doi.org/10.1002/cbdv.202100345

REVIEW

The Influence of Environmental Conditions on Secondary Metabolites in Medicinal Plants: A Literature Review

Poonam Pant,[a] Sudip Pandey,*[b] and Stefano Dall'Acqua*[c]

[a] Central Institute of Science and Technology, Kathmandu, Nepal
[b] Madan Bhandari University of Science and Technology, Lalitpur, Nepal, e-mail: sudip.pandey@mbustb.edu.np
[c] DSF Department of Pharmaceutical and Pharmacological Science, via Marzolo, University of Padova, 35121 Padova, Italy, e-mail: stefano.dallacqua@unipd.it

Medicinal plants, a source of different phytochemical compounds, are now subjected to a variety of environmental stresses during their growth and development. Different ecologically limiting factors including temperature, carbon dioxide, lighting, ozone, soil water, soil salinity and soil fertility has significant impact on medicinal plants' physiological and biochemical responses, as well as the secondary metabolic process. Secondary metabolites (SMs) are useful for assessing the quality of therapeutic ingredients and nowadays, these are used as important natural derived drugs such as immune suppressant, antibiotics, anti-diabetic, and anti-cancer. Plants have the ability to synthesize a variety of secondary metabolites to cope with the negative effects of stress. Here, we focus on how individual environmental variables influence the accumulation of plant secondary metabolites. A total of 48 articles were found to be relevant to the review topic during our systematic review. The review showed the influence of different environmental variables on SMs production and accumulation is complex suggesting the relationship are not only species-specific but also related to increases and decline in SMs by up to 50%. Therefore, this review improves our understanding of plant SMs ability to adapt to key environmental factors. This can aid in the efficient and long-term optimization of cultivation techniques under ambient environmental conditions in order to maximize the quality and quantity of SMs in plants.

Keywords: medicinal plants, environmental factors, secondary metabolites.

Introduction

Climate change is a serious threat that is afflicting many parts of the world with influence on plants survival, especially in some geographical areas. For example; in the case of Latin America, which accounts for one of the earth's largest concentration of biodiversity, the risk of biodiversity loss is expected to increase as a result of climate change.[1,2] In mountain regions, higher temperature leads to an upward shift of biotic zones and likely increase the frequency of forest fires.[3,4] Medicinal plant secondary metabolites (SMs) content is influenced by environmental factors including climate and ecologic issues, thus the possible changes to environmental conditions can raise issues for the production of some medicinal species. Furthermore, despite the large diffusion of synthetic and bio-ecological based drugs, plants are still one of the most significant sources of medicine and millions of people depend on herbal medicine for their cure and therapies.[5–7] Since ancient times, more than half of the world population depends on medicinal plants to cure different human ailments and is getting significant attention in global health.[8] There is an increasing demand from the occidental countries for new and 'natural' based remedies and products, with development of nutraceutical and growing of cosmetics. Many natural products are now searched

Supporting information for this article is available on the WWW under https://doi.org/10.1002/cbdv.202100345 for their claimed ability to reduce the risk of diseases and for healthy ageing.[9] Thus, different medicinal species have significant importance and different plant part (root, stem, leaves, flowers, fruits and seeds) can offer different SMs being a significant source of natural bioactive metabolites.

It is estimated that more than four billion people (80% of the world's population) living in developing countries rely on medicinal products as a source of healthcare and traditional medical practice.[10–12] According to World Health Organization (WHO), approximately 45,000 different plants in more than 21,000 species of plants are being used for medicinal purposes that can be verified by the Ayurveda.[13,14] Medicinal plants are good sources of chemical substances like terpenoids, phenols, steroids, flavonoids, tannins and aromatic compounds which are widely used in the pharmaceutical, cosmetics and food industry.[15] These chemical substances are commonly known as secondary plant metabolites (e.g., specialized products) which are not essential for the growth and development of the plant but are considered as defence compound to interact with its environment for adaptation.[16] There are over 2,140,000 secondary metabolites[17] and are divided into different groups consisting of 29,000 terpenoids, 12,000 alkaloids, 8,000 phenolics,[18] steroids, flavonoids, tannins, and more are in the process of identification. The demand for medicinal plants is profoundly increased in the recent decade due to enormous chemical diversity, and the

Professor Dr. Stefano Dall'Acqua works at Padova University involving in research and teaching within the Department of Pharmaceutical and Pharmacological Sciences. Graduated in Chemistry and Pharmaceutical Technology cum laude in 1998 at the University of Padova, PhD (2003) in Pharmaceutical Sciences at the same University defending a thesis titled "Bioactive compounds from Italian Plants". He worked in food, cosmetic and herbal medicine companies in years 2000–2005. He received several postdoc grants working in the chemistry of natural products. His research activity deal with the chemistry of bioactive natural products. The main topics are the isolation and structural determination of natural compounds with a high focus on 1D and 2D NMR and MS spectroscopy and the development of analytical methods for the determination of natural products in complex mixtures. Further research activity deals with in vivo absorption of natural products and in vivo and clinical effects of phytochemicals as well as a study of phytochemical effects by metabolomic approach. Author and co-author in more than 220 published articles.

Dr. Sudip Pandey holds double master degrees in Forestry and Natural Resource Management (Erasmus Mundus Programme, MEDfOR) with a scholarship from the European Union and the other in Environmental Science with specialization in mountain environment from Tribhuvan University, Nepal. He completed his doctoral degree in forest ecology (Professor Giai Petit) from the University of Padova, Italy in 2019. Dr Pandey is a consultant at Madan Bhandari University of Science and Technology (MBUST), Nepal. His research interests are climate change and its impacts on high altitude forest with the approach of dendroanatomy, forest inventory, park people conflict, forest ecology, human use of natural resources and phytochemical constituents of medicinal plants. He has published books, journal articles in reputed national and international journals.

Ms. Poonam Pant is a young pharmacist and emerging academic with expertise in pharmacology and clinical pharmacy. She is currently employed in the Department of Pharmacy as a lecturer in pharmacology at CiST college affiliated with Pokhara University, Nepal. Besides teaching her role in academics is to supervise or co-supervise bachelor as well as master students in their thesis. She holds a master degree in Pharmaceutical Care. Her research interest involved cancer, pharmacological interactions, essential oil composition and its antiproliferative activity.

opportunity to develop new products presenting few side effects and economic values.[19,20] Many studies have considered different classes of secondary metabolites as potential agents for the treatment or prevention of many serious diseases or syndromes like diabetes, tuberculosis, ulcers, asthma, cancer, Alzheimer's disease, and cardiovascular diseases, Parkinson's disease.[21–25]

Besides, the critical role of medicinal plants in different aspects of human lives, their growth and development are affected by environmental conditions like temperature variation, light intensity, elevated carbon dioxide, ultraviolet radiation, ozone, drought, salinity, and flood.[26–29] These environmental factors are important as each plant species needs special environmental conditions for growth. According to the Intergovernmental Panel of Climate Change (IPCC),[30] mean annual temperature is increasing faster to a rate of 0.06–0.1 °C/yr. with a CO_2 increase of 407.4 parts per million. Change in climatic conditions not only influences the normal behaviors of plants but also their physiology, ultimately affecting the secondary metabolites. Studies showed that some environmental factors like temperature,[31,32] elevated CO_2,[33–36] Ozone,[37,38] UV light,[39,40] drought[41,42] adversely affects the metabolites, growth and productivity in plants. However, these studies are in many cases sporadic and are still limited to fully understand the specific role of each environmental factor in SMs synthesis and accumulation. Furthermore, specific studies in medicinal plants are still lacking compared to commercial crops related to the food area. Medicinal species have a strong impact on the life of many people and entire populations with significant economic impact and value. Significant changes due to climate and ecological modifications can occur in the synthesis of secondary metabolites thus we can postulate that some medicinal species being a source of important active compound can be influenced by these factors in the production and accumulation of SMs, with relative problems for shortage, and for potential issues for industrial extraction and purification for the production of the medicinal product. In this regard, more research is needed on medicinal plants at the molecular level to better understand the specific role of each environmental parameter as they are potential sources of active molecules and compounds useful for the production of nutraceuticals.

In this study, we made a systematic review of the recent literature published in Google Scholar, PubMed and science direct to evaluate the influence of climatic parameters on secondary metabolites of medicinal plants. This review aims to enhance our understanding of the adaptability of plant SMs to key environmental factors. This can be of help in the optimization of cultivation techniques at ambient environmental conditions with maximization quality and quantity of SMs in plants efficiently and sustainably.

Results

The review was conducted in 48 articles with 10 articles published in 2015, 10 in 2016, 9 in 2017, 10 in 2018, 5 in 2019 and 4 in 2020. The articles were from 12 countries (China ($n=15$), Brazil ($n=5$), India ($n=5$), Iran ($n=8$), Canada ($n=1$), Saudi Arabia ($n=1$), Malaysia ($n=1$), Italy ($n=6$), Mexico ($n=1$), Australia ($n=1$), Germany ($n=3$) and Egypt ($n=1$)) analyzing the impacts of climate changes on secondary metabolites of medicinal plants found in the area (*Table 1*). The review was based on 34 different journals which are considered reputed in medicinal plant study.

