



Plants as Biofactories for Phenolic Compounds

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Abstract

For a long time, plants have been considered as healing agents for treating and preventing different diseases. These beneficial effects are mainly attributed to phenolic compounds. Phenolic compounds have as a basic structure one or more hydroxyl groups (–OH) attached to an aromatic ring. They are classified in two groups: flavonoids and phenolic acids. The regular intake of plant-based foods rich in phenolic compounds has been associated to the prevention and treatment of diseases such as Alzheimer's, Parkinson's, cardiovascular problems, atherosclerosis, metabolic syndrome, diabetes, and many types of cancer. Therefore, their demand has increased, so plants are now being used as biofactories for their production. By exposing plants to abiotic and biotic stress, phenolic compounds are synthesized in response to ROS overproduction. Their production has also been raised by increasing the expression of genes involved in phenolic compounds metabolic pathways. Present chapters address the use of biotic and abiotic stress as well as genetic engineering tools for increasing phenolic content in different plants.

Keywords

Plant · Phenolics · Biofactory · Stress · Biotic · Abiotic · ROS

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20.1 Introduction

Around 80% of people living in developing countries consider their native plants as the main healing agent for treating and preventing different diseases. This healing power has been attributed to their antioxidant activity and associated to the presence of phenolic compounds (Abdul Qadir et al. 2017).

Phenolic compounds are divided in two groups: flavonoids and phenolic acids. They are among the most investigated phytochemicals in both medicinal and nutritional areas (Del Rio et al. 2010).

Phenols were first isolated in 1834 by Friedlieb Ferdinand Runge and used as a wound dressing, antiseptic, and disinfectant in Germany. One of the first registers was in 1865 where the surgeon Joseph Lister employed them in a tibia fracture surgery (Hugo 1978). Currently, over 8000 different naturally occurring phenolic compounds are known, and the list grows (Tsao 2010).

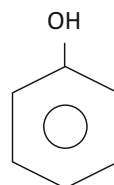
The main sources of flavonoids are parsley (*Petroselinum crispum*), celery (*Apium graveolens*), chamomile (*Matricaria chamomilla*), *Ginkgo biloba*, mint (*Mentha arvensis*), and red pepper (*Capsicum annum*) (Panche et al. 2016). While the main sources of phenolic acids are green tea (*Camellia sinensis*), coffee, berries, red wine, and whole cereals such as wheat (*Triticum* spp.), rice (*Oryza sativa*), corn (*Zea mays*), and oats (*Avena sativa*) (Weichselbaum and Buttriss 2010).

20.2 Chemical Characteristics

Phenolics are comprised in a wide array of compounds derived from the secondary metabolism of plants (Kutchan et al. 2015). Phenolic compounds have as a basic structure one or more hydroxyl groups (–OH) attached to an aromatic ring (Fig. 20.1). The presence of the hydrogen in the –OH groups makes phenolic compounds weak labile acids. Phenolic compounds can be ubiquitously found throughout the plant kingdom where they are usually present as esters or glycosides.

Nowadays, scientific literature uses the terms “phenolic compounds” and “polyphenols” to refer to the widespread subclasses of phenolic compounds, which are grouped according to their chemical characteristics related to their structure and type of compound. However, phenolic compounds are metabolically speaking, only metabolites derived from the shikimate phenylpropanoid and/or the polyketide pathways, with one or more phenolic rings and lacking of nitrogen-based functional groups (Quideau et al. 2011).

Fig. 20.1 Graphical representation of a phenol conformed of an aromatic ring with an hydroxyl group (–OH) attached



Phenolic compounds are the subject of many studies since they have been implicated in a myriad of health-promoting properties. The chronic intake of plant-based foods rich in phenolic compounds has been associated to an onset/prevention of noncommunicable diseases such as Alzheimer's, Parkinson's, cardiovascular problems, atherosclerosis, metabolic syndrome, diabetes, and many types of cancer (Del Rio et al. 2010; Fraga et al. 2010; Ozcan et al. 2014). These bioactive effects are attributed to the physicochemical properties related within the phenol functional group, which allows the –OH group to act as hydrogen-bond donor or as an acceptor (Quideau et al. 2011).

20.3 Classification

Phenolic compounds are a diverse group of organic compounds; at least 8000 phenolic structures have been elucidated. Phenolics have an important role in the protection of the plants against biotic or abiotic stress. These molecules are present in most plant tissues, for example, leaves, roots, and edible parts of the plant such as fruits (de la Rosa et al. 2019). Furthermore, phenolics can be found in nature conjugated to sugar moieties and organic acids.

There are several ways to classify phenolic compounds, and nowadays there is not a general agreement in how to categorize them. Besides, their classification can be dependent on the molecule's different properties. For example, (1) classifying phenolic compounds by their solubility is convenient for explaining the metabolic fate of phenolic compounds since it depends greatly on this property (Santana-Gálvez and Jacobo-Velázquez 2018); (2) based on the chemical structure, phenolic compounds can be categorized by the number of aromatic rings (Fig. 20.2), and this classification has been previously detailed (Santana-Gálvez and Jacobo-Velázquez 2018).

Phenolic compounds can be also classified in flavonoids and non-flavonoids. Flavonoids are the most abundant phenolics in plant kingdom. Its presence in nature is more commonly found in leaves and the skin of fruits (Crozier et al. 2009). The basic structure of flavonoids consists of 15 carbon atoms arranged in 2 phenyl rings named as A and B, linked through a heterocyclic pyran ring named as ring C (Fig. 20.3).

Flavonoids are subdivided into six groups of families, differing in their degree of oxidation and pattern of substitution of the C ring, whereas individual compounds in each family are differentiated by the pattern of hydroxylation and methylation of the rings A and B. The six groups of flavonoids are flavones, flavonols, flavonones, isoflavones, anthocyanidins, and flavan-3-ols (de la Rosa et al. 2019). From these subgroups, flavonols are the most abundant flavonoids; the most representative flavonols are kaempferol, myricetin, quercetin, and isorhamnetin (Crozier et al. 2009).

On the other hand, non-flavonoids consist of phenolic acids, stilbenes, lignans, and tannins (Oliveira et al. 2014). The most representative phenolic acid is gallic

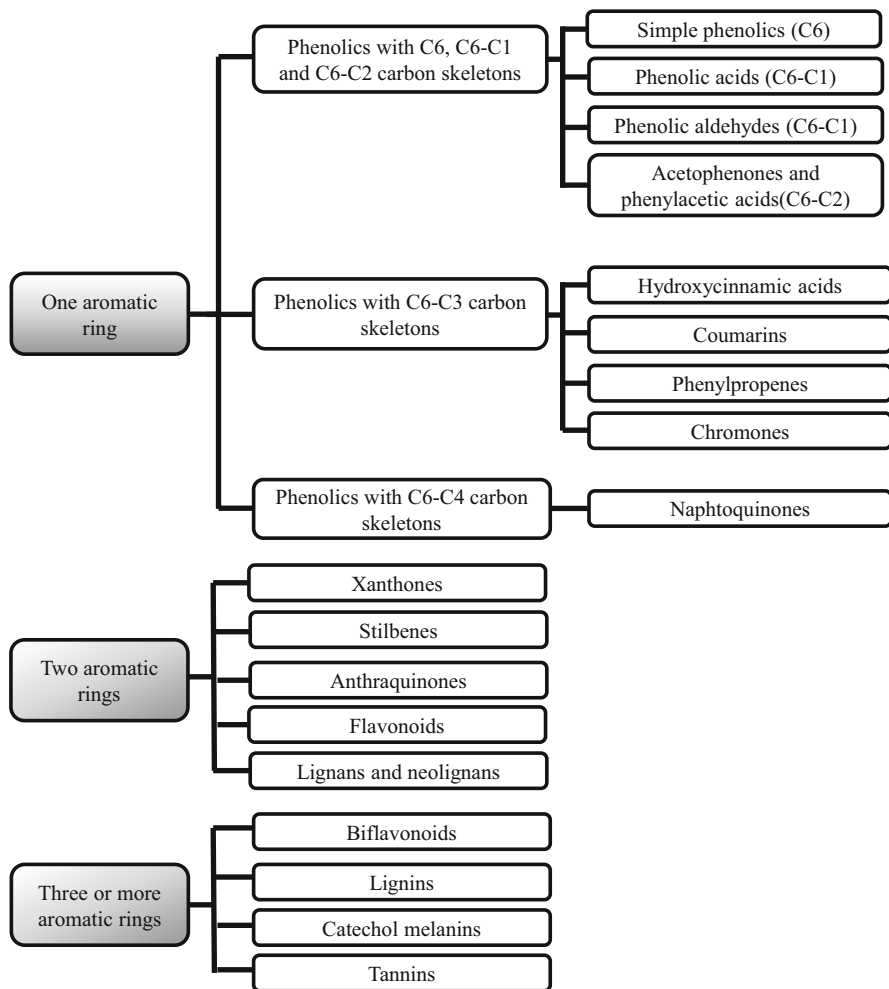


Fig. 20.2 Classification of phenolic compounds based on their basic chemical structure. Source: (Santana-Gálvez and Jacobo-Velázquez 2018)

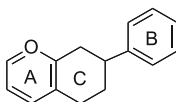


Fig. 20.3 Basic flavonoid skeleton

acid and acts as a precursor for the synthesis of other non-flavonoids such as hydrolysable tannins and stilbenes (Crozier et al. 2009).

