

Vertical Farming of Medicinal Plants



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Abstract Medicinal plants have been used in traditional medicine, health food supplements, rituals, and for health care purposes for thousands of years. According to the Food and Agriculture Organization of the United Nations (FAO), the worldwide production of medicinal and aromatic plants is estimated to be 330 million tons for a total area of 77 million ha. Nowadays, the sector of medicinal plants is subject to inconstancy, and issues about the yield, quality, and efficacy of plant extracts have been reported. The present review describes the current status of medicinal plants worldwide, including a detailed description of the sector in France. The suitability of vertical farming for the production of medicinal plants is discussed, and its advantages and drawbacks are presented. Indoor cultivation in a controlled environment requires appropriate adjustment of abiotic factors to optimize biomass and secondary metabolite contents. Light quantity and quality, nutrient solution, temperature, and CO₂ concentration are presented in relation with their impact on plants and on the production of the targeted phytochemical. A case-study on the technical feasibility and economic viability of producing a plant-based drug in a vertical container is presented, including plant cultivation and drug extraction steps. Based on the costs related directly to the production activity, it provides a rapid estimate of the direct production cost of each step. The largest contributor to cultivation costs is labor, averaging 48%, followed by energy (20%) and investment cost (20%). The largest contributor to extraction and purification costs is the operating and maintenance cost of equipment (47%), followed by energy cost (31%) and labor cost (16%). The largest contributor to the whole plant-based drug production process, from plant cultivation to drug production, is the research and development cost (98–67%), followed by cultivation and extraction costs (1–24%) and drug manufacturing costs (1–8%), depending on the number of containers, i.e., on the productivity of the cultivation and extraction steps.

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1 Introduction: Vertical Farming and Medicinal Plants

1.1 Current Challenges of Agriculture

Agriculture currently faces many challenges and difficulties in terms of environmental performances. Although the Organization for Economic Cooperation and Development (OECD) points out that agricultural nitrogen and phosphorous nutrient surpluses in the OECD countries steadily declined between 1990 and 2009, farmed soils still contain an average surplus of 63 kg/ha of nitrogen and 6 kg/ha of phosphorous. These levels remain very high as to their potential to cause surface, groundwater and coastal water pollutions (OECD 2013). In most European member states, agriculture is responsible for over a third of the total nutrient discharge into surface and coastal waters (OECD 2013). Agriculture is also the major user of pesticides, with 70% of the mean pesticide sales in OECD countries related to agriculture. As a result, agricultural soils are major reservoirs of pesticides that affect soil microbial communities and represent sources of water and air pollutants (Tao et al. 2008; OECD 2013; Hvězdová et al. 2018; Dou et al. 2020a, b). Almost a third of OECD member countries is affected by moderate to severe water-related soil erosion, while far fewer countries are suffering from wind-related erosion (OECD 2013). Erosion due to agricultural practices can be mainly attributed to continued cultivation on fragile and marginal soils, overgrazing of pasture, or unsuited farming and tillage practices (Bullock 2005; OECD 2013; Gebrehiwot 2022; Hassan et al. 2022). The mean energy consumption related to agriculture between 2008 and 2010 was low – 1.6% – but the sector is vulnerable to changes in crude oil prices, and sensitive to dramatic changes (OECD 2013). Although the OECD indicates that the agriculture sector reduced its water withdrawals over the past decade, agriculture remains a major user of water accounting for an average 44% of total water withdrawals (OECD 2013). Biodiversity as measured from farmland bird populations has been declining continuously in almost all countries over the 1990–2010 period (OECD 2013). The main reason is the considerable use of land and water resources on which wild species are highly dependent (OECD 2013). Agricultural intensification in recent decades has resulted in reduced crop diversity and losses of plant species (Storkey et al. 2012; Meyer et al. 2013; Abeli et al. 2022). Figure 1 shows the pressure exerted by agriculture in several sectors.

The value of primary agriculture round the world can be partly understood by looking at trade statistics from worldwide databases. Although trade data are never complete and products are categorized differently, they give a global picture of the importance of primary agriculture and the share of medicinal plants within primary agriculture. Customs nomenclature referring to primary agriculture includes several codes: 07 “Edible vegetables and certain roots and tubers,” 08 “Edible fruit and nuts;

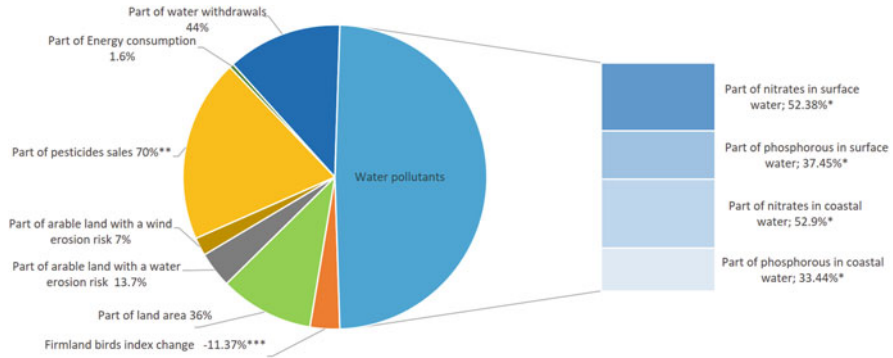


Fig. 1 Overview of the pressure exerted by agriculture in several sectors: water pollutants, energy consumption, water withdrawal, pesticide sales, land area, biodiversity, and water and wind erosion risk (OECD 2013). Each sector is represented on a 100% basis, in which the share of primary agriculture is indicated *Mean based on a limited number of OECD countries **The number of OECD countries monitoring pesticides in water systems is limited. However, data for Austria reveals that the development of pesticide sales is closely related to level of pesticides detected in surface waters ***Mean average annual percentage change

