages associated to proinflammatory processes related with obesity	Lee and Lee (2019)
Aristotelia chilensis	Maqui berry water extract	Reduction of MDA, NO, i-NOS, and COX2 in colon and MPO, TNF-α, and IL-1β in blood serum. Alleviation of intestinal histopathological damage. Increment of occludin expression. Regulation of gut microbiota in UC	Zhou et al. (2019)
V. ashei	Anthocyanin-rich extract	Prevention of body weight loss. Amelioration of diarrhea, morphology and histology scores. Reduction of NO, MPO, IL-12, TNF-α and IFN-g levels in induced-colitis in mice	Wu et al. (2011)
Ficus carica	Polysaccharides, phenolic acids (gallic, chlorogenic, syringic and ellagic acids), flavonoids (rutin, catechin, epicatechin and apeginine), carbohydrates	Amelioration of functional gastrointestinal and motility disorders in acute UC in rats. Improvement of fecal parameters, water content, lipid metabolism, and intracellular mediators, reduction of oxidative stress	Rtibi et al. (2018)
Lycium barbarum	Berry powder	Reduction of UC activity, body weight loss, diarrhea and gross bleeding. Suppression of 30% mortality rate in mice. Histologically amelioration of colonic edema, mucosal damage and neutrophil infiltration. Decreased expression of chemokines, IL-6 and COX-2. Protective effects against colitis	Kang et al. (2017)

Abbreviations: COX2: cyclooxygenase-2, GS: glycogen synthesis, GSH-Px: glutathione peroxidase, GSK-3β: glycogen synthesis kinase-3β, HDL-C: high-density lipoprotein colesterol; IFN: interferon; IL: imterleukin, i-NOS: nitric oxide synthase,, LDL-C: low-density lipoprotein colesterol; MDA: malondialdehyde, MeOH: methanol, MMP: matrix metalloproteinase, MPO: metalloprotein myeloperoxidase, NO: nitric oxide, PI3K: phosphatidylinositol-3-kinase, ROS: reactive oxygen species, SOD: superoxide dismutase, TNF-α: tumor necrosis factor-α, UC: ulcerative colitis

the hepatocyte growth factor, has been reported to activate several cellular signaling pathways, most of them involved in proliferation, motility, migration, and invasion. In vitro and in vivo studies using cloudberry showed that it diminishes cancer cell motility and tumor growth by inhibiting Met signaling and the consequential activation of phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) (Pajari et al. 2016). Similarly, an in vitro and in vivo study performed with blueberry extract showed its phytochemicals inhibited the metastatic potential and growth of breast cancer cell line (MDA-MB-231) by modulating the PI3K/AKT/Nuclear Factor κB (NFκB) pathway (Adams et al. 2010). Another study evaluated the phenolic extract obtained from *Rubus fairholmianus* roots using a methanolic column subfraction. The chemical analysis of the phenolic profile of this extract displayed the presence of α-tocopherol, apigenin, and flavonol glycoside. These phytochemicals were pointed as potential responsible for the reduction of the tumor volume weight and the increment of life span. Besides, they might be the probable reason for the reduced cellular activity, the increased cytotoxicity, the caspase-mediated apoptotic cells population and the reduced the population of viable cells (George et al. 2017).

Table 4 Clinical trials of berries tested against several conditions (https://clinicaltrials.gov/)