20.4 Health-Promoting Properties

20.4.1 Neurodegenerative Diseases

The overrun of the endogenous antioxidant system due to free radicals is one of the main factors involved in the onset of neurodegenerative diseases (Poprac et al. 2017). The adoption of a Mediterranean diet has been associated with a lower incidence of neurodegenerative diseases due to the inclusion of foods such as wine (Valls-Pedret et al. 2015).

The total phenolic compounds in red wine reaches up to 1000 mg/kg. These components exert their antioxidant activity by directly scavenging the reactive oxygen species (ROS) and nitrogen oxygen species (NOS), and by inducing phase II detoxifying enzymes via nuclear factor E2-related factor 2 (Nrf2) activation over in vitro models (Rodriguez-Morato et al. 2015). For the particular case of Parkinson's disease, (–)-epigallocatechin-3-gallate, the most abundant polyphenol found in tea, and quercetin also found in red wine, protects against oxidative hippocampal neurodegeneration at the time that inhibits L-DOPA (dopamine precursor) methylation on in vivo models (Kang et al. 2013). As for Alzheimer's, phenolic acids and polyphenols modified by microbiota inhibit amyloid β aggregation, which is associated to cognitive decile in Alzheimer's disease (Pistollato et al. 2016).

20.4.2 Inflammation

Inflammation is a natural defense process that recognizes harmful environmental stimuli (Neagu et al. 2018). Phenolic compounds such as epicatechin and caffeic acid, found in red Cannonau wine, diminish the intestinal inflammation induced by dietary oxysterols, which are cholesterol auto-oxidation products that may lead to colorectal cancer by preventing the induction of NF- κ B-dependent inflammatory events (Guina et al. 2015).

Oleocanthal is a phenolic compound isolated from virgin olive oil with an anti-inflammatory property similar to ibuprofen. It represents 10% of the olive oil phenolic fraction, and it inhibits cyclooxygenase pathway over in vitro monocytes and monocyte-derived macrophages (Lucas et al. 2011). Kaempferol is another phenolic compound with autoinflammatory activity and highly found in golden root (*Rhodiola sachalinensis*). It reduced nitric oxide production by inhibiting nitric oxide synthase over in vitro LPS-stimulated RAW 264.7 cells (Choe et al. 2012).

20.4.3 Cancer

Cancer is characterized by a loss of cell death capacity and an uncontrolled cell division (Wong 2011). One of the main responsible for cancer onset is ROS, known to regulate signaling molecules required for cell cycle progression and to control the

expression of various tumor suppressor genes. Phenolic compounds such as the anthocyanin delphinidin induce apoptosis and cell cycle arrest in several types of cancer by the suppression of the NF- κ B pathway. Another target for cancer treatment is matrix metalloproteinase, an enzyme capable of degrade extracellular matrix. It is regulated by peonidin-3-glucoside (Zhou et al. 2016). Many other phenolic compounds have been studied, mainly over in vitro cancer models where cinnamic acid, caffeic acid, coumaric acid, and ferulic acid outstand for their antiproliferative effect over melanoma, prostate, and breast cancer, respectively (Anantharaju et al. 2016).

20.4.4 Cardiovascular Health

The term “cardiovascular diseases” encompasses a set of conditions among which peripheral arterial disease, coronary heart disease, venous thromboembolism, and congenital heart diseases stand out. Foods such as garlic, onion, ginger, and dark chocolate were consumed for a long time for their cardioprotective effect. Know it is known that these effects are due to the high antioxidant contents mainly due to phenolic acid, flavonoids, lignans, and stilbenes (Olas 2017). A high source of stilbenes is grape pomace. Consuming it for 7 days has cardioprotective effects against isoprenaline-induced infarct-like lesion. The effect is associated to the stilbenes trans- and cis-resveratrol, glycosylated derivatives of resveratrol, trans- and cis-piceid, piceatannol, and viniferins (resveratrol dimmers), which reduce oxidative stress (Balea et al. 2018).

20.4.5 Diabetes

The fungi *Phellinus igniarius* is a rich source of 7,8-dihydroxycoumarin, 3,4-dihydroxybenzalacetone, 7,3'-dihydroxy-5'-methoxyisoflavone, and inoscavin C. These phenolics are considered as potent antidiabetic compounds. All of them increase glucose uptake over in vitro models by up to 2.34-fold. They activate GLUT4 translocation via AMPK pathway modulation (Zheng et al. 2018). Another source of antidiabetic phenolic compounds is *Senecio bialfrae* leaves rich in gallic, chlorogenic, and caffeic acid as well as rutin, quercetin, and kaempferol. Together, these compounds inhibit the activity of alpha-glucosidase preventing the conversion of complex carbohydrates in to simple glucose (Ajiboye et al. 2018).

20.4.6 Obesity

Obesity is a preventable condition characterized by overweight (Hruby and Hu 2015). Hydroxycinnamic acid is considered as a potential compound for the management of obesity health complications. It inhibits macrophage infiltration and NF- κ B activation in obese animals. Also, it inhibits the expression of adipokines

TNF- α at the time that prevents adipocyte differentiation (Alam et al. 2016). Also, the polyphenols flavan-3-ols, epigallocatechin gallate, genistein, daidzein, curcumin, resveratrol, and quercetin glycosides found mainly in black tea, green tea, soybean, turmeric, grapes, and onion, respectively, have been largely studied and recognized for their control in body weight and fat accumulation. This compound promotes energy dissipation by activating brown adipose tissue, increasing energy expenditure (Mele et al. 2017).

20.4.7 Hyperlipidemia

Hyperlipidemia is caused by an excess of cholesterol, triglycerides, or both, in the bloodstream (Karr 2017). Cinnamon polyphenols are able to inhibit hyperlipidemia in high-fat diet-fed rats by enhancing the expression of the transcription factors SREBP-1c, LXRs, NF- κ B, and Nrf2 as well as enzymes such as ACLY and FAS involved in lipid metabolism (Tuzcu et al. 2017).

The most abundant phenolics identified in cinnamon are catechin, (–)-epigallocatechin gallate, syringic acid, gallic acid, vanillic acid, and p-coumaric acid (Lv et al. 2012). Recent studies have shown that *Clinacanthus nutans* leaves, a medicinal plant endemic to Asia, given to rats for 7 weeks, attenuate the oxidative stress through increasing serum antioxidant activity and upregulating the expression of hepatic antioxidant genes. The effects are attributed to protocatechuic acid (Sarega et al. 2016).

20.4.8 Osteoprotective

Osteoporosis is characterized by bone mass decrease, which can lead to fractures. For a long time, ferns such as *Drynaria* species have been used to prevent bone loss, specially its rhizome. The active compounds were unknown until recently, where chlorogenic acid, syringic acid, trans-ferulic acid, (–)-epigallocatechin, epigallocatechin gallate, quercetin dehydrate, and luteolin were identified in *Drynaria* extracts. These extracts increase the cell viability of osteoblastic cells by around 40%, promoting a high cellular density (Kang et al. 2014).

Also, genistein aglycone, a soybean isoflavone, has been known for a long time as a phytochemical that induces bone formation and resorption through the osteoprotegerin-sRANKL system (Bitto et al. 2010). The medicinal effect of some phenolic compounds is described in Table 20.1.