peel of citrus fruit or melons,” 09 “Coffee, tea, maté and spices,” 10 “Cereals,” and 12 “Oil seeds and oleaginous fruits; miscellaneous grains, seeds and fruit; industrial or medicinal plants; straw and fodder,” Table 1 shows the exported value of primary agriculture and the relative significance of nomenclature 1211 corresponding to “Plants and parts of plants, incl. seeds and fruits, of a kind used primarily in perfumery, medicaments or for insecticidal, fungicidal or similar purposes, fresh or dried, whether or not cut, crushed or powdered.” It shows that the export value of medicinal plants represents a small percentage of primary agriculture (about 0.7%) but is constantly growing.

In 2019, the total exported quantities of code 1211 represented 731,606 tons and 2,892,682 euros. The exported value of code 1211 *per* ton was about ten times higher than those of rice (code 1006), cereals (code 1001), and potato (code 0701) and about three times higher than that of tomatoes (code 0702), showing that this category has a high added value.

1.2 The Current Status of Medicinal Plants

The Current Status of Medicinal Plants Round the World

Medicinal plants, including medicinal herbs, have long been used round the world. The use of medicinal plants is one of the oldest forms of treatment, coming from ancestral and empirical uses, that still plays a significant role in Africa and Asia (World Health Assembly 2003). The World Health Organization (WHO) reports that at least half of the world population do not receive the healthcare services they

Table 1 World total export value (€) of codes 07-08-09-10-12, world total export value (€) of code 1211, percentage of code 1211 in the total of codes 07-08-09-10-12, and annual export value growth of code 1211 from 2018 to 2021 (International Trade Center, no date)

Year	World total export value of primary agriculture codes 07-08-09-10-12 (€)	World total export value of code 1211 (€)	Percentage of code 1211 in the total export value of primary agriculture	Annual export growth of code 1211
2021	483,564,488	3,310,966	0.6847%	5.26% (2020–2021)
2020	431,281,779	3,145,490	0.7293%	8.74% (2019–2020)
2019	410,466,532	2,892,682	0.7047%	6.15% (2018–2019)
2018	387,958,090	2,725,045	0.7024%	–

Codes: 07, “Edible vegetables and certain roots and tubers”; 08, “Edible fruit and nuts; peel of citrus fruit or melons”; 09, “Coffee, tea, maté and spices”; 10, “Cereals”; 12, “Oil seeds and oleaginous fruits; miscellaneous grains, seeds and fruit; industrial or medicinal plants; straw and fodder”; 1211, “Plants and parts of plants, incl. seeds and fruits, of a kind used primarily in perfumery, medicaments or for insecticidal, fungicidal or similar purposes, fresh or dried, whether or not cut, crushed or powdered”

need and that about 80% are using traditional medicines to meet their healthcare needs (World Health Assembly 2003; World Health Organization 2022). One way of understanding the importance of the medicinal plant market at the level of a country is to look at the number of national research institutes dedicated to traditional and complementary medicines, which are fully or partially funded by the governments and indicate strong national policy support. The WHO report on traditional and complementary medicine shows that the highest number of countries reporting a national research institute were in the South-East Asia Region (64%), followed by the African Region (62%), the Eastern Mediterranean Region (48%), the Western Pacific Region (33%), the Region of the Americas (26%), and the European Region (21%) (Fig. 2) (WHO 2019). The regions with the highest percentage correspond to countries, where medicinal plants strongly belong to the traditional healthcare system (Pan et al. 2014; Howes et al. 2020).

The trade database shows that India and China are the major providers of medicinal plants round the world with 24.1 and 10.6% of the total export value in 2021 (Fig. 3), followed by Germany (6%), the USA (4.4%), Egypt (4.3%), Canada (4.1%), Spain (2.8%), Poland (2.6%), Korea (2.3%), and Mexico, Vietnam, France, all three at 1.8%. All other countries are below 1.8% and represent 33% of the total world exports.

Current Status of the Medicinal Plant Sector in Europe

In Europe, medicinal and aromatic plants are cultivated on more than 200,000 ha, most of which are located in France (52,000 ha), Poland (30,000 ha), Spain (27,800 ha), Bulgaria (16,800 ha), Germany (13,000 ha), Croatia (8500 ha), the Czech Republic (7225 ha), Italy (7191 ha), Greece (6800 ha), and Austria (4136 ha) (EIP-AGRI 2020). The export market of customs code 1211 in Europe in 2021 was dominated by Germany (26%), Spain (12%), Poland (12%), and France (8%),

