Chapter 4

Controlled Environment Production of Medicinal and Aromatic Plants

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Controlled environment (CE) technology enables the production of plants and their products inside structures such as greenhouses, growth chambers, and indoor plant factories. Growth conditions are managed to optimize the concentration of high value phytochemicals, maximize yields, and minimize microbial and insect contamination on a year round basis. CE technology removes the geographical constraints to production by enabling environmental (temperature, photoperiod, light quality, CO_2) and cultural (rooting media, nutrient composition, irrigation) factors to be managed and replicated anywhere in the world. CE technology has potential to increase availability, improve quality, and reduce over-harvesting pressures of medicinal and aromatic plants (MAPs) supplying the commercial market. Although CE is widely used for the production of vegetables and ornamental species, there is limited published data on growth, production, and chemistry of MAPs in CE. This article provides an overview of research conducted on production of MAPs in CE, provides examples of potential CE's to increase yield and quality, and suggests areas for future development.

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Introduction

It's estimated that up to 80% of the world's population use traditional herbal medicine as first, and often only, source of medicine. MAPs are botanical raw materials where their primary use is for therapeutic, aromatic and culinary purposes. They are components of medicinal production, additives to foods, and medicinal products (*1*). They are available as fresh or dried material, processed to essential oils, or processed to form extracts (*2*). These raw materials are used in a large number of products as constituents in prescription and over the counter drugs (*3*).

Although difficult to establish with any level of precision, it's been estimated that the global market value was $32.9 billion in 2013, up from $19.5 billion in 2009, an impressive 11.0% annual growth rate (*4*). Retail sales of herbal supplements in the US were estimated to be at least $6.4 billion in 2014, with an average growth rate of >4% per annum over the previous decade (*5*). Although thousands of plant species have some medicinal use, far fewer (<400) have established international trade markets, and a minority of these species account for the bulk of sales (*6*).

With increased demand for MAPs, issues of reliable product availability and concern on quality of the product with respect to constituents and composition are increasing (*7*). The number of incidents involving adulteration and contamination are on the rise, posing health risks to consumers, liability issues for producers, and regulatory issues for the industry (*8*).

Opportunities for CE and MAPs

The demand for MAPs threatens the availability of raw material, creating the need to develop sustainable collection practices from the wild (*3*), improve and expand cultivation techniques (*9–11*), and use biotechnology to increase the availability of plant material (*12–14*) and bioactive products (*15*, *16*). CE production can play a direct or supporting role in all these areas (*12*, *17*).

Although there is limited information on CE production for the majority of MAPs of commerce, there is growing literature on greenhouse production of species with both ornamental and medicinal application such as *Achillea millefolium*, *Artemisia vulgaris*, *Calendula officinalis*, *Capsicum* sp., *Echinacea* sp., *Inula helenium*, *Matricaria recutita, Salvia* sp., *Stellaria media*, *Tagete* sp., *Tanacetum parthenium, Taraxacum officinale*, and *Valeriana officinalis* (*18*, *19*).

Background on Controlled Environments

Controlled environment agriculture is the production of plants and their products inside structures, such as greenhouses, growth chambers and growth facilities. By using CE, temperature, relative humidity, nutrients and water can be optimized using environmental and control technology to increase yield and consistency in an efficient and sustainable manner. The ability to monitor and control the environment with CE technology removes climatic and geographic

barriers for production and enables year-round supply of plant material and product.

CE has particular advantage over field production of MAPs since the elevated CO_2 typically increases photosynthetic rate and yield (*20–23*). Similarly, higher quantities of light result in increased photosynthetic rates, and yields, as well (*24*). Both light and CO_2 concentration affect carbon partitioning and subsequent phytochemical content in the plant.

There is compelling evidence that CO_2 enrichment increases the total biomass produced by the plant, and generally increases the concentration of secondary metabolites produced. The effect of CO_2 concentration on plant physiology is species, and indeed cultivar, specific and with light intensity, temperature, nutrition and other environmental factors not well understood (*25–28*).

The following sections will summarize a cross-section of available literature to highlight to potential to increase the quality and quantity of MAPs in CE.