Environmental parameters i.e., temperature ($n=6$), carbon dioxide ($n=9$), ozone ($n=5$), light intensity ($n=11$) and soil ($n=17$) were considered in the study (*Figure 1*). HPLC, GC/MS, NMR were the most prevalent instruments used for metabolites profiling. Leaves (51%), whole plants (17%), and roots (13%) were commonly used parts for assessing climatic effects. Though the percentage is quite low some researcher also used stem, shoot, seed, flower and fruits.

Both *in vitro* and *in vivo* methods were utilized in most of the plants to have comparative effects of climatic parameters on the quality and quantity of SMs. Articles considered in the review showed plants species was extensively used for curing different illness

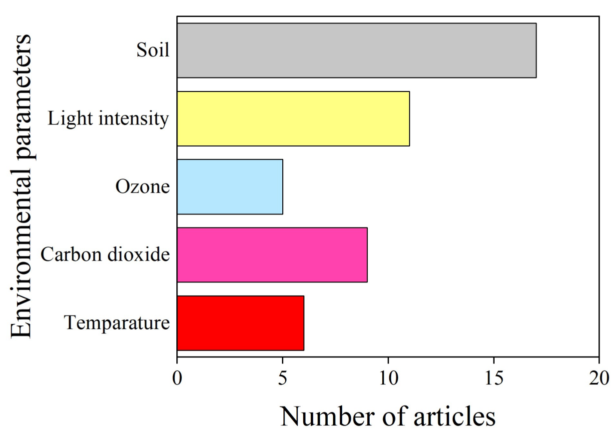

Figure 1. Environmental parameters considered in the study with the number of articles on assigned topics.

Table 1. Publications identified in the main databases (PubMed, Google Scholar and ScienceDirect) through systematic review.

Country	Plants	Parts used	Secondary metabolites	Environment factor	Concentration change	Ref.
Germany	*Duboisia myoporoides* R. Br.	Whole plant	Alkaloids	Temperature	Increase	[46]
China	*Salvia miltiorrhiza* Bunge	Roots	Tanshinone	Temperature	Increase	[47]
Brazil	*Tithonia diversifolia* (Hemsl.) A. Gray	Leaf, stems	Phenols	Temperature	Increase	[48]
China	*Camellia japonica* L.	Leaf	α-linolenic acid, Jasmonic acid (Fatty acid)	Low temperature	Increase	[49]
Iran	*Silybum marianum* (L.) Gaertn	Roots	Silymarin	Temperature	Decrease	[50]
China	*Dendrobium officinale* Kimura & Migo	Stems	Total Alkaloids and Total Flavonoid	Temperature	Decrease	[51]
India	*Hypericum perforatum* L.	Flowers and fruits	Hypericin	Elevated carbon dioxide [CO_2]	Decrease	[54]
Canada	*Arabidopsis thaliana* (L.) Heynh	Leaf	Glucosinolates	Elevated carbon dioxide [CO_2]	Decrease	[55]
China	*Paris polyphylla* var. *yunnanensis (Franch.)*	Rhizome	Saponins (Diosgenin and Pennogenin)	Elevated carbon dioxide [CO_2]	Increase	[56]
Iran	*Centella asiatica (L.) Urban*	Leaf	Flavonoid	Elevated carbon dioxide [CO_2]	Increase	[57]
Germany	*Stevia rebaudiana Bertoni*	Whole plant	Steviol Glycosides	Elevated carbon dioxide [CO_2]	Increase	[58]
Saudi Arabia	*Mentha piperita* L	Shoots	Flavonoids	Elevated carbon dioxide [CO_2]	Increase	[44]
Malaysia	*Hibiscus sabdariffa L.*	Calyx	Total Phenolic and Total Anthocyanins	Elevated carbon dioxide [CO_2]	Increase	[59]
India	*Valeriana jatamansi* Jones	Roots	Essential oil (patchouli alcohol, bornyl acetate, β-patchoulene, germacrene D)	Elevated carbon dioxide [CO_2]	Increase	[60]
Brazil	*Pfaffia glomerata* (Spreng.) Pedersen	Shoots	Saponins and Phytosteroids	Elevated carbon dioxide [CO_2]	Increase	[61]
Italy	*Hypericum perforatum* L.	Leaf	Total Phenols and Flavonoid	Elevated ozone	Increase	[66]
Italy	*Salvia officinalis* L.	Leaf	Phenols (Gallic acid, Caffeic acid, Rosmarinic acid)	Elevated ozone	Increase	[38]
Brazil	*Capsicum baccatum* L. var. Pendulum	Fruit	Capsaicin and Dihydrocapsaicin	Elevated ozone	Decrease	[37]
Italy	*Melissa officinalis* L.	Shoots	Total Carotenoids	Elevated ozone	Increase	[67]
Italy	*Melissa officinalis* L.	Shoots	Rosmarinic Acid	Elevated ozone	Increase	[68]
China	*Mahonia breviracema* Y.S. Wang & P.K. Hsiao	Leaf, stem and root	Alkaloids	Light intensity	Increase	[71]
China	*Mahonia bodinieri* Gagnep	Whole plant	Alkaloids	Light intensity	Increase	[72]
Mexico	*Flourensia cernua* DC.	Leaf	Total Phenolic	Light intensity	No effects	[73]
China	*Glechoma longituba* (Nakai) Kuprian	Leaf	Ursolic and Oleanolic acid	Light intensity	Decrease	[33]
Australia	*Centella asiatica (L.) Urban*	Whole plant	Phenols: Chlorogenic Acid	Full sunlight	Increase	[74]
China	*Erigeron breviscapus* (Vaniot) Hand. Mazz.	Leaf	Scutellarin (Flavonoids)	Sunlight	Increase	[75]
Brazil	*Hyptis marrubioides* Epling	Leaf	Rutin (Flavonoid)	Light intensity	Increase with white and blue light	[76]
China	*Chrysanthemum morifolium* Ramat	Flower	Phenols (Phenolic Acid)	Ultraviolet-B radiation	Increase	[77]
India	*Coleus forskohlii* Briquet	Leaf	Flavonoids and Phenolics	Ultraviolet-B radiation	Increase	[78]
China	*Prunella vulgaris* L. Spica	Whole plant	Total Flavonoids, Rosmarinic Acid, Caffeic Acid	Ultraviolet-B radiation	Increase	[39]
Brazil	*Kalanchoe pinnata* (Lam.)	Leaf	Phenolic Profile and Flavonoid Content	Ultraviolet-B radiation	Increase	[79]
China	*Scutellaria baicalensis* Georgi	Whole plant	Baicalin (Flavonoid)	Drought stress	Increase	[81]
Iran	*Glycyrrhiza glabra* L. (licorice)	Roots	Glycyrrhizin	Drought stress	Increase	[82]
India	*Ocimum tenuiflorum* L.	Leaf	Eugenol (Phenol)	Drought stress	Decrease	[83]
Egypt	*Mentha piperita* L.	Leaf	Phenol and Flavonoid	Drought stress	Decrease	[84]
China	*Catharanthus roseus* (L.) G. Don.	Leaf	Alkaloid	Drought stress	Increase	[85]
Iran	*Thymus vulgaris* L. and *Thymus kotschyanus* Boiss. & Hohen	Seed, leaf	Malic Acid and Succinic Acid, Trichloroacetic Acid	Drought stress	No effects	[86]
China	*Stellaria dichotoma* L. var. *lanceolata* Bunge	Leaves, roots	Total Saponins, Total Flavonoid	Drought stress	Increase	[87]
China	*Carthamus tinctorius* L.	Leaf	Flavonoids	Salinity stress	Increase	[89]
Iran	*Stevia rebaudiana* Bertoni	Leaf	Diterpene Glycosides	Salinity stress	Increase	[90]
Iran	*Plantago ovate* Forsk	Whole plant	Phenol	Salinity stress	Increase	[91]
Italy	*Brassica napus* var *oleifera* Del.	Seed	Total Phenolic, Non-Flavonoids, Tannins	Salinity stress	Increase	[92]
Iran	*Salvia macrosiphon* Boiss	Leaf	Total phenol	Salinity stress	Decrease	[93]
Germany	*Duboisia* species (*Duboisia myoporoides* R.Br. and *Duboisia leichhardtii* F. Muell)	Whole plant	Scopolamine (Alkaloid)	Fertility stress (nitrogen, calcium and potassium)	Decrease	[46]
Italy	*Lactuca sativa* L.	Leaf	Total Polyphenols	Fertility stress (nitrogen)	Increase	[94]
India	*Trigonella foenum-graecum* L.	Seed	Trigonelline (Alkaloid)	Fertility stress (phosphorous)	Increase	[95]

i.e., respiratory tract infection, stomach diseases, cancer, parkinsonism, depression etc. Most of the authors considered in the study were natural product expert with funding support from research institutes and government authorities. The biological analysis of plants used in the study showed the dominant of herbs and sub herbs. Most of the researcher raised concern on climatic issues in the context of medicinal plants and provide a necessary way for getting the better quality and quantity of SMs in medicinal plants which are useful in pharmaceutical industries, food beverages and cosmetic etc. This raised concern to many scientists to work further to have in-depth knowledge on it.