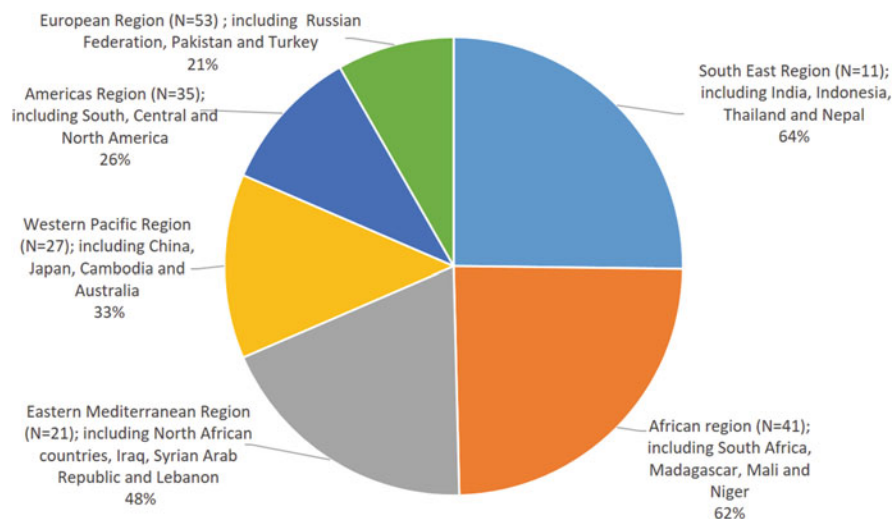


Fig. 2 Percentages of national research institutes for traditional and complementary medicines or herbal medicines in six regions of the planet. Each region is represented by N countries. The percentages represent the numbers of countries having a national research institute in a specific region. (WHO, 2019)

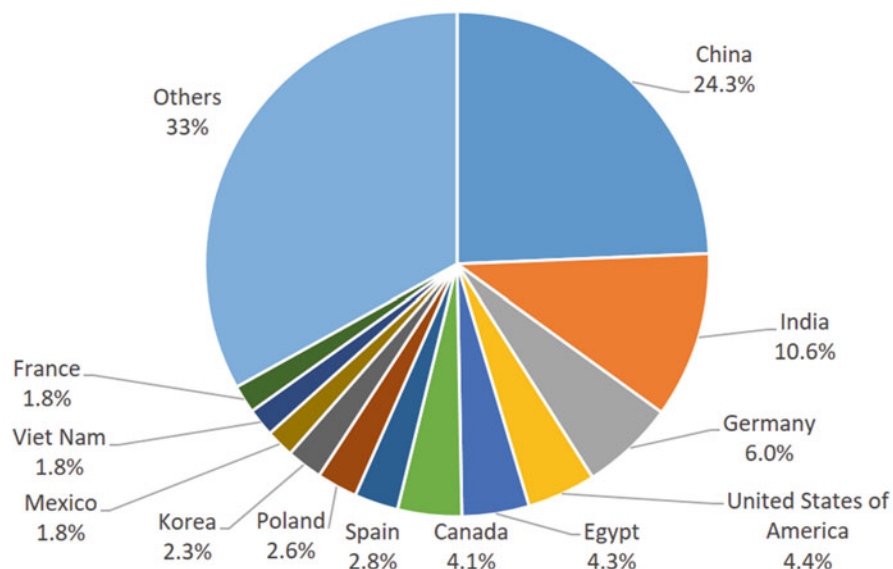


Fig. 3 Main exporter countries of medicinal plants in 2021. Export values in 2021 expressed as percentages, according to the trade database from the International Trade Center (no date). Export values were calculated from custom nomenclature 1211 “Plants and parts of plants, incl. seeds and fruits, of a kind used primarily in perfumery, medicaments or for insecticidal, fungicidal or similar purposes, fresh or dried, whether or not cut, crushed or powdered”

followed by Austria (5%), Italy and Bulgaria (4% each) (International Trade Center, no date). The current state of medicinal and aromatic plants in France is further studied in the following subchapter.

The French Perfume, Aromatic, and Medicinal Plant Sector (FranceAgriMer 2020, 2021)

The French perfume, aromatic, and medicinal plant sector includes the cultivation and regular picking of more than 300 species and more than 1000 products of marketed perfume, aromatic, and medicinal products. In 2021, this sector covered an area of 67,513 ha for 6527 producers. This area has been constantly increasing since the 2000s and has grown by more than 32% over the last 5 years. Perfume plants represent the largest surface area in the sector with 37,897 ha in 2021 and three predominant species: lavandin and lavender (33,094 ha) and clary sage (3400 ha). The farms have multiple profiles ranging from industrial cultivation to very small farms in disadvantaged areas. The sector had the strongest surface area growth in absolute value (>33%) between 2017 and 2021. Aromatic plants were grown on 9644 ha in 2021. The main species were coriander, parsley, thyme, fennel, mint, dill, tarragon, marjoram, oregano, basil, rosemary, and chives. This sector strongly grew (>66%) between 2017 and 2021. The medicinal plant sector includes the largest number of species (more than 150 species including poppy, chamomile, milk thistle, lemon balm, etc.). Its surfaces decreased by 4% to 19,972 ha in 2021 compared to 2020 (20,712 ha), but altogether increased by 19% between 2017 and 2021. Poppy (*Papaver somniferum* var. *nigrum*) and ginkgo biloba are exclusively produced under contract with the pharmaceutical industry. In 2021, the total area of the perfume, aromatic, and medicinal plant sector was 67,513 ha and represented less than 1% of French agricultural land, subdivided as follows:

- 56% for perfume plants (37,234 ha for lavender and lavandin areas, i.e., nearly 49%)
- 30% for medicinal plants
- 14.3% for aromatic plants

In 2020, medicinal plants had a turnover value of 3659 k€ for a volume of 385 tons. The main volume was reached by birch, followed by Roman chamomile and rose geranium (Table 2), but lemon balm ranked first in market value, followed by beech wood and birch (Table 2).

