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Bioactive compounds in lettuce: Highlighting the benefits to human health and impacts of preharvest and postharvest practices

Xiao Yang[1] | **María I. Gil**[2] | **Qichang Yang**[1] | **Francisco A. Tomás-Barberán**[2]

[1] Institute of Urban Agriculture, Chinese Academy of Agricultural Sciences (IUA-CAAS), Chengdu National Agricultural Science and Technology Center, Chengdu, China

[2] Centre for Applied Biology and Soil Science of Segura, Spanish National Research Council (CEBAS-CSIC), Murcia, Spain

Correspondence

Qichang Yang, Institute of Urban Agriculture, Chinese Academy of Agricultural Sciences (IUA-CAAS), Chengdu National Agricultural Science and Technology Center, Chengdu, 610213, China.
E-mail: yangqichang@caas.cn

Francisco A. Tomás-Barberán, Centre for Applied Soil Science and Biology of Segura, Spanish National Research Council (CEBAS-CSIC), Murcia 30100, Spain.
Email: fatomas@cebas.csic.es

Abstract

Lettuce is one of the most commonly consumed leafy vegetables worldwide and is available throughout the entire year. Lettuce is also a significant source of natural phytochemicals. These compounds, including glycosylated flavonoids, phenolic acids, carotenoids, the vitamin B groups, ascorbic acid, tocopherols, and sesquiterpene lactones, are essential nutritional bioactive compounds. This review aims to provide a comprehensive understanding of the composition of health-promoting compounds in different types of lettuce, the potential health benefits of lettuce in reducing the risks of chronic diseases, and the effect of preharvest and postharvest practices on the biosynthesis and accumulation of health-promoting compounds in lettuce.

KEYWORDS

(poly)phenols, bioactive compound, health benefits, *Lactuca sativa* L., vegetables

1 | INTRODUCTION

Lettuce (*Lactuca sativa* L.) is one of the most frequently consumed vegetable crop species globally. The modern types of cultivated lettuce are categorized based on their huge diversity in morphological features and are mainly classified as crisphead, butterhead, romaine, looseleaf, or stem lettuce (L. Zhang et al., 2017). Lettuce is commercially accessible year-round and grown in open fields, greenhouses, or the plant factory with artificial light systems (PFALs). The annual global production of lettuce (and chicory) is 27.2 million tons; China, the United States of America, India, Spain, and Italy are the top five producers (United Nations Food & Agriculture Organization, 2018).

Lettuce, a low-calorie, low-fat, and low-sodium salad vegetable, is rich in fiber, folate, and vitamin C, as well as essential minerals such as iron (M. J. Kim et al., 2016). Lettuce is also an abundant source of other natural health-promoting phytochemicals and vitamins, including glycosylated flavonoids, hydroxycinnamic acids, sesquiterpene lactones (e.g., lactucin and lactucopicrin), carotenoids, the group B vitamins, ascorbic acid, and tocopherols. Lettuce secondary metabolites are potentially associated with many health-beneficial properties, including antifree radical, anti-inflammatory, antidiabetic, anticancer, and

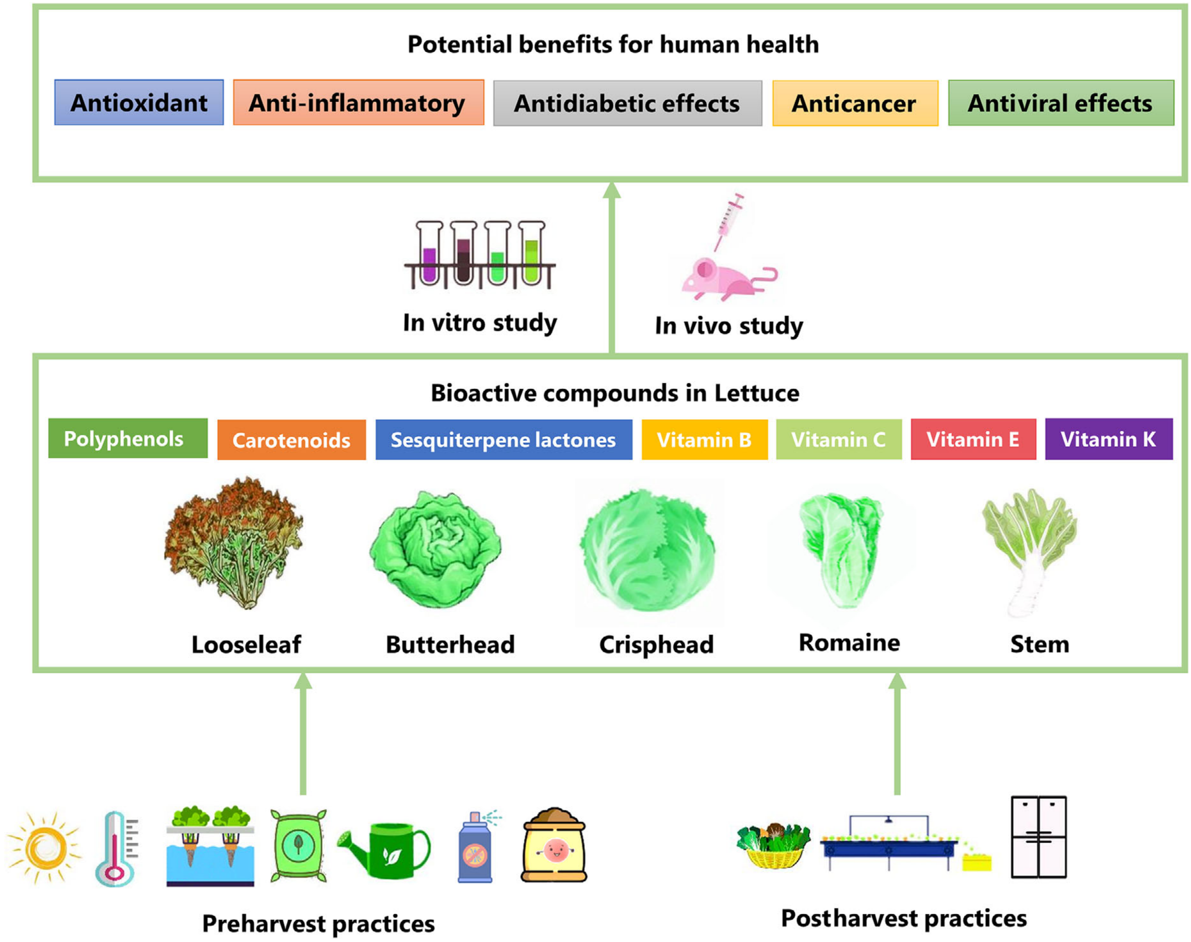

FIGURE 1 Illustration of the bioactive compounds in lettuce, their potential benefits for human health, as well as preharvest and postharvest practices that affect the constitution and concentrations of these health-promoting compounds

anticardiovascular diseases (CVDs) effects (M. J. Kim et al., 2016). Due to the minimal processing procedures, such as cutting, washing, drying, packing, and low-temperature distribution and storage, fresh-cut lettuce maintains its nutritional value and bioactivity (Cantwell & Kasmire, 2002). In Asian countries, lettuce and asparagus lettuce are traditionally cooked rather than consumed raw (Mou, 2008). However, given the growing predominance of ready-to-eat food/meals in these regions, notably in China, Japan, and Korea, the public increasingly prefers convenient fresh-cut products, particularly lettuce salads. As a result of changing consumer preferences and the advances in fresh-cut processing and storage technology, lettuce production has been consolidated worldwide; lettuce has become one of the most in-demand fresh-cut products.

Here we critically review the health-promoting effects of lettuce, including the composition, bioavailability, and metabolism of the constituents responsible for these health effects and explore how preharvest and postharvest practices affect the composition of bioactive compounds in lettuce (Figure 1).

2 | BIOACTIVE COMPOUNDS IN LETTUCE

2.1 | Normalization of the measurement of bioactive compounds in lettuce

Numerous studies have determined the contents of different (poly)phenol (PP) subgroups (i.e., phenolic acids, flavones, flavonols, and anthocyanins) in various lettuce cultivars. These investigations used different external standards as equivalents or expressed the contents relative to the fresh weight (FW) or dry weight using different drying techniques, complicating the standardization and limiting the comparison of quantitative data from various laboratories. Therefore, uniform equivalents and drying protocols are required to be established to enable data normalization and comparability across investigations.

Here, we propose that the results be reported converted to milligram of bioactive compound per 100 g FW. Additionally, considering that the water content of lettuce is around 90%, dry weight values should be converted into the content in FW. The determination of the values per 100 g FW is advantageous because the values can easily be extrapolated to the dietary intake of food items, which is vital in nutrition research.

2.2 | (Poly)phenols in lettuce

2.2.1 | Soluble (poly)phenols

PPs are the most abundant phytochemicals in lettuce. Antioxidant phenolics are produced via the shikimate, phenylpropanoid, flavonoid, and anthocyanin biosynthetic pathways. PPs are classified as flavonoids or nonflavonoids and can be further grouped according to their chemical structure. The main PP compounds identified in lettuce are shown in Table 1. Additionally, a soluble PPs fraction is often extracted using aqueous alcoholic solvents and referred to as the extractable PPs fraction (EPP), which is the main fraction in lettuce. The soluble PPs fraction consists of phenolic acids (such as hydroxybenzoic acid and hydroxycinnamic acid derivatives), flavonoids (such as flavones, flavonols, and anthocyanins), and trace quantities of coumarins (such as aesculin and 6,7-dimethoxy coumarin). Anthocyanins are the pigments found in red and green/red colored cultivars, with cyanidin glycosides being the most abundant.

2.2.2 | Bound (poly)phenols

Another fraction, the nonextractable PPs fraction (NEPP) contains phytochemicals that cannot be extracted with hydroalcoholic solvents (polymeric phenolics) and those that are chemically bound to other molecules (bound phenolics), such as oligomeric and polymeric carbohydrates and cell wall components. NEPPs are only released after chemical degradation (Perez-Jimenez & Saura-Calixto, 2015). Galieni et al. (2015) determined that the bound PP fraction represented an average of 33% of the total PP content (TPC) in romaine lettuce "Romana lentissima a montare 4," with a value of 82.4 mg gallic acid equivalent (GAE)/g FW. Hydroxybenzoic and hydroxycinnamic acids are the primary forms of bound PPs in lettuce, with respective contents of 65.6 and 1.1 mg/100 g FW (Perez-Jimenez & Saura-Calixto, 2015). López et al. (2014) reported that caffeic acid and *p*-coumaric acid were the most abundant bound PPs detected in different sizes of romaine lettuce; regular-size romaine lettuce had the highest concentrations of bound caffeic acid and *p*-coumaric acid, with average values of 5.18 and 0.25 mg/100 g FW, respectively; followed by mini-size, with 4.44 mg/100 g FW caffeic acid and 0.20 mg/100 g FW *p*-coumaric acid, while little gem size had the lowest concentrations of caffeic acid and *p*-coumaric acid, with average values of 2.99 and 0.12 mg/100 g FW, respectively. W. Zhou et al. (2018) identified that caffeoyl tartaric and caffeic acids were two main types of bound PPs in the leaves of "Lvluo" and "Ziluoma" lettuce using HPLC-DAD-ESI-MS.

2.2.3 | (Poly)phenols in different types of lettuce

Increasing evidence indicates that lettuce genotypes may contain varied TPC and levels of specific phenolic compounds. Numerous studies have examined the TPC of different types of lettuce (Table 2). The results suggest that the looseleaf type bears the highest TPC, while the iceberg type has the lowest TPC (Bunning et al., 2010; M. J. Kim et al., 2016, D. E. Kim et al., 2018; Liu et al., 2007; Llorach et al., 2008). For example, the TPC of 25 lettuce cultivars ranged between 104 and 857 mg GAE per 100 g FW; the looseleaf type had the highest TPC with an average value of 432 mg GAE/100 g FW, followed by the romaine type (363 mg GAE/100 g FW) and the butterhead type (151 mg GAE/100 g FW), while the iceberg type had the lowest TPC value of 104 mg GAE/100 g FW (Liu et al., 2007). Llorach et al. (2008) also reported the TPC of several types of lettuce, with Lollo rosso, a red looseleaf variety, having a higher TPC than red oak leaf (571 and 322 mg GAE/100 g FW, respectively), romaine (64 mg GAE/100 g FW), and iceberg (crisphead type, 18 mg GAE/100 g FW). The TPC values of two stem lettuce cultivars "Grüner stern" and "Karola" were reported to be 363.6 and 415.5 mg GAE/100 g FW after 8 weeks of growth, respectively (Malarz et al., 2021). Red lettuce cultivars have higher TPC values than the green lettuce types (Becker et al., 2015; D. E. Kim et al., 2018; Liu et al., 2007; Llorach et al., 2008). For instance, D. E. Kim et al. (2018) examined the variation in the TPC of green, green/red, and red lettuce cultivars and found that red lettuce cultivars had the highest TPC with an average value of 524 mg GAE/100 g FW, followed by red/green cultivars (average TPC of 227 mg GAE/100 g FW). In contrast, the green leaf cultivar had the lowest TPC (average value of 133 mg GAE/100 g FW). These findings can be explained by the fact that red lettuce varieties allocate carbon towards PP production rather than growth, which results in the accumulation of phenolic compounds (Neilson et al., 2013).

Phenolic acids, particularly hydroxybenzoic acid and hydroxycinnamic acid derivatives, represented the major forms of EPP and NEPP in lettuce. Chlorogenic acid, chicoric acid (dicaffeoyl tartaric acid), and caffeoyl tartaric acid were the leading phenolic acid derivatives identified (Llorach et al., 2008). The total amount of phenolic acids in different types of lettuce is shown in Table 3. The red

TABLE 1 The main phenolic compounds in lettuce

Polyphenol classes	Main compounds	References	Lettuce types
Phenolic acid derivatives			
Hydroxybenzoic acid derivatives	Hydroxybenzoic acid and isomers	1, 3, 6	Iceberg, romaine, looseleaf
	Hydroxybenzoic acid hexose	1, 3, 10	Iceberg, romaine, looseleaf
	Dihydroxybenzoic acid and isomers	1, 3, 10	Iceberg, romaine, looseleaf
	Dihydroxybenzoic acid hexose	1, 3, 10	Iceberg, romaine, looseleaf
	Galloyl-hexose and isomers	1, 3	Iceberg, romaine, looseleaf
	Vanillic acid glucoside	1, 10	Iceberg, romaine
	Syringic acid hexose	1, 3	Iceberg, romaine, looseleaf
	Hydroxybenzoyl gallic acid hexose	3	Looseleaf
	Hydroxybenzoyl-dihydroxybenzoic acid	3	Looseleaf
Hydroxyphenylacetic acid derivatives	4-Hydroxyphenylacetyl glucoside	1	Iceberg, romaine,
	4-Hydroxyphenylacetic acid	1, 3	Iceberg, romaine, looseleaf
	Di(4-hydroxyphenylacetyl)-hexose	1	Iceberg, romaine,
	Dihydrocaffeic acid hexose	1, 3, 10	Iceberg, romaine, looseleaf
	Dihydrocaffeic acid sulfate	1	Iceberg, romaine
	Caffeoyl hexose	1, 3, 10	Iceberg, romaine, looseleaf
	Caffeoyltartaric acid	1, 3, 5, 6, 8, 9	Iceberg, romaine, looseleaf
	Dicaffeoyltartaric acid	1, 2, 3, 5, 6, 7, 9, 10	Iceberg, romaine, looseleaf, butterhead
	Caffeic acid	1, 6, 8	Iceberg, romaine, looseleaf
	Caffeoylquinic acid and isomers	1, 2, 3, 5, 6, 7, 8, 9, 10	Iceberg, romaine, looseleaf, butterhead
	Caffeoylquinic acid hexose and isomers	3, 10	Looseleaf
	Dicaffeoylquinic acid and isomers	1, 2, 3, 5, 6, 10	Iceberg, romaine, looseleaf, butterhead
	Ferulic acid glucoside	1	Iceberg, romaine
	Ferulic acid methyl ester	1, 3	Iceberg, romaine, looseleaf
	Feruloyl tartaric acid	7	Butterhead
	Feruloylquinic acid	7	Butterhead
	Caffeoyl feruloylquinic acid	7	Butterhead
	Methylcaffeoylferuloyltartaric acid	7	Butterhead
	Caffeoylmalic acid	1, 5, 6, 10	Iceberg, romaine, looseleaf
	p-Coumaroylquinic acid	1, 3, 10	Iceberg, romaine, looseleaf
	p-Coumaroyl glucoside	1, 3, 10	Iceberg, looseleaf
	Coumaric acid and isomers	8	Romaine
	Coumaroyl-tartaric acid	1, 3	Iceberg, romaine, looseleaf
	Sinapoyl glucoside	1, 3	Iceberg, romaine, looseleaf

(Continues)

TABLE 1 (Continued)