Carbon Dioxide Enrichment and MAPs

Enriching the CE atmosphere with CO_2 is often used to increase yield, reduce harvest time, and enhance quality of ornamental, vegetable and fruit crops (*26*). While most of the research has focused on high value ornamental and horticultural species, there is growing evidence supporting the CO_2 enhancement of biomass production of MAPs including *Datura stramonium* (*29*), *Panax ginseng* (*30*), *Papaver setigerum* (*31*), *Echinacea* sp (*32*), *Podophyllum hexandrum* (*33*), *Hypericum perforatum L.* (*34*, *35*), *Digitalis lanata* (*36*, *37*), *Hymenocallis littoralis Jacq. Salisb* (*38*), *Labisia nigra L.* (*39*), *Taxus baccata* (*32*) and *Zingiber officinale* (*40*).

In addition to increase in biomass, the concentration bioactive compounds also increases in these species. Table 1 provides an overview of effect of elevated CO_2 on concentration of bioactive compounds in MAPs (*29–40*). The increase in bioactive compounds is consistent with increases reported in horticultural and agronomic species such as *Brassica oleracea va. Italic Plench* (*41*) and *Glycine max (*L.*) Merr.* (*42*, *43*).

Stutte *et al.* (*44*), grew *Scutellaria lateriflora* L., and *S. barbata* under fluorescent lamps in a controlled environment chamber at three CO_2 concentrations (400, 1200, and 3000 ppm). They reported more rapid flowering and and significant increases in flavonoid concentration in response to elevated CO_2 in both species. There was a 2.4X increase in total flavonoid concentration from 400 to 1200 ppm, and a 4.9X increase over ambient CO_2 at 3000 ppm in *S. lateriflora*. There was a similar response in total biomass observed with *S. barbat*a. When the combined effects of CO_2 enrichment on biomass and flavonoid concentration are taken together, this translates to a 13.7 fold increase in net production of bioactive compounds by increasing concentration from ambient (400 ppm) to 3000 ppm.

Similarly, Idso *et al*. (*28*) reported that increasing CO_2 from 400 to 700 ppm resulted in 48% increase in above ground and 56% increase in below ground (bulb) biomass and a mean increase of 12% in concentration of bioactive constituents, effectively increasing the amount of bioactive constituent per bulb by 75%.

Table 1. Summary of Selected Medicinal and Aromatic Plants That Have Shown Increases in Concentration of Bioactive Secondary Metabolites in Response to CO_2 Enrichment of the Atmosphere

Species	***Concentration (ppm)***	***Response***	***Reference***
Brassica oleracea va. Italic Plench	450, 750	Increase glycosinolates	(*41*)
Datura stramonium	294, 378, 690	Increase scopolamine	(*29*)
Digitalis lanata	350, 1000	Increase digoxin-momo-digitoxoside digoxin digitoxin	(*37*)
Echinacea sp	350, 500, 700	Increase in caftaric acid and total phenols in root	(*32*)
*Glycine max (*L.*) Merr.*	400, 700	Increase isoflavonoid concentration	(*42*)
	360, 650	Increase in daidzein, genistein, glycitein, diadzin, genistin, glycitin, 6"-O-acetyldaidzin, 6"-O-acetylgenistin, 6"-O-acetylglycitin, 6"-O-malonyldaidzin, 6"-O-malonylgenistin ,"-O-malonylglycitin	(*43*)
Hymenocallis littoralis Jacq. Salisb	400, 700	Increase bulb biomass, increase in 7-deoxynarciclasine , 7-deoxy-*trans*-dihydronarciclasine, pancratistatin, trans-dihydronarciclasine, narciclasine.	(*30*)
Hypericum perforatum L.	360, 1000	Iincrease hypericin and pseudohypericin concentration	(*35*)
	500, 100, 1500	Increase concentration of hypericin, pseudohypericin and hyperforin	(*34*)
	350, 500, 750	Increase total flavonoids	(*32*)
Labisia nigra L.	400, 800, 1200	Increase total flavonoids, total phenolics, antioxidant capacity	(*39*)
Nicotiana tabacum	294, 378, 690	Reduce nicotine	(*29*)

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Table 1. (Continued). Summary of Selected Medicinal and Aromatic Plants That Have Shown Increases in Concentration of Bioactive Secondary Metabolites in Response to CO_2 Enrichment of the Atmosphere

Species	*Concentration (ppm)*	*Response*	*Reference*
Panax ginseng	1, 2.5 and 5%	Increase total phenolics, total flavonoids	(*30*)
Papaver setigerum	300, 400, 500, 600	Increase in total alkaloid content	(*31*)
Scutellaria barbata	400, 1200, 3000	Increase concentration of scutellarein, baicain, apigenin	(*44*)
Scutellaria lateriflora	400, 1200, 3000	Increase concentration of baicalin, baicalein, wogonin and chrysin	(*44*)
Taxus bacatta	350, 500, 750	Increase taxol	(*32*)
Zingiber officinale	400, 800	Increase total phenols, total flavonoids, antioxidant potential	(*40*)