Discussion

The environmental factor is the major limiting factor for the survival and growth of medicinal plants. Studies showed plant of the same species grown in a different environment has a different concentration of a particular secondary metabolite.[16,43] This is because the plant has to produce a specified quantity and quality of SMs to counter the environmental stress. Thus, the study on each environmental factor is important to know the adaptability and availability of plant in a particular region.

Temperature Stress

Change in temperature affects plant growth and metabolic pathways involved in signalling, physiological regulation and defence responses.[44,45] Temperature as major weather variables can significantly influence the composition of SMs with disruption in photosynthesis activities to tolerate stressful condition. For example, vegetative development (node and leaf appearance rate) increases as temperature rise to species optimum level while cold temperature limit plant growth, leaf development and photosynthesis. Furthermore, we can also postulate those changes in season and the average temperature may in the future change the area of cultivation/growing of some species. For instance, the composition of alkaloids in *Duboisia myoporoides* R. Br. demonstrated a minor increase with temperature (4 °C).[46] Zhang et al.[47] indicated an increase in tanshinones accumulation in *Salvia miltiorrhiza* Bunge with an increase in temperature. Likewise, in *Tithonia diversifolia* A. Gary, there is an increase in phenolic compounds at 22 °C and a decrease afterwards.[48] *Camellia japonica* L. global gene regulation of unsaturated fatty acid and jasmonic biosynthesis pathways were deduced in the low temperature.[49] On contrary, high temperature reduce silymarin content in *Silybum marianum* L. roots showing SMs accumulation is a temperature-dependent process.[50] Also, Yuan et al.[51] observed the response of *Dendrobium officinal*e Kimura & Migo in three different cultivation modes namely, wild, bionic and greenhouse. The result showed polysaccharide, total alkaloid and total flavonoid was higher in wild followed by bionic and greenhouse. They found metabolites content decrease with the increase in temperature indicating it is a shade lover and too high temperature is detrimental for growth. This shows the influence of temperature on plant growth and SMs synthesis is not univocal indicating species-specific effects (*Table 1*).

CO_2 Stress

Carbon dioxide is considered a major greenhouse gas hampering the physiology of medicinal plants. Since the industrial revolution, the concentration of it is increasing rapidly from 270 parts per million (ppm) to 407.4 ppm.[52] Plant adapt to change in environment through metabolic plasticity, however, this affects the SMs which are the basis for their medicinal activity.[53] For example, *Hypericum perforatum* L. known for its use in moderate depression was treated with elevated CO_2 and found growth to be increased after 140 days compared to ambient conditions. In the same experiment, hypericin concentration significantly decreases by 22 % in elevated CO_2 (550 ± 50 μmol mol^{-1}) which further decrease to 19.30 % under combined effects of elevated CO_2 and temperature.[54] Similarly, phenological stages (bud and flower formation) were advanced by 4 days under 140 days of CO_2 enrichment as compared to ambient condition. A study conducted by Paudel et al.[55] in *Arabidopsis thaliana* (L.) Heynh found a distinct metabolite signature under elevated CO_2 with a lower concentration of defence compounds such as Glucosinolates. They suggest that changing atmospheric condition and nitrate fertilization may affect plant's ability to identify and cope with oxidative stress (e.g., insect damages). Atmospheric CO_2 level and nitrate fertilization play an important role in shaping the constitutive and wound-induced metabolic profile in Arabidopsis leaves. *Paris polyphylla* var. *yunnanensis*, a traditional Chinese medicinal plant showed stronger photosynthetic activity and higher content of bioactive compounds in western Yunnan than in cultivar from central Yunnan under elevated

CO_2. In western Yunnan, the growth rate increases higher at first and decrease with further CO_2 increase. On the contrary, in central Yunnan growth rate is lower at first and increase afterwards suggesting western Yunnan cultivars to be sensitive to atmospheric CO_2 concentration. Contents of bioactive compound diosgenin of western Yunnan cultivars increased under elevated CO_2 suggesting *Paris polyphylla* var. *yunnanensis* a potential candidate for industrial cultivation in a high CO_2 environment.[56]

A study on *Centella asiatica* (L.) urban used as medicinal herbs for its multiple therapeutic properties showed improved photosynthetic efficiency initially with a higher concentration of flavonoids under CO_2 levels at 400 and 800 $\mu mol\,mol^{-1}$. Furthermore, there was an increase in flavonoids concentration in the irradiated plants with rising CO_2 concentration from 400 to 800 $\mu mol\,mol^{-1}$ suggesting *C. asiatica* grown under CO_2 is more capable of overcoming the detrimental impacts of gamma radiation.[57] In *Stevia rebaudiana* Bertoni, elevated CO_2 increased Steviol glycosides content, a low-calorie sweetener.[58] It was observed that elevated CO_2 enhanced photosynthetic rate and water use efficiency thereby reducing the threat of oxidative stress.

A similar study conducted on *Mentha piperita* L. showed an increase in flavonoids concentration with the application of elevated CO_2 of 360 ppm and 620 ppm.[44] In a typical study on *Hibiscus sabdariffa* L. var. UKMR-2 elevated CO_2 levels from 400 to 800 $\mu mol\,mol^{-1}$ showed an increase in calyx yields and total phenol concentration.[59] Moreover, it is also predicted that an increase in CO_2 may result in greater height and higher fresh yields than ambient CO_2. Kaundal et al.[60] subjected *Valeriana jatamansi* Jones to elevated CO_2 levels (550 $\mu mol\,mol^{-1}$) and observed an increase in essential oil content by 17.7 %. Chemical constituents such as patchouli alcohol, bornyl acetate, β-patchoulene, germacrene D significantly increase at elevated CO_2 and decrease with increasing temperature compared to ambient condition. This finding indicates that elevated CO_2 in future could have positive effects while temperature has negative effects on essential oil composition in *V. jatamansi. In vitro* study performed with Brazilian ginseng (*Pfaffia glomerata* (Spreng.)) showed increased phytoecdysteroid 20-hydroxyecdysone under CO_2 enrichment (1000 $\mu L\ CO_2 L^{-1}$). This study was important in demonstrating the best culture conditions and increasing the development and production of 20-hydroxyecdysone in the species.[61] The overall trend in such finding showed the importance of secondary metabolites of medicinal plants with respects to CO_2 besides seasonal variation, time duration and nutrient availability. This can provide insight into the role of elevated CO_2 in altering the metabolic plasticity of medicinal plants providing appropriate conservatory practices in the long run.

Ozone Stress

Ozone is considered as a bio protector from ultraviolet radiations, however, at ground level, they affect both animals[62,63] and plants.[64,65] *Hypericum perforatum* L. (St. John's wort) showed an increment of total phenols and flavonoids (quercetin) with activation of peroxidase activity by ozone (110 ppb, 5 hrs.) confirming that ozone is an elicitor of bioactive secondary metabolites.[66] Similarly, at 24 h of exposure (110 ppb), the increase of quercetin was replaced by a raise of Kaempferol (another flavonol) while isoquercitrin and quercitrin remain unchanged. This suggests that ozone treatment can be considered to enhance the concentration of antioxidants phytochemical increasing the beneficial properties of medicinal plants. Similarly, a study on ecophysiological and antioxidant traits of *Salvia officinalis* L. under ozone stress (120 ± 13 ppb for 90 consecutive days) showed an increase in phenolic content; notably Gallic acid (2-fold increase), Caffeic acid (8-fold increase) and Rosmarinic acid (122 % increase on 60th day of treatment).[38] *Capsicum baccatum* L. var. Pendulum plants were studied by Brazilian scientist to check the effects of chronic ozone exposure, showing a decrease in capsaicin (50 %) and dihydrocapsaicin in ozone exposed pericarp.[37] Furthermore, capsaicin content was reduced in the seeds of the plant while no change was observed in dihydrocapsaicin as compared to control plants. Also, total carotenoid and phenolic content in the pericarp increased by 52.8 and 17 %, respectively. A study on *Melissa officinalis* L., a traditional medicinal plant with a large number of uses including dementia and anxiety showed an increase in total anthocyanins to a substantial extent along with phenolic and rosmarinic acid in plants subjected to ozone treatment (200 ppb, 3 h).[67,68] Literature search on ozone influence on quality of plants revealed many studies on edible crops while limited specifically related to medicinal plants. Thus, more studies with wide perspectives and plan are needed for depicting the role of this treatment as enhancer of production of secondary metabolites as well as to understand the role of increased oxidative stress conditions on the conservation and management of cultivated as well as spontaneous medicinal plants.