Polyphenol classes	Main compounds	References	Lettuce types
Coumarin derivatives			
	Aesculin	1, 10	Iceberg, romaine
	6,7-Dihydroxycoumarin	1, 10	Iceberg, romaine
Flavonoids			
Flavonols			
Quercetin glycosides	Quercetin-3-glucoside	1, 3, 4, 5, 6, 7, 10	Iceberg, romaine, looseleaf, butterhead
	Quercetin-3-galactoside	1, 3, 4	Iceberg, romaine, looseleaf, butterhead
	Quercetin-3-glucuronide	1, 3, 4, 5, 6, 10	Iceberg, romaine, looseleaf, butterhead
	Quercetin-3-rhamnoside	1, 4	Iceberg, romaine
	Quercetin-3-arabinoside	1	Iceberg, romaine
	Quercetin-3-rutinoside	1, 4, 5, 10	Iceberg, romaine, looseleaf, butterhead
	Quercetin 3-neohesperidoside	10	Iceberg, romaine, looseleaf, butterhead
	Quercetin 3-(6′'-malonyl)-glucoside 7-glucuronide	1, 3, 5, 6, 10	Iceberg, romaine, looseleaf
	Quercetin 3-(6′'-malonyl)-glucoside 7-glucoside	1, 3, 4, 5, 6, 10	Iceberg, romaine, looseleaf
	Quercetin-3-(6′'-malonyl)-glucoside	1, 2, 3, 4, 5, 6, 10	Iceberg, romaine, looseleaf, butterhead
	Quercetin 3-glucoside −6′'-acetate	10	Iceberg, romaine, looseleaf, butterhead
	Quercetin diglucoside	3, 6, 10	Looseleaf
	Quercetin hexoside glucuronide	1, 3, 10	Looseleaf
	Quercetin rhamnosyl-glucuronide	3	Looseleaf
Kaempferol glycosides	Kaempferol 3-glucoside	3	Looseleaf
	Kaempferol 3-glucuronide	2, 7	Iceberg, romaine, looseleaf, butterhead
	Kaempferol 3-(6′'-malonyl)-glucoside	2, 3	Iceberg, romaine, looseleaf, butterhead
	Kaempferol	3	Looseleaf
Others	Isorhamnetin-3-glucuronide	7	Butterhead
	Myricetin-hexoside	11	Looseleaf
Flavanones	Naringenin 7-neohesperidoside	1	Iceberg, romaine
	Hesperetin 7-rutinoside	1	Iceberg, romaine
	Eriodictyol-glucuronide	3	Looseleaf
Flavones			
	Luteolin-7-glucoside	1, 3, 5, 10	Iceberg, romaine, looseleaf, butterhead
	Luteolin-7-glucuronide	1, 3, 4, 5, 6, 10	Iceberg, romaine, looseleaf, butterhead

(Continues)

TABLE 1 (Continued)

Polyphenol classes	Main compounds	References	Lettuce types
Luteolin glycosides	Luteolin-7-rutinoside	3, 5	Looseleaf
	Luteolin-7-rhamnosyl-hexoside	3, 10	Looseleaf
	Luteolin-hydroxymalonyl-hexoside	3	Looseleaf
	Luteolin diglucoside	1	Iceberg, romaine
	Luteolin-malonyl-hexoside	1	Iceberg, romaine
	Luteolin	1	Iceberg, romaine
	Luteolin 6-C-glucoside	11	Looseleaf
	Luteolin 8-C-hexosyl-hexoside	11	Looseleaf
	Luteolin-7-neohesperidoside	10	Iceberg, romaine, looseleaf, butterhead
Apigenin glycosides	Apigenin-7-glucoside	1, 3, 10	Iceberg, romaine, looseleaf, butterhead
	Apigenin-7-glucuronide	1, 3, 10	Iceberg, romaine, looseleaf, butterhead
	Apigenin-rhamnosyl-glucoside	3	Looseleaf
	Apigenin diglucoside	10	Iceberg, romaine, looseleaf, butterhead
Others	4′-methyl-apigenin rutinoside	1	Iceberg, romaine
	Chrysoeriol	11	Looseleaf
	Chrysoeriol-malonyl-hexoside	11	Looseleaf
	Chrysoeriol-7-rutinoside	11	Looseleaf
	Chrysoeriol-ferulic acid	11	Looseleaf
	Chrysoeriol-5-hexoside	11	Looseleaf
	Chrysin-hexoside	11	Looseleaf
	Chrysin-malonyl-hexoside	11	Looseleaf
Anthocyanins			
Cyanidin glycosides Others	Cyanidin 3-glucoside	2, 3, 4	Iceberg, romaine, looseleaf
	Cyanidin 3-galactoside	10	Looseleaf, butterhead
	Cyanidin 3-(6′′-malonyl)-glucoside	3, 4, 5, 10, 12	Looseleaf
	Cyanidin 3-(3′′-malonyl)-glucoside	3	Looseleaf
	Cyanidin 3-(6′′-acetyl)-glucoside	3, 12	Looseleaf
	Cyanidin 3, 5-diglucoside	4	Looseleaf
	Malvidin 3-glucoside	11	Looseleaf
	Delphinidin 3-glucoside	11	Looseleaf
	Peonidin 3-glucoside	12	Romaine, looseleaf

Note: 1, a Waters ACQUITY UPLC coupled to a Bruker Daltonics micrOTOF-QTM (Abu-Reidah et al., 2013); 2, a Waters UPLC coupled to a SYNAPT G2-Si HDMS (Assefa et al., 2019); 3, a Waters ACQUITY UPLC coupled to a SYNAPT G2-Si HDMS (Viacava et al., 2017); 4, an Agilent Hewlett-Packard 1100 HPLC system coupled to a Micromass ACPI-based MS and JEOL GX400 NMR spectrometer (DuPont et al., 2000); 5, an Agilent 1100 Series LC coupled to a G2445A ion trap mass spectrometer (Llorach et al., 2008); 6, an Agilent 1200 liquid chromatograph coupled to an Agilent ion trap 6320 mass spectrometer (Santos et al., 2014); 7, a Shimadzu Nexera UHPLC system coupled to a Shimadzu IT-TOF mass spectrometer (Pepe et al., 2015); 8, an Agilent Series 1200 HPLC coupled to a triple quadrupole mass spectrometer (López et al., 2014); 9, a Bruker AVANCE AQS600 spectrometer (Sobolev et al., 2005); 10, a Waters ACQUITY UPLC coupled to a Waters Vion IMS Qtof MS (Yang, Wei, et al., 2018); 11, an ACQUITY UPLC I-Class coupled to a Xevo G2-S QTOF(Qin et al., 2018). 12, Waters Acquity UPLC H-Class system (Medina-Lozano et al., 2021).

TABLE 2 Total poly)phenols content (TPC) in different types of lettuce (mg gallic acid equivalent/100 g FW)

Lettuce type	TPC	Variety	References
Looseleaf type	103.0	Cheongchima (G)	D. E. Kim et al. (2018)
	133.0	Cheongha (G)	D. E. Kim et al. (2018)
	212.0	Concept (G)	Liu et al. (2007)
	317.9	Crisp and green (G)	Bunning et al. (2010)
	307.0	Crisp and green (G)	Liu et al. (2007)
	264.0	Envy (G)	Liu et al. (2007)
	337.0	Green vision (G)	Liu et al. (2007)
	181.0	Hacheong (G)	D. E. Kim et al. (2018)
	244.0	Marin (G)	Liu et al. (2007)
	91.0	Shenxuan 1 (G)	Yang et al. (2017)
	130.7	Simpson elite (G)	Z. Li et al. (2010)
	347.0	Thai green (G)	Liu et al. (2007)
	210.0	Two star (G)	Liu et al. (2007)
	140.0	Asia oraedda jeokchima (R)	D. E. Kim et al. (2018)_
	218.0	Asia yeoreum jeokchima (R)	D. E. Kim et al. (2018)
	739.0	Black jack (R)	Liu et al. (2007)
	297.0	Dduksum jeokchukmyeon (R)	D. E. Kim et al. (2018)
	857.0	Galactic (R)	Liu et al. (2007)
	282.2	Galactic (R)	Z. Li et al. (2010)
	320.0	Haetsal jeokchukmyeon (R)	D. E. Kim et al. (2018)
	176.0	Heukssamchima (R)	D. E. Kim et al. (2018)
	287.0	Hongha jeokchukmyeon (R)	D. E. Kim et al. (2018)
	186.0	Jangsu (R)	D. E. Kim et al. (2018)
	456.0	Jeokcima (R)	D. E. Kim et al. (2018)
	86.0	Jeoksangchae (R)	D. E. Kim et al. (2018)
	589.0	Jinbballolla (R)	D. E. Kim et al. (2018)
	130.0	Lollo rossa (R)	Yang et al. (2017)
	571.2	Lollo rosso (R)	Llorach et al. (2008)_
	552.0	New red fire (R)	Liu et al. (2007)
	591.0	Rave (R)	Liu et al. (2007)
	322.1	Red oak leaf (R)	Llorach et al. (2008)
	870.0	Rutgers scarlet lettuce (R)	Cheng, Pogrebnyak, Kuhn, Poulev, et al. (2014)
	106.0	Seonhong jeokchukmyeon (R)	D. E. Kim et al. (2018)
	684.0	Vulcan (R)	Liu et al. (2007)
	495.8	Vulcan (R)	Bunning et al. (2010)
Butterhead type	151.0	Unknown (G)	Liu et al. (2007)
	222.1	Lochness	Bunning et al. (2010)
	71.2	Lores	Viacava et al. (2018)
Crisphead type	92.0	Abata (G)	D. E. Kim et al. (2018)
	83.0	Arirang (G)	D. E. Kim et al. (2018)
	18.2	Iceberg (G)	Llorach et al. (2008)
	90.0	Salad express (G)	D. E. Kim et al. (2018)
	128.3	Crispino	Bunning et al. (2010)
	12.9	Unknown	Ketnawa et al. (2020)

(Continues)

TABLE 2 (Continued)

Lettuce type	TPC	Variety	References
Romaine type	291.0	Asia heuk romaine (G)	D. E. Kim et al. (2018)
	122.0	Caesar green (G)	Kim et al. (2018)
	184.0	Claremont (G)	Liu et al. (2007)
	146.0	Esse (G)	D. E. Kim et al. (2018)
	221.0	Green forest (G)	Liu et al. (2007)
	172.1	Green forest (G)	Bunning et al. (2010)
	227.0	Medallion (G)	Liu et al. (2007)
	63.5	Romaine (G)	Llorach et al. (2008)
	79.7	Romaine (G)	Msilini et al. (2013)
	95.0	Saengchae (G)	D. E. Kim et al. (2018)
	638.0	Caesar red (R)	D. E. Kim et al. (2018)
	431.0	Cimmaron (R)	Liu et al. (2007)
	520.0	Eruption (R)	Liu et al. (2007)
	429.0	Integrata (R)	Liu et al. (2007)
	564.0	Outredgeous (R)	Liu et al. (2007)
	347.0	Super caesar red (R)	D. E. Kim et al. (2018)
Stem type	363.6	Grüner stern	Malarz et al. (2021)
	415.5	Karola	Malarz et al. (2021)

Note: The letters R and G denote the red and green leaf lettuce varieties, respectively. If the content was originally reported as dry weight in the reference, we converted the value to fresh weight (FW) using an average water content of 10% of lettuce (fresh wight = dry weight * 10). Then, all data from various sources were normalized to the units gallic acid equivalent (GAE) mg/100 g FW.

TABLE 3 Total phenolic acid content in different types of lettuce

Lettuce type	Total phenolic acid content	Variety	References
Looseleaf type	66.3 mg DTE/100 g FW [a]	Oak leaf	Nicolle, Carnat, et al. (2004)
	231.3 mg DTE/100 g FW [a]	Red oak leaf	Nicolle, Carnat, et al. (2004)
Butterhead type	78.6 mg DTE/100 g FW [a]	Unknown	Nicolle, Carnat, et al. (2004)
	98.5 mg DTE/100 g FW [a]	Unknown	Nicolle, Carnat, et al. (2004)
	5.9 mg/100 g FW [b]	Green salanova	El-Nakhel et al. (2020)
	21.7 mg/100 g FW [b]	Red salanova	El-Nakhel et al. (2020)
Crisphead type	80.4 mg CAE/100 g FW [c]	Asdrubal	Cantos et al. (2001)
	64.7 mg CAE/100 g FW [c]	Green queen	Cantos et al. (2001)
	129.4 mg CAE/100 g FW [c]	Little gem sandra	Cantos et al. (2001)
	64.4 mg CAE/100 g FW [c]	Mikonos	Cantos et al. (2001)
	89.7 mg DTE/100 g FW [a]	Unknown	Nicolle, Carnat, et al. (2004)
	85.9 mg DTE/100 g FW [a]	Unknown	Nicolle, Carnat, et al. (2004)
Romaine type	65.3 mg CAE/100 g FW [c]	Cazorla	Cantos et al. (2001)
	28.3 mg CAE/100 g FW [c]	Modelo	Cantos et al. (2001)

Note: If the content was originally reported as dry weight in the reference, we converted the value to fresh weight (FW) using an average water content of 10% of lettuce (fresh wight = dry weight * 10). Then, all data from various sources were normalized to the units gallic acid equivalent (GAE) mg/100 g FW.

[a]DTE represents dicaffeoyl tartaric acid equivalent.

[b]Total phenolic acid content = chicoric acid content + chlorogenic acid content + caffeoyl tartaric acid content + caffeoyl-meso-tartaric acid.

[c]CAE represents chlorogenic acid equivalent.

types contain higher levels than the green types (El-Nakhel et al., 2020; Nicolle, Carnat, et al., 2004). For example, the total phenolic acid content of red oak leaf lettuce was 231 mg/100 g FW dicaffeoyl tartaric acid equivalent, which was 3.5 times higher than that of green oak leaf lettuce (Nicolle, Carnat, et al., 2004). A previous study revealed that the total flavonoid content (without anthocyanins) of lettuce samples varied from 2.3 to 22.0 mg quercetin equivalent/100 g FW, and looseleaf types exhibited the highest flavonoid content (Gan, & Azrina, 2016). Yang, Wei, et al.

TABLE 4 Total anthocyanin contents in different types of lettuce

Lettuce type	Total anthocyanin content	Variety	References
Looseleaf type	17.4 mg CRE/100 g FW [a]	Galactic	Z. Li et al. (2010)
	12.7 mg/100 g FW [b]	Likarix	Medina-Lozano et al. (2021)
	0.06 mg CE/100 g FW [c]	Lollo rossa	Rouphael et al. (2019)
	45.6 mg CRE/100 g FW [a]	Lollo rosso	Llorach et al. (2008)
	7.3 mg CGE/100 g FW [d]	Lollo rosso	Dupont et al. (2000)
	95 mg CMGE/100 g FW [e]	Lollo rosso	Ferreres et al. (1997)
	8.95 mg/100 g FW [b]	Lollo rosso	Medina-Lozano et al. (2021)
	5.8 mg/100 g FW [b]	Nestorix	Medina-Lozano et al. (2021)
	25.9 mg CRE/100 g FW [a]	Red oak leaf	Llorach et al. (2008)
	2.3 mg CGE/100 g FW [d]	Red oak leaf	Dupont et al. (2000)
	0.16 mg CE/100 g FW [c]	Red oak leaf	Rouphael et al. (2019)
	6.1 mg/100 g FW [b]	Red sails	Medina-Lozano et al. (2021)
	3.8 mg/100 g FW [b]	Revolution	Medina-Lozano et al. (2021)
	6.0 mg/100 g FW [b]	Romired	Medina-Lozano et al. (2021)
Butterhead type	0.06 mg CE/100 g FW [c]	Red salanova	Rouphael et al. (2019)
	0.13 mg CE/100 g FW [c]	Red salanova	El-Nakhel et al. (2020)
Romaine	2.2 mg/100 g FW [b]	Lechuga de bureta	Medina-Lozano et al. (2021)
	1.2 mg/100 g FW [b]	Morada de belchite	Medina-Lozano et al. (2021)
	1.1 mg/100 g FW [b]	Morada de sorripas	Medina-Lozano et al. (2021)

Note: If the content was originally reported as dry weight in the reference, we converted the value to fresh weight (FW) using an average water content of 10% of lettuce (fresh wight = dry weight * 10). Then, all data from various sources were normalized to the units gallic acid equivalent (GAE) mg/100 g FW.
[a]CRE represents cyanidin-3-rutinoside equivalent.
[b]Total anthocyanin content = peonidin 3-glucoside content + cyanidin 3-(6′-malonyl)-glucoside content + cyanidin 3-(6′-acetyl)-glucoside content.
[c]CE represents cyanidin equivalent.
[d]CGE represents cyanidin 3-glucoside equivalent.
[e]CMGE represents cyanidin 3-malonyl-glucoside equivalent.

(2018) used a metabolomic approach to quantify the relative abundance of glycosylated flavonoids in 30 lettuce cultivars. They found that looseleaf types contained higher concentrations of glycosylated quercetin and luteolin than head lettuce (butterhead, iceberg, and romaine), which may result from the more extensive open/exposed leaf area to light and UV irradiation in the looseleaf types than in closed head types.