Berry and/or phytochemicals	Clinical study design	Status and inference*	Clinical trial No./ References
Daily juice plus + with vegetable, fruit, and berry capsule	Clinical periodontal outcomes N = 60, randomized, triple masking	Completed (Improvement of initial pocket depth reduction in patients)	NCT00952536
High-polyphenol diet (includes 1 daily berry portion)	Cardiovascular risk and vascular function N = 104, randomized, single masking	Completed (polyphenolics in diet improve cardiovascular risk markers)	NCT01319786
Punica granatum and *Alpinia galanga extracts*	Poor semen quality N = 70, randomized, double masking	Completed (increased sperm motility, not sperm morphology changes)	NCT01357044
Punica granatum var pleniflora (Golnaar) mouth rinse	Gingivitis N = 80, randomized, quadruple masking	Completed (safe and effective in gingivitis)	NCT02227485
Punica granatum extract	Obesity, diabetes, cardiovascular disease N = 55, randomized, triple masking	Ongoing (reduction of hypertension)	NCT02017132
Standardized maqui berry extract	Bioavailability study N = 12, cohort, prospective	Completed	NCT03485885
300 g of strawberry, raspberry and cloudberry	Metabolic syndrome, impaired glucose tolerance, low-grade inflammation, dyslipidaemia N = 56, randomized, open label	Completed (Strong dependance within the bioavailability and bioactivity of berries constituents and gut microbiota composition)	NCT01414647
Meals containing starch (bread) or sucrose are consumed with berries (150 g) or berry nectars (300 mL)	Blood glucose, postprandial blood insulin, postprandial hyperglycaemia N = 20, randomized, open label	Completed (Improvement of postprandial metabolic responses to sucrose by the berries and other supplements)	NCT01580150
Fresh berry extract	Effect on mood and cognition N = 36, randomized, double masking	Completed	NCT01605682
Strawberry	Aging, age-related cognitive decline, obesity N = 46, randomized, double masking	Ongoing	NCT03162913
Strawberry	Aging, age-related memory disorders N = 54, randomized, double masking	Completed (polyphenols were absorbed and extensively metabolized)	NCT02051140
Freeze-dried strawberry powder	Childhood obesity and cardiovascular disease N = 32, randomized, triple masking	Completed	NCT01705093

Table 4 continued

Berry and/or phytochemicals	Clinical study design	Status and inference*	Clinical trial No./ References
Freeze-dried strawberry powder	Cardiovascular Risk Factors N = 50, randomized, double masking	Ongoing	NCT03522974
Strawberries	Hyper-LDL-cholesterolemia, metabolic syndrome N = 40, randomized, single masking	Ongoing	NCT03441620
Strawberry powder	Cardiovascular disease N = 50, randomized, quadruple masking	Ongoing	NCT02557334
Freeze-dried strawberry powder	Hypertension, cardiovascular diseases, vascular diseases N = 60, randomized, double masking	Completed (improvement of vascular health, blood pressure and arterial stiffness)	NCT02099578
Strawberry beverage	Pre-hypertension N = 50, randomized, double masking	Completed	NCT01190319
Strawberry meal	Cardiovascular disease N = 34, randomized, double masking	Completed (no alterations of vascular function)	NCT01989637
Strawberry	Osteoarthritis N = 20, randomized, triple masking	Completed (substantial analgesic and anti-inflammatory effects in knee osteoarthritis patients)	NCT02518347 Schell et al. (2017)
Strawberry	Insulin resistance, nutritional disease, metabolic disease N = 45, randomized, single masking	Ongoing	NCT01457612
Freeze-dried strawberries	Dyslipidaemia, obesity N = 60, randomized, single masking	Completed (Not significant anti-obesity effect. Author claimed for additional and larger trials)	NCT01883401
Strawberry beverage	Hypercholesterolemia, glycemic response N = 50, randomized, quadrupole masking	Ongoing	NCT02612090
Freeze dried Strawberry Powder	Microbial colonization, cardiovascular diseases, obesity. N = 20, randomized, triple masking	Ongoing	NCT03283969
Strawberries	Nutritional and metabolic diseases, inflammation, physiological responses N = 25, randomized, single masking	Ongoing	NCT01199848

Clinical studies of wild berries and fruits

Apart from the multiple in vivo and in vitro assays performed to assess the bioactivities of the berry phytochemicals, several extracts, purified compounds, or dietary supplements produced from berries have successfully undergone multiple clinical trials against a wide range of disease conditions (Table 4). Even though their antioxidant activity is the key one, many other clinical benefits, similar to those previously mentioned, were recorded from the berries, i.e., antidepressant, anti-anxiety, anti-inflammatory and antidiabetic effects, effect on cognitive impairment, anticancer, antihyperlipidemic, ulcerative colitis, myocardial infractions, and different diseases that are associated with the cholesterol accumulations.