20.5 Strategies to Enhance Phenolic Compounds in Plants

Nowadays phenolic compounds are of greater interest. Their demand has increased by several factors such as a lot of studies attributing them potential health benefits, consumer health concerns, as well as an increased rate of diseases related to aging.

Table 20.1 Medicinal effect of phenolic compounds

Disease	Phenolic compounds	Source	Mechanism	References
Neurodegeneration	Hydroxytyrosol	Red wine	Scavenging of ROS and phase II detoxifying enzymes induction via Nrf2 activation	Rodriguez-Morato et al. (2015)
Parkinson	(-)-Epigallocatechin-3-gallate and quercetin	Green tea and red wine, respectively	Inhibition of L-DOPA methylation	Kang et al. (2013)
Inflammation	Epicatechin and caffeic acid Oleocanthal Kaempferol	Red Cannonau wine Virgin olive oil Golden rice (<i>Rhodiola sachalinensis</i>)	Prevention over the induction of NF- κ B-dependent inflammatory events via ROS scavenging Inhibition of cyclooxygenase pathway Inhibition of nitric oxide synthase	Guina et al. (2015), Lucas et al. (2011), Choe et al. (2012)
Cancer	Delphinidin Peonidin-3-glucoside		Suppression of the NF- κ B pathway Inhibition of matrix metalloproteinase	Zhou et al. (2016)
Cardiovascular health	Stilbenes	Grape pomace	Isoprenaline-induced infarct-like lesion reduction via oxidative stress reduction	Balea et al. (2018)
Diabetes	7,8-dihydroxycoumarin, 3,4-dihydroxybenzalacetone, 7,3'-dihydroxy- 5'-methoxyisoflavone and inosocavin C Rutin, quercetin and kaempferol	<i>Phellinus igniarius</i> <i>Senecio bialifrae</i>	Glucose uptake increment by activation of GLUT4 translocation Inhibition of alpha-glucosidase activity	Zheng et al. (2018) Ajiboye et al. (2018)
Obesity	Hydroxycinnamic acid, epigallocatechin gallate, genistein, daidzein, curcumin, and resveratrol	Black tea, green tea, soybean, turmeric, grapes, and onion, respectively	Inhibition of macrophage infiltration and NF- κ B activation in obese animals, inhibition of adipokines TNF- α expression, prevention of adipocyte differentiation, and energy dissipation promotion by brown adipose tissue activation, promoting energy expenditure	Alam et al. (2016), Mele et al. (2017)

Hyperlipidemia	Catechin, (-)-epigallocatechin gallate, syringic acid, gallic acid, vanillic acid, and p-coumaric acid Protocatechuic acid	Cinnamon <i>Cinnacanthus nutans</i>	Enhancement in the expression of the transcription factors SREBP-1c, LXRs, NF- κ B, and Nrf2 Increased serum antioxidant activity and upregulation of the expression of hepatic antioxidant genes	Tuzcu et al. (2017)
Osteoporosis	Chlorogenic acid, syringic acid, trans-ferulic acid, (-)-epigallocatechin, epigallocatechin gallate, quercetin dehydrate, and luteolin	<i>Drynaria</i> species	Induction of bone formation and resorption through the osteoprotegerin-sRANKL system	Bitto et al. (2010)

Plants are the main source for obtaining phenolic compounds, so techniques have been introduced to increase the plant phenolic content (Ameer et al. 2017). Among them, the use of abiotic and biotic conditions has been found to increase the bioactive compounds such as polyphenols and flavonoids in response to ROS overproduction. By exposing different types of plants to these types of stresses, vegetable tissues with higher antioxidant capacity can be obtained (Abdi et al. 2019; Khan et al. 2019). Another strategy for phenolic increase in plants is genetic manipulation, which has recently emerged since the biosynthetic pathways for phenolic production have been unveiled. Therefore, the expression of genes involved in all of them, especially transcription factors that allow the control of specific enzymes, has been engineered as a promising strategy for medicinal plant production.

These three topics will be discussed in detail throughout this chapter.

20.5.1 Abiotic Stress and Phenolic Compounds in Plants

Plants are continuously subjected to different types of stresses, affecting their normal growth, for example, adverse abiotic conditions such as cold, heat, drought, excess of salt or toxic metals, as well as nutrient imbalance (Zhu 2016).

Abiotic stresses are major limiting factors and responsible for enormous crop yield losses worldwide (Jorge et al. 2016), so omics and biology tools have been used to elucidate the pathways responding to different abiotic stresses conditions.

Over the time, it has been found that these types of stresses are mainly mediated by the overproduction of signaling molecules such as ROS and phytohormones like methyl jasmonate and ethylene. These trigger the overproduction of some phytochemical compounds, for example phenolics, promoting its accumulation (Jacobo-Velázquez and Cisneros-Zevallos 2012).

Phenolic compounds are highly valued biomolecules, so different strategies have been applied to increase its production, including the induction of adverse abiotic conditions. This strategy has been suggested as a replacement of genetic tools; technologies are still considered hazardous.

In Fig. 20.4, the abiotic stress strategies employed for phenolic overproduction in plants are classified.

20.6 Radiation

20.6.1 Light

Visible light is the electromagnetic spectrum visible to the human eye, from 380 to 740 nm. Visible light overexposure triggers strategies of photoprotection to counteract the damage, so it induces photosynthesis to occur, therefore promoting other metabolic pathways to increase (Younis et al. 2010).

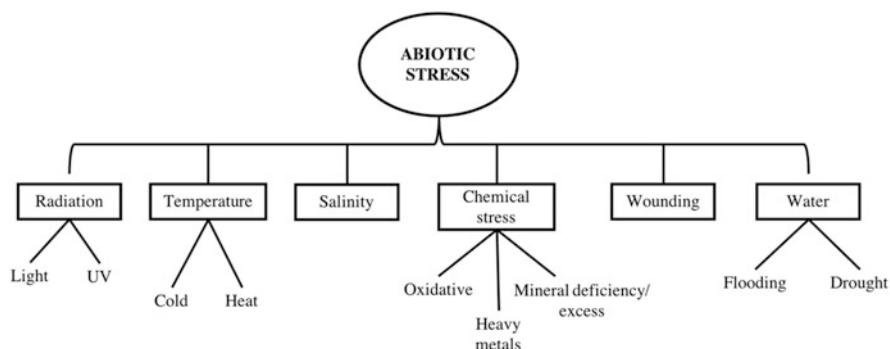


Fig. 20.4 The abiotic stress strategies employed for phenolic production in plants

Given the above, light-emitting diodes (LEDs) have been used lately to produce crops with special features, including improved nutritional profiles. Red and blue light going from 625–740 to 400–500 nm, respectively, is the most used spectra.

Monochromatic blue LED stimulates the biosynthesis of total phenolics and flavonoids in 2-week-old cherry tomato seedlings after 4 weeks exposure. Total phenolic and flavonoid content increased up to 33.33 and 75%, respectively (Kim et al. 2014). The same happens when applying blue LED over red leaf lettuce plants (Johkan et al. 2010).

In addition of being used for the increase of total phenolic content, LEDs have also been tested for raising particular compounds concentration. Blue and red LEDs tested separately promoted the accumulation of particular compounds in peas. After 4 days exposure, red LED increased catechin content by 14.3%, while chlorogenic acid and rutin content were increased by 26.3 and 18%, respectively, when applying blue LED (Liu et al. 2016).

Besides blue and red LEDs, the white one has been tested. Kale sprouts grown under white or blue LEDs showed an increase of total phenolic compounds of 34.55% and 69.09%, respectively. On the other side, the particular contents of anthocyanin in white, red, and blue LED-exposed grown sprouts were 8.69-, 5.94-, and 18.16-fold higher, respectively, as compared to nonexposed sprouts (Qian et al. 2016).

The combined effect of LEDs has also been evaluated. Blue and red LED increases total phenolic concentration in Sunmang and Grand Rapid lettuces by 55% and twofold, respectively (Son and Oh 2013). Also, chlorogenic acid, vitexin, rutin, quercetin, cyanidin 3-*O*-glucoside, and cyanidin 3-*O*-rutinoside concentrations are increased in Tartary buckwheat submitted to blue- and red-combined LED treatment (Seo et al. 2015).

The mechanism by which light radiation exposure works is by overexpressing *FtDFR* and *FtANS*. These genes are overexpressed up to 7.1-fold.