The main anthocyanins, a subgroup of flavonoids found in lettuce that contribute to leaf pigmentation, are cyanidin derivatives (Table 1). The anthocyanin content varies significantly across cultivars but not between the horticultural types (Table 4). Assefa et al. (2019) found that cyanidin was the single major anthocyanin in 15 lettuce varieties, with levels ranging from 3 (“Sunredbutter”) to 97 mg/100 g FW (“Tomalin”) at the mature stage. According to Rouphael et al. (2019), the looseleaf lettuce “Lollo rossa” and the butterhead lettuce “Red salanova” contained 0.062 and 0.063 cyanidin equivalent (CE) mg/100 g FW, respectively, whereas the looseleaf lettuce “Red oak leaf” contained 0.164 CE mg/100 g FW. These values were lower than those reported in previous studies. For example, Dupont et al. (2000) found that the anthocyanins contents of the “Red oak leaf” and “Lollo rosso” cultivars were 2.3 and 7.3 mg cyanidin 3-glucoside equivalent/100 g FW, respectively. However, higher values were of 25.9 mg cyanidin 3-rutinoside equivalents/100 g FW for “Red oak leaf” and 95.0 mg cyanidin 3-malonyl-glucoside equivalent/100 g FW for “Lollo rosso” were found for lettuce grown in open fields (Ferreres et al., 1997; Llorach et al., 2008). The low values reported in the study of Rouphael et al. (2019) may result from different lettuce growing conditions and the use of a different anthocyanin standard for measurement. Most recently, Medina-Lozano et al. (2021) revealed that cyanidin 3-(6′-malonyl glucoside) was the most abundant anthocyanin, accounting for 97% of the total anthocyanins content in most of the looseleaf and romaine lettuce cultivars, while trace amounts of peonidin 3-glucoside were detected in several lettuce cultivars.

2.3 | Terpenoids in lettuce

2.3.1 | Carotenoids

Carotenoids are a lipid-based class of phytochemicals essential for plant growth and defense and have been associated with health benefits to human health due to their antioxidant properties (Bohn, 2019). Carotenoids serve as adjunct pigments in photosynthesis to protect plants from photo-oxidative stress. They are the primary source of provitamin A (most notably β-carotene) in the diet (Nisar et al., 2015). The primary carotenoids found in lettuce are β-carotene, β-cryptoxanthin, and lutein, although their concentrations vary across varieties (Table 5). Romaine lettuce had the highest content of lutein and β-carotene, while crisphead lettuce contained the lowest contents; the amount of β-cryptoxanthin varied from 2.57 mg/100 g FW in "Lollo verde" to 10.46 mg/100 g FW in "Red salanova" as indicated in Table 5. Additionally, neoxanthin, violaxanthin, zeaxanthin, and lactucaxanthin have been detected in lettuce (Cruz et al., 2014; López et al., 2014). López et al. (2014) and Nicolle, Carnat, et al. (2004) examined the levels of lactucaxanthin, violaxanthin, and neoxanthin in several romaine lettuce cultivars. The lactucaxanthin content varied between 0.59 and 0.63 mg/100 g FW, the violaxanthin levels ranged between 0.50 and 0.69 mg/100 g FW, and the neoxanthin content ranged between 0.23 and 0.46 mg/100 g FW. According to Cruz et al. (2014), looseleaf lettuce contained 0.2, 1.3, and 0.8 mg/100 g FW lactucaxanthin, neoxanthin, and violaxanthin, respectively. Most recently, five apocarotenoid compounds were identified in stem lettuce using ^{1}H nuclear magnetic resonance (NMR) and HPLC/DAD UV spectrum data; these compounds were (−)-loliolide, (+)-dehydrovomifoliol, blumenol A, (6S,9S)-vomifoliol, and corchoionoside C (Malarz et al., 2021). In Europe, the population reference intake (PRI) for vitamin A is 750 μg retinol equivalent/day for adult males and 650 μg retinol equivalent/day for adult females (European Food Safety Authority, 2019). A serving of fresh lettuce (100 g) can provide as much as 2075 μg retinol equivalent of vitamin A, which meets the EU PRIs for adults. Moreover, the same amount of lettuce provides up to 1038 μg retinol activity equivalent of vitamin A, which meets the Chinese recommended nutrient intake (RNI) of vitamin A for adults of 800 and 700 μg retinol activity equivalent/day for adult males and females, respectively (National Health Commission, 2018). Therefore, some varieties of lettuce could be considered as rich dietary sources of provitamin A.

2.3.2 | Sesquiterpene lactones

Lettuce is the primary dietary source of sesquiterpene lactones due to its high level of consumption. Oxalate and sulfate conjugates of lactucin, deoxylactucin, and lactucopicrin are the main sesquiterpene lactones primarily found in the laticifer of lettuce leaves, stems, and flowering heads (Figure 2) and are mainly released in response to various stresses (Sessa et al., 2000). These compounds have been reported to exert potential antiobesity and antimalaria effects (Bischoff et al., 2004; Wang et al., 2020). To date, more than 20 compounds belonging to the sesquiterpene lactone group have been identified in lettuce, and these compounds are responsible for the bitterness of vegetable salads (Mai & Glomb, 2016; Sessa et al., 2000). Sessa et al. (2000) isolated and characterized sesquiterpene lactone conjugates in lettuce, including lactucin-15-oxalate, 15-deoxylactucin-8-sulfate, lactucin, 8-deoxylactucin 15-oxalate, 15-*p*-hydroxyphenyl acetyl lactucin-8-sulfate, 11,13 dihydro-8-deoxylactucin-15-glycoside, and lactucopicrin. Three novel sesquiterpene lactones were annotated from asparagus lettuce using ^{1}H and ^{13}C NMR, namely 1β-O-β-D-glucopyranosyl-4β-hydroxyl-5α, 6β, 11βH-eudesma-12, 6α-olide, 1β-hydroxyl-15-O-(*p*-methoxy phenylacetyl) -5α, 6β, 11βH-eudesma-3-en-12, 6α-olide, and β-D-glucopyranosyl-15-hydroxyl-5α, 6βH-guaiane-10(14), 1(13)-dien-12, 6α-olide (Y. F. Han et al., 2010). Abu-Reidah et al. (2013) putatively identified 10 sulfate and amino acid conjugates of sesquiterpene lactones in iceberg and romaine lettuce using mass spectrometry (MS). Lettucenin A, lettucenin A1, lettucenin B, and lettucenin B1 were identified as prominent colored lettucenins that contribute to browning in iceberg cultivars using NMR and MS techniques (Mai & Glomb, 2014). Three novel sesquiterpene lactones were isolated from iceberg lettuce via preparative HPLC and identified using NMR and MS techniques: 11β, 13-dihydro-lactucin-8-O-sulfate (jaquinelin-8-O-sulfate), cichorioside B, and 8-deacetylmatricarin-8-O-sulfate (Mai & Glomb, 2016). Recently, 9α-hydroxy-11β,13-dihydrozaluzanin C was isolated from stem lettuce and annotated by ^{1}H NMR (Malarz et al., 2021).

Sesquiterpene lactones have been linked to the degree of bitterness in lettuce and have been shown to vary between cultivars (Table 6) (Chadwick et al., 2016). The total content of the bitter sesquiterpene lactones varied significantly between 10 looseleaf cultivars. These included lactucin (0.03–0.17 mg/100 g FW), 8-deoxylactucin (0.03–0.17 mg/100 g FW), and lactucopicrin (0.09–0.36 mg/100 g FW), with the total sesquiterpene lactone concentrations ranging from 0.15 to 0.68 mg/100 g FW (Seo et al., 2009). Lactucin and lactucopicrin accumulated at higher levels in lettuce leaves during the bolting stage than the mature stage. According to Assefa et al. (2019), the total content of sesquiterpene lactones (measured as the sum of lactucin and lactucopicrin) in 22 lettuce cultivars ranged from 0.12 ("Superseonpung") to 3.87 ("Sunredbutter") mg/100 g FW at the mature stage, whereas "Cheonsang" and "Superseonpung" had the lowest and highest total sesquiterpene lactones contents at the bolting stage, with respective values of 2.13 and 41.01 mg/100 g FW.

TABLE 5 Major carotenoid contents in different types of lettuce (mg/100 g FW)

Lettuce type	Lutein	β-Carotene	Variety	References
Looseleaf type	2.66	1.13	Asia Oraedda Jeokchima	D. E. Kim et al. (2018)
	3.19	1.13	Asia Yeoreum Jeokchima	D. E. Kim et al. (2018)
	3.20	1.06	Cheongchima	D. E. Kim et al. (2018)
	2.53	0.86	Cheongha	D. E. Kim et al. (2018)
	1.90	0.53	Dduksum Jeokchukmyeon	D. E. Kim et al. (2018)
	4.05	5.65	Grand rapids	Mou (2008)
	7.46	8.31	Greengo	Mou (2008)
	2.00	0.70	Hacheong	D. E. Kim et al. (2018)
	2.23	0.76	Haetsal Jeokchukmyeon	D. E. Kim et al. (2018)
	2.94	0.82	Heukssamchima	D. E. Kim et al. (2018)
	1.87	0.54	Hongha Jeokchukmyeon	D. E. Kim et al. (2018)
	2.56	0.95	Jangsu	D. E. Kim et al. (2018)
	2.41	0.80	Jeokcima	D. E. Kim et al. (2018)
	2.17	0.71	Jeoksangchae	D. E. Kim et al. (2018)
	3.13	0.90	Jinbballolla	D. E. Kim et al. (2018)
	3.25	4.21	Lolla rossa	Mou (2008)
	2.37	1.91	Lollo rossa	Rouphael et al. (2019)
	1.81	1.29	Lollo verde	Rouphael et al. (2019)
	5.92	6.46	Merlot	Mou (2008)
	6.15	7.52	PI 206963	Mou (2008)
	5.87	6.08	Prizehead	Mou (2008)
	6.11	3.59	Red oak leaf	Rouphael et al. (2019)
	3.89	5.04	Ruby	Mou (2008)
	4.70	6.68	Salad bowl	Mou (2008)
	1.98	0.63	Seonhong Jeokchukmyeon	D. E. Kim et al. (2018)
	8.29	9.22	Waldmann's green	Mou (2008)
Butterhead type	7.35	7.51	Bibb	Mou (2008)
	6.41	6.87	Buttercrunch	Mou (2008)
	1.66	1.94	Dark green boston	Mou (2008)
	1.54	2.05	Dynamite	Mou (2008)
	2.17	2.12	Epic	Mou (2008)
	4.00	3.68	Four seasons	Cruz et al. (2014)
	1.81	1.10	Green salanova	El-Nakhel et al. (2020)
	2.43	1.63	Green salanova	Rouphael et al. (2019)
	5.65	3.19	Red salanova	El-Nakhel et al. (2020)
	7.39	4.04	Red salanova	Rouphael et al. (2019)
	1.38	2.66	Salanova Rossa	El-Nakhel et al. (2020b)
	0.56	1.52	Salanova Verde	El-Nakhel et al. (2020b)
Crisphead type	1.64	0.42	Abata	D. E. Kim et al. (2018)
	3.09	1.15	Arirang	D. E. Kim et al. (2018)
	1.75	1.40	Bronco	Mou (2008)
	0.89	0.87	Calmar	Mou (2008)
	2.12	1.77	Climax	Mou (2008)
	0.99	0.69	Empire	Mou (2008)
	0.99	0.74.	Francisco	Mou (2008)
	1.17	1.32	Glacier	Mou (2008)

(Continues)

TABLE 5 (Continued)

Lettuce type	Lutein	*β*-Carotene	Variety	References
	0.45	0.47.	Great lakes	Mou (2008)
	0.81	0.82.	Green lake	Mou (2008)
	1.32	0.69.	Ice cube	Mou (2008)
	0.45	0.42.	Imperial 44	Mou (2008)
	0.76	0.78.	King crown	Mou (2008)
	2.97	2.01	Legacy	Mou (2008)
	0.82	0.63	Mohawk	Mou (2008)
	0.69	0.65	Monterey	Mou (2008)
	1.09	0.80	Niner	Mou (2008)
	2.94	0.79	Salad express	D. E. Kim et al. (2018)
	1.85	1.54	Salinas 88	Mou (2008)
	1.59	1.13	Sniper	Mou (2008)
	1.32	0.97	Thompson	Mou (2008)
	2.79	2.06	Tiber	Mou (2008)
	1.66	1.02	Top gun	Mou (2008)
	0.58	0.41	Vanguard 75	Mou (2008)
	1.78	1.29	Yuma	Mou (2008)
Romaine type	1.39	3.49	Aitana	López et al. (2014)
	1.34	3.39	Alhama	López et al. (2014)
	1.41	3.30	Ar-29213	López et al. (2014)
	2.05	0.48	Asia Heuk Romaine	D. E. Kim et al. (2018)
	6.09	3.72	Baby romaine	Rouphael et al. (2019)
	2.20	0.75	Caesar green	D. E. Kim et al. (2018)
	3.62	1.06	Caesar red	D. E. Kim et al. (2018)
	1.17	2.64	Carrascoy	López et al. (2014)
	1.16	3.20	Collado	López et al. (2014)
	9.67	10.00	Darkland	Mou (2008)
	1.00	2.46	Espuña	López et al. (2014)
	3.63	1.29	Esse	D. E. Kim et al. (2018)
	3.37	5.50	Heart's delight	Mou (2008)
	0.77	2.01	Isasa	López et al. (2014)
	5.71	9.53	Parris island	Mou (2008)
	1.82	0.49	Saengchae	D. E. Kim et al. (2018)
	3.82	1.33	Super caesar red	D. E. Kim et al. (2018)
	7.22	10.22	Tall guzmaine	Mou (2008)
	6.74	12.45	Valmaine	Mou (2008)
Stem type	6.36	7.15	Da ye wo ju	Mou (2008)

Note: If the content was originally reported as dry weight in the reference, we converted the value to fresh weight (FW) using an average water content of 10% of lettuce (fresh wight = dry weight * 10). Then, all data from various sources were normalized to the units gallic acid equivalent (GAE) mg/100 g FW.

2.4 | Vitamins in lettuce

2.4.1 | The vitamin B complex

The vitamin B complex is a group of eight water-soluble B vitamins that are required in cellular metabolism. Folate (vitamin B_9) has been extensively documented in lettuce, which is a substantial source of folates in the diet. The three primary forms of folates found in butterhead, romaine, looseleaf, and crisphead lettuce were tetrahydrofolate, 5-methyl-tetrahydrofolate, and 5-formyl-tetrahydrofolate (Johansson et al., 2007). Folates serve as donors and acceptors in one-carbon metabolism and are involved in the biosynthesis of nucleotides, amino acids,