In the medicinal plant category, most of the commercial value relates to essential oils (355 k€) for an extremely low volume (154 kg). Lemon balm essential oil was sold between 2000 and 2600 €/kg in 2020, and thyme was the most representative aromatic plant (PA) in market value with a turnover of 630 k€. In 2020, the marketing value of “dry” products represented 44% of all aromatic plants. It was 29% for fresh products (including frozen ones) and 25% for essential oils (Fig. 4). The market shares of dried plants predominated over all medicinal plants with 36%, followed by “fresh/frozen” processed plants (31%). The market share of essential oils was 27%, and the remaining 6% included hydrolates, oily macerates, and stabilized extracts (Fig. 4). This shows that dried plants had the main market

Table 2 Major medicinal plants produced in France. Surfaces (ha), market volumes (t), market values (k€), and main uses

	2021 Surfaces (ha)	2020 Market volume (tons)	2020 Market value (k€)	Main form
<i>Betula s.l.</i>	/	21	202	Concentrated bud macerates, sap, traditional health syrup
<i>Chamaemelum nobile</i>	362 (2017)	14	60	Essential oil, tea, floral water, health food supplement, extract
<i>Pelargonium 'rosat'</i>	/	14	/	Essential oil, mother tincture, tea, concentrated bud macerates
<i>Filipendula ulmaria</i>	/	10	88	Tea, health food supplement, hydroalcoholic extract
<i>Aloysia citrodora</i>	/	9	100	Tea, essential oil, extract, mother tincture
<i>Centaurea cyanus</i>	22 (2017)	9	55	Floral water, tea, extract, hydrolat
<i>Calendula officinalis</i>	/	8	/	Extract, tea, hydroalcoholic extract, mother tincture, oily macerate
<i>Melissa officinalis</i>	260	8	404	Essential oil, health food supplement, extract, tea, hydrolat
<i>Arnica montana</i>	/	3–10 (harvest)	66	Mother tincture, oily macerate, extract, vegetable oil
<i>Leontopodium alpinum</i>	/	/	78	Flower extract, flower essence
<i>Vitis vinifera</i>	/	/	87	Health food supplement, water extract
<i>Gentiana lutea</i>	/	1600 (harvest-2017)	91	Extract, tea, mother tincture, health food supplement
<i>Fagus s.l.</i>	/	/	300	Concentrated bud macerates
<i>Ribes nigrum</i>	603 (perfume and essential oil)	30 (bud-harvest-perfume and essential plant) 60 (leaf-harvest-medicinal plant)	1443 (perfume and essential plant)	Concentrated bud macerates, health food supplement, extract, mother-tincture, macerate
<i>Thymus</i>	955 (aromatic plant)	328 (aromatic plant)	630 (aromatic plant)	Essential oil, healthy traditional syrup, concentrated bud macerates, health food supplement

(continued)

Table 2 (continued)

	2021 Surfaces (ha)	2020 Market volume (tons)	2020 Market value (k€)	Main form
<i>Salvia rosmarinus</i>	204 (aromatic plant)	60 (aromatic plant)	153 (aromatic plant)	Essential oil, concentrated bud macerates, health food supplement, extract, tea
<i>Silybum marianum</i>	300	/	/	Health food supplement, extract
<i>Cynara cardunculus</i>	250	/	/	Health food supplement, tea, extract
<i>Angelica archangelica</i>	179	/	/	Mother-tincture, extract, health food supplement, essential oil
<i>Plantago afra</i> L.	74	/	/	Seed, health food supplement
<i>Lavandula</i> L.	33,094	140 (Lavander – essential oil) 2000 (Lavandin – essential oil)	/	Essential oil, health food supplement
<i>Papaver</i>	10,000 (estimation)	/	/	License with a pharmaceutical company – derivatives for the production of alkaloids

Source: FranceAgriMer (2020, 2021)

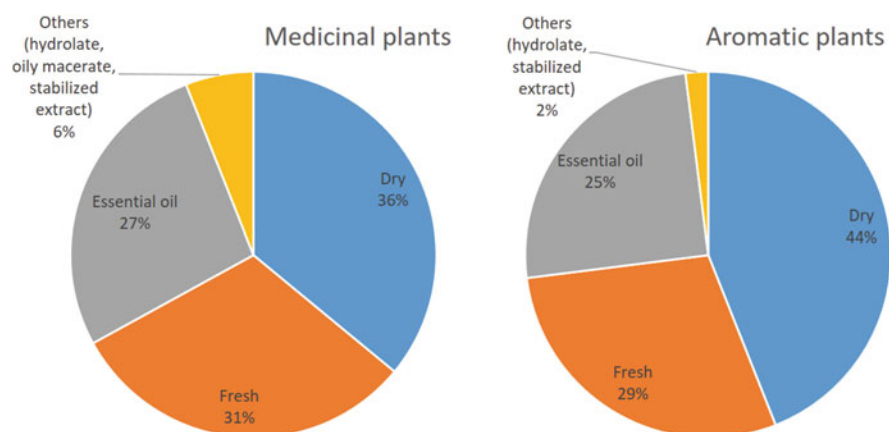


Fig. 4 Share of the marketing value of medicinal plants and aromatic plants according to the type of processing in France in 2020. (FranceAgriMer 2021)

value in both the medicinal and aromatic plant markets, followed by fresh plants and essential oils.