20.6.2 UV

Ultraviolet (UV) radiation is classified as UV-A, UV-B, and UV-C, in the range of 320–400, 280–320, and 100–280 nm, respectively (Edward et al. 2014). The application of UV rays affects plants by changing the normal metabolic pathways of photosynthesis, cell division, and any other process related to plant growth and development (Surjadinata et al. 2017). These effects are mainly promoted by reactive species accumulation which induces the expression of antioxidant genes already linked to the UV resistance 8 locus pathway. The above results in the activation of the plant defense system, including the triggering of the phenylpropanoid metabolism which results in the accumulation of secondary metabolites such as phenolic antioxidants. Consequently, UV radiation has been proposed, alone or in combination, as a cheap tool to enhance phenolic compound content in horticultural crops during postharvest life (Formica-Oliveira et al. 2017).

Lettuce, a very important crop worldwide, has been used as a plant factory to accumulate phenolic compounds. Total phenolic content (especially anthocyanins) and total antioxidant capacity were increased by 30 and 40%, respectively, without growth inhibition after 4 d UV-A exposure. The above was attributed to an increase in phenylalanine ammonia lyase (PAL) gene expression (a key gateway gene for the biosynthesis of phenolic compounds), and therefore PAL activity was increased (Lee et al. 2013). PAL is the first enzyme in the phenylpropanoid pathway.

On the other hand, UV-B applied to plants such as *Vitis vinifera* grape skin after defoliation and until harvest, alters the expression of 121 phenylpropanoid biosynthesis-related genes, including *VvFLS1*, *VvGT5*, *VvGT6*, *VvHYS-1*, *VvHYS-2*, and *VvRU*. Also, PAL and chalcone synthase gene expression was increased. These gene products are involved in the flavonol and monoterpenoid biosynthetic pathways. Among the compounds which concentration was highly increased by UV-B light application, there was syringic acid, caffeoyl tartaric acid, and resveratrol, which increased by 13%, 40%, and twofold, respectively, as compared to nonexposed plants (Rodríguez-Calzada et al. 2019).

The exposure to UV-C also increases resveratrol production in grapes, especially in *Vitis amurensis* and *Vitis labrusca* grapes. The mechanism is by PAL and stilbene synthase increased expression, where PAL is the first enzyme of the phenylpropanoid pathway, and stilbene synthase is responsible for catalyzing the reaction of resveratrol formation. Also, chalcone synthase gene had higher expressions. As for epigenetic changes, UV-C decreases methylation levels of *VaSTS2*, *VaSTS6*, and *VaSTS10* genes (Tyunin and Kiselev 2016). The above has also been documented for other plants such as shell ginger (*Alpinia zerumbet*) and in lemon pomace (Xuan et al. 2016; Papoutsis et al. 2016).

The effect of different types of UV radiation has been compared. For example, UV-A and UV-B over broccoli sprouts both particularly change their phenolic profiles. Applying UV-A during 120 min increased gallic acid hexoside I (~14%), 4-*O*-caffeoylquinic acid (~42%), gallic acid derivative (~48%), and 1-sinapoyl-2,2-diferuloyl-gentiobiose (~61%), and by applying UV-B, sinapoyl malate (~12%),

gallotannic acid (~48%), and 5-sinapoyl-quinic acid (~121%) were increased (Moreira-Rodríguez et al. 2017).

UV irradiation must be exploited for the production of functional foods rich in bioactive phytochemicals. This has been highly recognized and utilized for sunscreens and cosmetics production (Takshak and Agrawal 2019).

The results obtained in terms of phenolic accumulation in different plant materials by applying radiation are summarized in Table 20.2.

20.7 Temperature

20.7.1 Cold

Cold stress has been applied to different plant materials. It is classified as either chilling or freezing, above and below 0 °C, respectively (Pareek et al. 2017). This condition promotes stress, affecting physiological, biochemical, molecular, and developmental processes of plants. Different results have been found when it comes to cold stress and phenolics plant production. In some cases, the content increases, but in others it is reduced or maintained. These will depend mainly on the intensity and duration of the stress, as well as on the plant material (Hajihashemi et al. 2018).

For example, when exposing *Vitis vinifera* leaves at 7 °C during a week, a reduction in total phenolic content of up to 22.05% has been observed, especially in caffeic acid, p-coumaric acid, ferulic acid, and caffeic acid. Also, tannin content of *Vitis vinifera* leaves exposed below 0 °C was reduced up to 15.9% (Król et al. 2015).

On the contrary, low temperatures increase phenolic content in other plants such as kale, cabbage, papaya, and olive tree leaves. In Kale and cabbage stored at 12 °C, phenolic content was increased by 65.71 and 60%, respectively, as compared to normal temperature conditions (Soengas et al. 2018). Regarding to Maradol papaya, storing it at chilling conditions (1 °C) promotes phenolic accumulation compared with those stored at normal 25 °C conditions. The compounds increased after 8 days of storage were ferulic acid and caffeic acid by 40 and by twofold, respectively. As for freezing, olive tree leaves submitted below -7 °C for 15 days showed an increase in PAL expression by up to 4.8-fold, promoting a total phenolic increase of 12% (Ortega-García et al. 2008).

It was found that low-temperature exposure changed gene expression after 24 h treatment. Genes codifying for enzymes such as PAL and chalcone synthase were increased by 8- and 50-fold, respectively, and 4-coumarate, CoA ligase and chalcone isomerase, increased by threefold. The expression of these genes is back to normal after returning the plants to 25 °C during 2 days (Christie et al. 1994).

Also, in other plants such as chickpea, submitting the seeds to cold stress promoted an increased expression of PAL and cinnamyl alcohol dehydrogenase genes. This indicates the crucial role of phenylpropanoid pathway in creating cold tolerance (Rakei et al. 2016).

Table 20.2 Phenolic accumulation in plant materials by radiation exposure

Radiation type	Plant material	Effects	Mode of action	References
Visible light				
Blue	Tomato seedlings and red leaf Lettuce Peas Kale sprouts	<p>↑ Phenolic and flavonoid content by 33.33 and 75%, respectively</p> <p>↑ Chlorogenic acid and rutin content by 26.3 and 18%, respectively</p> <p>↑ Phenolic and anthocyanin content by 69.9% and 18.16-fold, respectively</p>	Overexpression of <i>FtDFR</i> and <i>FtANS</i> genes by 7.1-fold	Kim et al. (2014) Liu et al. (2016), Johkan et al. (2010) Qian et al. (2016)
Red	Peas Kale sprouts	<p>↑ Chlorogenic acid by 14.3%</p> <p>↑ Anthocyanin content by 5.94-fold</p>		Liu et al. (2016), Qian et al. (2016)
White	Kale sprouts	↑ Phenolic and anthocyanin content by 34.55% and 8.69-fold, respectively		Qian et al. (2016)
Blue + red	Sunmang lettuces Grand Rapid Tartary buckwheat	<p>↑ Phenolic content by 55%</p> <p>↑ Phenolic content by twofold</p> <p>↑ Chlorogenic acid, vitexin, rutin, quercetin, cyanidin 3-<i>O</i>-glucoside, and cyanidin 3-<i>O</i>-rutinoside content</p>		Seo et al. (2015)
UV				
UV-A	Lettuce Broccoli sprouts	<p>↑ Phenolic content by 30%</p> <p>↑ Gallic acid hexoside, 4-<i>O</i>-caffeoylquinic acid, gallic acid derivative, and 1-sinapoyl-2,2-diferuloyl-gentiobiose by 14, 42, 48, and 81%, respectively</p>	Overexpression of <i>PAL</i> and <i>chalcone synthase</i> genes	Lee et al. (2013)
UV-B	<i>Vitis vinifera</i> grapes skin Broccoli sprouts	<p>↑ Syringic acid, caffeoyl tartaric acid and resveratrol, by 13%, 40%, and twofold</p> <p>↑ Sinapoyl malate, gallotannic acid, and 5-sinapoyl-quinic acid by 12, 48, and 121%, respectively</p>		Rodríguez-Calzada et al. (2019), Moreira-Rodríguez et al. (2017)

20.7.2 Heat

The main use of heat in food industry is for reducing microbial levels. Nevertheless, it has been found that a lot of biochemical pathways are overexpressed in plants subjected to high temperature which in turn increases phytochemicals synthesis (Zhu 2016).