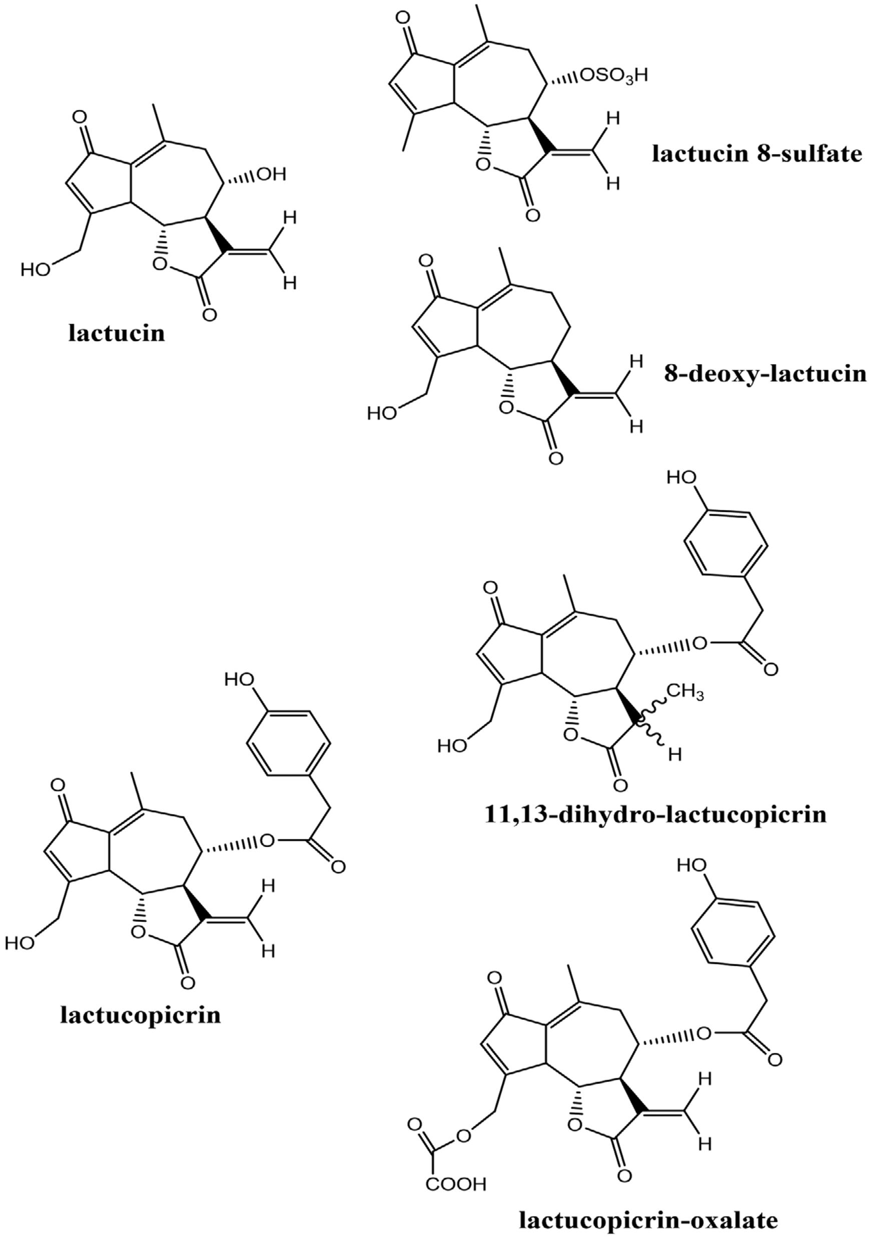

FIGURE 2 Sesquiterpene lactones present in lettuce. Sulfate and oxalate derivatives are also found as well as some glycosidic forms

formyl-methionyl tRNA, and pantothenate (Blancquaert et al., 2010). The total folate concentration varies between lettuce cultivars (Table 7). Simonne et al. (2002) quantified the folate content of 17 cultivars, including looseleaf, romaine, butterhead, and crisphead lettuce; the looseleaf types with green leaves had a significantly higher average folate contents than crisphead types; the looseleaf variety "Nevada" and crisphead cultivar "Legacy" had the highest and lowest folate contents of 0.10 mg/100 g FW and 1.73×10^{-2} mg/100 g FW, respectively. In addition, D. E. Kim et al. (2018) found that the total folate content of 23 lettuce varieties, including looseleaf, crisphead, and romaine types, ranged from 6.51×10^{-2} mg/100 g FW ("Caesar green") to 9.73×10^{-2} mg/100 g FW ("Asia heuk romaine"). A recent study demonstrated that stem lettuce might also be a substantial source of folate in the diet. 10-Formyl-folic acid, 5-formyl-tetrahydrofolate, and tetrahydrofolate were identified as the three primary forms in cooked stem lettuce. A total folate value of 5.77×10^{-2} mg/100 g FW was found; whereas two major vegetables, spinach, and broccoli, were found to contain 6.96×10^{-2} and 4.44×10^{-2} mg/100 g FW folate, respectively, after cooking (Islam et al., 2020). For adults, a serving of fresh lettuce (100 g) offers up to 25% of the RNI of folate for the Chinese population and up to 31% of the PRI for folate in the EU (European Food Safety Authority, 2019; National Health Commission, 2018). For pregnant women, 100 g fresh lettuce provides up to 17% of the RNI of folate in China and 17% of the EU adequate intake (AI) of folate (European Food Safety Authority, 2019; National Health Commission, 2018).

TABLE 6 Main sesquiterpene lactone contents in different types of lettuce (mg/100 g FW)

	Lactucin		Lactucopicrin		8-Deoxy-lactucin		
Lettuce type	**Mature [a]**	**Bolting [b]**	**Mature**	**Bolting**	**Mature**	**Variety**	**References**
Looseleaf type	0.04	–	0.15	–	0.07	Bulkkotchukmyeon	Seo et al. (2009)
	0.05	0.12	0.60	2.12	–	Cheongchima	Assefa et al. (2019)
	0.06	–	0.16	–	0.06	Cheonghacheongchima	Seo et al. (2009)
	0.26	0.90	1.24	5.22	–	Chunhachujeokchima	Assefa et al. (2019)
	0.02	0.18	0.61	6.28	–	Chunpungjeokchukmyeon	Assefa et al. (2019)
	0.04	–	0.15	–	0.07	Daetongyeoleumjeokchukmyeon	Seo et al. (2009)
	0.04	–	0.13	–	0.05	Ganghancheongchima	Seo et al. (2009)
	0.04	0.18	0.65	6.63	–	Gohong	Assefa et al. (2019)
	0.03	0.10	0.61	8.15	–	Gopungjeokchukmyeon	Assefa et al. (2019)
	0.06	0.36	0.99	11.76	–	Hacheong	Assefa et al. (2019)
	0.07	–	0.36	–	0.16	Hajicheongchukmyeon	Seo et al. (2009)
	0.03	–	0.09	–	0.03	Hanbatcheongchima	Seo et al. (2009)
	0.05	1.72	0.51	4.38	–	Hyeseonmanchudae	Assefa et al. (2019)
	0.03	0.42	0.46	5.93	–	Jangsu	Assefa et al. (2019)
	0.10	0.85	1.24	12.28	–	Jeokdan	Assefa et al. (2019)
	0.05	1.00	0.80	11.57	–	Jeokhagye	Assefa et al. (2019)
	0.15	0.80	0.62	2.08	–	Mansang	Assefa et al. (2019)
	0.02	0.11	0.63	5.79	–	Mihong	Assefa et al. (2019)
	0.05	0.25	0.75	15.37	–	Miseonjeokchukmyeon	Assefa et al. (2019)
	0.05	0.21	1.03	5.40	–	Sambokhacheong	Assefa et al. (2019)
	0.07	–	0.34	–	0.13	Seonpungpochapjeokchukmyeon	Seo et al. (2009)
	0.02	2.13	0.10	38.88	–	Superseonpung	Assefa et al. (2019)
	0.04	–	0.13	–	0.05	Taepungyeoleumjeokchukmyeon	Seo et al. (2009)
	0.04	1.19	0.69	9.86	–	Tomalin	Assefa et al. (2019)
	0.07	–	0.14	–	0.06	Waolhajeokchukmyeon	Seo et al. (2009)
	0.02	0.73	0.52	9.95	–	Yelpungjeokchima	Assefa et al. (2019)
	0.07	–	0.31	–	0.17	Yeonsanhongjeokchukmyeon	Seo et al. (2009)
Butterhead type	0.05	1.75	0.29	6.15	–	Adam	Assefa et al. (2019)
	0.42	0.74	3.45	5.94	–	Sunredbutter	Assefa et al. (2019)
Crisphead type	0.02	1.81	0.29	12.56	–	Pungseong	Assefa et al. (2019)
Romaine type	0.14	0.44	0.52	1.69	–	Cheonsang	Assefa et al. (2019)
Unknown	0.07	0.82	0.65	13.97	–	Jeoksagye	Assefa et al. (2019)

Note: If the content was originally reported as dry weight in the reference, we converted the value to fresh weight (FW) using an average water content of 10% of lettuce (fresh wight = dry weight * 10). Then, all data from various sources were normalized to the units gallic acid equivalent (GAE) mg/100 g FW.

[a]At mature stage.

[b]At bolting stage.

However, few studies have quantified other members of the vitamin B complex, including thiamine, riboflavin nicotinamide, pantothenic acid, and pyridoxine, in lettuce. For example, Cataldi et al. (2003) reported that the riboflavin content of crisphead lettuce was 0.06 mg/100 g FW, which is considered a moderate content of riboflavin compared to other common vegetables. In addition, Santos et al. (2012) determined the water-soluble vitamin contents of green and red looseleaf lettuce. They found that green lettuce contained 7.9×10^{-2} mg thiamine (B_1)/100 g FW, 2.8×10^{-2} mg riboflavin (B_2)/100 g FW, 0.13 mg nicotinamide (B_3)/100 g FW, 0.14 mg pantothenic acid (B_5)/100 g FW, and $2{\times}10^{-3}$ mg pyridoxine (B_6)/100 g FW, while ruby red lettuce contained 6.8×10^{-2} mg thiamine/100 g FW, 2.8×10^{-2} mg riboflavin/100 g FW, 0.19 mg nicotinamide/100 g FW, $7.7 {\times}10^{-2}$ mg pantothenic acid/100 g FW, and $1.5{\times}10^{-2}$ mg pyridoxine/100 g FW. However, due to the lack of relevant studies, it is difficult to

TABLE 7 Folate content in different types of lettuce (mg/100 g FW)

Lettuce type	Folate	Variety	References
Looseleaf	7.74×10^{-2}	Asia oraedda jeokchima	D. E. Kim et al. (2018)
	9.01×10^{-2}	Asia yeoreum jeokchima	D. E. Kim et al. (2018)
	4.47×10^{-2}	Big curly	Simonne et al. (2002)
	7.45×10^{-2}	Brunia	Simonne et al. (2002)
	3.65×10^{-2}	Cabernet red	Simonne et al. (2002)
	7.59×10^{-2}	Cheongchima	D. E. Kim et al. (2018)
	7.50×10^{-2}	Cheongha	D. E. Kim et al. (2018)
	8.30×10^{-2}	Dduksum jeokchukmyeon	D. E. Kim et al. (2018)
	5.53×10^{-2}	Greengo	Simonne et al. (2002)
	9.09×10^{-2}	Hacheong	D. E. Kim et al. (2018)
	9.16×10^{-2}	Haetsal Jeokchukmyeon	D. E. Kim et al. (2018)
	7.88×10^{-2}	Heukssamchima	D. E. Kim et al. (2018)
	8.35×10^{-2}	Hongha jeokchukmyeon	D. E. Kim et al. (2018)
	8.32×10^{-2}	Jangsu	D. E. Kim et al. (2018)
	9.39×10^{-2}	Jeokcima	D. E. Kim et al. (2018)
	9.07×10^{-2}	Jeoksangchae	D. E. Kim et al. (2018)
	8.43×10^{-2}	Jinbballolla	D. E. Kim et al. (2018)
	10.24×10^{-2}	Nevada	Simonne et al. (2002)
	4.13×10^{-2}	Red Salad Bowl	Simonne et al. (2002)
	2.20×10^{-2}	Redprize	Simonne et al. (2002)
	9.43×10^{-2}	Salanca GM	Simonne et al. (2002)
	7.80×10^{-2}	Seonhong jeokchukmyeon	D. E. Kim et al. (2018)
	5.62×10^{-2}	Sierra	Simonne et al. (2002)
	2.62×10^{-2}	Slobolt	Simonne et al. (2002)
Butterhead type	3.32×10^{-2}	Nancy	Simonne et al. (2002)
	4.44×10^{-2}	Optima	Simonne et al. (2002)
	5.73×10^{-2}	Ostinata	Simonne et al. (2002)
Crisphead type	7.79×10^{-2}	Abata	D. E. Kim et al. (2018)
	7.60×10^{-2}	Arirang	D. E. Kim et al. (2018)
	3.42×10^{-2}	Epic	Simonne et al. (2002)
	4.78×10^{-2}	Frillice lettuce	Johansson et al. (2007)
	1.73×10^{-2}	Legacy	Simonne et al. (2002)
	8.91×10^{-2}	Salad express	D. E. Kim et al. (2018)
	2.13×10^{-2}	Salinas 88	Simonne et al. (2002)
Romaine type	4.00×10^{-2} [a]	Aitana	López et al. (2014)
	2.10×10^{-2} [a]	Alhama	López et al. (2014)
	2.90×10^{-2} [a]	Ar-29213	López et al. (2014)
	9.73×10^{-2}	Asia heuk romaine	D. E. Kim et al. (2018)
	6.51×10^{-2}	Caesar green	D. E. Kim et al. (2018)
	7.74×10^{-2}	Caesar red	D. E. Kim et al. (2018)
	3.10×10^{-2} [a]	Carrascoy	López et al. (2014)
	1.80×10^{-2} [a]	Collado	López et al. (2014)
	2.80×10^{-2} [a]	Espuña	López et al. (2014)
	7.72×10^{-2}	Esse	D. E. Kim et al. (2018)
	0.80×10^{-2} [a]	Isasa	López et al. (2014)

(Continues)

TABLE 7 (Continued)

Lettuce type	Folate	Variety	References
	4.36×10^{-2}	Parris Island	Simonne et al. (2002)
	5.66×10^{-2}	Romaine lettuce	Johansson et al. (2007)
	7.77×10^{-2}	Saengchae	D. E. Kim et al. (2018)
	7.89×10^{-2}	Super caesar red	D. E. Kim et al. (2018)

Note: If the content was originally reported as dry weight in the reference, we converted the value to fresh weight (FW) using an average water content of 10% of lettuce (fresh wight = dry weight * 10). Then, all data from various sources were normalized to the units gallic acid equivalent (GAE) mg/100 g FW.
[a]Total folate content = 5-methyl-tetrahydrofolate content + tetrahydrofolate content.

assess the contribution of dietary lettuce to the daily intake of these B vitamins, which should be studied further.

2.4.2 | Vitamin C

Ascorbic acid, an antioxidant that plays a significant role in plant defense and survival and functions as a modulator of plant growth and development through phytohormones signaling, is mainly biosynthesized via de novo pathways (Pastori et al., 2003; Valpuesta & Botella, 2004). Fruit and vegetables are the primary sources of vitamin C (ascorbic acid and dehydroascorbic acid). The vitamin C content in lettuce, in particular, exhibits significant diversity in terms of leaf shape and color, as shown in Table 8 (Hao et al., 2018; Simonne et al., 2002; van Treuren et al., 2018). The vitamin C concentration of 74 lettuce cultivars varied from 3.35 to 60.99 mg/100 g FW. Forty cultivars had between 10 and 20 mg/100 g FW, and nine purple-leaf types of lettuce contained more than 40 mg/100 g FW (Hao et al., 2018). Among the various horticultural types, crisphead lettuce has the lowest levels of vitamin C, with an average level of 8.52 mg/100 g FW, followed by butterhead (9.27 mg/100 g FW), looseleaf (10.39 mg/100 g FW), and romaine (29.60 mg/100 g FW). In contrast, stem type has the highest average of 42.39 mg/100 g FW (van Treuren et al., 2018). Previously studies suggested that lettuce contained one of the lowest concentrations of vitamin C of the most frequently consumed fruit and vegetables (Bahorun et al., 2004; Chu et al., 2002; Proteggente et al., 2002). Here, according to our calculations (Table 8), a serving of fresh lettuce (100 g) could provide 5–28% of the RNI of vitamin C for adults in the Chinese population (National Health Commission, 2018), 4–26% of the PRI of vitamin C for European adult males, and 5–30% of the PRI of vitamin C for European adult females (European Food Safety Authority, 2019). Thus, due to its widespread consumption, lettuce may represent a moderate source of vitamin C in the diet.

2.4.3 | Vitamin E

Vitamin E is a significant lipid-soluble antioxidant present in cell membranes as α-, β-, γ-, and δ-forms of tocopherols and tocotrienols. The α-, and γ- tocopherols predominate in lettuce (Table 9). The α-tocopherol content of 17 cultivars ranged from 0.22 mg/100 g FW in the "Legacy" cultivar (crisphead type) to 2.27 mg/100 g FW in the "Salanca" cultivar (looseleaf type). Meanwhile, the γ-tocopherol content ranged from 0.09 and 0.51 mg/100 g FW (Simonne et al., 2002). The total vitamin E content ranged from 0.33 to 1.10 mg/100 g FW (Chun et al., 2006). The same authors compared four types of lettuce, including iceberg, looseleaf, butterhead, and romaine. They observed that the looseleaf lettuce contained the highest amount of γ-tocopherol (0.74 mg/100 g FW), while the highest α-tocopherol content (0.55 mg/100 g FW) was found in romaine. Only trace amounts of β-tocopherol (0.01 mg/100 g FW) were found in looseleaf lettuce (Chun et al., 2006). The AI of vitamin E for adults in the Chinese population is 14 mg α-tocopherol equivalents per day (National Health Commission, 2018). Thus, a serving of fresh lettuce (100 g) could provide 16% of the AI of vitamin E, up to 21% of the AI of vitamin E for adult females, and up to 17% of the AI of vitamin E for adult males in the European population (European Food Safety Authority, 2019).