The use of medicinal plants is increasing in industrialized countries; the percentages of the population that had used a plant-based medicine at least once were 70% in Canada, 49% in France, 48% in Australia, 42% in the United States of America, and 31% in Belgium (World Health Assembly 2003). The global market value of herbal products is predicted to grow to US\$ 5 trillion by 2050 (Pan et al. 2014). The increasing demand for medicinal plants has serious consequences such as overharvesting, quality inconsistencies, and uncertain efficacy (World Health Assembly, 2003; Howes et al. 2020; Zobayed 2020; Singh et al. 2022).

Overharvesting of medicinal plants has a major impact on biodiversity; for example, (1) Asian *Taxus brevifolia* Nutt., *T. chinensis*, *T. mairei*, and *T. contorta* Giff. populations harvested for paclitaxel extraction have undergone significant population reductions, (2) *Encephalartos woodii* Sander is extinct in the wild, (3) about 80% of Ethiopian medicinal plants are harvested from the wild with serious threats on their preservation, or (4) *Arnica montana* L. has been overexploited in Europe for its anti-inflammatory properties and shows decreasing populations; it is now included in the red list of several European countries (Balabanova and Vitkova 2010; Howes et al. 2020; Vera et al. 2020).

Medicinal plants are mainly harvested from wild plants (Zobayed 2020). Under field cultivation, some methods have had a negative impact on the environment. For example, field cultivation of *Panax ginseng* Meyer in Asia led to deforestation and soil microbial diversity losses in farmlands, which in turn brought about serious soil-borne diseases affecting the quality and yield of *P. ginseng* (Tong et al. 2021). The quality of medicinal plants is subject to inconsistencies, and issues about the quality and efficacy of plant extracts have been reported (World Health Assembly 2003). Outdoor plants are exposed to variations of their growing conditions in water content, temperature, light characteristics (photoperiod, intensity, ozone and UV radiation), and soil characteristics. All these parameters vary according to the season, annual climate changes, and location and impact the plant contents in specific metabolites. Moreover, open-field harvesting is often seasonal and conditions the annual yield. Issues related to quality, efficacy, microbial and pollutant contamination, and contamination with misidentified plant species are often reported (World Health Assembly 2003; Zobayed 2020).

1.3 General Interest of Vertical Farming

Vertical farming consists in growing vegetables in vertically/horizontally stacked layers made of hydroponic or aeroponic soilless crop units mounted in (1) an indoor closed production system with artificial light, where environmental factors (airflow, temperature, CO₂, humidity and nutrients) are completely controlled, or (2) a greenhouse with vertically stacked layers, in semi-closed production systems, possibly adding artificial light to natural sunlight.

Vertical farming could contribute to answer some challenges of outdoor agriculture:

- First of all, *yields* in vertical farming are widely described as being significantly higher than in conventional agriculture, because they combine three factors: (1) the yield per square meter is increased thanks to a reduced land footprint resulting from the vertical succession of crop production units, (2) the photosynthetic rate is better as a result of a constant and ideal combination of environmental factors, and (3) production is possible all year round (Banerjee and Adenaueer 2014; Barbosa et al. 2015; Avgoustaki and Xydis 2020a, b). The yield depends on the number of plants *per* square meter and on the maximizing of the vertical indoor space, which implies plants no taller than 30 cm, such as leafy greens, herbs, transplants, and medicinal plants (Kozai and Niu 2020).
- Secondly, *water use* is significantly lowered, because plants are grown hydroponically, irrigation water is supplied in a closed loop, and drought events are absent – climate is stable (Barbosa et al. 2015; Benke and Tomkins 2017; Graamans et al. 2017, 2018; Kalantari et al. 2018; Avgoustaki and Xydis 2020a).
- Thirdly, *pesticide use* is dramatically lowered, because exposure to the outdoor environment is reduced, although the risk of pest contamination cannot be completely excluded (Cowan et al. 2022). Moreover, if a pest appears, it is likely to spread exponentially because of the interconnected irrigation system and the high plant density.
- Fourthly, nitrogen and phosphorous *nutrient losses* in soil and aquatic sources are reduced, because the nutrient solutions are recirculated in a closed-loop system (Cowan et al. 2022). However, the recycling of the nutrient solution is not complete: nutrient imbalance gradually appears, and the nutrient solution has to be replaced unless a dynamically managed system is used (Silberbush and Ben-Asher 2001; Zeidler et al. 2017; Michael et al. 2021; Cowan et al. 2022).
- Finally, *farmland use* is reduced because crop production is soilless, the crop system is multilayered and can be implemented in urban areas and hostile places, such as desert, tundra, polluted and cold regions (Cowan et al. 2022).