Therefore, several clinical studies were performed on the safety and efficacy of various berries and fruits

Table 4 continued

Berry and/or phytochemicals	Clinical study design	Status and inference*	Clinical trial No./ References
Strawberry and sea buckthorn	Insulin sensitivity, glucose intolerance N = 18, randomized, single masking	Completed (reduced and delayed insulin response, improved glycaemic profile for sea buckthorn)	NCT02412995
Strawberry dietary intervention	Hyperlipidaemia, cardiovascular diseases, hypercholesterolemia. N = 50, randomized, open label	Completed (Strawberries enhanced diet palatability and reduced the oxidative damage to LDL)	NCT00345722
Glucola beverage	Gestational diabetes mellitus. N = 617, non-randomized, open label	Ongoing	NCT02610179
Dried cranberries, Strawberry fruit pieces	Urinary tract infection N = 65, randomized, single masking	Completed	NCT01219595
Strawberry, raspberry, and cloudberry	Metabolic syndrome, impaired glucose tolerance, low-grade inflammation, dyslipidaemia N = 56, randomized, open label	Completed (Bioavailability dependance on gut microbiota)	NCT01414647
Aronia berry/ chokeberry	Vascular function N = 66, randomized, double masking	Completed	NCT03041961
Mixed berry diet	Effects on healthy humans N = 36, randomized, double masking	Ongoing	NCT03458858
Flavanol-berry blend and others flavonols	Pharmacokinetic study on healthy subjects N = 23, randomized, single masking	Ongoing	NCT03526094
Ficus carica	Functional constipation N = 80, randomized, double masking	Completed	NCT02138851
Ficus carica	Functional constipation N = 40, randomized, triple masking	Completed	NCT01185431

against numerous disorders or quality of life-associated parameters. The identified completed and ongoing clinical studies are listed in Table 4, and some recent studies are discussed below.

A study on the *Cydonia oblonga* Mill fruit extract, which is also known as quince sauce, revealed similar and even quicker efficacy than the control drug ranitidine against gastroesophageal reflux disease in pregnant women (Shakeri et al. 2018). Thus, quince sauce may stand for a natural, cheap, safe, and effective alternative medicine for such patients. Similarly, another clinical trial compared the effect of *C. oblonga* fruit against vitamin B6 conducted in 76 pregnant women of gestational age between 6 and 14 weeks. The results of this trial showed that quince syrup reduced nausea and vomiting in pregnant women (Jafari-Dehkordi et al. 2017).

An equivalence trial was conducted in 45 children between 4 months and 14 years of age to explore the aqueous extract of fig (*Ficus carica*) fruit against atopic dermatitis compared to the standard drug hydrocortisone (1%). Fig extract can be effectively used in mild to moderate atopic dermatitis cases because it reduced the scoring atopic dermatitis index (Greta et al. 1996).

Fifty-six days double-blind, placebo-controlled clinical study of the herbal formulation LI13109F (AlvioLife®) holding extracts of *Aegle marmelos* fruit and *Boswellia serrata* gum resin against asthmatic patients showed a significant reduction in interleukin-4 (IL-4) and upsurge in serum interferon-gamma (IFNγ). The combination of both was quite effective against mild to moderate asthmatic conditions. The formulation was also tolerable to the human subjects and did not show any adverse events during the study (Yugandhar et al. 2018). Another clinical study on the fruit extract of *Hovenia dulcis* Thunb. revealed anti-hangover effects from alcohol in 26 males. This effect was due to the homeostatic regulation of inflammatory responses. However, due to the presence of cytochrome P450-2E polymorphisms, the impact might be variable (Kim et al. 2017). Finally, a clinical study on 105 healthy overweight subjects using a standardized aqueous extract of *Terminalia chebula* fruit showed positive effects on functional joint capacity and mobility (Lopez et al. 2017).

A 12-week randomized, control, double-blind clinical study was conducted with 44 NAFLD patients to see the protective effects of fruit pickles of *Capris spinosa*. A significant decrease in the body mass index and weight of the treated group was observed in NAFLD patients compared to control accompanied of an improvement of the biochemical parameters (Khavasi et al. 2017). In a randomized crossover study, a mixture of different types of berries viz. blueberries (150 g), blackcurrant (50 g), elderberry (50 g), lingonberries (50 g), strawberry (50 g), and tomatoes (100 g) were given for 5 weeks to 40 healthy individuals to measure cardiometabolic risk markers and cognitive functions. Compared to the baseline and control groups, the berry mixture significantly decreased total cholesterol, including low density lipoproteins (LDL). Moreover, the berry mixture improved cognitive performance and CRM, correlated with preventive potential against various disease conditions such as cardiovascular diseases, metabolic syndrome, and cognitive decline (Nilsson et al. 2017).