2.4.4 | Vitamin K

Vitamin K is a liposoluble vitamin that has been shown to decrease the risk of bone fracture, protect against CVD, and aid in blood coagulation (Booth, 2012; Shea et al., 2021). Phylloquinone is the primary dietary supply of vitamin K, and vegetables are the primary source of phylloquinone. In particular, lettuce is one of the most abundant vegetable sources of vitamin K in certain populations due to its high consumption levels (Harshman et al., 2017). The amount of phylloquinone varies in different kinds of lettuce. Specifically, green looseleaf lettuce has an average phylloquinone content of 127 mg/100 g FW, followed by red looseleaf lettuce (123 mg/100 g FW), romaine lettuce (103 mg/100 g FW), and butterhead lettuce (102 mg/100 g FW). In comparison, crisphead lettuce has the lowest phylloquinone content of these five types with 24.1 mg/100 g FW (Damon et al., 2005). A serving of fresh lettuce (100 g)

TABLE 8 Vitamin C content in different types of lettuce (mg/100 g FW)

Lettuce type	Vitamin C	Variety	References
Looseleaf type	28.4	Begoña	Medina-Lozano et al. (2021)
	10.8	Big curly	Simonne et al. (2002)
	14.1	Brunia	Simonne et al. (2002)
	17.5	Cabernet red	Simonne et al. (2002)
	18.6	Greengo	Simonne et al. (2002)
	21.9	Likarix	Medina-Lozano et al. (2021)
	17.2	Lollo rosso	Medina-Lozano et al. (2021)
	19.7	Morada de bernués	Medina-Lozano et al. (2021)
	15.3	Nestorix	Medina-Lozano et al. (2021)
	9.9	Nevada	Simonne et al. (2002)
	19.7	Red sails	Medina-Lozano et al. (2021)
	22.3	Red salad bowl	Simonne et al. (2002)
	14.9	Redprize	Simonne et al. (2002)
	18.8	Revolution	Medina-Lozano et al. (2021)
	19.6	Romired	Medina-Lozano et al. (2021)
	13.3	Salanca GM	Simonne et al. (2002)
	12.1	Sierra	Simonne et al. (2002)
	26.2	Slobolt	Simonne et al. (2002)
Butterhead type	21.2	Lechuga del valle de tena	Medina-Lozano et al. (2021)
	17.9	Nancy	Simonne et al. (2002)
	17.8	Optima	Simonne et al. (2002)
	8.3	Ostinata	Simonne et al. (2002)
	55.1	Salanova rossa	El-Nakhel et al. (2020)
	11.5	Salanova verde	El-Nakhel et al. (2020)
	16.3	Winter crop	Medina-Lozano et al. (2021)
Crisphead type	15.8	Epic	Simonne et al. (2002)
	4.8	Legacy	Simonne et al. (2002)
	10.6	Salinas 88	Simonne et al. (2002)
Romaine type	10.0	Aitana	López et al. (2014)
	9.3	Alhama	López et al. (2014)
	10.9	Ar-29213	López et al. (2014)
	7.5	Carrascoy	López et al. (2014)
	9.0	Collado	López et al. (2014)
	19.9	Dolomiti G12	Medina-Lozano et al. (2021)
	10.4	Espuña	López et al. (2014)
	6.9	Isasa	López et al. (2014)
	23.4	Lechuga de beceite	Medina-Lozano et al. (2021)
	25.7	Lechuga de bureta	Medina-Lozano et al. (2021)
	21.0	Lechuga de ensalada	Medina-Lozano et al. (2021)
	18.8	Lechuga de híjar	Medina-Lozano et al. (2021)
	22.5	Lechuga de subías	Medina-Lozano et al. (2021)
	26.4	Lechuga del pirineo	Medina-Lozano et al. (2021)
	28.0	Lechuga Romana zaragozana	Medina-Lozano et al. (2021)
	15.8	Morada de belchite	Medina-Lozano et al. (2021)
	18.1	Morada de sorripas	Medina-Lozano et al. (2021)
	24.8	Oreja de mulo	Medina-Lozano et al. (2021)

(Continues)

TABLE 8 (Continued)

Lettuce type	Vitamin C	Variety	References
	23.3	Parris island	Simonne et al. (2002)
	24.8	Romana inverna	Medina-Lozano et al. (2021)

Note: If the content was originally reported as dry weight in the reference, we converted the value to fresh weight (FW) using an average water content of 10% of lettuce (fresh wight = dry weight * 10). Then, all data from various sources were normalized to the units gallic acid equivalent (GAE) mg/100 g FW.

TABLE 9 Vitamin E content in different types of lettuce (mg/100 g FW)

	Vitamin E			
Lettuce type	α-Tocopherol	γ-Tocopherol	Variety	References
Looseleaf type	1.23	0.09	Big curly	Simonne et al. (2002)
	0.58	0.51	Brunia	Simonne et al. (2002)
	0.82	0.17	Cabernet red	Simonne et al. (2002)
	0.96	0.19	Greengo	Simonne et al. (2002)
	0.54	0.18	Nevada	Simonne et al. (2002)
	0.98	0.16	Red salad bowl	Simonne et al. (2002)
	0.72	0.25	Redprize	Simonne et al. (2002)
	1.00	–	Ruby red lettuce	Santos et al. (2012)
	2.27	0.08	Salanca GM	Simonne et al. (2002)
	0.63	0.14	Sierra	Simonne et al. (2002)
	0.98	0.31	Slobolt	Simonne et al. (2002)
	0.31	0.74	Unknown	Chun et al. (2006)
	0.15	0.51	Unknown	Cruz and Casal (2013)
	0.36	0.49	Unknown	Cruz and Casal (2013)
Butterhead type	1.73	1.40	Four seasons	Cruz and Casal (2014)
	0.76	0.20	Nancy	Simonne et al. (2002)
	0.63	0.15	Optima	Simonne et al. (2002)
	0.56	0.09	Ostinata	Simonne et al. (2002)
	0.23	0.27	Unknown	Chun et al. (2006)
	0.34	0.63	Unknown	Cruz et al. (2013)
Crisphead type	0.56	0.26	Epic	Simonne et al. (2002)
	0.22	0.05	Legacy	Simonne et al. (2002)
	0.36	0.11	Salinas 88	Simonne et al. (2002)
	0.22	0.11	Unknown	Chun et al. (2006)
Romaine type	0.98	0.14	Parris island	Simonne et al. (2002)
	0.55	0.36	Unknown	Chun et al. (2006)

Note: If the content was originally reported as dry weight in the reference, we converted the value to fresh weight (FW) using an average water content of 10% of lettuce (fresh wight = dry weight * 10). Then, all data from various sources were normalized to the units gallic acid equivalent (GAE) mg/100 g FW.

could supply up to 127 mg of vitamin K in the form of phylloquinone, which is sufficient to satisfy the AI of vitamin K recommended by the EU and Chinese dietary reference intakes, which are 70 and 80 µg/day of vitamin K as phylloquinone for adults, respectively (European Food Safety Authority, 2019; National Health Commission, 2018). As a result, looseleaf, romaine, and butterhead lettuce could be significant sources of dietary phylloquinone.

2.5 | Bioactive compounds vary in lettuce types

The nutritional value of lettuce varies between different horticultural types. To compare the content of dietary vitamins (or provitamins) and TPC among different lettuce types, we calculated the average values for these health-promoting compounds (Figure 3). The contribution of lettuce to dietary micronutrient levels in the diet is of

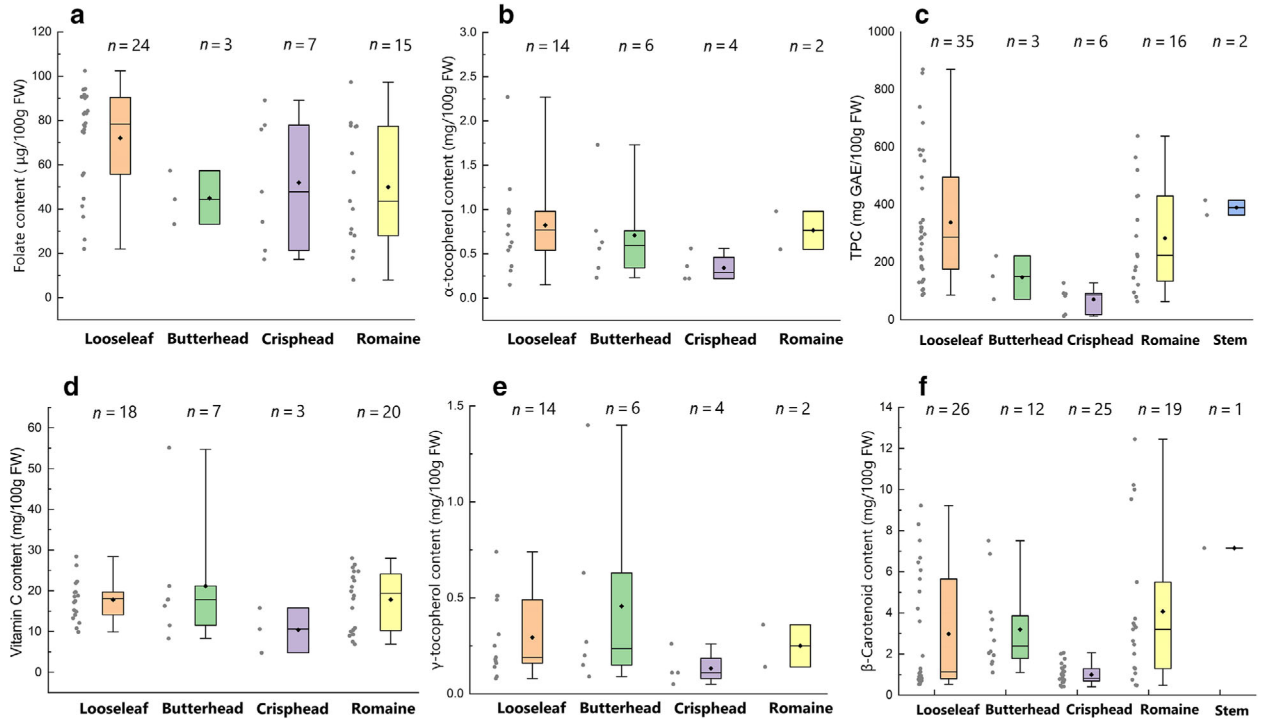

FIGURE 3 Contents of health-promoting compounds in looseleaf, butterhead, crisphead, and romaine types of lettuce. (a) Folate contents (see Table 7); (b) α-tocopherol contents (see Table 9); (c), TPC contents (see Table 2); (d) vitamin C contents (see Table 8); (e) γ-tocopherol contents (see Table 9); (f) β-carotenoid contents (see Table 5). The horizontal lines and rhombic symbols inside the box plots represent the median and mean values

public importance, as various types of lettuce are widely consumed in different regions of the world (Křístková et al., 2008; Mampholo et al., 2016). Among the looseleaf, butterhead, crisphead, and romaine types of lettuce, looseleaf was found to be a rich source of folate (7.2×10^{-2} mg/100 g FW), α-tocopherol (0.82 mg/100 g FW), and TPC (338.08 mg/100 g), and a moderate source of vitamin C and β-carotene. Romaine lettuce had the highest average values of γ-tocopherol (0.77 mg/100 g FW) and β-carotene (4.06 mg/100 g FW) among these four types of lettuce. Butterhead lettuce contained the highest levels of vitamin C, with an average of 21.16 mg/100 g FW. In contrast, crisphead lettuce was a poor source of all these phytochemicals compared to the other horticultural types of lettuce. Stem lettuce originated in China and is primarily consumed in Asian countries like China and India (L. Zhang et al., 2017). Previous studies indicated stem lettuce might be a significant source of β-carotene and TPC; however, the nutritional value of stem lettuce is difficult to assess due to the lack of comprehensive phytochemical analyses.

3 | POTENTIAL BENEFITS FOR HUMAN HEALTH

Lettuce is consumed worldwide as a ready-to-eat vegetable, and its contribution to micronutrient levels and potential health benefits are of public interest. Lettuce consumption has been associated with a reduction in the risk of several chronic diseases, and these health benefits are attributed to the presence of health-promoting compounds. Here, the in vitro and in vivo evidence of the benefits of lettuce to human health are summarized and critically discussed.

3.1 | In vitro evidence

Despite high lettuce consumption in both Asian and Western diets, most of the evidence for the health advantages of lettuce was obtained in vitro. However, in vivo evidence from either preclinical or clinical studies is still very limited. So far, consumption of fresh lettuce and lettuce extracts has been reported to improve the antioxidant status, suppress inflammation, prevent diabetes, inhibit the proliferation of specific cancer cell lines, and exert antiviral effects in vitro (M. J. Kim et al., 2016). However, there are only a small number of studies, and they often have many constraints.

3.1.1 | Antioxidant bioactivity

Numerous studies have shown that lettuce extracts can scavenge reactive oxygen species (ROS) and, therefore, decrease free radicals induced by oxidative stress. Multiple approaches have been used to assess antioxidant bioactivity in vegetables, including the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activity assay, the ferric reducing antioxidant power assay (FRAP), the 2,2′-azinobis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) free radical scavenging activity assay, the cellular antioxidant activity assay (CAA), and the cellular H_2O_2 scavenging capability assay. Lettuce has a relatively low antioxidant capacity compared to other commonly consumed vegetables (Chu et al., 2002; Song et al., 2010).

Previous studies suggested that red or purple pigmented lettuce has higher antioxidant activity than green leaf cultivars. For instance, Liu et al. (2007) compared the DPPH antioxidant activity of red and green colored looseleaf, romaine, and crisphead lettuce. They found that red-pigmented types of looseleaf and romaine lettuce had higher antioxidant activity than the respective green types no significant difference was observed between green and red crisphead lettuce. D. E. Kim et al. (2018) also indicated that red lettuce cultivars had higher DPPH and ABTS free-radical scavenging activities than green/red and green cultivars.

The total antioxidant activity positively correlates with the content of PP compounds in lettuce. Nicolle, Carnat, et al. (2004) reported that total phenolics contributed to more than 60% of the total antioxidant capacity in lettuce; specifically, dicaffeoyl tartaric acid, chlorogenic acid, and quercetin 3-glucuronide accounted for 55.8%, 4.6%, and 3.8%, respectively, of DPPH free-radical scavenging activity in green cultivars. In addition, using the loading plot of principal component analysis, D. E. Kim et al. (2018) found that cyanidin derivatives and TPC strongly correlated with antioxidant activities measured using the DPPH and ABTS assays. Moreover, Yang et al. (2017) observed that FRAP, CAA units, and H_2O_2 scavenging capability were significantly and positively correlated with TPC and with the relative abundances of glycosylated flavonoids, including apigenin 7-glucuronide and luteolin 7-glucoside, and quercetin derivatives, including quercetin 3-(6′′-malonyl)-glucoside 7-glucoside, quercetin 3-(6′′- malonyl)-glucoside 7-glucuronide, quercetin glucose acetate, quercetin glucoside, and quercetin hexoside glucuronide.

The total antioxidant activity of lettuce varies according to cultivar, plant and leaf portion, and harvesting time. The antioxidant capacity of horticultural types follows the order of looseleaf > romaine > butterhead > crisphead. Liu et al. (2007) indicated that looseleaf lettuce showed the highest DPPH free-radical scavenging activity, followed by romaine, butterhead, and crisphead cultivars when cultivated under the same environmental conditions, while seasonal production also affected the total antioxidant activity, with lettuce grown in July having higher levels than lettuce planted in September. Llorach et al. (2008) found that the free radical scavenging ability varied across five lettuce types widely cultivated in Spain. The looseleaf cultivar "Lollo rosso" had the highest antioxidant activity, followed by "Red oak leaf," "Continental," and "Romaine," whereas "Iceberg" had the lowest. In addition, Cano and Arnao (2005) evaluated the hydrophilic and lipophilic antioxidant activity of three lettuce varieties (iceberg, romaine, baby head) using the ABTS assay and found that romaine lettuce had the highest hydrophilic and lipophilic antioxidant activities. Moreover, the lipophilic antioxidant activity in different organs of lettuce was in the following order: outer leaf > inner leaf > middle leaf > stem, while the hydrophilic antioxidant activity was in the following order: outer leaves > mid leaves > inner leaves > stems.

To date, most investigations of the antioxidant bioactivity of lettuce have tested extracts directly prepared from lettuce products. A recent study compared the in vitro antioxidant potential of crisphead lettuce extracts before and after gastrointestinal digestion and found that digestion decreased antioxidant bioactivities as measured by the DPPH (48–76%) and ABTS (5–39%) radical scavenging methods, FRAC (14–30%), and metal ion chelating activity (27–68%) assays (Ketnawa et al., 2020).

However, the antioxidant tests carried out in vitro have limited physiological relevance and, in more cases, reflect the content of PPs in the assayed sample. The main problem with these assays is that they do not consider the digestion events and the intestinal and systemic metabolism of the food components, which render metabolites with a very different antioxidant activity. Thus, the in vitro free-radical scavenging assays do not parallel what happens in vivo. An excellent example to show the lack of relevance of the antioxidant tests evaluated in vitro with foods or food extracts is the case of pomegranate juice. Pomegranate is one of the foods with the highest antioxidant activity due to its ellagitannin content. Pomegranate antioxidants are not absorbed, and gut microbiota metabolizes them, leading to urolithins which are readily absorbed. Urolithins, however, show a relatively low antioxidant activity, although they have other relevant biological effects (Cerdá et al., 2004; Gil et al., 2000).

3.1.2 | Anti-inflammatory effects

Lettuce is an abundant natural source of antioxidants and exerts an intense anti-inflammatory activity when evaluated in cell lines (Table 10). In the J774A.1 mouse monocyte-macrophage cells, extracts from the green lettuce cultivar "Maravilla de Verano" promoted nuclear translocation of Nrf2, decreased ROS formation, and nitric oxide release inhibited NF-κB nuclear translocation and suppressed the expression of inducible NOS (iNOS) and COX-2. These effects were attributed to the high concentrations of quercetin glycosides in the lettuce extract. However, significant amounts of other phenolics (feruloyl tartaric, feruloyl quinic, chlorogenic, caftaric acid, chicoric acid, esculetin, and kaempferol glycosides) were also present in the extract (Adesso et al., 2016; Pepe et al., 2015).