However, several challenges are reported for vertical farming:

- Vertical farming *requires energy*, hence a carbon footprint. More electricity is required than in open-field and greenhouse farming; these high energy expenses are mainly linked to lighting and air and hydric management (Zeidler et al. 2017; Graamans et al. 2018; Sparks and Stwalley III 2018; Avgoustaki and Xydis 2020a; Bafort et al. 2022; Cowan et al. 2022).
- Other difficulties are the *global cost* to start vertical farming, linked to high start-up costs, high property costs in urban areas, high labor requirements, and the low market price of leafy-green crops challenging its viability (Zeidler et al. 2017; Bafort et al. 2022).
- The use of *mineral nutrients* has a big impact on soil resources and ecology. Other nutrient sources should be considered. Organic nutrient sources are often described, e.g., manures, bulky organic manures, or organic fertilizers. Most organic nutrient sources, including waste materials, have widely varying compositions and often only a low concentration of variably available nutrients and need to be processed before use (Szekely and Jijakli 2022).

- *Plastic* is largely used in hydroponics: the materials used for hydroponic culture (nutrient film technique, ebb-and-flow systems, deep water systems, aeroponics systems, and drip irrigation systems) are mainly plasticware. Efforts to decrease the use of plastic in hydroponics materials should be done.
- Rockwool is mainly used as a *substrate* in hydroponics. However, it has low durability as it has to be discarded after one or two cultivation cycles and requires high energy during its manufacturing process (Bar-Tal et al. 2019). To increase the durability of rockwool, its reuse has been developed as raw material for horticultural and insulation applications and in brick production in European countries, but this reuse network is not well developed yet (Bar-Tal et al. 2019). Clay beads are characterized by a very good long-term stability that allows for their reuse. Reuse induces increased costs because workforce and water are needed to rinse and clean the clay beads. Coco fiber is natural and recyclable, but its use in deep-water systems causes filtering problems, because coco fibers are degraded rapidly, so that more labor work needed to clean the filtering system very regularly (Bafort et al. 2022). As a consequence, the use of ecological hydroponic media should be emphasized.

Figure 5 summarizes the main challenges of outdoor farming and vertical farming.

1.4 Interest of Vertical Farming for Growing Medicinal Plants

The economic viability of leafy vegetable cultivation in indoor vertical farms with artificial lighting is complex, in particular on the European market because of their low market price, and high start-up, energy, and labor costs. In the United States, only 50% of container farms and 27% of indoor vertical farms reported operating profitability after 7 years of existence (Agrilyst 2017). Several studies on leafy greens in container farms reported that production costs were too high for them to be viable (Sparks and Stwalley III 2018; Debusschere and Boekhout 2021; Bafort et al. 2022). The selling prices in a simulated multilayer vertical farm – two layers containing four levels of lettuce each and two layers containing 18 rows of tomato each – were calculated to be 5.81 €/kg for an annual yield of 810 tons for lettuce and 9.94 €/kg for an annual yield of 215 tons for tomato, making profitability impossible (Zeidler et al. 2017). In Europe, several cases of bankruptcy of vertical farms have been reported, confirming the difficulty for vertical farming to be economically feasible (Sijmonsma 2019; VerticalFarmDaily.com 2021; Perreau 2022). Diversification by cultivating high-added-value plants, such as medicinal plants, could be less challenging economically. The economic approach of vertical farming of medicinal plants is discussed in Sect. 3.

Vertical farming is particularly suitable for producing medicinal plants. The stability of the environment makes it possible to increase stable and predictable yields and provide a stable quality with regular and high concentrations in phy-

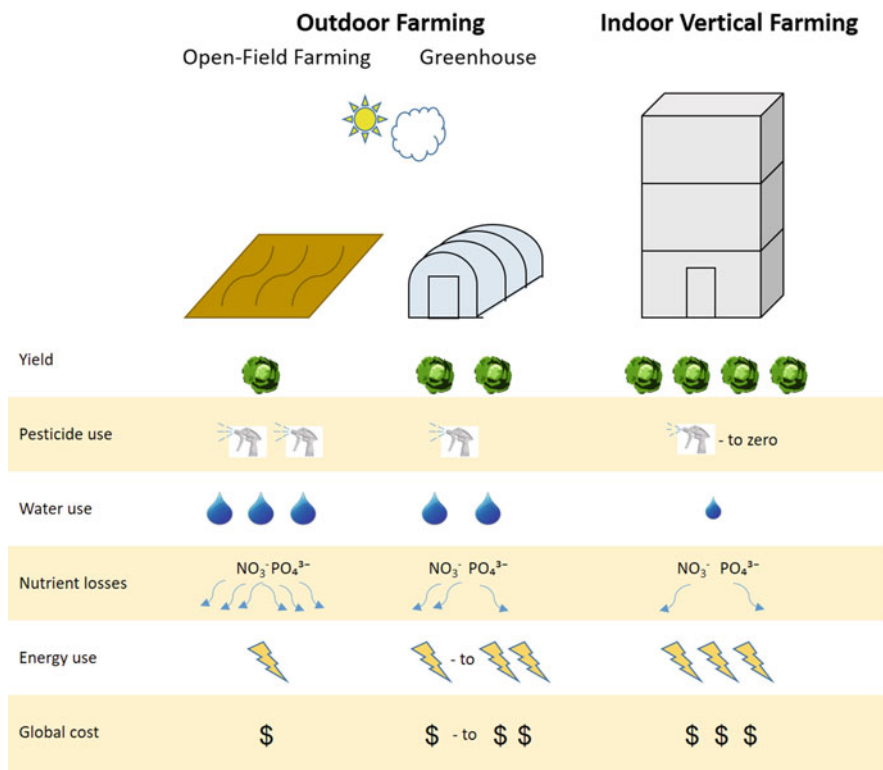


Fig. 5 Schematic overview of the current challenges of traditional farming and vertical farming. Please note that many forms of greenhouses exist, from plastic tunnels to fully automated greenhouses with complementary lighting devices