The effect of a capsule formulation of an herbal composition containing *Terminalia chebula* fruit extract (200 mg), *Commiphora myrrha* oleo-gum-resin (200 mg), and *Commiphora mukul* (200 mg) was evaluated in female diabetes patients. The formulation decreased LDL, total cholesterol, and fasting blood glucose and enhanced high density lipoprotein (HDL) levels. Thus, this combination can improve the lipid and glycemic profiles of hyperlipidemic type-2 diabetes affected women without any adverse events (Shokoohi et al. 2017).

Similarly, a commercial product named Juice-Plus + ®, which is an encapsulated concentrate of vegetable and juice powder (concentrate of *Acerola* cherry, beetroot, sugar beet, cabbage, cranberry, apple, kale, garlic, pineapple, tomato, *Lactobacillus acidophilus*, *Spirulina pacifica*, oat bran, broccoli, carrot, and dates and spinach) was tested for its ability to improve the quality of life and postoperative morbidity. The results showed that the postoperative quality of life was higher in the treatment group compared to placebo. Hence, pre-operative consumption of vegetable and fruit supplementation may improve postoperative quality of life and reduce surgical complications (Gorecki et al. 2018).

A randomized placebo-control trial with *Rosa canina* fruit as an intervention was carried out to investigate its effect on the incidence of urinary tract infection. The administrated *R. canina* fruit capsules reduced urinary tract infections after cesarean section and, thus, may have potentially beneficial effects on maternal health (Seifi et al. 2018).

A parallel, double-blind, randomized clinical trial in 41 subjects was performed to see the effect of cranberry and strawberry polyphenols. There was an increase in insulin sensitivity in the intervention group, and the first-phase insulin secretion response was also lower. However, no marked effect was observed in the risk factors associated with cardiometabolic diseases (Paquette et al. 2017). Also, a 12-week randomized clinical study conducted on 72 participants showed that ginseng berry extracts improved glucose metabolism (Choi et al. 2018).

Although there is a lack of clinical trials that demonstrate the weight loss potential of berry interventions, there are positive findings in short-term feeding studies, achieving interesting results in indirect calorimetry. This is a key factor to verify if the berry or berry products consumption can be used in nutritional interventions for the treatment of obesity, since weight changes can be predicted with indirect calorimetry. In this way, the study of the effects of cyanidin-3-glucoside and blackberry extract on cellular respiration of a fatty acid matrix in 3T3-L1adipocytes. After treating cells with different concentrations of cyanidin-3-glucoside or blackberry extracts, results showed a decrease in the mitochondrial content with higher doses of cyanidin-3-glucoside and blackberry extract (Solverson et al. 2022).

These clinical studies using berries, either alone or in different formulations, revealed beneficial health effects from diverse disease conditions. These studies point to berries as potential ingredients to be utilized as functional foods. In fact, various berries products are now available as dietary supplements, probiotics, medicines. Few examples are represented by 'Cranberry U.T. Complete' that contains cranberry extract to treat urinary tract infection; 'Cranberry Gold' is a dietary supplement; 'Green Baver' is a skincare product; or 'Organic Traditions' which is used as probiotics, among many other (https://fruitdornutraceuticals.ca/consumer-products). In addition, various products of berries are available as an extract or fermented juice, which serve as potent antioxidants and have been included as ingredients of commercialized products, such as the Açaí berry juice, popularly sold as 'Red Bull Energy drink' (https://www.redbull.com) or yogurt drinks with wild berries for increasing its nutritional and taste attributes (https://world.openfoodfacts.org/product/4002971775402/yogurt-drink-ehrmann). Furthermore, *Berberis vulgaris* fruits are commercialized as ingredients that complemented common foods, such as rice, meat products, cereals, among others as a taste enhancer and for its medicinal attributes (https://zereshk.com). In this way, the results of the studies included in this section may serve as a precedent to promote the development of perspectives in relation to the supplementation with these fruits and, consequently, also live trials where their complete innocuousness and safety should be assessed.