Light Stress

Light is essential for plant metabolism and life due to photosynthesis. Therefore, the survival of plants depends on their ability to sense different light spectra present in solar radiation.[69] Also, the light at different intensity impacts the levels of a broad range of secondary metabolites in the complex biochemical interaction.[69,70]

A study on plants of the genus *Mahonia* (*Mahonia bodinieri* (Gagnep.) Laferr and *Mahonia breviracema* Y.S. Wang & P.K. Hsiao) well-known traditional Chinese medicine used for the treatment of tuberculosis, dysentery, periodontitis, pharyngolaryngitis, eczema and wounds showed a higher yield of alkaloids under I_{50} (50% of sunlight) followed by I_{30} (30% of sunlight) than under I_{10} (10% of sunlight) and I_{100} (Full sunlight).[71,72] Therefore, I_{30} and I_{50} were beneficial for the synthesis and accumulation of SMs indicating noticeable effects of photoperiod and light intensity. Rarely, the opposite situation was also reported like in *Flourensia cernua* DC, a Mexican traditional medicine used to treat indigestion, respiratory tract infection, tuberculosis showed higher total phenolic compounds under partial shade than on fully irradiated conditions.[73] In some plants, the higher irradiance is helpful for plant growth and SMs production.[33] For example, the amount of scutellarin (flavone glycoside) in *Erigeron breviscapus* (Vaniot) Hand. Mazz. and chlorogenic acid (phenols) in *Centella asiatica* (L.) Urban was higher in sun-developed leaves than in shade-developed leaves.[74,75] Both these species (*E. breviscapus* and *C. asiatica*) are well-known for their medicinal applications and understanding the role of light can be crucial for selecting proper cultivation sites, as well as for the collection of spontaneous populations. *Hyptis marrubioides*, a medicinal plant used against gastrointestinal infection was cultured *in vitro* supporting the culture using different wavelengths (white, blue, green, red, and yellow).[76] They found white and blue lights promote flavonoids (Rutin) accumulation, whereas red light induces plant growth and increase leaf number and dry weights. This provides a theoretical basis for studies related to quality control of growth and production of secondary metabolism of *H. marrubioides.* Also, this aspect strongly shows the influence of different latitude and/or potential cultivation conditions on the medicinal plants. Furthermore, it opens a significant potential role in the cultivation of such species in indoor systems where light exposure can be controlled by specific lamps and systems.

Ultraviolet Radiation Stress

Ultraviolet (UV) light is also an important abiotic factor that stimulates the production of secondary metabolites, and hence many studies were conducted considering the factor. For example, the concentrations of flavonoids and phenolic acids increased in response to increasing UV–B radiation of *Chrysanthemum morifolium* Ramat.[77] Similarly, a study on *Coleus forskohlii* Briquet leaves by Takshak and Agrawal[78] showed an increase in flavonoids and phenolic content under UV–B stress. When the plant *Prunella vulgaris* L. spica was irradiated with UV–B, the production of total flavonoids, rosmarinic acid, caffeic acid was enhanced.[39] However, these contents differ in development stages and the best harvest stage was between budding and full-flowering for the best medicinal values. Nascimento et al.[79] found that the level of phenolic profile and flavonoids content in *Kalanchoe pinnata* (Lam.) leaves increase in response to UV–B irradiation. The content was further increased in the combination of white light providing higher diversity of phenolic compound and a larger amount of quercitrin. These studies highlighted the importance of photoperiod and light intensity for photosynthesis, growth and accumulation of secondary metabolites in medicinal plants. Thus, medicinal properties yield might be achieved by proper adjustment of light quality and quantity in future.

Soil Stress

Soil influence the growth and development of plants, and SMs accumulation is strongly dependent on soil water (drought stress), soil salinity and soil fertility.

Soil Water Stress (Drought Stress)

Drought stress is an important environmental factor affecting the content of secondary metabolites in plants. A larger number of studies manifested that plants exposed to drought stress accumulate a higher concentration of secondary metabolites than those cultivated under well-watered conditions.[80] In *Scutellaria baicalensis* Georgi, a traditional medicinal herb mild drought stress increase baicalin but decrease under severe stress.[81] This result demonstrates that an appropriate degree of drought stress may promote baicalin accumulation by stimulating the expression and activities of the key enzymes involved in the biosynthesis of the compound. Therefore, for appropriate protective enzyme activity and increase baicalin content, *Scutellaria baicalensis* soil moisture should be properly controlled. A similar study was conducted on *Glycyrrhiza glabra* L. at slight, moderate and intense drought.[82] It showed drought promoted the synthesis of glycyrrhizin with an increase in glycyrrhizin biosynthesis pathway. But, in extreme drought condition, there is a decrease in the amount of glycyrrhizin content compared to slight and moderate drought. Further, they found glycyrrhizin yields in response to drought differ between genotypes of plants. Rastogi et al.[83] found *Ocimum tenuiflorum* L. was able to sustain the severe drought for 30 days. They provide insight into transcriptomic changes so we can identify the putative genes of medicinal plants. Alhaithloul et al.[84] reported that in *Mentha piperita* L. and *Catharanthus roseus* (L.) G. Don. drought stress decreases total phenols, flavonoids and saponin content, however, the level of other SMs including tannins, terpenoids and alkaloids increased under stress in both plants. In contrast to this, Liu et al.[85] demonstrated an increased accumulation of alkaloids and the expression of genes regulating secondary metabolite accumulation in drought-stressed *Catharanthus roseus* (L.) G. Don. There was a study by Ashrafi et al.[86] on *Thymus vulgaris* L. (drought-sensitive) and *Thymus kotschyanus* Boiss. & Hohen (drought-tolerant species) under different drought condition. In both the plants, sugars, amino acids, and energy metabolism were significantly affected by drought stress thus, new technologies such as transcriptomics and proteomics could be helpful to understand in-depth knowledge on enhanced drought tolerance. Zhang et al.[87] showed the total saponin content increased at first and decreased afterwards in *Stellaria dichotoma* L. var. *lanceolata* Bge. Thus, moderate water stress was suitable for active ingredient accumulation which was affected by endogenous hormones and water status. These all studies revealed the concentration of SMs in plants significantly differ under different drought stress condition. However, there are still few researches on medicinal plants and need more studies.

Soil Salinity Stress

Salinity stress significantly affects the accumulation of secondary metabolites in plant tissues. Increased salt levels in soil also cause nutritional imbalances, hyperosmotic stress, and decrease photosynthesis, growth, and nutrient uptake in plants.[88] In the leaves of *Carthamus tinctorius* L., the flavonoids, which are an important curative component of the safflower leaves increased significantly under different NaCl concentration (50, 100 and 150 mM).[89] Another study in *Stevia rebaudiana* Bertoni under low level of NaCl concentration (30 mM) increased diterpene glycosides content (8.25 %) and further increment in NaCl concentration (90 mM) showed a decrease (4.2 %).[90] The concentration of phenol in *Plantago ovate* Forsk increase under different salinity stress (25, 50, 100, 200 and 300 mM NaCl).[91] Furthermore, increasing salinity (25, 50 100, 200 mM) can change the contents of total phenolics, non-flavonoids, tannins and phenolic acids in *Brassica napus* var *oleifera* Del. (rapeseed). In early sprout stage, total phenolic content increased by 35 % (up to 50 mM NaCl) and then decreased slightly. Similarly, non-flavonoids showed 30 % increment (25 mM NaCl) and total-tannins increased with increasing salt concentration up to 50 mM and remained in high concentration in 100 mM and 200 mM, while salinity did not give a clear effect on total-phenolic acids content.[92] Valifard et al.[93] reported that the content of total phenol in *Salvia macrosiphon* Boiss decreased with all the treatment of different NaCl concentration (0.4 (control), 2.3, 4.5 and 6.8 dSm^{-1}). The content of total phenolics was reduced by 2.6 times on increasing NaCl concentration (6.8 dSm^{-1}).