tochemicals, without soil contamination by microbes or pollutants (Goto 2012; Zobayed 2020). However, high biomass is contradictory with high concentrations in secondary metabolites, and a combination of these two criteria both important to reach economic viability is difficult to reach. Biomass increases are obtained by an ideal combination of abiotic factors – the most important variables are light, the water status, and the CO_2 concentration – so that photosynthesis is promoted and the production of primary metabolites such as starch and sucrose is promoted. Primary metabolites (lipids, proteins, and carbohydrates) are critical for plant growth and development. Plant growth is closely related to photosynthesis and respiration, and more than 90% of the crop biomass is derived from photosynthesis (Yamori 2020). Based on primary metabolites, plants metabolize various molecules with complex structural compositions called secondary metabolites (Naik and Al-Khayri 2016; Twajj and Hasan 2022). When plants encounter abiotic or biotic stresses, secondary metabolites are synthesized to communicate and act as a defense mechanism (Naik and Al-Khayri 2016; Dadhich et al. 2022). Plant secondary metabolites are usually

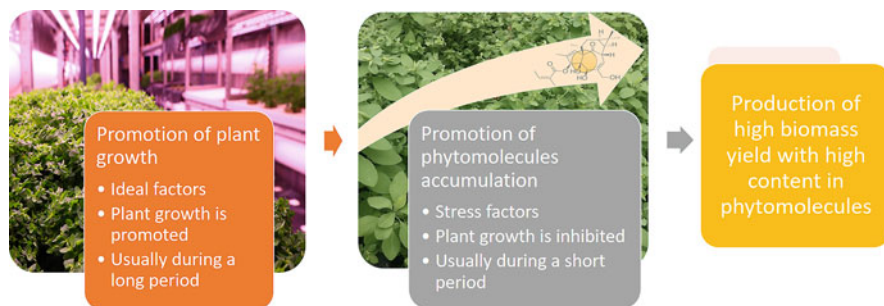


Fig. 6 Schematic overview of a two-step production principle allowing medicinal crop production with a significant biomass yield and an increased content in phytomolecules. The plant illustrated in the figure is *Euphorbia peplus* for its ingenol-mebutate content

classified in four major groups: (1) phenolics; (2) terpenes, saponins, and steroids; (3) nitrogen-containing compounds (such as alkaloids); and (4) glycosides (Hussein and El-Anssary 2018; Twaij and Hasan 2022). Following their specific presence and concentration, they characterize the medicinal property of the plant and its interest for the healthcare and pharmaceutical sector. However, the stress-induced enhancement of secondary metabolites alters plant development and growth (Itoh 2018; Dadhich et al. 2022). The enhancement of biomass is antagonistic with the enhancement of secondary metabolite production. Therefore, a dynamic two-step production of medicinal compounds has been proposed (Itoh 2018; Zobayed 2020) (Fig. 6).

2 Abiotic Factors Affecting the Quality of a Medicinal Crop

The environmental factors that play a role on plant photosynthesis and respiration also have an impact on plant growth and the accumulation of crop biomass. Ensuring the best environmental factors in a closed and controlled environment allows for a stable, maximized yield of high-quality plants, while stressing them may reallocate carbon to secondary metabolite production. Secondary metabolites are described as nonessential molecules for plant growth and biomass accumulation but are crucial for their interaction and adaptation to environmental fluctuations. Producing secondary metabolites is costly for plants because it requires primary metabolites, enzymes, cofactors, and energy. Secondary metabolites do not all have the same cost: terpenoids require less photosynthetically-produced carbon than alkaloids do (Gulmon and Mooney 1986; Cipollini et al. 2017). Plants' environments are usually classified in three main categories: (1) adverse biotic factors, such as fungi, bacteria, viruses, herbivores, and competing plants; (2) favorable biotic factors, such as symbiotic microorganisms, pollinators, seed dispersers, and plant-to-plant communication; and (3) abiotic factors, such as light, water availability, minerals

availability, soil fertilization, temperature, and, in closed environment, the CO₂ level (Yang et al. 2018). There is a general consensus that abiotic factors can significantly affect the accumulation of secondary metabolites and in turn the medicinal value of the plant. Therefore, it is crucial to correctly manage those factors during the production process.

2.1 Light

Light affects plants in two ways – as an energy source and as an information medium (Dou and Niu 2020). The energy of light is transmitted by the photons, and about 10% of sunlight are converted into chemical energy – carbohydrates – through photosynthesis, while the remaining 90% are converted into heat energy (Dou and Niu 2020). The absorption of light for photosynthesis is initiated by photosynthetic pigments – chlorophylls and carotenoids; chlorophylls strongly absorb red and blue light, and carotenoids strongly absorb blue light (Yamori 2020). Chloroplasts and whole leaves absorb most of the light, including green light (Yamori 2020). Plant photoreceptors measure the light composition variations and trigger plant responses independently from photosynthesis, as in photoperiodism and photomorphogenesis, and regulate the expression of genes associated with cell division and enlargement (Dou and Niu 2020). Five classes of photoreceptors have been described. They allow plants to perceive a broad spectrum of light from ultraviolet to far-red wavelengths and to regulate multiple physiological and metabolomic responses (Fig. 8).