Trends and challenges associated with berries research

World's population is estimated to rise to over 10 billion by 2050, an increment that will be accompanied by an increase of food demand by up to 50% compared to 2013 (Bvenura and Sivakumar 2017). Current models of foods production have augmented their productivity over the last decades, however the proportion of undernourished people substantially increased. In fact, malnutrition is considered a major health concern worldwide, suggesting that exploration of more food resources with high nutritional value will be essential to meet additional food requirements of people.

In this sense wild food may stand for an important proportion of the global food basket. Among them, wild fruits/berries, would provide even better nutritional value than common fruits, since they are considered healthy and balanced food choices, safe to consumers and containing high amounts of essential dietary constituents such as vitamins, dietary fibers, and antioxidant phytochemicals. Therefore, wild fruits/berries contain unique and abundant ingredients with health benefits that highlight their utilization and consumption as functional foods and potential preventive or therapeutic products. Indeed, wild fruits/berries are the most favored group of edible plants for medicinal uses, owing to their antioxidant, antimicrobial, anti-fungal, anti-viral, anti-inflammatory, anti-cancer, cardioprotective, and neuroprotective bioactivities (Bvenura and Sivakumar 2017). This preferential use of wild fruits/berries is due to the extensive scientific reports annually published and that provide deeper knowledge regarding their distribution, ecology, uses, and applications. A recent Scopus search (www.scopus.com, accessed on June 2, 2021) with the keywords ["wild fruits" OR "wild berries"] revealed anthocyanins, flavonoids, phenolic compounds, and phenolic acids are the main bioactive secondary metabolites reported from berries and fruits along with few reports on carotenoids and alkaloids (Fig. 4A). Antioxidant activity is one of the most well-investigated bioactivities of wild fruits/berries, followed by their functional food properties, nutraceutical, and antibacterial/antimicrobial properties (Fig. 4B). Notably, wild fruits/berries antioxidants have great potential as preventive and therapeutic agents for managing multiple chronic diseases, including diverse inflammatory diseases, Alzheimer's, and cancer. Furthermore, most wild fruits and berries can be used in baking products, including jelly, jam, preserves, marmalade, butter, syrup, and candy. Besides, the increasing interest in wild fruits/berries is international with USA leading the number of research publications but followed by China, India, Finland, Spain, etc. (Fig. 4C). However, despite all these efforts and their reported benefits, wild fruits/berries are so far underutilized, and their nutritional value nearly lags that of cultivated species (Bharucha and Pretty 2010).

Therefore, about the (bio)chemical properties of wild fruits/berries, further characterizations of macro- and micro-nutrients and secondary metabolites are critical for better exploiting their properties. Besides, it is also essential to disclose of mechanism(s) of action through in vitro and in vivo models as well as toxicological evaluations to ensure their adequacy for human consumption (Bvenura and Sivakumar 2017).

Regarding their production, commercialization and efficient use, there are different priorities that may have strong impact for reaching their maximal high throughput. Regarding the production, harvesting wild fruits/berries is one delicate step which becomes performed manually since otherwise it requires little specialized equipment which is not selective. It collects leaves and twigs which need to be further clean using traditional approaches (*e.g.*, by floating the leaves and twigs in water) or other specialized equipment, such "huckleberry combine" (Kuhnlein and Turner 2020). Even though, the use of mechanical techniques may increase harvesting yield, they usually cause issues associated with fruits degradation (Kuhnlein and Turner 2020; Pinela et al. 2017). Indeed, shelf-life of most wild berries is short and, even though, their raw consumption provides higher nutritional value than preserved forms, the cost of harvesting, packaging, and shipping strongly increase their commercial value (Ciacco and Ranatunga 2009). Therefore, their commercialization is dependent on processed rather than fresh products. Hence, storage and processing methods that allow their further preservation are of key importance (Kuhnlein and Turner 2020; Tikkanen 2015). Regarding the storage techniques, small-scale producers use very cold chest freezers and bag them while flash-freezing represents a cost-effective approach for larger producers (Tikkanen 2015). Alternative storage systems that significantly extend shelf-life of certain types of wild fruits/berries includes dehydrating or drying. Besides, this approach is convenient for trade purposes since the product becomes lighter and more compact (Pinela et al. 2017; Tikkanen 2015). Other processing methods that may increase shelf-life of wild fruits/berries like irradiation, innovative packaging systems, or pulsed electric fields have been recently proposed for better commercialization and consumers acceptance (Pinela et al. 2017). Moreover, new pathways for the quality improvement of food products are being explored, being nanotechnology one of these alternatives (Sahoo et al. 2021). Regarding the processing products, the most common presentations of wild fruits/berries is as part of baked pastry and/or as jams, jellies, syrups, or fillers. Besides, the development of optimized protocols for recovery enriched extracts of wild edible plants containing high added-value compounds such as polyphenols and terpenoids may provide alternatives to commercialize them as natural healthy products, or functional, premium or high value-added ingredients which are of interest for different industrial sectors like nutraceutical, pharmaceutical, medicinal or cosmetics (Ciacco and Ranatunga 2009; Pinela et al. 2017; Tikkanen 2015).