Heat shock at 100 °C was applied over fresh-cut carrots, increasing their phenolic content by 73.98% after 7 days of the heat shock application. Nevertheless, after 10 days the content starts to decrease. Phenolic compound accumulation was due to phenylpropanoid pathway activation. The most increased compound in wounded carrot is caffeoylquinic acid (Alegria et al. 2012). Six wheat genotype seedlings submitted to 45 °C during 20 h showed an increase of total phenolic content by about 40% in all genotypes (Ahmad et al. 2014).

The production and accumulation of phenolics according due to high temperatures will depend on the vegetable tissue. For example, fresh-cut carrots and onions accumulate more phenolics at 20 °C, while celery does it at 10 °C (Xiaoan et al. 2017).

Heat effect, as for the other stresses, is mainly the same. During heat, cell disruption may occur, liberating cytosolic ATP into the extracellular matrix. This ATP is recognized by receptors in the far cell's membrane increasing cytosolic Ca²⁺ concentrations, which activates NADPH oxidase and thus ROS and NOS production. ROS and NOS act as signals to activate PAL, and the plants answers back by producing antioxidant molecules as a defense system (Jacobo-Velázquez et al. 2011). The results obtained in terms of phenolic accumulation in some plant materials by applying different temperatures are summarized in Table 20.3.

20.8 Salinity

Around 20% of the world's irrigated lands have an excess of salt content, known as salinity. Salinity affects plants in multiple ways, for example, blocking respiration, inhibiting photosynthesis, and disordering metabolism and growth processes (Zhao et al. 2017). Nutritional quality of buckwheat sprouts under salinity was estimated. Here, the exposure time (from 1 to 7 days) and the salt concentrations (10, 50, and 100 mM) were evaluated. It was concluded that the most extreme conditions (100 mM for 7 days) resulted in the most effective condition to increase the phenolics content by 153%. The main increased phenolics were isoorientin, orientin, rutin, and vitexin. Previous studies have shown most of the phenolic compounds are generated by the phenylpropanoid pathway, which is stimulated by biotic and abiotic stresses (Lim et al. 2012). This effect is also associated to the increased in plant hormones production, including jasmonic acid and its methylated deriviate (methyl jasmonic acid). These hormones induce enzyme production involved in the phenylpropanoid pathway, including PAL, thereby resulting in the accumulation of phenolic compounds (Lim et al. 2012).

Table 20.3 Phenolic accumulation in plant materials by low- or high-temperature exposure

Temperature type	Plant material	Effect	Mode of action	References
Cold				
Chilling	<i>Vitis vinifera</i> leaves	↓ Phenolic content by 22.05%	Overexpression of <i>PAL</i> and <i>chalcone synthase</i> genes by up to 8- and 50-fold, respectively	Król et al. (2015)
	Kale	↑ Phenolic content by 65.71%		
Freezing	Cabbage	↑ Phenolic content by 60%		Król et al. (2015) Ortega-García et al. (2008)
	Papaya	↑ Ferulic acid and caffeic acid by 40- and twofold, respectively		
Freezing	<i>Vitis vinifera</i> leaves	↓ Phenolic content by 15.9%		Król et al. (2015) Ortega-García et al. (2008)
	Olive tree leaves	↑ Phenolic content by 12%		
Heat				
100 °C	Fresh-cut carrots	↑ Phenolic content by 73.98%	Increasing cytosolic Ca ²⁺ concentrations, which activates NADPH oxidase and thus ROS and NOS production overexpressing <i>PAL</i> gene	Alegria et al. (2012)
45 °C	Wheat	↑ Phenolic content by 40%		Ahmad et al. (2014)

Biosynthesis of phenolics was also stimulated in other plants such as olive cultivar leaves by irrigating them every 3 days during 1 month with 125 mM NaCl. Salinity stimulated the biosynthesis of phenolics by increasing its total content up to 129%. From them, the content of oleuropein, the most abundant phenolic from olive tree and oil, was increased by 3.8-fold (Petridis et al. 2012a). Similarly, a high salinity concentration of 300 mM NaCl was evaluated over *Salvia coccinea* leaf, increasing the total phenolic content by 17% (Grzeszczuk et al. 2018).

Salinity stress (5 dS/m) was applied to both susceptible and tolerant rice varieties. Total phenolics and flavonoids, as well as vanillin, ferulic acid, p-coumaric acid, and protocatechuic acid, were increased in tolerant varieties. Phenolic compounds were increased around 48% while flavonoids only 17.15%. In contrast they were markedly reduced in the susceptible cultivars (Jamalian et al. 2013). The enhancement in the synthesis of flavonoids and phenolics of strong tolerant varieties might be due to the adaptive mechanism of rice under salt stress. The presence of ferulic acid under osmotic stress may be related to the strengthening of the plant cell wall and the overall cell elongation. Also, they are possibly found in bounded forms with sugar or glycoside (Minh et al. 2016). It is believed that the salinity stress also enhances the phenolic compound production by the abscisic acid increased content in plants. The results obtained in terms of the phenolic accumulation in different plant materials by applying different salinity stresses are summarized in Table 20.4.

Table 20.4 Phenolic accumulation in plant materials by high salinity exposure

Salinity (NaCl)	Plant material	Effects	Mode of action	References
100 mM	Buckwheat sprouts	↑ Phenolic content by 153%, mainly isoorientin, orientin, rutin and vitexin	Increased plant hormones production, including jasmonic acid and methyl jasmonic acid which overexpresses <i>PAL</i> gene	Lim et al. (2012)
125 mM	Olive leaves	↑ Phenolic and oleuropein content by 129% and 3.8-fold, respectively		Petridis et al. (2012a)
300 mM	<i>Salvia coccinea</i> leaves	↑ Phenolic content by 17%.		Grzeszczuk et al. (2018)
5 dS/m	·Susceptible rice varieties Tolerant rice varieties	↓ Phenolic content ↑ Phenolic and flavonoid content by 48 and 17.15%, respectively ↑ Flavonoids, vanillin, ferulic acid, p-coumaric acid, and protocatechuic acid		Minh et al. (2016)

20.9 Chemical Stress

20.9.1 Oxidative

Oxidative stress is the result of unfavorable biotic and abiotic conditions. It also can be artificially induced by ROS such as superoxide (O_2^-) and hydrogen peroxide (H_2O_2) addition.

Common daisy (*Bellis perennis L.*) callus was submitted to 10 mM H_2O_2 for 10 h. The treatment with H_2O_2 allowed the detection of kaempferol, myricetin, quercetin, and isorhamnetin, compounds not detected in the control (0 mM H_2O_2). Also, total phenolic content was increased by 29.25% after H_2O_2 exposure. Furthermore, as a result of oxidative stress, SOD and CAT were increased.

It was found that CAT, SOD, total phenolic, total flavonoid, and proline activity had a significant positive correlation with the phenolic accumulation under H_2O_2 pretreatment. The in vitro culture methods under controlled laboratory conditions, such as the one studied in this investigation, have been of great interest for the production of bioactive molecules (Karakas et al. 2015).

20.9.2 Heavy Metals

Heavy metals are considered as one of the most dangerous pollutants (Morkunas et al. 2018). When plants are in the presence of these compounds, phytochemicals such as phenolic compounds are overproduced and accumulated to protect the plant against toxicity. When plants are exposed to heavy metals, phenolic compounds are mostly increased, since they function as metal chelators and participate in ROS scavenging (Malčovská et al. 2014).

Cadmium (Cd^{2+}) and lead (Pb^{2+}) exposure (50 and 10 ppm, respectively) during 2 weeks increased the total phenolics in corn (*Zea mays*) leaves by around 41.17 and 47%, respectively. The main phenolic compounds increased were chlorogenic acid and rutin; on the other hand, the level of other compounds such as caffeic acid and ferulic acid was decreased (Kısa et al. 2016). Another heavy metal evaluated over plants is nickel (Ni). When exposing chamomile (*Matricaria chamomilla*) to 120 μM Ni during 10 days, polyphenol oxidase activity was decreased, but an increase in the total phenolic compounds (by 18%) and in PAL activity as well as in shikimate dehydrogenase was observed. Another enzyme production, such as cinnamyl alcohol dehydrogenase, was not affected. Also, in leaf rosettes it was detected an increase in chlorogenic acid accumulation (9.02%), as well as protocatechuic acid (7.47%) (a compound with chelating strength) and caffeic acid (153%) (Kováčik et al. 2007).