Soil Fertility Stress

For healthy growth, plants require many chemicals in the form of nutrients, fertilizers, growth regulators, and so on, including SMs biosynthesis. Chemical stress, on the other hand, occurs when these substances are not present in the proper concentration. Fertilizers (nitrogen, calcium, potassium) in soil can affect scopolamine biosynthesis of *Duboisia* species (*Duboisia myoporoides* R.Br. and *Duboisia leichhardtii* F. Muell). It showed that nitrogen and calcium negatively correlated with scopolamine content at increased levels above 1 mM. Similarly, potassium does not affects scopolamine production within the tested concentration range (0.05–4 mM).[46] *Lactuca sativa* L. is used in medicine for its anodyne, antispasmodic, digestive, diuretic, hypnotic, narcotic and sedative properties. Nitrogen-free fertilization allowed *Lactuca sativa* L. to obtain the highest total polyphenols content, as well as a favorable anti-radical activity.[94] Tariq et al.[95] found that with the application of foliar spray of irradiated sodium alginate alone or in combination with soil-applied phosphorus in Trigonella foenum-graecum L. (Fenugreek) increased the seed yield by 131.0 %, trigonelline content by 17.84 %, trigonelline yield by 174.0 %, seed alkaloid content by 32.98 % and seed alkaloid yield by 208.64 % over the control.

Conclusions

Medicinal plants are rich sources of chemically active constituents which are used as raw materials in nutraceutical, fragrance, dyes, cosmetic and pharmaceutical. The constituents commonly known as SMs are used for adaptation by the plant during stress condition such as temperature, carbon dioxide, ozone, light and soil. These abiotic stresses not only modify plant structurally and anatomically but also lead to fluctuation in their chemical constituents' quantities. Thus, knowledge of abiotic stress and SMs help to protect the plant sources which are under pressure due to excessive exploitation. In this review, we have provided evidence on how secondary metabolites show diversified and changeable responses to different environmental stresses. Interestingly, we have found individuals stress selectively alter the content of several SMs in plants. This clearly showed the synthesis of natural products can be altered by different abiotic stresses. However, further research is needed at a molecular level to understand the synergistic effect of multiple environmental factors using new techniques such as metabolomics, proteomics and transcriptomics for improvement of the growth and productivity of plants.

Experimental Section

General

We used a standard method called PRISMA for systematic literature review which includes resources eligibility and exclusion criteria, the systematic review process, and data abstraction and analysis.[96] The review was based on a systematic search of research articles from electronic databases: PubMed, Google Scholar and ScienceDirect (*Table 2*). We choose these databases as they cover about 256 disciplines with +300 minor disciplines (e.g., health science, life science, social science physical science) such as science, social science, arts and humanities. The advanced search tool in databases was used for rigorous search on assigned topics (*Appendix I*). All the searched articles were imported into Mendeley reference management software and duplicates were deleted.

Inclusion and Exclusion Criteria

All original articles collected from search engine were compiled. We selected only peer-reviewed articles which were based on climatic variation and its effects on secondary metabolites of the plant with specific methods and results. The printed and online journal registered on the journal website were included for study. Valuable sources of information from news articles, case studies, technical notes, educational materials were excluded as they are not peer-reviewed. To make a concise and systematic review we choose only articles published in English between January 1st 2015 to May 31st 2020. Studies that were related to study topics but not to climatic parameters were excluded (*Table 3*).

Table 2. Search manual used.

Search term used	PubMed	Google Scholar	ScienceDirect
Secondary metabolites and medicinal plants	59	85	17
Medicinal plants and climate change	6	39	3
Secondary metabolites and temperature	28	9	12
Total	93	133	32

Table 3. The inclusion and exclusion criteria.

Criterion	Eligibility	Exclusion
Literature type	Research articles (journal)	Review journal articles, book, book chapter, book series, conference article, report, proceeding
Language	English	Non-English
Timeline	Between 2015 and 2020	<2014
	Full-length article peer-reviewed journal	Published abstract

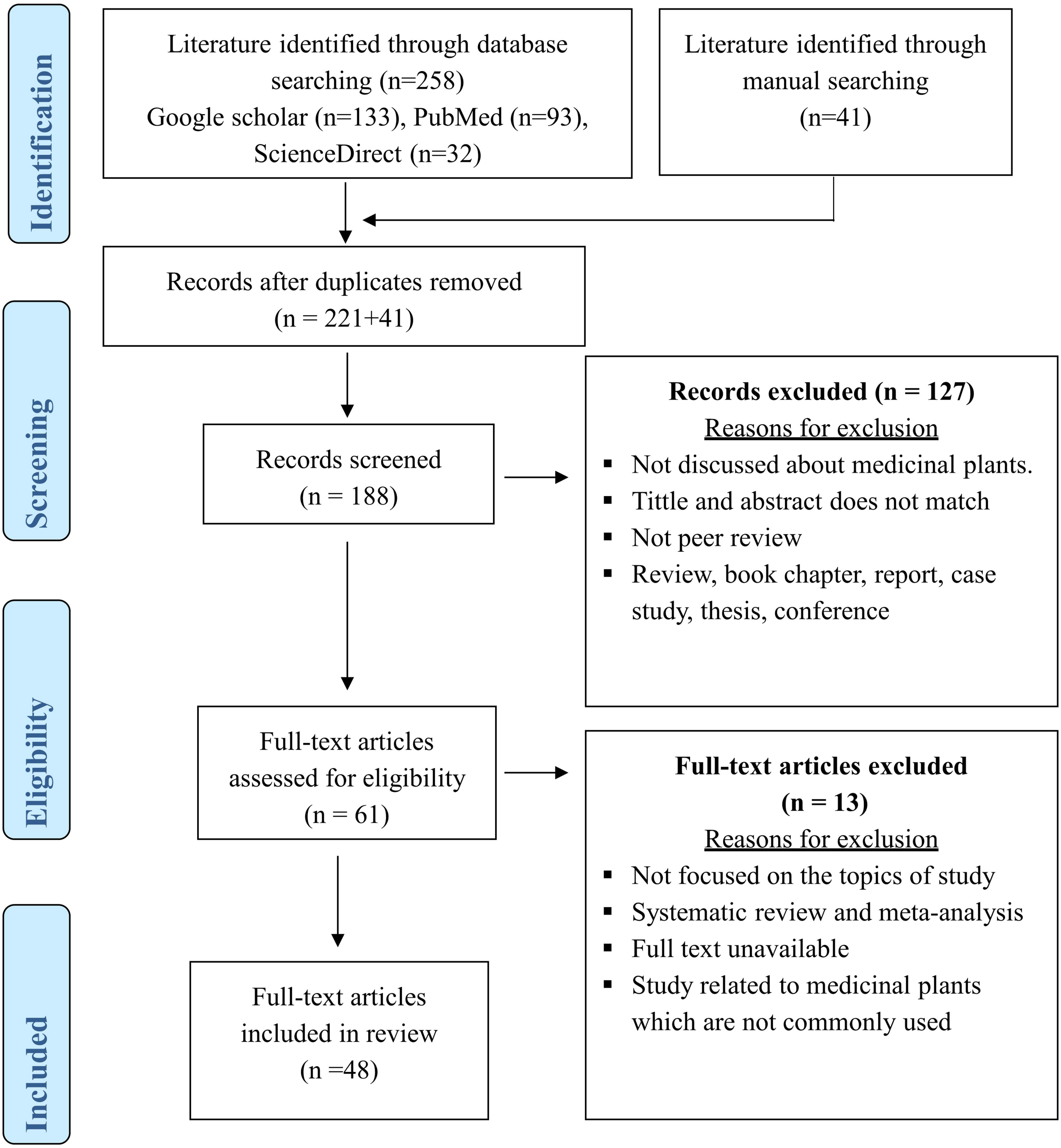

Figure 2. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the study.

Data Extraction

All the searched articles were imported into Mendeley reference management software (Mendeley Desktop version 1.19.4). A total of 258 articles were found through databases: 133 articles in Google scholars, 93 articles in PubMed and 32 articles in ScienceDirect. From this database, 37 duplicates articles were removed. The first screening of the articles consisted of reading the title and abstracts and 61 articles were identified as eligible for full text, and 48 research studies were finally included in the data analysis. This review process is based on the PRISMA flowchart (*Figure 2*). Moreover, the references of the analyzed articles were accessed to identify other studies that had not been found in the consulted databases. Thus, 41 new articles added, totaling 299 articles were used in the preparation of this review articles.

Information was extracted from all articles, including study methodology, aim and importance of secondary metabolites where available using data extraction form. Title, abstract and full-text reviews of the publication were done independently. The abstract, geographical location of the study, the methods used were manually screened based on the eligibility criteria and exclusions cross-checked by a member of the team. We also contacted the authors for additional information whenever necessary. Disagreement about any article's eligibility was resolved by consent.

Quality Assessment

A review of the articles was done to identify if there is any potential systematic error in data extraction. The quality assessment is based on different categories: rationale for research studies, reproducibility, robustness in methodology, and significance of the study. With this criterion, a table was made and an assessment was made with Yes, or No corresponding to each category. Agreement and disagreement of rating were discussed and final scores were given to the publication. Moreover, articles with the same plant species with similar climatic parameters were grouped into a single set and data extraction were made from those groups. We reviewed reference lists of some review articles with similar heading to assess articles of our interest.

Acknowledgements

The study was supported by Madan Bhandari University of Science and Technology Board (MBUSTB), Lalitpur, Nepal. Open Access Funding provided by Universita degli Studi di Padova within the CRUI-CARE Agreement.