Stutte (unpublished) found that increasing CO_2 concentration from 400 to 1200 ppm resulted in a 106% increase in shoot length, 64% increase in dry mass, and 12.8 % increase in anti-oxidant potential of *Prunella vulgaris* L. grown for 54 d under triphosphor fluorescent lamps at 300 µmol m^{-2} s^{-1} photosynthetically active radiation (PAR) on 18h light/ 6 h dark photoperiod (19.4 Mol m^{-2} d^{-1} PAR). This was equivalent to a 69% increase in antioxidant potential (Table2).

Table 2. Effect of Elevated CO_2 on Shoot Length, Fresh Mass, Dry Mass, And Anti-Oxidant Potential of 54 Day Old *Prunella vulgaris* Grown under Controlled Environment Conditions[1]

CO_2 (ppm)	*Shoot Length (mm)*	*Fresh Mass (g)*	*Dry Mass (g)*	*ORAC (µmol TE/g FM)*	*ORAC (µmol TE/plant)*
400	71.8	25.8	3.26	20.6	529
1200	148.3	35.8	5.63	23.1	895
Significance[2]	***	***	***	**	***

[1] Plant were grown at 23°C, 65% RH, and 300 µmol m^{-2} s^{-1} PAR on a 16h light/8h dark photoperiod under triphosphor fluorescent lamps. [2] Tukey t-test, significant at P≥0.01=**, P≥ P.001=***.

Light Quantity and Quality in CE

Light quantity and quality both had significant impacts on growth and quality of MAPs. Increasing the quantity of light by increasing intensity or duration generally results in an increase in plant biomass (*24*) of horticultural and agronomic species (*45*).

The University of Wisconsin and the Wisconsin Center for Space Automation and Robotics evaluated the use of LEDs for plant growth in the late 1980s, and patents were awarded for this application in 1991 (*45*). Work at Kennedy Space Center (KSC) in Florida indicated that lettuce, wheat, spinach, and radish plants would grow and complete their life cycles under red light alone, but growth and development were significantly better when a small amount of blue light was added to the red (*47*). Since that initial work in the late 1980, early 1990's a substantial body of literature has developed demonstrating the potential of LEDs as supplemental and sole-source lighting in horticultural applications (*46–50*).

There is strong evidence suggesting that total yield of biomass increases with increasing quantity of light reaching the canopy. The quantity can be increased through either increasing the intensity or duration of a lighting cycling. The specific light response curves are dependent upon the species and cultivar. The effect of light intensity on yield and composition has been reported for a number of medicinal plants, including *Glycyrrhiza uralensis* (*51*), *Hypericum perforatum* (*29*, *52*, *53*), *Rhodiola sachalinensis* (*54*), *Tabernaemontana pachysiphon* (*55*), *Tanacetum parthenium* (*27*),and *Zingiber officinale* (*56*).

Figure 1 illustrates the effect of light intensity on size and flower number of *Tagetes patella* grown under cool white fluorescent lamps on 16 hr light/ 8 hr dark cycle at 22°C, 60% RH and elevated (1000 ppm) CO_2 for 79 days in a controlled environment chamber. Doubling the light intensity from 300 to 600 µmol m^{-2} s^{-1} resulted in a 58% increase in total plant dry mass, with a 117% increase in dry mass partitioned to the flowers/calyx. There was an 18% increase in lutein concentration/g in flowers/calyx resulting in an effective 2.6X increase in lutein content per plant (Stutte, unpublished).

In addition to using LEDs to increase yield, there is a growing literature demonstrating the use of LEDs to increase the concentration and composition of secondary metabolites (i.e. polyphenolics and glucosinolates) for many species, among which are included commercially valuable crops such as strawberry (*Fragaria vesca*) (*57*), tomato (*Solanum lycopersicum*) (*58*, *59*), kale (*Brassica oleracea* L. var. *acephala)* (*60*), salad greens (e.g., *Lactuca sativa*) (*61*, *62*), and microgreens (e.g., *Brassica oleracea*) (*63*).