3.1.3 | Antidiabetic effects

In vitro evidence suggests that the "Rutgers scarlet" lettuce extract and its primary phenolic compound, chlorogenic acid, exerted a glucose-lowering impact in H4IIE rat hepatoma cells (Table 10) (Cheng, Pogrebnyak, Kuhn, Poulev, et al., 2014). However, this study is of limited physiological relevance as metabolism and absorption of metabolites in lettuce extract are not considered. Besides, the carotenoid lactucaxanthin, a typical carotenoid isolated from lettuce, exerted antidiabetic effects by reducing the activity of α-amylase (IC_{50} of 435.5 µg/mL) and α-glucosidase (IC_{50} of 1.84 mg/mL), which are two main targets of clinical therapeutic strategies for diabetes (Gopal et al., 2017).

3.1.4 | Anticancer effects

Lettuce extracts can inhibit cancer cell growth and potentially exert anticancer effects (Table 10). Qin et al. (2018) reported that red pigmented lettuce extracts exerted growth inhibitory effects against A549 human lung adenocarcinoma cells, Bel7402 human hepatoma cells, HepG2 human colorectal cancer cells, and HT29 human colon cancer cells, and these effects were attributed to anthocyanins, flavones, and phenolic acids. In addition, bioactive compounds isolated from lettuce also exhibited the potential to prevent cancer. For instance, lactucin was reported to induce apoptosis and sub-G1 cell cycle arrest, thus exerting potential anticancer effects in HL-60 human leukemia cancer cells (F. H. Zhang et al., 2016). Lactucaxanthin, violaxanthin, lutein, and 9-Z-neoxanthin isolated from lettuce reduced the cell viability of cervical (HeLa) and lung cancer (A549) cells. Of these xanthophyll compounds, 9-Z-neoxanthin had the lowest IC_{50}, at 3.8 µM for HeLa cells and 9.1 µM for A549 (Saini et al., 2018).

3.1.5 | Other effects

Lettuce extracts have also demonstrated potentially protective effects against hepatitis B virus and glucose/serum deprivation (GSD)-induced neurotoxicity (Table 10). A lettuce extract and its active component luteolin-7-glucoside inhibited hepatitis B surface antigen and hepatitis B virus replication and transcription in HepG2 cells (Cui et al., 2017). Lettuce was also reported to exert a protective effect against GSD-induced neurotoxicity by decreasing intracellular ROS formation, lipid peroxidation, and oxidative DNA damage and attenuating the upregulation of proapoptotic antiapoptotic proteins by GSD (Ghorbani et al., 2015).

3.2 | In vivo evidence

3.2.1 | Preclinical studies

The preclinical evidence for anti-CVD, anti-diabetic, and anti-inflammatory effects of lettuce extracts are summarized in Table 11. Regular consumption of lettuce improves cholesterol metabolism and the antioxidant defense systems and thus reduces the risk of CVD in animal models. Nicolle, Cardinault, et al. (2004) reported that a diet containing 20% lettuce decreased the liver cholesterol Low-density lipoprotein/High-density lipoprotein ratio and reduced apparent absorption of dietary cholesterol in rats. Moreover, the same diet increased the total concentration of steroids excreted in feces and increased the plasma antioxidant levels, including carotenoids and vitamins C and E. These results suggest that lettuce exerts beneficial effects on lipid metabolism and antioxidant status and may potentially contribute to the protection against CVD. Daily feeding of a high-fat, high-cholesterol diet containing 8% lettuce reduced the total plasma cholesterol, LDL cholesterol, and triacylglycerol concentrations in mice. The activities of enzymes involved in the antioxidant defense system also increased in mice receiving the lettuce diet. These further indicate that lettuce consumption may help reduce CVD risk (J. H. Lee et al., 2009).

Dietary supplementation of lettuce also decreased total liver lipids and improved glucose metabolism in C57BL/6 mice with high-fat diet-induced obesity, suggesting that

TABLE 10 Bioactivity of lettuce extracts reported by in vitro studies

Bioactivity	Extract details	Cell lines	Assay conditions	Main effects and related mechanisms	References
Anti-inflammatory	**Variety**: Maravilla de verano **Organ**: Leaf **Solution**: Methanol: HCl (37%) = 49: 1 (v/v)	J774A.1 murine monocyte macrophage cell line	Dried extracts diluted to 10–250 μg/mL	**Reduction** 1. NO_2^- release (25, 50, 150, 250 μg/mL) 2. Nitric oxide synthase (iNOS) expression (25, 50, 150, 250 μg/mL) 3. ROS formation (25, 50, 150, 250 μg/mL) 4. Cycloxygenase-2 (COX-2) expression (25, 50, 150, 250 μg/mL) **Induction** 5. Heme-oxygenase enzyme (OH-1) expression (150, 250 μg/mL)	Pepe et al. (2015)
	Variety: Maravilla de verano **Organ**: Leaf **Solution**: Methanol: HCl (37%) = 49: 1 (v/v) **Treatment**: Lettuce is grown with 120 ton of cattle manure per ha (LC) or 150 kg nitrogen per ha mineral fertilization (LK)	J774A.1 murine monocyte macrophage cell line	Dried extracts diluted to 10–250 μg/mL	**Reduction**: 1. NO_2^- release (25, 50, 150, 250 μg/mL of LC and 10, 25, 50, 150, 250 μg/mL of LK) 2. iNOS expression (25, 50, 150, 250 μg/mL of LC and 10, 25, 50, 150, 250 μg/mL of LK) 3. COX-2 expression (25, 50, 150, 250 μg/mL of LC and 10, 25, 50, 150, 250 μg/mL of LK) 4. Tumor necrosis factor-α (TNF-α) production (10, 25, 50, 150, 250 μg/mL of LC and 10, 25, 50, 150, 250 μg/mL of LK) 5. Interleukin-6 (IL-6) production (25, 50, 150, 250 μg/ mL of LC and 10, 25, 50, 150, 250 μg/mL of LK) 6. NF-κB nuclear translocation (50, 150 μg/ mL of LC and 50, 150 μg/mL of LK) 7. ROS formation (10, 25, 50, 150, 250 μg/ mL of LC and 10, 25, 50, 150, 250 μg/mL of LK) 8. Nitrotyrosine formation (10, 25, 50, 150, 250 μg/ mL of LC and 10, 25, 50, 150, 250 μg/mL of LK) **Induction**: 9. Nuclear factor-erythroid 2-related factor 2 (Nrf2) nuclear translocation (50, 150 μg/mL of LC and 50, 150 μg/mL of LK) 10. HO-1 expression (25, 50, 150, 250 μg/mL of LC and 25, 50, 150, 250 μg/mL of LK)	Adesso et al. (2016)

(Continues)

TABLE 10 (Continued)

Bioactivity	Extract details	Cell lines	Assay conditions	Main effects and related mechanisms	References
Antidiabetic effect	**Variety**: Rutgers Scarlet **Organ**: Leaf **Solution**: 100 °C water, pH 2.0	H4IIE rat hepatoma cells	Dried extract (1 µg/mL −20 µg/mL)	**Reduction** Glucose production (10 and 20 µg/mL)	Cheng, Pogrebnyak, Kuhn, Poulev, et al. (2014)
Anticancer	**Variety**: Red-pigmented leafy lettuce B-2 **Organ**: Leaf **Solution**: 80% ethanol	Human lung adenocarcinoma cell line A549, human hepatoma cell line Bel7402, human colorectal cancer cell line HepG2, colon cancer cell HT29	Dried lettuce extracts diluted to 10, 30, 50, 100, 200 µg/mL; thiazolyl blue tetrazolium bromide (MTT) assay for the relative number of viable cells; trypan blue (TB) assay for tumor cell viability	**Reduction** 1. Relative amount of viable cells of human lung adenocarcinoma cell line A549, human hepatoma cell line Bel7402, human cancer colorectal adenoma cell line HepG2, and colon cancer cell line HT-29 (100 and 200 µg/mL) 2. Cell viability of human lung adenocarcinoma cell line A549, human hepatoma cell line Bel7402, human cancer colorectal adenoma cell line HepG2, and colon cancer cell line HT-29 (100 and 200 µg/mL)	Qin et al. (2018)

(Continues)

TABLE 10 (Continued)

Bioactivity	Extract details	Cell lines	Assay conditions	Main effects and related mechanisms	References
Antihepatitis B virus	**Variety**: Lollo Rossa **Organ**: Leaf **Solution**: 80% methanol **Treatment**: 1 Lettuce is grown with nitrogen fertilizer as 9 mM $NaNO_3$ (S11) 2. Lettuce is grown with nitrogen fertilizer as 9 mM glycine (S15)	HBV-producing cell lines HepG2.2.15, HepAD38 and parental cell line HepG2	Dried lettuce extracts diluted to 2, 5, 10 μg/μL	**Reduction** 1. Hepatitis B surface antigen (HBsAg) and HBsAg expression in HepG2.2.15 cells, HpeAD38 cells and HepG2 cells (2, 5, 10 μg/μL of S11 and 2, 5, 10 μg/μL of S15) 2. HBV replication in HepG2.2.15 cells (5, 10 μg/μL of S11 and 5, 10 μg/μL of S15), HpeAD38 cells (5, 10 μg/μL of S11 and 5, 10 μg/μL of S15), and HepG2 cells (2, 5, 10 μg/μL of S11 and 5, 10 μg/μL of S15) 3. HBV transcription in HepG2.2.15 cells and HpeAD38 cells (2, 5, 10 μg/μL of S11 and 2, 5, 10 μg/μL of S15) 4. HBV viral antigen secretion, replication and transcription in HepG2.2.15 cells (10 μg/μL of S15) 4. ROS levels in HepG2.2.15 cells (S11 and S15)	Cui et al. (2017)
Protective effects on glucose/ serum deprivation-induced neurotoxicity	Lettuce whole plant extracts by 70% ethanol	Neuron-like cells, N2a, and PC12 cells	Dried lettuce extracts diluted to 50–400 μg/mL Glucose/serum deprivation-induced neurotoxicity model	**Reduction**: 1. Intracellular ROS content of N2a and PC12 cells (100 μg/mL, 200 μg/mL, 400 μg/mL) 2. Lipid peroxidation in N2a and PC12 cells (50 μg/mL, 400 μg/mL) 3. DNA damage of N2a and PC12 (50 μg/mL, 400 μg/mL) 4. Proapoptotic (Bax and aspase-3) and antiapoptotic (Bcl-2) protein expression in PC12 cells (400 μg/mL)	Ghorbani et al. (2015)

TABLE 11 Bioactivity of lettuce extracts in preclinical studies

Bioactivity	Extracts details	Subjects	Assay conditions	Main effects and related mechanisms	References
Anti-CVD effects	**Variety**: Red oak leaf	Male Wistar rats (150 g)	Freeze-dried lettuce 20% in the diet for 3 weeks	**Reduction**: 1. Plasma and liver total cholesterol 2. Digestive neutral sterols balance (intake-excreted) and total digestive steroids balance 3. TBARS in heart tissue **Induction**: 4. Fecal cholesterol, fecal coprostanol, and total neutral sterols 5. Vitamin E concentration in plasma 6. Antioxidant capacity and vitamin C in plasma 2 h and 4 h after intake of a single meal.	Nicolle, Cardinault, et al. (2004)
	Red-pigmented leafy lettuce	Male C57BL/6J mice (25-30 g)	Freeze-dried red lettuce powder (8%) in the diet for 4 weeks.	**Reduction** 1. Plasma triacylglycerols (TAG), total cholesterol, and LDL-cholesterol 2. Atherosclerotic index 3. Thiobarbituric acid-reactive substances (TBARS) values in plasma, liver, heart, and kidney tissues 4. Tail DNA (%), tail extent moment, olive tail moment, and a tail length of hepatocytes DNA oxidative damage 5. Tail DNA (%), tail extent moment, and olive tail moment of lymphocyte DNA oxidative damage **Induction**: 6. Total glutathione content, glutathione S-transferase activity, and glutathione peroxidase activity in liver 7. Paraoxonase activity in plasma	J. H. Lee et al. (2009)

(Continues)

TABLE 11 (Continued)

Bioactivity	Extracts details	Subjects	Assay conditions	Main effects and related mechanisms	References
Antidiabetic effects	**Variety**: Beizisheng No. 4, whole plant	Male C57BL/6J mice	Dried lettuce 1. 2.5% lettuce in high-fat diet (2.5% LD); 2. 5% lettuce in high-fat diet (5% LD); 3. 10% lettuce in high-fat diet (10% LD) Diet-induced obese (DIO) mouse model	**Reduction** 1. Body weight (2.5% LD, 5% LD, 10% LD) 2. Fat/body weight ratio (10% LD) 3. Fasting glucose level in the blood (2.5% LD, 5% LD, 10% LD) 4. Ttriglyceride and free fatty acid contents (2.5% LD, 5% LD, 10% LD) 5. Serum low-density lipoprotein (5% LD, 10% LD) 6. Alanine aminotransferase and aspartate aminotransferase activity (2.5% LD, 5% LD, 10% LD) 7. Firmicutes, Proteobacteria and Deferribacteres phyla in intestinal microbiota of DIO mice **Induction**: 8. Body temperature (2.5% LD, 5% LD, 10% LD) 9. Insulin sensitivity (2.5% LD, 5% LD, 10% LD) 10. Blood urea nitrogen (2.5% LD, 10% LD) 11. Creatinine (2.5% LD)	Y. Y. Han et al. (2018)
	Variety: Rutgers Scarlet **Organ**: Leaf **Solution**: 100°C water, pH 2.0	Male C57BI/6J mice	DIO mouse model 1. Dried lettuce extracts (100 mg/kg) 2. Dried lettuce extracts (300 mg/kg)	**Reduction**: 1. Liver weight to body weight (100 mg/kg, 300 mg/kg) 2. Total liver lipid content (300 mg/kg) **Induction**: 3. Glucose metabolism (100 mg/kg, 300 mg/kg)	Cheng, Pogrebnyak, Kuhn, Poulev, et al. (2014)
	Variety: Rutgers Scarlet **Organ**: Leaf **Solution**: Methanol/water/acetic acid = 85:14.5:0.5, v/v/v	Male C57BI/6J mice	DIO mouse model 1. Dried lettuce extracts (100 mg/kg) 2. Dried lettuce extracts (300 mg/kg)	**Reduction**: 1. Fasting blood glucose after 6 h (100 mg/kg, 300 mg/kg) **Induction**: 2. Insulin sensitivity (100 mg/kg, 300 mg/kg)	Cheng, Pogrebnyak, Kuhn, Krueger, et al. (2014)

(Continues)

TABLE 11 (Continued)

Bioactivity	Extracts details	Subjects	Assay conditions	Main effects and related mechanisms	References
Anti-inflammatory	**Organ**: Seed **Solution**: Methanol: petroleum ether = 70: 30, v/v	Male Wistar rats (200-240 g)	Dried extracts Carrageenan-induced paw edema model	**Reduction** Paw edema volume (0.5 g/kg – 4 g/kg)	Sayyah et al. (2004)
	Variety: Grand rapids **Organ**: Leaf and seed **Solution**: Methanol: chloroform = 1: 1 (v/v); Water (100%)	Adult albino rats (150-200 g)	Dried extracts including 1. Organic leaf extract (1 g/kg); 2.Organic seed extract (1 g/kg); 3. Aqueous leaf extract (1 g/kg); 4. Aqueous seed extract (1 g/kg); 5. Cell suspension exudate (1 mL/kg). Carrageenan-induced hind paw edema model	**Reduction**: 1. Leaf extracts > cell suspension exudate > seed extracts 2. Aqueous extracts > organic extracts	Ismail and Mirza (2015)

lettuce consumption may help prevent diabetes (Cheng, Pogrebnyak, Kuhn, Krueger, et al., 2014; Cheng, Pogrebnyak, Kuhn, Poulev, et al., 2014). A recent study had reported that feeding C57BL/6J DIO mice with purple lettuce reduced the accumulation of fat mass and increased energy expenditure to maintain body weight. Lettuce consumption was also associated with reduced triglyceride and free fatty acid levels and improved glucose homeostasis and insulin sensitivity, suggesting lettuce may protect against metabolic disorders (Y. Y. Han et al., 2018).

Lettuce seeds are used in many countries as traditional medicine. Recently, lettuce seed extracts were reported to exert anti-inflammatory effects in an animal model, the carrageenan-induced hind paw edema assay (Ismail & Mirza, 2015; Sayyah et al., 2004). Moreover, a mixture of lettuce seeds and skullcap root improved sleep behavior in vertebrate models and could potentially be used to treat sleep disorders (Hong et al., 2018).