Author Contribution Statement

Sudip Pandey conceived and designed the manuscript. Sudip Pandey and Poonam Pant wrote the manuscript and contributed equally. Stefano Dall'Acqua revised and proofread the manuscript.

References

[1] A. Boit, B. Sakschewski, L. Boysen, A. Cano-Crespo, J. Clement, N. Garcia-alaniz, K. Kok, M. Kolb, F. Langerwisch, A. Rammig, R. Sachse, M. van Eupen, W. von Bloh, D. Clara Zemp, K. Thonicke, 'Large-scale impact of climate change vs. land-use change on future biome shifts in Latin America', *Glob. Chang. Biol.* **2016**, *22*, 3689–3701.

[2] B. Locatelli, V. Evans, A. Wardell, A. Andrade, R. Vignola, 'Forests and climate change in latin America: Linking adaptation and mitigation', *Forestry* **2011**, *2*, 431–450.

[3] S. Hoffmann, S. D. H. Irl, C. Beierkuhnlein, 'Predicted climate shifts within terrestrial protected areas worldwide', *Nat. Commun.* **2019**, *10*, 1–10.

[4] Y. Telwala, B. W. Brook, K. Manish, M. K. Pandit, 'Climate-Induced Elevational Range Shifts and Increase in Plant Species Richness in a Himalayan Biodiversity Epicenter', *PLoS One* **2013**, *8*, 57103.

[5] G. M. Cragg, D. J. Newman, 'Natural products: A continuing source of novel drug leads', *Biochim. Biophys. Acta* **2013**, *1830*, 3670–3695.

[6] M. Rafieian-Kopaei, R. D. E. Sewell, 'The history and ups and downs of herbal medicines usage', *J. HerbMed Pharmacol.* **2014**, *3*, 1–3.

[7] D. S. Fabricant, N. R. Farnsworth, 'The value of plants used in traditional medicine for drug discovery', *Environ. Health Perspect.* **2001**, *109*, 69–75.

[8] N. I. Mongalo, L. J. McGaw, T. V. Segapelo, J. F. Finnie, J. Van Staden, 'Ethnobotany, phytochemistry, toxicology and pharmacological properties of *Terminalia sericea* Burch. ex DC. (Combretaceae) – A review', *J. Ethnopharmacol.* **2016**, *194*, 789–802.

[9] D. J. Newman, G. M. Cragg, 'Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019', *J. Nat. Prod.* **2020**, *83*, 770–803.

[10] G. Bodeker, G. Burford, 'Traditional, complementary and alternative medicine: Policy and public health perspectives', *Int. J. Health Care Qual. Assur.* **2006**, *9*, 1–454.

[11] M. Ekor, 'The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety', *Front. Pharmacol.* **2014**, *4*.

[12] W. M. Bandaranayake, in *Mod. Phytomedicine Turn. Med. Plants into Drugs* (Eds.: I. Ahmad, F. Aqil, M. Owais), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2006**, pp. 25–57.

[13] D. J. Taur, R. Y. Patil, 'Some medicinal plants with anti-asthmatic potential: A current status', *Asian Pac. J. Trop. Med.* **2011**, *1*, 413–418.

[14] World Health Organization, WHO Global Report on Traditional and Complementary Medicine, **2019**.

[15] T. Efferth, H. J. Greten, 'The European directive on traditional herbal medicinal products: Friend or foe for plant-based therapies?', *J. Chin. Integr. Med.* **2012**, *10*, 357–361.

[16] A. Ramakrishna, G. A. Ravishankar, 'Influence of abiotic stress signals on secondary metabolites in plants', *Plant Signaling Behav.* **2011**, *6*, 1720–1731.

[17] D. Thirumurugan, A. Cholarajan, S. S. S. Raja, R. Vijayakumar, in *Second. Metab. - Sources Appl.* (Ed.: R. Vijayakumar), InTech, **2018**.

[18] P. Kumar, P. Sharma, V. Kumar, M. Markandeshwar, in *Ind. Biotechnol. Plant Syst. Resour. Prod.* (Eds.: M. Yadav, V. Kumar, N. Sehrawat), De Gruyter, **2019**, pp. 89–103.
[19] R. Verpoorte, J. Memelink, 'Engineering secondary metabolite production in plants', *Curr. Opin. Biotechnol.* **2002**, *13*, 181–187.
[20] K. Anand, C. Tiloke, P. Naidoo, A. A. Chuturgoon, 'Phytonanotherapy for management of diabetes using green synthesis nanoparticles', *J. Photochem. Photobiol. B* **2017**, *173*, 626–639.
[21] A. Crozier, I. B. Jaganath, M. N. Clifford, 'Dietary phenolics: Chemistry, bioavailability and effects on health', *Nat. Prod. Rep.* **2009**, *26*, 1001–1043.
[22] K. Davies, R. Espley, 'Opportunities and challenges for metabolic engineering of secondary metabolite pathways for improved human health characters in fruit and vegetable crops', *J. Crop Hortic. Sci. (New Zeal.)* **2013**, *41*, 154–177.
[23] J. Fang, H. Nakamura, H. Maeda, 'The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect', *Adv. Drug Delivery Rev.* **2011**, *63*, 136–151.
[24] P. E. Miller, D. C. Snyder, 'Phytochemicals and Cancer Risk', *Nutr. Clin. Pract.* **2012**, *27*, 599–612.
[25] A. Basu, V. Imrhan, 'Tomatoes versus lycopene in oxidative stress and carcinogenesis: Conclusions from clinical trials', *Eur. J. Clin. Nutr.* **2007**, *61*, 295–303.
[26] Y. Li, D. Kong, Y. Fu, M. R. Sussman, H. Wu, 'The effect of developmental and environmental factors on secondary metabolites in medicinal plants', *Plant Physiol. Biochem.* **2020**, *148*, 80–89.
[27] S. R. Imadi, A. G. Kazi, A. Hashem, E. F. Abd-Allah, A. A. Alqarawi, P. Ahmad, in *Plant-Environment Interact. Responses Approaches to Mitigate Stress* (Eds.: M. Azooz, P. Ahmad), John Wiley & Sons, Ltd, Chichester, UK, **2015**, pp. 300–310.
[28] A. Gupta, P. P. Singh, P. Singh, K. Singh, A. V. Singh, S. K. Singh, A. Kumar, in *Clim. Chang. Agric. Ecosyst. Curr. Challenges Adapt.* (Eds.: K. Choudhary, A. Kumar, A. Singh), Elsevier, 2019, pp. 181–209.
[29] M. Elena, K. Katarína, V. Ivana, K. Zuzana, in *Handb. Plant Crop Stress* (Ed.: M. Pessarakli), CRC Press, **2020**, pp. 713–753.
[30] IPCC, Climate Change 2014: Synthesis Report. Contribution of Working Groups I, II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change, The Intergovernmental Panel on Climate Change, Geneva, Switzerland, **2014**.
[31] B. Singh, R. A. Sharma, in *Second. Metab. Med. Plants*, Wiley, **2020**, pp. 1470–1472.
[32] A. M. Shohael, M. B. Ali, K. W. Yu, E. J. Hahn, K. Y. Paek, 'Effect of temperature on secondary metabolites production and antioxidant enzyme activities in Eleutherococcus senticosus somatic embryos', *Plant Cell Tissue Organ Cult.* **2006**, *85*, 219–228.
[33] L. X. Zhang, Q. S. Guo, Q. S. Chang, Z. B. Zhu, L. Liu, Y. H. Chen, 'Chloroplast ultrastructure, photosynthesis and accumulation of secondary metabolites in *Glechoma longituba* in response to irradiance', *Photosynthetica* **2015**, *53*, 144–153.
[34] A. Ghasemzadeh, H. Z. E. Jaafar, A. Rahmat, 'Elevated Carbon Dioxide Increases Contents of Flavonoids and Phenolic Compounds, and Antioxidant Activities in Malaysian Young Ginger (*Zingiber officinale* Roscoe.) Varieties', *Molecules* **2010**, *15*, 7907–7922.
[35] L. H. Ziska, S. Panicker, H. L. Wojno, 'Recent and projected increases in atmospheric carbon dioxide and the potential impacts on growth and alkaloid production in wild poppy (*Papaver setigerum* DC.)', *Clim. Change* **2008**, *91*, 395–403.
[36] M. H. Ibrahim, H. Z. E. Jaafar, 'Impact of elevated carbon dioxide on primary, secondary metabolites and antioxidant responses of *Eleais guineensis* jacq. (oil palm) seedlings', *Molecules* **2012**, *17*, 5195–5211.
[37] R. C. Bortolin, F. F. Caregnato, A. M. Divan Junior, A. Zanotto-Filho, K. S. Moresco, A. de Oliveira Rios, A. de Oliveira Salvi, C. F. Ortmann, P. de Carvalho, F. H. Reginatto, D. P. Gelain, J. C. Fonseca Moreira, 'Chronic ozone exposure alters the secondary metabolite profile, antioxidant potential, anti-inflammatory property, and quality of red pepper fruit from *Capsicum baccatum*', *Ecotoxicol. Environ. Saf.* **2016**, *129*, 16–24.
[38] E. Pellegrini, A. Francini, G. Lorenzini, C. Nali, 'Ecophysiological and antioxidant traits of *Salvia officinalis* under ozone stress', *Environ. Sci. Pollut. Res. Int.* **2015**, *22*, 13083–13093.
[39] Y. Chen, X. Zhang, Q. Guo, L. Liu, C. Li, L. Cao, Q. Qin, M. Zhao, W. Wang, 'Effects of UV–B Radiation on the Content of Bioactive Components and the Antioxidant Activity of *Prunella vulgaris* L. Spica during Development', *Molecules* **2018**, *23*.
[40] S. Takshak, S. B. Agrawal, 'The role of supplemental ultraviolet-B radiation in altering the metabolite profile, essential oil content and composition, and free radical scavenging activities of *Coleus forskohlii*, an indigenous medicinal plant', *Environ. Sci. Pollut. Res. Int.* **2016**, *23*, 7324–7337.
[41] M. R. Amirjani, 'Effects of drought stress on the alkaloid contents and growth parameters of *Catharanthus roseus*', *J. Agric. Biol. Sci.* **2013**, *8*, 745–750.
[42] H. Liu, X. Wang, D. Wang, Z. Zou, Z. Liang, 'Effect of drought stress on growth and accumulation of active constituents in *Salvia miltiorrhiza* Bunge', *Ind. Crops Prod.* **2011**, *33*, 84–88.
[43] J. Radušienė, B. Karpavičienė, Ž. Stanius, 'Effect of External and Internal Factors on Secondary Metabolites Accumulation in St. John's Worth', *Bot. Lith.* **2013**, *18*, 101–108.
[44] S. Al Jaouni, A. M. Saleh, M. A. M. Wadaan, W. N. Hozzein, S. Selim, H. AbdElgawad, 'Elevated CO_2 induces a global metabolic change in basil (*Ocimum basilicum* L.) and peppermint (*Mentha piperita* L.) and improves their biological activity', *J. Plant Physiol.* **2018**, *224–225*, 121–131.
[45] S. Pandey, M. Carrer, D. Castagneri, G. Petit, 'Xylem anatomical responses to climate variability in Himalayan birch trees at one of the world's highest forest limit', *Perspect. Plant Ecol. Evol. Syst.* **2018**, *33*, 34–41.
[46] S. F. Ullrich, A. Rothauer, H. Hagels, O. Kayser, 'Influence of Light, Temperature, and Macronutrients on Growth and Scopolamine Biosynthesis in Duboisia species', *Planta Med.* **2017**, *83*, 937–945.
[47] C. Zhang, D. Yang, Z. Liang, J. Liu, K. Yan, Y. Zhu, S. Yang, 'Climatic factors control the geospatial distribution of