There is also growing evidence that quality and composition of medicinal and aromatic plants can be managed through spectral quality. Stutte et al. (*61*), reported that addition of blue (440 nm) light affects not only morphology, but concentration of anthocyanin in *Lactuca sative* L. cv. Outredgeous (Figure 2) well. Addition of blue light during final week of development increased anthocyanin content four fold over controls.

Figure 1. Tagetes patula grown for 79 days in CE chamber at 22°C, 60% RH and 16 hr light/ 8 hr dark photoperiod at 300 µmol m^{-2} s^{-1} (17.28 M m^{-2} d^{-1})(left) or 600 µmol m^{-2} s^{-1} PAR (34.56 M m^{-2} d^{-1})(right) from high pressure sodium lamps at 1000 ppm CO_2.

Figure 2. Twenty-eight day old Lactuca sativa cv. Outredgeous grown under either red (660 nm (left)) or blue/red (440/660 nm) (right) LEDs at 280 µmol m^{-2} s^{-1} PAR on 16h light/ 8 hr dark photoperiod at 23°C at ambient (365 ppm) CO_2. [Reproduced with permission from reference (50). Copyright 2015, Amer. Soc. Hort. Sci.].

Samuoline *et al*. (*64*), reported that light intensity and quality affected the concentration of phenolics, anthocyanins and ascorbic acid in sprouts of *Amaranthus cruentus*, *Ocimum basilicum, Brassica oleracea* cultivars, *Brassica juncea*, *Atriplex hortensis* L., *Borago officinalis*, *Beta vulgaris, Petroselinum crispum* and *Pisum sativum.* The responses were species specific, highlighting the need to optimize spectral quality and quantity for each species being considered.

Similarly, Tarakonaov *et al*. (*65*) found that altering the spectral composition with blue and red LEDs had varying effects on chlorophyll a/b, carotenoids and anthocyanin content and concentration of *Brassica juncea, Lactuca sativa, Ocimum gratissimum, Coleus blumei* and *Tagetes patula.* Park *et al.* (*66*) used narrow spectra LEDs to treat *Panax ginseng* Mayer roots with different wavelengths of light (380, 450, 470 or 660 nm) and found that blue wavelengths (450 and 470 nm) significantly increased the production of ginsenosides in the root tissue.

Nishimura et al. (*67*) found that growing *H. perforatum* under red, blue or white fluorescent lights in a controlled environment chamber at 27/24°C thermoperiod, and 16 hr photoperiod at 1000 µmol mol^{-1} CO_2 at 250 µmol m^{-2} s^{-1} PAR increased total biomass, as well as concentration of hypericin, hypeicin, and pseudohypericin. Plants grown under red (600-700 nm) light had higher biomass that those grown under blue (400-500 nm) or white (400-700 nm), but spectral quality did not significantly affect the concentration of bioactive constituents. Doubling the light intensity from 250 µmol m^{-2} s^{-1} PAR (14.4 Mol m^{-2} d^{-1}) to 500 µmol m^{-2} s^{-1} PAR (28.8 Mol m^{-2} d^{-1}) increased the biomass per plant for each light level approximately 2 fold (range 1.5-2.6X). Although biomass of plants grown at 250 µmol m^{-2} s^{-1} PAR was lower , the concentration of hypericin, hyperorin and pseudohypericin was at least 2 fold higher, with greatest effect under red light (3.1-3.5X higher).

Solar light contains both UV-A (320-400 nm) and UV-B (280-320 nm) wavelengths that plants are adapted to, so indoor agriculture scenarios providing electrical sources of sole source lighting, especially of the narrow-spectrum type, may encounter situations in which produce quality and/or appearance may reflect a lack of UV radiation.

It has been hypothesized that the production of secondary products is reduced when UV-B is removed from the light spectra of plants grown in the greenhouse or under electric lamps. The effects of UV-B on plant production of secondary metabolites has been the subject of recent reviews (*68*, *69*).

The addition of UV-B to the spectra has been shown to increase the production of hyperforin, pseudohypericin and hypercin in *Hypericum perforatum* (*70*), essential oil content and composition of *Nepata cataria* L., *Melissa officinalis* L. and *Salvia officinalis* L. (*69*), anthocyanin, total phenolics , anti-oxidant capacity and rosmarinic acid content of *Ocimum basilicum* L. (*71*, *72*), melatonin concentration in *Glycyrrhiza uralensis* roots (*73*), brachycerine concentration of *Psychotria brachyceras* (*74*), and terpene content of *Mentha x peperita* L. (*75*).