Transcriptional and post-transcriptional analysis of soybean and lupine roots exposed to Cd^{2+} (25 mg/l) or Pb^{2+} (350 mg/l) was carried out. Here, it was found that under heavy metal stress, there was a transcriptional and post-transcriptional control of PAL expression. For soybean, both metals increased PAL expression, while for lupin only Pb^{2+} . Due to the above, it is concluded that heavy metal stress imposed by Cd^{2+} and Pb^{2+} can cause an induction in the phenylpropanoid pathways of soybean and lupin (Pawlak-Sprada et al. 2011).

Cd^{2+} effect (5 $\mu\text{g/g}$ soil) was also evaluated over *Erica andevalensis*. This heavy metal increased cinnamic acid derivatives (by threefold), epigallocatechin (81.78%), and rutin (32.32%). Nevertheless, when cadmium concentration was increased up to 50 $\mu\text{g/g}$, the synthesis and release of phenolics were reduced. So, the excess of cadmium may reduce the synthesis of phenolics to avoid deleterious effect caused by the phenoxy radicals' production. The overall results showed that the phenolic compounds play an important role in the cadmium defense of *E. andevalensis* (Márquez-García et al. 2012).

Maize plants (*Zea mays L.*) have also been exposed to a Cd^{2+} stress (50 μM). Hydroponically grown maize superoxide radicals were increased by up to 1.6-fold. Nevertheless, total phenolic content in maize leaf was barely increased by this Cd^{2+} concentration. It is thought that the presence of high amounts of Cd^{2+} is related to the phenolics involvement in lignin biosynthesis, affecting the pool of free phenols in the plant tissue, which has also been reported in cucumber plants (Malčovská et al. 2014).

Besides Cd^{2+} , Pb^{2+} , and Ni, other heavy metals such as cobalt (Co^{2+}) and silver (Ag^{+}) have been tested. Solutions of 5 μM of Co^{2+} , Ag^{+} , and Cd^{2+} have been

Table 20.5 Phenolic accumulation in plant materials by heavy metal exposure

Heavy metals	Plant material	Effects	Mode of action	References
Cadmium	Corn leaves <i>Erica andevalensis</i>	↑ Phenolic content by 41.17% ↑ Cinnamic acid derivatives, epigallocatechin, and rutin by threefold, 81.78%, and 32.32%, respectively	Overexpression of <i>PAL</i> and <i>shikimate dehydrogenase</i> genes	Kisa et al. (2016) Márquez-García et al. (2012)
Lead	Corn leaves	↑ Phenolic content by 47%.		Kisa et al. (2016)
Nickel	Chamomile leaf rosettes	↑ Phenolic content by 18% and ↑ chlorogenic acid, protocatechuic acid, and caffeic acid by 9.02, 7.47, and 153%, respectively		Kováčik et al. (2007)
Cobalt and silver	<i>Vitis vinifera</i>	↑ 3- <i>O</i> -glucosyl-resveratrol by 1.6-fold		Cai et al. (2013)

added to *Vitis vinifera* cell suspension cultures. An increase of 3-*O*-glucosyl-resveratrol up to 1.6-fold after 4 h exposure was observed, not affecting cell viability. Cell viability was only affected when heavy metal concentrations increased up to 25 μM (Cai et al. 2013). Other studies in terms of phenolic accumulation in different plant materials by applying different heavy metals are summarized in Table 20.5.

20.10 Mineral Deficiency and Excess

Plants need at least 14 minerals to grow optimally. If there is a deficit or an excess of one of them, crop yield may be affected. There are some minerals required in large amounts (nitrogen, phosphorus, potassium, calcium, magnesium, and sulfur), while others are needed to a lesser extent (chlorine, boron, iron, manganese, copper, zinc, nickel, and molybdenum). It has been observed that the concentration of nutrient elements, such as minerals, is related with the accumulation of plant defense metabolites.

The excess of minerals such as copper (Cu) has a pronounced effect increasing *PAL*, shikimate dehydrogenase, cinnamyl alcohol dehydrogenase, polyphenol oxidase, and ascorbate peroxidase activity in chamomile plants exposed to 10 μM Cu during 7 days. Due to this, protocatechuic acid, *p*-OH benzoic, vanillic acid, syringic acid, *p*-coumaric acid, ferulic acid, and chlorogenic acid were increased by 63.47, 137.5, 44, 33.55, 76.38, 58.33, and 107%, respectively (Kováčik et al. 2009).

Cu excess effect has also been evaluated over other plants. It has been reported that 1.0 μM of Cu increases total phenolic content by 19% in rosemary leaves (*Rosmarinus officinalis* L.), compared to normal levels. Cu excess in sorghum also increases total phenolic content (Hejazi et al. 2012). Cu levels of 0.5 mM in red cabbage increased anthocyanin concentrations by 126.7% due to oxidative stress

Table 20.6 Phenolic accumulation in plant materials submitted to mineral excess or deficiency

Mineral	Plant material	Effects	Mode of action	References
Excess				
Copper	Chamomile Rosemary leaves Red cabbage	↑ Vanillic acid, syringic acid, p-coumaric acid, ferulic acid, and chlorogenic acid by 63.47, 137.5, 44, 33.55, 76.38, 58.33, and 107%, respectively ↑ Phenolic content by 19% ↑ Anthocyanin by 126.7%	Overexpression of <i>PAL</i> , <i>shikimate dehydrogenase</i> , <i>cinnamyl alcohol dehydrogenase</i> , <i>polyphenol oxidase</i> , and <i>ascorbate peroxidase</i> genes expression	Kováčik et al. (2009) HEJAZI et al. (2012)
Deficiency				
Nitrogen	Tomato leaf	↑ Chlorogenic acid and rutin by 136 and 117%, respectively	Nothing reported yet	Bénard et al. (2011)
Nitrogen and potassium	American ginsengs	↑ Vanillic acid, p-coumaric acid, and trans-cinnamic acid		Du et al. (2011)
Phosphorus	American ginsengs	↓ Phenolic content		Du et al. (2011)

induction and enhancement of thiobarbituric acid reactive substances in all the plant, suggesting that these flavonoids are synthesized to neutralize ROS (Posmyk et al. 2009). The excess of some minerals induces other many alterations in plants, for example, it affects the uptake of other essential nutrients.

Mineral deficiency also alters the content of phenolic compounds. Nitrogen and potassium deficiency in American ginseng increases the concentration of vanillic acid, p-coumaric acid, and trans-cinnamic acid. Nevertheless, the opposite effect was observed after phosphorus deficiency, where total phenolic content decreased (Du et al. 2011).

Nitrogen deprivation during 19 days on tomato (*Solanum lycopersicum*) leaf increases chlorogenic acid and rutin by 136 and 117%, respectively. It was reported that this increase in phenolic compounds was maintained even when the plant was again exposed to normal nitrogen levels (Bénard et al. 2011). When nitrogen deprivation is combined with an exposure to 12 °C for 8 days, flavonoids levels are also enhanced. The responsible are structural genes in the phenylpropanoid and flavonoid pathway enhancement. From this, eight of the ten structural genes involved in flavonol metabolism showed enhanced expression, including phenylalanine ammonia lyase, chalcone synthase, flavanone 3-hydroxylase, and flavonol synthase (Løvdaal and Lillo 2009).

Data in terms of phenolic accumulation in different plant materials by submitting them to mineral excess or deficiency is summarized in Table 20.6.

20.11 Water

20.11.1 Flooding

Flooding, also known as submergence, is a scenario where the plant is totally or partially immersed in water. Due to limited oxygen uptake, anaerobic metabolism may result in the accumulation of phytochemical end-products generated for the plant to survive. Different varieties of sweet potatoes, Taoyuan 2, Sushu 18, and Simon 1, have been tested after flooding treatments where flavonoid content was increased by 11, 4, and 4%, respectively (Lin et al. 2006). More studies are required in this and other plant species to investigate the underlying mechanism.

20.11.2 Drought

Water deficiency promotes a change in biological processes such as photosynthesis, respiration, nutrient metabolism, and secondary metabolism which results in reduced plant growth and also in phytochemicals accumulation (Jaleel et al. 2009; Marchese et al. 2010).