3.2.2 | Human intervention trials

The protective effects of lettuce against colorectal, lung, esophageal, breast, and liver cancers have also been demonstrated in epidemiologic studies (Table 12). A previous case-control study compared the risk of colorectal cancer in 220 subjects, including 112 patients and 108 controls with a family history of colorectal cancer. A significant negative association was observed between lettuce consumption and colorectal cancer (relative risk [RR] = 0.3, 95% confidence interval [CI] [0.1, 0.6], $p < .05$), and β-carotene and ascorbic acid present in lettuce were associated with a reduced incidence of colorectal cancer (Fernandez et al., 1997). Brennan et al. (2000) conducted a multicenter case-control study of 1551 subjects, including 506 nonsmoking incidental lung cancer cases and 1045 nonsmoking controls, to investigate the association between dietary intakes and lung cancer. High consumption of lettuce was associated with a protective effect against lung cancer (odd ratio [OR] = 0.6; 95% CI [0.3, 1.2], $p = .02$). More recently, a Swedish nationwide and population-based case-control study investigated the association of dietary patterns and esophageal cancer risk. The results suggested that a daily diet rich in lignans, quercetin, and resveratrol (from tea, wine, lettuce, mixed vegetables, tomatoes, and whole-grain bread) were strongly associated with a decreased risk of esophageal adenocarcinoma (181 cases and 806 controls, OR = 0.24, 95% CI [0.12, 0·49], $p < .05$), esophageal squamous cell carcinoma (158 cases and 806 controls, OR = 0·31, 95% CI [0.15, 0·65], $p < .05$), and gastroesophageal junctional adenocarcinoma (255 cases and 806 controls, OR = 0·49, 95% CI [0.28, 0.84], $p < .05$) (Lin et al., 2014).

In addition, regular lettuce consumption was reported to be negatively associated with the risk of estrogen receptor-negative breast cancer in women (Farvid et al., 2019; Jung et al., 2013). Jung et al. (2013) found that the daily intake of 56 g of lettuce was negatively associated with the risk of estrogen receptor-negative breast cancer among 993,466 women followed for 11 to 20 years in 20 cohort studies (RR = 0.91, 95% CI [0.84, 0.98], $p = .02$). Farvid et al. (2019) reported that every two servings/week of lettuce was associated with a reduced risk of estrogen receptor-negative breast cancer among 182,145 women aged 27–59 (1794 cases, hazard ratio [HR] = 0.96, 95% CI [0.93, 0.99], $p < .05$). Moreover, epidemiological evidence indicated that a high intake of stem lettuce and garland chrysanthemum were associated with a reduced risk of liver cancer among 132,837 women and men from Shanghai, China (W. Zhang et al., 2013).

Most recently, Moghadam et al. (2020) performed a randomized, double-blinded clinical trial to investigate the hypolipidemic effect of lettuce seed extracts. A total of 140 patients were randomly enrolled and completed the 12-week clinical trial. The 70 patients in the treatment group received atorvastatin (20 mg/day) and a capsule containing 1000 mg dried lettuce seed extract, while the 70 patients in the placebo group took atorvastatin (20 mg/day) with a placebo capsule. Nutritional supplementation with lettuce seed extracts significantly reduced triglycerides, total cholesterol content, and low-density lipoprotein compared to the placebo group. The study also demonstrated that the ability of lettuce seed extract to improve lipid profiles might be clinically relevant for the treatment of dyslipidemia. However, further randomized clinical trials are required to confirm the health effects of lettuce or lettuce extracts in humans.

4 | PREHARVEST APPROACHES THAT AFFECT BIOACTIVE COMPOUNDS

4.1 | Environmental factors

4.1.1 | Temperature

Temperature and light are the most relevant environmental factors that positively influence the growth and quality of the crop. Temperature affects the accumulation of bioactive compounds in lettuce, as low temperature generally increases the accumulation of phenolic compounds. Boo et al. (2011) reported that lettuce cultivated at an average temperature of 13/10°C (day/night) accumulated higher levels of phenolic compounds and anthocyanins and had higher activities of the enzymes polyphenol oxidase (PPO) and phenylalanine ammonia-lyase (PAL) compared to

TABLE 12 Anticancer bioactivity of lettuce consumption in human intervention trials

Cancer types	Subjects	Main effects and related mechanisms	References
Colorectal cancer	220 subjects 1. 112 colorectal cancer patients 2. 108 controls with a family history of colorectal cancer	Lettuce consumption was negatively associated with colorectal cancer incidence (RR = 0.3, 95% CI [0.1, 0.6], $p < .05$)	Fernandez et al. (1997)
Lung cancer	1551 subjects 1. 506 with nonsmoking incidental lung cancer 2. 1045 nonsmoking controls	Protective effect against lung cancer was observed for high consumption of lettuce (OR = 0.6; 95% CI [0.3, 1.2], $p = .02$)	Brennan et al. (2000)
Esophageal adenocarcinoma	181 cases and 806 controls	Daily consumption of tea, wine, lettuce, mixed vegetables, tomatoes, and whole-grain bread was strongly associated with a decreased risk of esophageal adenocarcinoma (OR = 0.24, 95% CI [0.12, 0·49], $p < .05$).	Lin et al. (2014)
Esophageal squamous cell carcinoma	158 cases and 806 controls	Daily consumption of tea, wine, lettuce, mixed vegetables, tomatoes, and whole-grain bread was strongly associated with a decreased risk of esophageal squamous cell carcinoma (OR = 0·31, 95% CI [0.15, 0·65], $p < .05$).	Lin et al. (2014)
Gastro-esophageal junctional adenocarcinoma	255 cases and 806 controls	Daily consumption of tea, wine, lettuce, mixed vegetables, tomatoes, and whole-grain bread was strongly associated with a decreased risk of gastro-esophageal junctional adenocarcinoma (OR = 0·49, 95% CI [0.28, 0.84], $p < .05$)	Lin et al. (2014)
Estrogen receptor-negative breast cancer	3828 cases among 993466 women followed for 11 to 20 years in 20 cohort studies	Fifty-six grams lettuce per day was negatively associated with the risk of estrogen receptor-negative breast cancer (RR = 0.91, 95% CI [0.84, 0.98], $p = .02$)	Jung et al. (2013)
	1794 cases among 182145 women aged 27 to 59-years-old	Every 2 servings/week of lettuce was associated with a reduced risk of estrogen receptor-negative breast cancer (HR = 0.96, 95% CI [0.93, 0.99], $p < .05$)	Farvid et al. (2019)
Liver cancer	132 837 women and men	Daily intake of stem lettuce and garland chrysanthemum was negatively associated with the risk of liver cancer. 1. Daily intake ≤0.06 g, HR = 1, $p < .01$ (90 cases) 2. Daily intake ≤0.71 g, HR = 0.90, 95% CI [0.66, 1.23], $p < .01$ (73 cases) 3. Daily intake ≤2.25 g, HR = 0.81, 95% CI [0.58, 1.12], $p < .01$ (64 cases) 4. Daily intake > 2.25 g, HR = 0.48, 95% CI [0.33, 0.71], $p < .01$ (40 cases)	W. Zhang et al. (2013)

Note: 95% CI, 95% confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.

lettuce cultivated at 20/13°C, 25/20°C, or 30/25°C. Previous studies suggested that the increased levels of anthocyanins induced by low temperature were due to the accumulation of cyanidin-3-(6″-malonyl) glucoside in lettuce leaves (Becker, Klaering, Kroh, et al., 2014; Marín et al., 2015). However, near-freezing temperatures can adversely affect the accumulation of phenolic compounds. Lettuce cultivated at 4°C during the night had lower concentrations of caffeic acid, dicaffeoyl tartaric acid, 3,5-dicaffeoylquinic acid, and quercetin 3-glucoside than lettuce cultivated at 12 or 20°C at night (Jeong et al., 2015).

4.1.2 | Light

The quality, intensity, and duration of light are critical factors that dramatically affect the biosynthesis and accumulation of various phytochemicals related to lettuce quality. Generally, blue and UV light induce the biosynthesis of phenolic acids and flavonoids in lettuce (Q. Li & Kubota, 2009; M. J. Lee et al., 2014). The blue light was reported to induce the accumulation of total carotenoids, xanthophylls, and β-carotene in lettuce, while supplemental far-red light decreased carotenoid content by 11% (Q. Li & Kubota, 2009). When additional LED lighting was included in the lighting formula, supplemental green LED light (535 or 505 nm), or blue light (470 or 455 nm) had positive effects on the accumulation of vitamin C and tocopherol in the order 535 > 505 > 455 > 470 nm (Samuoliene et al., 2012). In addition to light quality, exposure to high light intensity resulted in the accumulation of bioactive compounds in lettuce, particularly chlorogenic acid, flavonols, anthocyanins, and vitamin C (Becker, Klaering, Schreiner, et al., 2014; García-Macías et al., 2007; Pérez-López et al., 2018; Shimomura et al., 2020). For instance, Pérez-López et al. (2018) reported that the concentrations of flavonols (quercetin, quercetin-3-glucuronide, kaempferol, quercitrin, and rutin) increased in lettuce grown under high light intensity as a response to oxidative stress. Moreover, a suitable duration of light is beneficial for the accumulation of phytochemicals in lettuce. Chen et al. (2017) reported that lettuce exposed to alternating red/blue lighting ratio intervals for 4 h over a 16-h photoperiod accumulated higher levels of ascorbic acid than lettuce treated with the same daily light interval and a similar red/blue ratio, but different red/blue alternating intervals. A preharvest short-term continuous illumination was recently emphasized as a valuable strategy for the nutritional management of lettuce. Bian et al. (2016) found that 12 h continuous illumination with LED light (red: blue: green = 4:1:1) before harvest enhanced phenolic compounds and carotenoids accumulation.

4.2 | Agricultural practices

4.2.1 | Cultivation systems

Numerous agricultural practices can influence the content of bioactive compounds in lettuce and affect the postharvest quality. Research has suggested that lettuce cultivated in the open field have a higher content of flavonoids than lettuce grown in a protected cultivation system, as bioactive compounds accumulate in plant vacuoles to increase crop resistance and enable adaption to adverse environmental conditions (Gil, 2016; Selma et al., 2012; X. Zhao et al., 2007). In addition, soilless cultivation can offer growers a range of benefits for the production of fresh-cut lettuce. For instance, “Lollo rosso” lettuce cultivated in a soilless system had higher contents of phytochemicals, including vitamin C and individual and total phenolics, than the same genotype grown in soil (Selma et al., 2012).

4.2.2 | Application of nitrogen fertilizer

There is growing interest in the relationship between primary nutrients, such as nitrogen, and the accumulation of bioactive compounds in lettuce after fertilization. Previous studies indicated that a low nitrate supply or nitrogen deficiency is beneficial for the biosynthesis of phenolic acids, flavonols, anthocyanins, and ascorbic acid in lettuce. For example, W. Zhou et al. (2019, 2021) demonstrated that application of a low concentration of nitrate during the cultivation of the red-pigmented lettuce “Ziluoma” significantly increased TPC, the flavonoid content, and vitamin C levels, as well as the levels of major phenolic compounds such as chicoric acid, chlorogenic acid, quercetin, and luteolin, though this strategy decreased carotenoids.

In addition, a sufficient nitrate supply has a detrimental effect on polyphenol biosynthesis, though the impact varies between green and red lettuces. Generally, in red-colored lettuce varieties, photosynthetically generated carbon molecules are more used for the biosynthesis of phenolic acids and flavonoids than for plant growth and yield formation compared to green cultivars (Becker et al., 2015; Mampholo et al., 2016). For example, Becker et al. (2015) observed that the concentrations of phenolic compounds, including flavonoid glycosides and caffeic acid derivatives, decreased significantly as the amount of nitrate applied increased (0.75, 3, 12 mM), while the carotenoid concentrations (β-carotene, neoxanthin, lactucaxanthin, and all-*trans*- and *cis*-violaxanthin) increased. Additionally, the concentrations of cyanidin 3-(6″-malonyl)-glucoside, quercetin 3-(6″-malonyl)-glucoside, quercetin 3-glucuronide, and luteolin 7-glucuronide were lower in a red lettuce cultivar supplied with 12 mM nitrogen than 0.75 mM nitrogen; while the quercetin and luteolin glycosides concentrations decreased in green lettuce as the concentration of nitrate applied increased (Becker et al., 2015).

Moreover, the supply of organic nitrogen fertilizer (using glycine as a model) has been reported to affect the levels of bioactive compounds in lettuce significantly. An adequate supply of glycine during cultivation promoted the accumulation of ascorbic acid and glycosylated flavones and flavonols, such as quercetin 3-glucoside, quercetin 3-(6′′-malonyl-glucoside), luteolin 7-glucuronide, and luteolin 7-glucoside (Yang et al., 2017; Yang, Feng, et al., 2018). Thus, nitrogen limitation and appropriate glycine supply could represent beneficial preharvest strategies to increase the accumulation of bioactive compounds in lettuce.

4.2.3 | Irrigation

The use of reduced irrigation strategies through innovative technologies has been suggested as a novel opportunity to increase the content of phytochemicals during lettuce production. The water-saving practice of deficit irrigation functions as abiotic stress that promotes the biosynthesis of phytochemicals in lettuce; 50% deficit irrigation has been recommended as a strategy to increase the dietary phytochemicals in lettuce and improve crop quality without compromising the fresh mass (Malejane et al., 2018). However, when the concentrations of phenolic compounds increase, browning and pinking can negatively affect the sensory properties (Monaghan et al., 2017). It is known that when the concentration of hydroxycinnamic acid derivatives increases, lettuce quality after cutting and storage decrease as these metabolites can be substrates for PPO, an enzyme implicated in enzymatic browning of lettuce (C. Luna et al., 2012; M. C. Luna et al., 2013). Several studies that explored the effects of deficit or excess irrigation on the responses of lettuce to browning indirectly examined the changes in bioactive compounds, mainly phenolic compounds, to understand their impact as natural substrates of PPO (C. Luna et al., 2012; M. C. Luna 2013). C. Luna et al. (2012) observed that deficit irrigation increased phenolic compounds, mainly caffeic acid derivatives, in iceberg lettuce. These changes were associated with low PPO activity, less browning, and low consumption of PPO substrates. Reduced irrigation also significantly increased the content of phenolic compounds in romaine lettuce. In contrast, a high browning reaction occurred in the excess irrigated crop as a direct consequence of the action of PPO on phenolic compounds (M. C. Luna et al., 2013).

4.2.4 | Pesticides

It is crucial to understand the possible impacts of pesticides on the nutritional value of edible lettuce, as pesticides have direct effects on human health. For example, exposure of expanded "Queen of May" lettuce leaves to mancozeb, an ethylenebisdithiocarbamate salt widely used in vegetable production, decreased the concentrations of phenylalanine (a precursor of phenylpropanoid pathway) and polyphenols by approximately 40% and 50%, respectively (Pereira et al., 2014). Moreover, L. Zhao et al. (2016) observed that foliar-sprayed $Cu(OH)_2$ nanopesticides decreased the levels of phenolic compounds (such as *cis*-caffeic acid, 3,4-dihydroxycinnamic acid, and chlorogenic acid) and dehydroascorbic acid and also decreased the antioxidant capacity by 20–23% compared to controls. These studies indicate that pesticides may have a detrimental influence on the accumulation of health-promoting compounds and the total antioxidant activity of lettuce by increasing the consumption of antioxidants as a plant defense strategy after exposure to pesticides.

4.2.5 | Application of fungi

Growing evidence indicates that mycorrhizal fungi colonize the roots of lettuce plants to establish a beneficial mutualistic relationship with the host plant that promotes the accumulation of antioxidants, including phenylpropanoid and carotenoid intermediates. However, these beneficial effects vary between cultivars and fungal species. According to Baslam et al. (2011), the application of arbuscular mycorrhizal fungi (AMF) species, for example, *Glomus fasciculatum* and a mixture of *G. intraradices* and *G. mosseae*, increased the total concentrations of anthocyanins, carotenoids, and phenolics in lettuce grown in a greenhouse. However, the benefits varied depending on the mycorrhizal inoculum, lettuce variety, and leaf position. Baslam et al. (2012) reported that the application of AMF (a mixture of *G. intraradices* and *G. mosseae*) improved the nutritional quality of greenhouse-cultivated lettuce, including the levels of soluble phenolic compounds, carotenoids, anthocyanins, and total ascorbate. However, elevated atmospheric CO_2 levels may mitigate this benefit. Recently, Avio et al. (2017) found that inoculation of looseleaf type lettuce with the AMF species *Rhizoglomus irregulare* significantly increased the levels of phenolics and anthocyanins (in red leaf cultivars), as well as the total antioxidant activity, compared to noninoculated plants.

4.2.6 | Other factors

Other factors, such as microelements and plant growth regulators, can strongly affect the accumulation of bioactive compounds in lettuce. Exogenous application of appropriate amounts of selenium (Se) or iodine (I) during lettuce cultivation increased the levels of phenolic acids, flavonoids, and ascorbic acid without reducing plant FW (Blasco et al., 2008; Ríos et al., 2008; Smoleń et al., 2014). Also, applying specific concentrations of plant growth regulators prior to harvest can increase bioactive phytochemicals. For example, application of 1 μM jasmonic acid, 100 μM arachidonic acid, or 100 μM abscisic acid increased flavonoid levels; 100 μM abscisic acid or 1 μM jasmonic acid induced the accumulation of carotenoids; while 100 μM jasmonic acid or 100 μM abscisic acid increased the concentration of ascorbic acid (Złotek et al., 2014). On the other hand, several agronomic techniques can negatively affect the content of bioactive compounds in lettuce. For example, Stagnari et al. (2015) reported that shading (a loss of more than 50% of photosynthetically active radiation reduction) reduced the accumulation of phenolic compounds and carotenoids in cultivar "Bionda degli ortolani selection Siusi" in greenhouse lettuce cultivation. Ntsoane et al. (2016) also compared the influence of different colored shade nets on lettuce phytochemicals accumulation. These authors found that lettuce cultivar-specific responses were observed for different colored shade nets in terms of the accumulation of -carotene, ascorbic acid, and flavonoids. Thus, the black net (25% shade) showed positive effects on the enhancement of ascorbic acid, flavonoids, and β-carotene in "Askbrook" and "Exbury" varieties. However, T. Li et al. (2017) reported a decrease in flavonol and anthocyanin content of other lettuce cultivars when shading was applied. The lack of consistency in the results observed indicates that more research is needed to understand the effects of light and shading on the biosynthesis of lettuce bioactives.