active ingredients in *Salvia miltiorrhiza* Bunge in China', *Sci. Rep.* **2019**, *9*, 1–11.
[48] B. L. Sampaio, R. Edrada-Ebel, F. B. Da Costa, 'Effect of the environment on the secondary metabolic profile of *Tithonia diversifolia*: a model for environmental metabolomics of plants', *Sci. Rep.* **2016**, *6*, 1–11.
[49] Q. Li, S. Lei, K. Du, L. Li, X. Pang, Z. Wang, M. Wei, S. Fu, L. Hu, L. Xu, 'RNA-seq based transcriptomic analysis uncovers α-linolenic acid and jasmonic acid biosynthesis pathways respond to cold acclimation in *Camellia japonica*', *Sci. Rep.* **2016**, *6*.
[50] S. Rahimi, T. Hasanloo, 'The effect of temperature and pH on biomass and bioactive compounds production in *Silybum marianum* hairy root cultures', *Res. J. Pharmacogn.* **2016**, *3*, 53–59.
[51] Y. Yuan, X. Tang, Z. Jia, C. Li, J. Ma, J. Zhang, 'The effects of ecological factors on the main medicinal components of *Dendrobium officinale* under different cultivation modes', *Forestry* **2020**, *11*, 94.
[52] World Meteorological Organization and Global Atmosphere Watch, *WMO Greenhouse Gas Bulletin* (*GHG Bulletin*) – *No. 15*, WMO, Geneva, **2019**.
[53] L. Yang, K. S. Wen, X. Ruan, Y. X. Zhao, F. Wei, Q. Wang, 'Response of plant secondary metabolites to environmental factors', *Molecules* **2018**, *23*, 762.
[54] S. Sharma, S. Walia, S. Rathore, P. Kumar, R. Kumar, 'Combined effect of elevated CO_2 and temperature on growth, biomass and secondary metabolite of *Hypericum perforatum* L. in a western Himalayan region', *J. Appl. Res. Med. Arom. Plants* **2020**, *16*.
[55] J. R. Paudel, A. Amirizian, S. Krosse, J. Giddings, S. A. A. Ismail, J. Xia, J. B. Gloer, N. M. van Dam, J. C. Bede, 'Effect of atmospheric carbon dioxide levels and nitrate fertilization on glucosinolate biosynthesis in mechanically damaged *Arabidopsis* plants', *BMC Plant Biol.* **2016**, *16*.
[56] Q. Qiang, Y. Gao, B. Yu, M. Wang, W. Ni, S. Li, T. Zhang, W. Li, L. Lin, 'Elevated CO_2 enhances growth and differentially affects saponin content in *Paris polyphylla* var. *yunnanensis*', *Ind. Crops Prod.* **2020**, *147*, 112124.
[57] S. Siavash Moghaddam, R. Ibrahim, C. A. Damalas, S. A. Noorhosseini, 'Effects of Gamma Stress and Carbon Dioxide on Eight Bioactive Flavonoids and Photosynthetic Efficiency in *Centella asiatica*', *J. Plant Growth Regul.* **2017**, *36*, 957–969.
[58] S. Hussin, N. Geissler, M. M. M. El-Far, H. W. Koyro, 'Effects of salinity and short-term elevated atmospheric CO_2 on the chemical equilibrium between CO_2 fixation and photosynthetic electron transport of *Stevia rebaudiana* Bertoni', *Plant Physiol. Biochem.* **2017**, *118*, 178–186.
[59] S. A. M. Ali, C. R. C. M. Zain, J. Latip, 'Influence of elevated CO_2 on the growth and phenolic constituents production in *Hibiscus sabdariffa* var. UKMR-2', *J. Teknol.* **2019**, *81*, 109–118.
[60] M. Kaundal, V. Bhatt, R. Kumar, 'Elevated CO_2 and Temperature Effect on Essential Oil Content and Composition of *Valeriana jatamansi* Jones. with Organic Manure Application in a Western Himalayan Region', *J. Essent. Oil-Bear. Plants* **2018**, *21*, 1041–1050.
[61] P. R. B. Ferreira, A. C. F. da Cruz, D. S. Batista, L. A. Nery, I. G. Andrade, D. I. Rocha, S. H. S. Felipe, A. D. Koehler, A. Nunes-Nesi, W. C. Otoni, 'CO_2 enrichment and supporting material impact the primary metabolism and 20-hydroxyecdysone levels in Brazilian ginseng grown under photoautotrophy', *Plant Cell Tissue Organ Cult.* **2019**, *139*, 77–89.
[62] J. J. Zhang, Y. Wei, Z. Fang, 'Ozone pollution: A major health hazard worldwide', *Front. Immunol.* **2019**, *10*, 2518.
[63] L. S. Jaffe, 'The Biological Effects of Ozone on Man and Animals', *Am. Ind. Hyg. Assoc. J.* **1967**, *28*, 267–277.
[64] N. E. Grulke, R. L. Heath, 'Ozone effects on plants in natural ecosystems', *Plant Biol.* **2020**, *22*, 12–37.
[65] B. S. Felzer, T. Cronin, J. M. Reilly, J. M. Melillo, X. Wang, 'Impacts of ozone on trees and crops', *Comptes Rendus – Geosci.* **2007**, *339*, 784–798.
[66] E. Pellegrini, A. Campanella, L. Cotrozzi, M. Tonelli, C. Nali, G. Lorenzini, 'Ozone primes changes in phytochemical parameters in the medicinal herb *Hypericum perforatum* (St. John's wort)', *Ind. Crops Prod.* **2018**, *126*, 119–128.
[67] F. D'Angiolilloa, M. Tonellia, E. Pellegrini, C. Nalia, G. Lorenziniab, L. Pistellibc, L. Pistelliab, 'Can ozone alter the terpenoid composition and membrane integrity of in vitro *Melissa officinalis* shoots?', *Nat. Prod. Commun.* **2015**, *10*, 1055–1058.
[68] M. Tonelli, E. Pellegrini, F. D'Angiolillo, M. Petersen, C. Nali, L. Pistelli, G. Lorenzini, 'Ozone-elicited secondary metabolites in shoot cultures of *Melissa officinalis* L.', *Plant Cell Tissue Organ Cult.* **2015**, *120*, 617–629.
[69] K. Kazan, J. M. Manners, 'The interplay between light and jasmonate signalling during defence and development', *J. Exp. Bot.* **2011**, *62*, 4087–4100.
[70] J. Rozema, J. Van De Staaij, L. O. Björn, M. Caldwell, 'UV–B as an environmental factor in plant life: Stress and regulation', *Trends Ecol. Evol.* **1997**, *12*, 22–28.
[71] Y. Li, D. Kong, H. L. Liang, H. Wu, 'Alkaloid content and essential oil composition of *Mahonia breviracema* cultivated under different light environments', *J. Appl. Bot. Food Qual.* **2018**, *91*, 171–179.
[72] D. X. Kong, Y. Q. Li, M. L. Wang, M. Bai, R. Zou, H. Tang, H. Wu, 'Effects of light intensity on leaf photosynthetic characteristics, chloroplast structure, and alkaloid content of *Mahonia bodinieri* (Gagnep.) Laferr.', *Acta Physiol. Plant.* **2016**, *38*, 1–15.
[73] R. E. Estell, E. L. Fredrickson, D. K. James, 'Effect of light intensity and wavelength on concentration of plant secondary metabolites in the leaves of *Flourensia cernua*', *Biochem. Syst. Ecol.* **2016**, *65*, 108–114.
[74] A. Alqahtani, W. Tongkao-On, K. M. Li, V. Razmovski-Naumovski, K. Chan, G. Q. Li, 'Seasonal Variation of Triterpenes and Phenolic Compounds in Australian *Centella asiatica* (L.) Urb', *Phytochem. Anal.* **2015**, *26*, 436–443.
[75] R. Zhou, W. H. Su, G. F. Zhang, Y. N. Zhang, X. R. Guo, 'Relationship between flavonoids and photoprotection in shade-developed *Erigeron breviscapus* transferred to sunlight', *Photosynthetica* **2016**, *54*, 201–209.
[76] R. C. N. Pedroso, N. A. A. Branquinho, A. C. B. A. M. Hara, A. C. Costa, F. G. Silva, L. P. Pimenta, M. L. A. Silva, W. R. Cunha, P. M. Pauletti, A. H. Januario, 'Impact of light quality on flavonoid production and growth of *Hyptis marrubioides* seedlings cultivated in vitro', *Braz. J. Pharmacogn.* **2017**, *27*, 466–470.
[77] C. H. Ma, J. Z. Chu, X. F. Shi, C. Q. Liu, X. Q. Yao, 'Effects of enhanced UV–B radiation on the nutritional and active ingredient contents during the floral development of