Brechner *et al*. (*70*) found that a single 40 minute exposure of UV-B to 55 day old *H. perforatum* grown at 400 µmol m^{-2} s^{-1} PAR increased the concentration of hypericin, hyperorin and pseudohypericin from 2.5 to 3.7 fold within 24 hours. There was no additional benefit from additional or longer exposures. The effect of

UV-B treatment during flowering, the highest period of production of bioactives, is not known.

Constraints To Use of CE for MAPs

Although CE technology is widely used to insure quality and consistency of production of vegetable and ornamental crops, limited published information exists on the use of CE to produce MAPs. This is probably not surprising, given that MAPs requiring long harvest cycles, (e.g. *Ginseng panex, Hydrastis canadensis*, *Actaea racemosa)*, large volumes (e.g. *Humulus lupulus*) or both (e.g. *Uncaria tomentosa)* are not economically viable for production.

Bioactives derived from byproducts of commercial horticulture (e.g. *Allium sativum, Vaccinium macrocarpon, Vaccinium microcarpom, Vitis vinifera* seed, *Citrus* sp. oil), agronomic (e.g. *Glycine max)* and forage (e.g. *Trifolium pratense, Medicago sativa)* crops are readily and cheaply available making it difficult to justify the capital investment and operating cost for CE production. Similarly CE production of bioactives derived from trees (e.g. *Crataegus monogyna, Ginkgo biloba, Serenoa repens)* is generally not economical due to long life cycle and large size.

However, there is significant opportunity to use CE technology for the production of uniform, high quality transplants for commercial cultivation. This has potential to significantly reduce time to harvest, reduce harvest pressure on endangered populations and increase profitability for the grower.

Summary

Controlled environment technology has a role in addressing several issues facing the medicinal and aromatic plant industries. Controlled environments and biotechnology have application in the propagation of threatened and endangered species to reestablish and preserve them in their native range. Availability of high quality, certified plant material for cultivation enables the commercial production of high value plant material to meet the increasing market demand. By providing a consistent supply of cultivated material to the market, the harvest pressures on wild populations should be reduced.

The risk of accidental and incidental contamination and adulteration of plant material grown under CE is inherently lower than that of plant material harvested from either wild or cultivated populations. The conditions are known, and opportunities for introduction of unknown or undesirable species is limited. The use of CE would conceivably be a key good manufacturing practice for production of standards to determine purity of product on the market.

The photoregulation of secondary metabolism through active management of spectral quality has been demonstrated to significantly enhance concentration of anthocyanins, glycosinolates, phenolics, flavonoids and other secondary metabolites. The increasing availability and reduced cost of LEDs for lighting holds great promise for enabling the consistent production of plant material with ‘custom’ biochemical constituents.

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The yield of MAP per unit area can be greatly increased using CE technology through use of CO_2 enrichment. By leveraging faster life cycle, higher yield, and year round production that can be achieved with CE, there are significant opportunities to achieve high quality, consistent production (Table 3). For example, assuming that the average yield from a 90 day seed to harvest cycle of hypothetical medicinal plant is '1', and assuming that CO_2 enrichment to 1000 ppm will reduce seed to harvest cycle from 90 to 60 days and double plant size, the yield per m^2 is increased a minimum of 12 fold!

Table 3. Hypothetical Comparison of Productivity Per Unit Area of Medicinal Crop Grown under Either Field or Controlled Environment (CE) Conditions. This Assumes Year Round Production on a Single Layer under Elevated CO_2 Conditions.

Variable	***Field***	***CE***
Growth Cycle (days)	90	60
Harvest(no/yr)	1	6
Yield/(unit/m^2)	1	2
Total (unit/m^2/yr)	**1**	**12**

CE technology and LED lighting also enables vertical production of plants in vertical farms or plant factories (*76*). If a typical production of 5 layers of plants is assumed the productivity will increase 60 fold/m^2/year!

It is clear that the productivity and composition are affected by the growth environment, and that active management of these factors, specifically light quantity, quality and CO_2 concentration can have significant beneficial effects on the phytochemical composition. When targeting growth of a medicinal plant in CE in order to increase phytochemical production, the decision on what conditions to use will involve trade-offs on production of target compound versus potential changes in phytochemical profile, increases in productivity versus operating costs. However, from a technical perspective, there are significant opportunities to increase the yield of high quality MAPs with consistent phytochemical profiles. The diversity, high value, and unique properties of medicinally active plants make them promising candidates for production in CE.

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