4.3 | Optimizing preharvest management to improve the accumulation of bioactive compounds

The sections above illustrate how environmental factors and agronomic management induce phytochemical changes in lettuce. Laboratory studies typically examine the effects of a single preharvest factor or a combination of two preharvest factors on phytochemical changes in lettuce. In this section, as an example, we discuss the effects of preharvest management on free phenolics. Numerous single preharvest techniques, including low temperature (such as 13/10°C, day/night), light quality (blue and UV), high light intensity, open-field cultivation, nitrogen deficiency, 50% deficit irrigation, appropriate concentrations of AMF, microelements (such as Se and I), and plant growth regulators (e.g., jasmonic acid, arachidonic acid, or abscisic acid) could represent practical approaches to improve the accumulation of phenolic compounds in the leaves of lettuce. However, in agricultural practice, the accumulation of phenolics is affected by coupling numerous environmental factors and agricultural management. Thus, additional research is necessary to elucidate the coupled effects of preharvest management on the accumulation of phytochemicals to provide growers with a comprehensive understanding of how to improve the nutritional value of lettuce through agricultural practices. In this regard, identifying the metabolic networks that connect agronomic factors with signal transduction, transcription factors, structural genes, and target metabolites could pave the way towards a better understanding of the mechanisms that regulate the biosynthesis of phytochemical compounds (such as the phenylpropanoid pathway and flavonoid pathway for phenolic compounds) in lettuce. Furthermore, additional applied research and horticultural practices are required. They should be initiated to optimize and balance lettuce yield and quality using various preharvest factors, including those discussed in this review.

5 | POSTHARVEST APPROACHES THAT AFFECT BIOACTIVE COMPOUNDS

5.1 | Maturity

The stage of maturity at harvest significantly influences the quality, shelf life (Gil et al., 2012), and composition of lettuce, particularly the content of phytochemicals. Lettuce leaves harvested at an immature stage, with an optimum leaf length of 10 cm to meet processing requirements for quality, contain higher contents of phenolic compounds than older leaves (Martínez-Sánchez et al., 2012). This observation can be explained by the fact that baby leaves have more rapid metabolism as they are actively growing. Many of these phytochemicals protect the tissue from photochemical reactions induced by UV irradiation (Y. H. Zhou et al., 2009). Looseleaf lettuce harvested at a mature stage to ensure high quality has a higher content of vitamin C compared to the immature stage or leaves from a more mature stage, such as whole heads (40, 22, 20 mg per 100 g, respectively) (Martínez-Sánchez et al., 2012). One of the goals of lettuce breeders is to select varieties with a high content of bioactive compounds to meet consumers' demand for a healthy diet. The Salanova® lettuce bred by Rijk Zwaan (https://www.rijkzwaan.com/salanova-teenleaf) separates into countless small leaves with just one cut. This innovative product offers an excellent cultivar with a high content of phytochemicals that can be produced through high-density growing practices, mechanically harvested at a later stage than the baby leaves, resulting in higher yields of more robust and more colorful leaves. For romaine lettuce, Castañer et al. (1999) studied the differences in the phenolic content between baby and whole heads. The main differences were observed between the photosynthetic and midrib tissues; the photosynthetic tissue contained higher phenolic contents than the midribs at both maturity stages. The authors recommended that more elevated amounts of green tissues should be included in salad mixes for a healthy diet. Additionally, the cut-and-regrow practice used in the production of baby salad greens has been shown to affect phytochemicals. In the future, it will be interesting to evaluate the antioxidant capacities of leaves obtained from sequential harvests.

5.2 | Minimal processing

Minimal processing involves several procedures such as cutting or shredding, washing, drying, and packaging that do not affect the "fresh-like" appearance of the product. Lettuce is a primary relevant ready-to-eat product with a high economic value than other vegetables (Martínez-Sánchez et al., 2012). Apart from the high content of bioactive compounds, innovations related to lettuce as a raw fresh-cut material have focused on creating premium quality convenience products, including freshness, on satisfying the expectations of consumers. Gil and Kader (2008) the effect of minimal processing operations and postharvest storage on antioxidant compounds and other bioactive health-promoting constituents in lettuce. In this regard, cutting operations induce a wounded tissue stress response in lettuce, which leads to a wounding signal that elicits various physiological and biochemical reactions in adjacent and distant cells (Saltveit, 2003; Tomás-Barberán et al., 1997). Several wound-induced changes have been reported, including moisture loss, elevated respiration, and the activation of phenylpropanoid metabolism, resulting in the accumulation of phenolic compounds and subsequent tissue browning (Saltveit, 1997). Nutrient losses may also be accelerated when lettuce tissues are wounded, and after cutting, bioactive compounds can be degraded when exposed to oxygen or light. Thus, the consequences of injuring should be minimized to prolong the shelf life and maintain the phytochemicals. García et al. (2019) identified positive and negative correlations between the development of browning and chlorogenic acids and sinapaldehyde derivatives, respectively, as phenolic biomarkers. These authors stated that cutting would lead to a fast-browning development if the biosynthetic machinery is balanced towards the biosynthesis of PPO substrates, such as caffeoylquinic derivatives. In contrast, if precursors for lignin biosynthesis that are not PPO substrates such as sinapaldehyde derivatives predominate, cutting will lead to wound healing and a delayed browning development.

The quality of fresh-cut lettuce, including the content of phytochemicals, can also be affected by the preparation method (i.e., by the sharpness of the cutting tools) and the size and surface area of the cut pieces. Shredding of lettuce leaves followed by exposure to light led to a reduction of up to 94% of flavonoid moieties in "Green oak leaf" compared to a loss of 6% in "Lollo rosso," whereas Cos and "Green salad bowl" samples did not exhibit losses overall. These authors identified the amounts and position of the substituents of flavonoids in salads and observed a significant malonic acid removal of both the quercetin and cyanidin glucosides in lettuce (DuPont et al., 2000). In addition, the sharpness of the cutting knife may influence the content of phytochemicals, including vitamin C, as lettuce cut with a sharp knife loses less ascorbic acid than if cut with a dull knife or when bruised (Barry-Ryan & O'Beirne, 1999).

In terms of washing, little is known about the effect of sanitizers on the phytochemical content of fresh-cut lettuce. Some studies have focused on the association between washing and browning. Fukumoto et al. (2002) investigated the effect of the washing water temperature and chlorination on phenolic metabolism in the photosynthetic and vascular tissues of inner and outer leaves and the properties of photosynthetic and vascular tissues stored at 5°C. Variations were observed between different tissue types during storage, and browning of cut edges consequently varied among tissues. Baur et al. (2004) studied the effect of different washing procedures on phenolic metabolism in shredded iceberg lettuce. Chlorinated water reduced PAL activity and minimized 3,5-dicaffeoylquinic acid accumulation compared to washing with ozonated water or tap water. However, other phenolic acids, including caffeoyl tartaric (caftaric acid), dicaffeoyl tartaric (chicoric acid), 5-caffeoylquinic (chlorogenic acid isomer), and caffeoyl malic acid, were less influenced by the different washing treatments. Vandekinderen et al. (2009) examined other hygienization agents, including sodium hypochlorite, electrolyzed water, peroxyacetic acid, and gaseous chlorine dioxide. Rinsing with water decreased the vitamin C content by 35% and polyphenol content by 17%, while the carotenoid and tocopherol contents were not affected by washing.

5.3 | Storage

Fresh and fresh-cut lettuce are susceptible to deterioration between harvest and consumption, depending on the storage conditions, particularly the temperature and relative humidity (RH). Preserving the content of bioactive compounds throughout the shelf life depends on a combination of proper cooled storage throughout the entire chain, modified atmosphere packaging (MAP) conditions, and good manufacturing and handling practices (Kader, 2002b). Storage conditioning generally refers to the storage or holding temperature, the time/temperature, and RH of the fresh-cut products may encounter. For fresh-cut lettuce, low temperatures (< 7°C) with 95% RH are recommended to slow the respiration rate, enzymatic processes, microbial activity, and the degradation of polyphenols substrates of PPO. Castañer et al. (1999) found that storage of romaine lettuce at 5 and 13°C increased the content of total phenolics in midribs, while total phenolics in photosynthetic tissue increased after 2 days of storage followed by a more marked decrease at 13°C than at 5°C due to the inappropriate temperature far from the recommended storage conditions between 1 and 4°C.

Preharvest practices such as nitrogen application also affect the bioactive compounds in lettuce. They might be a valuable strategy for extending the shelf life and preventing browning during fresh-cut processing and storage. Mampholo et al. (2019) demonstrated that preharvest nitrogen application of less than 120 mg/L could be a useful approach to avoid browning during storage; and in particular, 90 mg/L nitrogen supply could maintain ascorbic acid and dicaffeoyl tartaric acid concentrations, resulting in the extended shelf life of red looseleaf lettuce for 6 days.

Some studies have shown that removing surface moisture and subsequent handling conditions (packaging, cooling speed), maintaining optimum temperature ranges, and RH can change the phytochemical content (Kader, 2002a). Regarding packaging, the most studied packaging method is MAP. Low O_2 concentrations reduce the respiration rate, chlorophyll degradation, and ethylene biosynthesis, while high CO_2 concentrations reduce the respiration rate and slow plant metabolism. Packaging aims to create an atmosphere that slows produce respiration so that the minimal necessary O_2 concentration or maximum tolerated CO_2 concentration of the packaged product is not exceeded. Both fermentation and other metabolic disorders are avoided to prevent loss of the phytochemical content (Jacxsens et al., 2002). Beltrán et al. (2005) studied individual and total phenolic compounds changes during storage for 13 days at 4°C in the air or MAP (0.5–2 kPa of O_2 and 18–22 kPa of CO_2). These authors observed that chlorogenic and isochlorogenic acid contents increased noticeably after 13 days, while monocaffeoyl tartaric and dicaffeoyl tartaric acids remained unchanged. MAP effectively suppressed the accumulation of caffeoyl quinic derivatives, whereas caffeoyl tartaric derivatives decreased during MAP storage to reach similar levels. In addition, the content of vitamin C (ascorbic acid and dehydroascorbic acid) decreased during storage, particularly under MAP. When intact heads and cut leaf iceberg lettuce were stored under a 20% CO_2-enriched atmosphere, their TPCs reduced due to decreased PAL activity (Mateos et al., 1993). The responses of intact heads and cut lettuce tissues to elevated CO_2 varied: CO_2 had smaller effects on phenolics and PAL in entire heads than in cut tissue.

6 | CONCLUSIONS AND FUTURE PERSPECTIVES

This review has provided a comprehensive overview of the constitution and concentration of health-promoting compounds in different types of lettuce and shown that lettuce is a relevant dietary source of many bioactive compounds. The effects of different preharvest and postharvest managements on the accumulation of health-promoting compounds indicate that the contents of bioactive compounds in lettuce can be optimized using these agronomic and technological treatments. However, some knowledge gaps obstruct a complete understanding of the bioactive compounds in various types of lettuce, their benefits to human health, and the impacts of preharvest and postharvest practices.

6.1 | To enable comparability, measurement units for bioactive chemicals in lettuce should be standardized

The measurement of different bioactive compounds in lettuce, including PPs, sesquiterpene lactones, carotenoids, vitamin C, and vitamin E, should be given as mg/100 g FW in future works. The total contents of PPs, phenolic acids, flavonoids, and anthocyanins should be reported with uniform external standards as equivalents. For example, gallic acid can be used to measure TPC, chlorogenic acid to measure the total phenolic acid content, and cyanidin-3-rutinoside to measure anthocyanin contents in future studies. Also, further studies should be carried out to compare the constitution and content of health-promoting compounds between rare types of lettuce (such as stem, Latin, and oilseed) and common types. Consequently, uniform equivalents and units could facilitate comparisons between studies and make it easier to calculate the dietary intake of bioactive compounds in lettuce in nutritional studies.

6.2 | The in vivo health effects of lettuce are mostly unknown and need additional investigation

In vitro and in vivo evidence suggest consumption of lettuce exerts protective effects on human health. However, in vivo evidence in humans, particularly from randomized clinical trials, is very limited and should be obtained in the future, as lettuce is one of the main vegetables consumed raw in the diet. In addition, lettuce extracts were used directly on cell lines for most in vitro bioassays without submitting the extracts to a digestion process. Therefore, bioavailability and metabolism in the systemic circulation were not taken into consideration. Consequently, the physiological relevance of the results reported is of very limited applicability. Moreover, the preparation of purified phytochemicals isolated from lettuce extracts may provide a basis for further research to reveal the associations between lettuce consumption and human health using in vivo models and enable the development and application of efficient functional foods. Such research will help further understand the composition of health-promoting compounds in lettuce and its relevant health benefits.

6.3 | Innovative breeding technologies and PFALs may help to improve the nutritional quality of lettuce

In general, both breeding and preharvest practices are critical strategies for increasing the health-promoting compounds in lettuce; while breeding lays the groundwork for the optimum preharvest practices to ensure the quality of the lettuce. As a result, breeding and pre-harvest methods should be complementary.

Numerous innovative breeding strategies have focused on enhancing antioxidants and vitamins, along with other lettuce quality characteristics, as an opportunity to improve human disease prevention via phytochemicals (Damerum et al., 2020). Proper breeding selection programs may make it possible to achieve high levels of these bioactive compounds in lettuce cultivars and increase the upper limits of both quality and yield.

On the other hand, investigating and elucidating the underlying coupled effects of multiple preharvest factors on crop quality may aid improvements in the levels of bioactive compounds in lettuce. PFALs represent a novel lettuce production system in this regard, as they enable precise control of preharvest factors such as lighting, temperature, humidity, CO_2, fertilizers, and fertigation conditions (SharathKumar et al., 2020). Thus, PFALs provide an excellent opportunity to investigate the coupled effects of preharvest factors on the accumulation of phytochemicals in lettuce.

6.4 | Microbiological safety issues in lettuce

Lettuce and leafy greens have also been identified as one of the priority commodities of fresh produce microbial safety globally (EFSA, 2014; FDA, 2020). Most of the contamination events have been traced back to inappropriate practices in primary production, including growing fields and adjacent land, animal intrusions, manure-based soil amendments, agricultural water, worker hygiene, harvesting practices, and unsafety equipment conditions. Several mitigation strategies from production to processing have been proposed to ensure food safety (Gil et al., 2015; Julien-Javaux et al., 2019). Among these strategies, the use of disinfectants to reduce or eliminate contamination of agricultural water is recommended. The main disinfection processes for irrigation water include chlorine, peracetic acid, UV radiation, ozone, and chlorine dioxide treatment. Risk mitigation at the processing includes wash water disinfection using chlorine or peracetic acid. The potential impact of these essential safety strategies on bioactive compounds should be estimated as so far are entirely unknown. Efforts should be conducted on prevention, including good agricultural practices and good manufacturing practices, to verify that the microbial contamination likely occurs, including checklists for the agricultural inputs (e.g., agricultural water or soil amendments) or disinfection of process wash water. A multidisciplinary farm to fork strategy is required to deal with food safety, including microbiological and chemical issues such as disinfection by-products and pesticide residues associated with leafy greens.

The incidence of plant pathogens also represents a significant problem in most lettuce production areas and systems in which integrated production systems, based on accurate identification of plant pathogens and appropriate risk assessments, are required. Biocontrol agents have been applied in soils infested for disease control, but their use in practice should be integrated with other control strategies (Gilardi et al., 2019). These safety issues have to be strictly considered when designing strategies to enhance the bioactive content in lettuce using preharvest and postharvest approaches.

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AUTHOR CONTRIBUTIONS

Xiao Yang: conceptualization; funding acquisition; visualization; writing-original draft; writing-review and editing. María I. Gil: supervision; writing-original draft; writing-review and editing. Qichang Yang: funding acquisition; supervision; writing-original draft; writing-review & editing. Francisco A. Tomás-Barberán: conceptualization; funding acquisition; supervision; visualization; writing-original draft; writing-review & editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Xiao Yang https://orcid.org/0000-0002-2511-4640
María I. Gil https://orcid.org/0000-0003-4340-7727
Qichang Yang https://orcid.org/0000-0003-3657-7023
Francisco A. Tomás-Barberán https://orcid.org/0000-0002-0790-1739

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