Regarding the primary strategy for marketing wild and other non-timber forest fruits/berries they represent sustainable and cost-effective products. Species of wild berry that supply larger annual yields should be selected and domesticated for marketing programs. Their commercial successes are critically dependent on a standardized system that can assess their quality and assure their supply for future uses. Without such systematization, the wild berries could not compete with commercial crops grown for consumption, and

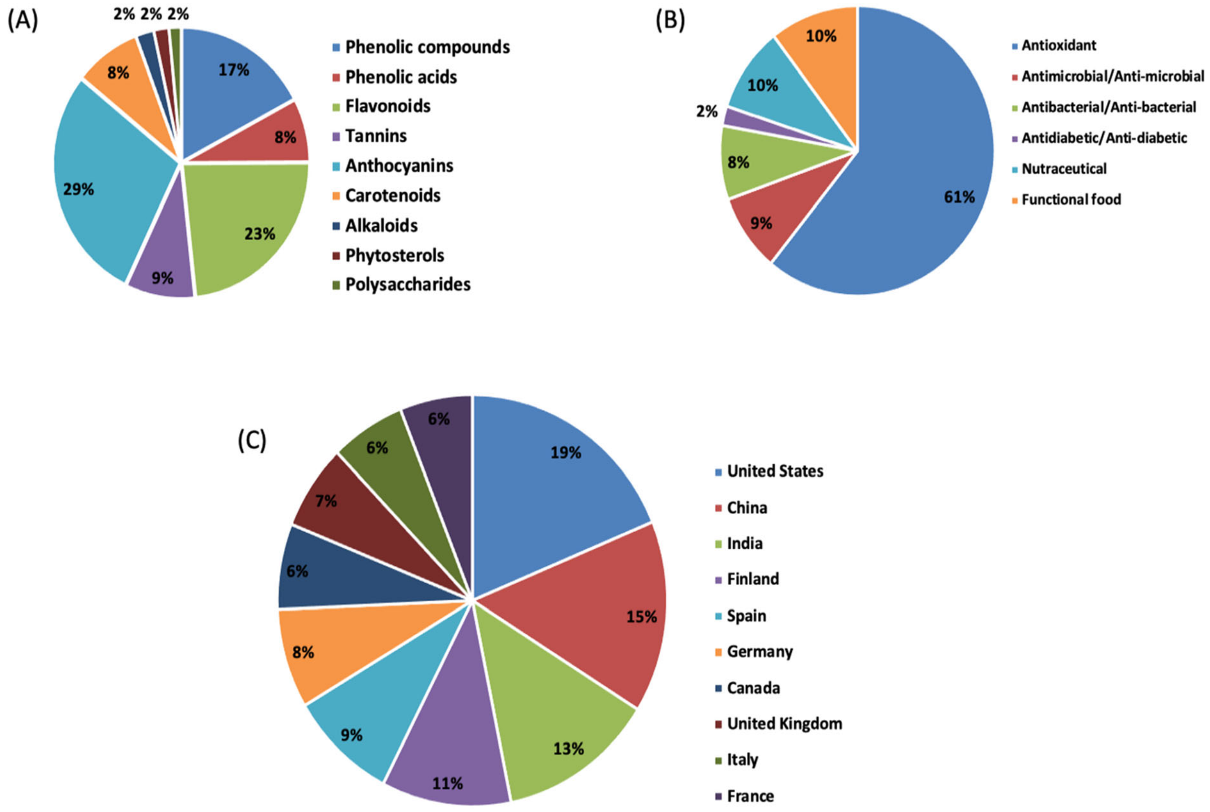


Fig. 4 Published papers (%) related to wild edible berries and fruits on mentioning different chemical classes (n = 261) (**A**); biological activities (n = 230) (**B**); and top 10 countries of author affiliations (n = 549) (**C**) from 2000–2021 (June)