Agave salvia, a plant used in the central and north regions of Mexico for the elaboration of alcoholic beverages, has been exposed to drought conditions not showing differences in its phenolic profile, nor in the concentration as compared to normal conditions. This is because *Agave salmiana* is a stress-tolerant plant, so its phenylpropanoid biosynthesis is not affected (Puente-Garza et al. 2017).

In the case of plants such as *Vitis vinifera*, a change in their phenolic content was seen after drought stress. *Vitis vinifera* roots and leaves under drought stress showed a reduction in total phenolic compounds by 9 and 30%, respectively. Caffeic acid, p-coumaric acid, and ferulic acid were the main phenolic compounds affected. The above promote a lowering on the antioxidant potential (Król et al. 2014). This reduction may be explained by the phenylpropanoid and shikimate pathway enzymes reducing their activity under drought stress, which has been observed in other plants.

On the contrary, other plants increase its phenolic compound production to avoid the oxidative damage caused by the lack of water, mainly those not used to drought conditions.

Plants such as *Aristotelia chilensis*, a berry native to Chile, increased anthocyanin concentration by upregulation of key anthocyanin pathway genes such as *dihydroflavonol 4-reductase*, *UDP-glucose: flavonoid 3-O-glucosyl transferase (UFGT)* and MYB R2R3-type transcription factors such as Myeloblastosis A1 (MybA1) and Myeloblastosis 5A (González-Villagra et al. 2018). This mechanism of enhanced phenolic compounds due to drought stress has also been observed in *Achillea* species and *Amaranthus tricolor*, where a 75% of water supply reduction increased the total phenolic and total flavonoid content by up and twofold and 38%, respectively (Sarker and Oba 2018). Also, a reduction of 67% water supply in olive

Table 20.7 Phenolic accumulation in plant materials submitted to water deficiency

Plant material	Effects	Mode of action	References
<i>Agave salmiana</i>	No changes in phenolic content or profile		Puente-Garza et al. (2017)
<i>Vitis vinifera</i> roots	↓ Phenolic content by 9%	Under expression of phenylpropanoid and shikimate pathway genes	Król et al. (2014)
<i>Vitis vinifera</i> leaves	↓ Phenolic content by 30%		Król et al. (2014)
<i>Aristolotelia chilensis</i>	↑ Anthocyanin	Upregulation of key anthocyanin pathway genes such as <i>dihydroflavonol 4-reductase</i> , <i>UDP-glucose: flavonoid 3-O-glucosyl transferase (UFGT)</i> and MYB R2R3-type transcription factors such as Myeloblastosis A1 (MybA1) and Myeloblastosis 5A	González-Villagra et al. (2018)
<i>Achillea species</i>	↑ Phenolic content by twofold		Sarker and Oba (2018)
<i>Amaranthus tricolor</i>	↑ Phenolic content by 38%		Sarker and Oba (2018)
Olive tree	↑ Phenolic content by 35%		Petridis et al. (2012b)

tree (*Olea europaea*) increased the phenolic compounds by around 35% (Petridis et al. 2012a).

After a long drought stress exposure of 3 weeks, *Codonopsis lanceolata* leaf and roots showed a total phenolic content increase up to 150%, being the predominant compounds catechin, benzoic acid, chlorogenic acid, ferulic acid, gallic acid, rutin, and vanillic acid. The responsible mechanism was an overexpression of 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase, an enzyme in the shikimate pathway, involved in the synthesis of aromatic amino acids such as phenylalanine and tyrosine, the precursors in the phenylpropanoid biosynthesis (Ghimire et al. 2017).

Gene expression is also very affected after drought stress in plants such as potato, where PAL, HCT, HQT, C3H, CHS, CHI, F3H, DFR, and AN1 expression was induced, which is related to an altered sucrose flux. The overexpression of HQT has also been documented in Solanaceae species exposed to drought, like in the case of tomatoes, where chlorogenic acid is accumulated in response that overexpression of HQT (André et al. 2009). The results obtained in terms of phenolic accumulation in different plant materials by submitting them to water deficiency are summarized in Table 20.7.

20.12 Wounding

Wounding methods have been applied as postharvest strategies for increasing phenolic content in different plants. Potato tubers are one of them. They were sliced, pie-cutted, or shredded followed by 144 h at 10 °C storage. The highest phenolic

compound content was found in sliced potato tubers, where the content of these compounds increased by twofold. The most abundant phenolic compounds were chlorogenic acid (CGA), neo-chlorogenic acid (neo-CGA), and crypto-chlorogenic acid (crypto-CGA). Wounding stressed potato could be used as a starting material for the extraction of high-value antioxidant phenolic compounds with potential applications in the pharmaceutical and dietary supplement industries (Torres-Contreras et al. 2014).

One of the vegetables more studied in terms of wounding is carrots, where it has been found that the higher the wounding intensity, the higher the phenolic accumulation. It is possible to increase the total phenolic content by 2.5-fold and the antioxidant capacity to 12.4-fold when wounding at 23.5 cm²/g. By this it is induced the synthesis of chlorogenic acid and 3,5-dicaffeoylquinic acid (Surjadinata and Cisneros-Zevallos 2012).

Other vegetables such as lettuce, cilantro, cabbage, green beans, apples, plums, peaches, strawberries, bell peppers, asparagus, celery, carrots, radishes, potatoes, and jicama have been submitted to wounding stress and exogenous ethylene and methyl jasmonate. The combination of wound stress and phytohormones resulted in increased PAL activity in some vegetables. Nevertheless, the response was tissue-dependent since the phenolic content of asparagus, cabbage, apples, tomatoes, and pears was not affected (Heredia and Cisneros-Zevallos 2009). Wounded vegetables that are included in most people regular diet may be considered as an inexpensive source to obtain phenolic compounds and thereby to promote the increase in antioxidants ingest.

20.13 Biotic Stress and Phenolic Compounds in Plants (Gabriela)

Phenolic compounds are synthesized by the secondary metabolism of plants, and it is used as a mechanism of defense against different biotic and abiotic stress. The metabolic pathways for the synthesis of phenolic compounds and other secondary metabolites can be manipulated, specifically promote their synthesis. Therefore, the study of the methods that enhance the production of secondary metabolites is currently of scientific interest. Biotic elicitors are molecules produced by living organisms, such fungus or formed by the plant itself. Plant cell cultures have been used to study the potential of some elicitors in the production of phenolic compounds. Chitosan has been the most reported biotic elicitor in the recent years. Chitosan is a polysaccharide composed of β -(1–4)-linked d-glucosamine and N-acetyl-d-glucosamine randomly distributed within the polymer. This polysaccharide is a structural component of the cell wall of fungi which are pathogens to plants. In plants, chitosan acts as elicitor of plant defensive mechanisms (Cheung et al. 2015; Ferri and Tassoni 2011).

The application of chitosan and irrigation frequencies has been evaluated for the enhancement of essential oils and phenolic content of *Salvia officinalis* L. The foliar application of chitosan (0.5 g/L) and reduced irrigation showed the maximum concentration of phenolic compounds in *Salvia officinalis* L. (Vosoughi et al.

2018). Chitosan has been applied as elicitor in many plants. For instance, in spinach, chitosan (0.1 mg/mL) increased the content of phenolic and flavonoids, with an increase in the antioxidant activity (Singh 2016). Other biotic elicitors are yeasts, and they have been evaluated and compared to the action of chitosan. Yeast and chitosan were evaluated as the biotic stressors on *Rumex cyprius* and showed to enhance the phenolic accumulation with an increase in the antioxidant activity. The maximum antioxidant activity was obtained with yeasts at 200 and 400 mg/mL, whereas the level of chitosan was not a determinant of the antioxidant activity since the low and high levels showed significant results. Furthermore, yeast showed to promote the formation of new phenolics such as gallic and chlorogenic acid (Al Khateeb et al. 2016). Furthermore, low concentration of yeast (50 mg/L) has been reported to enhance the production of phenolic compounds in adventitious root cultures of *Polygonum multiflorum* (Ho et al. 2018b).

The mechanism of action of fungal chitosan is the induction of the activities of defensive enzymes, as showed in *Zanthoxylum bungeanum* stems, where this effect triggers the total phenolic content production (Li et al. 2016). Therefore, fungal elicitors can stimulate the secondary metabolite production. These elicitors can enhance the enzymatic activity of defensive enzymes such as PAL and chalcone isomerase (Simic et al. 2015).