medicinal chrysanthemum', *J. Photochem. Photobiol. B* **2016**, *158*, 228–234.

[78] S. Takshak, S. B. Agrawal, 'Defence strategies adopted by the medicinal plant *Coleus forskohlii* against supplemental ultraviolet-B radiation: Augmentation of secondary metabolites and antioxidants', *Plant Physiol. Biochem.* **2015**, *97*, 124–138.

[79] L. B. D. S. Nascimento, M. V. Leal-Costa, E. A. Menezes, V. R. Lopes, M. F. Muzitano, S. S. Costa, E. S. Tavares, 'Ultraviolet-B radiation effects on phenolic profile and flavonoid content of *Kalanchoe pinnata*', *J. Photochem. Photobiol. B* **2015**, *148*, 73–81.

[80] M. Kleinwächter, D. Selmar, 'New insights explain that drought stress enhances the quality of spice and medicinal plants: potential applications', *Agron. Sustainable Dev.* **2015**, *35*, 121–131.

[81] L. Cheng, M. Han, L. min Yang, Y. Li, Z. Sun, T. Zhang, 'Changes in the physiological characteristics and baicalin biosynthesis metabolism of *Scutellaria baicalensis* Georgi under drought stress', *Ind. Crops Prod.* **2018**, *122*, 473–482.

[82] M. S. Hosseini, D. Samsampour, M. Ebrahimi, J. Abadía, M. Khanahmadi, 'Effect of drought stress on growth parameters, osmolyte contents, antioxidant enzymes and glycyrrhizin synthesis in licorice (*Glycyrrhiza glabra* L.) grown in the field', *Phytochemistry* **2018**, *156*, 124–134.

[83] S. Rastogi, S. Shah, R. Kumar, D. Vashisth, M. Q. Akhtar, A. Kumar, U. N. Dwivedi, A. K. Shasany, '*Ocimum* metabolomics in response to abiotic stresses: Cold, flood, drought and salinity', *PLoS One* **2019**, *14*, 0210903.

[84] H. A. Alhaithloul, M. H. Soliman, K. L. Ameta, M. A. El-Esawi, A. Elkelish, 'Changes in ecophysiology, osmolytes, and secondary metabolites of the medicinal plants of *Mentha piperita* and *Catharanthus roseus* subjected to drought and heat stress', *Biomol. Eng.* **2020**, *10*.

[85] Y. Liu, Q. Meng, X. Duan, Z. Zhang, D. Li, 'Effects of PEG-induced drought stress on regulation of indole alkaloid biosynthesis in *Catharanthus roseus*', *J. Plant Interact.* **2017**, *12*, 87–91.

[86] M. Ashrafi, M. R. Azimi-Moqadam, P. Moradi, E. Mohseni-Fard, F. Shekari, M. Kompany-Zareh, 'Effect of drought stress on metabolite adjustments in drought tolerant and sensitive thyme', *Plant Physiol. Biochem.* **2018**, *132*, 391–399.

[87] W. Zhang, Z. Cao, Z. Xie, D. Lang, L. Zhou, Y. Chu, Q. Zhao, X. Zhang, Y. Zhao, 'Effect of water stress on roots biomass and secondary metabolites in the medicinal plant *Stellaria dichotoma* L. *var. lanceolata* Bge', *Sci. Hortic.* **2017**, *224*, 280–285.

[88] A. Banerjee, A. Roychoudhury, in *Med. Plants Environ. Challenges*, Springer International Publishing, **2017**, pp. 177–188.

[89] Z. Gengmao, H. Yu, S. Xing, L. Shihui, S. Quanmei, W. Changhai, 'Salinity stress increases secondary metabolites and enzyme activity in safflower', *Ind. Crops Prod.* **2015**, *64*, 175–181.

[90] M. Aghighi Shahverdi, H. Omidi, S. J. Tabatabaei, 'Stevia (*Stevia rebaudiana* Bertoni) responses to NaCl stress: Growth, photosynthetic pigments, diterpene glycosides and ion content in root and shoot', *J. Saudi Soc. Agric. Sci.* **2019**, *18*, 355–360.

[91] N. Verma, S. Shukla, 'Impact of various factors responsible for fluctuation in plant secondary metabolites', *J. Appl. Res. Med. Arom. Plants* **2015**, *2*, 105–113.

[92] B. Falcinelli, V. Sileoni, O. Marconi, G. Perretti, M. Quinet, S. Lutts, P. Benincasa, 'Germination under moderate salinity increases phenolic content and antioxidant activity in rapeseed (*Brassica napus* var *oleifera* Del.) Sprouts', *Molecules* **2017**, *22*, 1377.

[93] M. Valifard, S. Mohsenzadeh, B. Kholdebarin, 'Salinity effects on phenolic content and antioxidant activity of *Salvia macrosiphon*', *Iran. J. Sci. Technol. Trans. A Sci.* **2017**, *41*, 295–300.

[94] A. Galieni, C. Di Mattia, M. De Gregorio, S. Speca, D. Mastrocola, M. Pisante, F. Stagnari, 'Effects of nutrient deficiency and abiotic environmental stresses on yield, phenolic compounds and antiradical activity in lettuce (*Lactuca sativa* L.)', *Sci. Hortic.* **2015**, *187*, 93–101.

[95] T. A. Dar, M. Uddin, M. M. A. Khan, A. Ali, L. Varshney, 'Modulation of alkaloid content, growth and productivity of *Trigonella foenum-graecum* L. using irradiated sodium alginate in combination with soil applied phosphorus', *J. Appl. Res. Med. Arom. Plants* **2016**, *3*, 200–210.

[96] A. Liberati, D. G. Altman, J. Tetzlaff, C. Mulrow, P. C. Gøtzsche, J. P. A. Ioannidis, M. Clarke, P. J. Devereaux, J. Kleijnen, D. Moher, 'The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and Elaboration', *PLoS Med.* **2009**, *6*.

Received May 13, 2021
Accepted September 16, 2021