thus it is unlikely that they may enter the consumption market (Tikkanen 2015). In this sense, it must be considered the impact that the climatic change has in crop yields and so in food availability. This phenomenon includes natural disasters and extreme weather conditions such as high temperatures and water stress that favors plant pests and pathogens that affect their productivity in terms of quantity and quality, and their final composition of phytochemicals (Bharucha and Pretty 2010; Bvenura and Sivakumar 2017). As previously exposed, climate is a determining factor that increases the regional pattern of berry composition. Nevertheless, the development of agricultural systems, domestication of wild fruit tree species, and training farmers on adaptation and mitigation strategies may help save wild fruit trees from climate changes (Zhang et al. 2017). Furthermore, monitoring programs can help detect and predict changes in species composition and climate change, and vulnerable wild fruits/berries species can be selected to evaluate their potential as climate refugia. In addition, the uses of biotechnology and related techniques can smoothen the path of discovering new genes to develop new plant variants that can better adapt to environmental conditions. For instance, CRISPR and omics-based technologies can help profile, modify, or transfer genes of interest to improve the nutritional quality and quantity of wild fruits/berries (Zhang et al. 2017). These may help solve concerns about the adverse effects of climate fluctuation and environmental stresses for wild fruits/berries and improve food security.

Little accessibility and lack of interest in consuming wild fruits are two main limiting factors for their use in a food basket. Educating people about the nutritional and health benefits of these wild foods and drawing public attention to the use of wild fruits/berries in restaurants and food shops can address concerns (Bharucha and Pretty 2010). Domestication can aid in addressing accessibility issues, particularly for those popular species that are difficult to access. In parallel, governments should supply policies to encourage farmers to cultivate wild fruits/berries. However, it should also be considered that wild species might decrease their bioactivities after domestication. In addition, the further relevant consideration is that excessive exploitation of wild fruits/berries may destruct their ecosystem and affect environmental balance.

Conclusions

Wild fruits/berries have multiple health benefits mainly associated to their high content in polyphenolic compounds and other antioxidant phytochemicals involved in their therapeutic effects against multiple human chronic diseases. Moreover, wild fruits/berries provide different organoleptic properties (*e.g*., texture and flavor), making them suitable for their use in several food preparations and products. Despite these valued properties, wild fruits/berries face some challenges that counteract their use as functional food and industrial products. To minimize these drawbacks, it is necessary to perform a better evaluation of their chemical composition and toxicological profile, develop more validating clinical trials, address the impact that climate change may have on their properties and production, and improve their harvesting, processing, and commercialization issues by using new strategies such as novel food packaging that extend the shelf-life of perishable products. Moreover, the value chain from the local inhabitant to the seller should be kept for their sustainable utilization and appropriate distribution and commercialization. In this way, developing a tight union between local communities and industry could help in the fair sell of these products. Furthermore, investing in research and development, and improving communication and marketing efforts could be interesting actions for guaranteeing sustainability from an environmental and economic point of view.

In conclusion, the consumption of wild fruits/berries as part of a healthy and balanced diet has been repeatedly proved to provide health benefits. Nevertheless, despite the potential of wild berries and fruits, more research needs to be done to optimize their availability and distribution from farms to industries to finally offer pharmaceutical, nutraceutical, cosmetics, or food products. For this aim, it is required the application of a multidisciplinary approach that includes ensure and standardize bulk availability, optimize harvesting, storing, and processing techniques (supply chain), innovate in the development of product formulations, and enhance marketing campaigns and mass communication to promote that all socioeconomical positions include their daily consumption.

Acknowledgements The research leading to these results was supported by MICINN supporting the Ramón y Cajal grant for M.A. Prieto (RYC-2017-22891) and by Xunta de Galicia for supporting the program EXCELENCIA-ED431F 2020/12 and the post-doctoral grant of M. Fraga-Corral (ED481B-2019/096).

Funding M. A. Prieto reports financial support was provided by Government of Spain. M. Fraga-Corral reports financial support was provided by Government of Galicia.

Declarations

Conflict of 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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