20.14 Genetic Enhancement of Phenolic Compounds in Plants

As it has been previously mentioned, several strategies have been studied to enhance the content of phenolic compounds in plants, most of them involve physiological approaches such as manipulation of biotic and abiotic stresses in plants to trigger the metabolic biosynthetic pathways leading to the overproduction of phenolic compounds. These works have combined high-throughput massive DNA sequencing and metabolic profiling technologies, leading to the development of a new area of study called phytochemical genomics. Thus, the physiological manipulation of phenolic compounds enhancement has led to the discovery of the metabolic pathway of phenolics biosynthesis through the identification of key genes involved in the phenolic pathway (Saito 2013). On this subject, there are different genomic techniques from which plants can be genetically modified. Eckerstorfer et al. (2019) listed some of the most widely used GM techniques such as “genome editing with site-directed nucleases, genome editing directed by synthetic oligonucleotides, RNA directed DNA methylation, cisgenesis and intragenesis, transgrafting, agro-infiltration, haploid induction and accelerated breeding.” For a more detailed research on this matter, we recommend the work by Eckerstorfer et al. (2019). A summary of recent studies regarding functional genomics on enhancement of phytochemical content of plants is found on Table 20.8. However, even though genomic manipulation is a promising technique to enhance phenolic compounds in crops and medicinal plants, the regulatory framework in the world limits its widespread distribution. In this regard, some authors have published strategies and recommendations for countries that desire to regulate GMO applications;

Table 20.8 Summary of some works of functional genomics applied to enhance phenolic content

Plant	Genomic modification	Result	References
<i>Glycine max</i> L.	Not specified	Non-GM soybean had highest polyphenol and sterol content of than GM soybean; non-GM methanol extract was more potent against colon carcinoma cells	Marrelli et al. (2013)
<i>Brassica rapa</i> ssp. <i>Rapa</i>	Increased expression of the genes BrMYB28, BrMYB29, BrMYB34, BrMYB51, BrMYB122, CYP79, and CYP83 in turnip hairy root	Higher flavonol, hydroxybenzoic acid, and hydroxycinnamic acid content in GM turnip hairy root; GM turnip also showed higher antioxidant, antimicrobial, and antiproliferative activity	Chung et al. (2016)
<i>Codonopsis lanceolata</i>	Transgenic plants with overexpression of γ -tocopherol methyl transferase gene	Transgenic plants had higher chlorogenic acid, luteolin, apigenin, protocatechuic acid, rutin, quercetin, salicylic acid, and caffeic acid. Also transgenic plants showed increased antimicrobial activity against <i>Staphylococcus aureus</i> , <i>Salmonella typhimurium</i> , <i>Klebsiella pneumoniae</i> , and <i>Escherichia coli</i>	Ghimire et al. (2017)
<i>Strawberry</i>	Transformed strawberry with a construct containing an anthocyanidin synthase gene	GM strawberry line ANS L18 had the highest total phenolic, total flavonoid content. Line ANS L15 had highest anthocyanin concentration	Giampieri et al. (2018)
<i>Artemisia dubia</i> WALL	Transgenic lines of <i>Artemisia dubia</i> WALL transformed with <i>Agrobacterium tumefaciens</i> harboring <i>rol</i> <i>ABC</i> genes	Increased production of flavonoids up to 71.1% and up to 110.8% higher total phenolic content in transgenic plants. GM plants showed higher antibacterial, antifungal, cytotoxicity, antitumor, and antioxidant activities	Kiani et al. (2015)
<i>Nitraria schoberi</i> L.	Transformed primary leaves with a wild strain of <i>Agrobacterium rhizogenes</i> 15,834 SWISS	Increased biosynthesis of flavonoids and hydroxycinnamic acids. 3.8-fold higher content of catechin in ethanol extracts of GM <i>N. schoberi</i> ; higher antiviral activity in GM plants against influenza [A(H5N1), A(H3N2)]	Zheleznichenko et al. (2018)

(continued)

Table 20.8 (continued)

Plant	Genomic modification	Result	References
<i>Polygonum multiflorum</i>	Transgenic transformation of hairy root lines of <i>P. multiflorum</i> with <i>A. rhizogenes</i> strain KCCM 11879, followed by exposure to methyl jasmonate	GM HR-01 line showed increased total phenolic content and higher quercetin, myricetin, kaempferol, cinnamic acid, chlorogenic acid, caffeic acid, ferulic acid, coumaric acid, gallic acid, protocatechuic acid, biochanin, hesperidin, naringenin	Ho et al. (2018a)
<i>Taraxacum antungense</i>	Induced overexpression of chlorogenic acid biosynthetic gene (HQT)	Chlorogenic acid levels increased up to 82.49% in transgenic lines	Liu et al. (2018)
<i>Mitracarpus hirtus</i>	Hairy root of <i>M. hirtus</i> was modified utilizing a root-inducing plasmid using <i>A. rhizogenes</i> A13-mediated transformation and also treated with 2-chloro-4-pyridyl-N-phenylurea	Increased secondary metabolite production; higher levels of chrysophanol (2.23-fold) and 2-methoxy-4-vinylphenol (1.95-fold)	Pansuksan et al. (2014)
<i>Nicotiana tabacum</i> cv. Petit Havana	Agrobacterium-mediated transformation of tobacco plants with MYB transcription factor AtMYB11	Flavonols such as quercetin, rutin, kaempferol and kaempferol-3-rutinoside, and chlorogenic acid biosynthesis was enhanced in GM tobacco plants	Pandey et al. (2015)

nonetheless, regulation frameworks vary among countries; thus there is currently no international harmonization (Eckerstorfer et al. 2019). Release of GMOs is regulated by government agencies; for instance, the US Department of Agriculture, the Food and Drug Administration, and the Environmental Protection Agency are the organizations that regulate release of GMO in the USA; Europe is regulated by the European Food Safety Authority; England is regulated by the Department for Environment Food and Rural Affairs; Mexico is regulated by the Federal Commission for the Protection Against Sanitary Risk (Eckerstorfer et al. 2019; Estados Unidos Mexicanos 2005). On this subject, Ichim (2019) stated that Romania was one of the first European countries adopting GM crops for commercial cultivation; however after 17 years, cultivation stopped, but it's expected to continue with this activity in spite of the European Union block on authorization regarding the cultivation of GM crops. Up to date, France, Germany, Poland, Italy, Austria, Hungary, Lithuania, Latvia, Bulgaria, and Greece are European countries that still restrict the cultivation of GM crops (Ichim 2019). Restrictions arise not due to concerns regarding safety to human and animal health but to concerns regarding the release in the environment of authorized or unauthorized GM crops (Rostoks et al. 2019).

20.15 Conclusions

Phenolic compounds are in great demand, mainly for their potential in treating and preventing noncommunicable diseases. Harvest and postharvest exposure to unfavorable conditions such as abiotic stress can be used as an alternative to accumulate total or specific phenolic compounds in different plant materials. By abiotic stress exposure, high commercially valued plants with high antioxidant activity can be produced. These adverse conditions mediate the overproduction of signaling molecules, such as reactive oxygen species and phytohormones like methyl jasmonate and ethylene, triggering the overproduction of phenolics, mainly by the overexpression of phenylalanine ammonia lyase, the enzyme involved in the first step of the phenylpropanoid metabolism. The production and accumulation of phenolic compounds by abiotic stress induction depend on the stimulus intensity as well as on the vegetable tissue. Generally, the more the plant is removed from its comfort zone, the greater the production of these phytochemicals. One of the most promising strategies of abiotic stress induction is by wounding plant matrices. This strategy that can be even carried out household to increase the consumption of antioxidant compounds.

Another tool for phenolic compound overproduction is biotic stress, where elicitors are mainly used for increasing the production of phenolic compounds in plants cell culture. This is a promising strategy for the production and subsequent recovery and purification of compounds of interest, aiming to generate food supplements or drugs.

Because of the metabolic pathway for phenolic compounds synthesis is now known, genetic engineering has emerged as another option to increase their production. However, since the regulatory framework has not been developed enough, the use of this particular tool is still limited. Numerous *in vivo* and *in vitro* studies have shown the bioactivity of polyphenols, so increasing the consumption of these natural compounds emerges as a promising alternative for treating and preventing health disorders related to oxidative stress. Here, we discussed three alternatives to achieve it.

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