2.1.1 Effect of the Quantity of Light

In controlled environments, artificial light is usually constant without the seasonal variation in intensity, duration, and spectrum of natural sunlight to which plant growth is subjected under natural conditions. The daily light integral (DLI) describes the total amount of photosynthetically active photons that are delivered to a specific area over a 24-hour period; it usually has a linear relationship with crop yield in controlled environments (Dou et al. 2018). The effects of three DLI levels of 8.64, 14.4, and 28.8 mol m⁻² d⁻¹ under a 16-h photoperiod were tested on the shoot biomass and the accumulation of a diterpene – ingenol-mebutate – by the medicinal plant *Euphorbia peplus* (Bafort et al. 2022). Increasing DLIs had a positive effect on yield, with shoot fresh biomass rises of 111% and 212% compared to the values obtained with a DLI of 8.64 mol m⁻² d⁻¹ (Fig. 7). The same trend was observed for shoot dry biomass. The calculated positive correlation was relatively low. It was attributed to the low homogeneity of the yield, which varied dramatically with the position of the plant in the vertical container, especially under the lowest DLI. In the same study, the content in ingenol-mebutate of *E. peplus* was not modified with the DLI level.

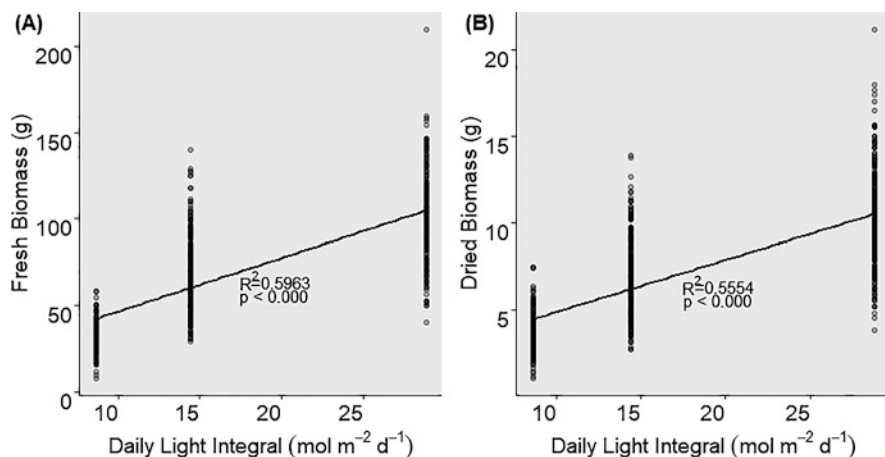


Fig. 7 Correlations and p-values between the shoot fresh biomass (a), the shoot dried biomass (b), and the daily light integral (DLI) of *Euphorbia peplus* grown at different DLI levels (8.64, 14.4, and 28.8 mol m⁻² d⁻¹) in a vertical container farm for 47 days. (Bafort et al. 2022)

In a completely closed and controlled environment, the DLI is modulated in two ways: (1) by adjusting the light intensity and (2) by adjusting the photoperiod.

Several studies have addressed the *role of the DLI* on yields and secondary metabolite contents by acting on the light intensity (photosynthetic photon flux density; PPFD) or on the photoperiod, or on both (Table 3). Basil (*Ocimum basilicum* L.) and lettuce (*Lactuca sativa*) are ideal crops for vertical farming, because they are well adapted to closed controlled and soilless environments, have short cultivation cycles and a limited height. Therefore, they have been extensively studied to determine the effect of environmental factors. The plant biomass is generally proportional to the DLI within a certain range (Dou and Niu 2020; Xu et al. 2021). Increasing the DLI increased the shoot fresh biomass yield of *O. basilicum* L., because of a higher photosynthetic rate and a linear accumulation of anthocyanins, phenols, and flavonoids *per plant* (Dou et al. 2018). However, the positive biomass correlation of basil with the DLI was also found cultivar dependent. For example, the Ararat variety had the largest weight at a DLI of 6.34, while the Yerevan sapphire variety reached its best yield at a DLI of 9.79 (Kondrat'Ev et al. 2021). A fixed DLI of 12.9 did not cause the yield of basil to vary, whatever the photoperiod-PPFD combination (Dou and Niu 2020). Red perilla shoot dry weight increased with the DLI but not in a linear manner, because light utilization efficiency decreased with increased PPFD (Yoshida et al. 2022). Anthocyanins accumulated *per dry weight unit* with higher DLI, but the essential oil perillaldehyde did not (Yoshida et al. 2022).

The effect of an *extended photoperiod* has been studied. Compared to DLIs of 5.8, 8.6, and 11.6, basil and lettuce growth were improved under a DLI of 14.4 corresponding to a PPFD of 250 $\mu\text{mol m}^{-2} \text{s}^{-1}$ under a 16 h photoperiod, and so were the

Table 3 Effect of the light quantity on plant growth and on secondary metabolite accumulation

Plant species	Daily light integral (mol m ⁻² d ⁻¹)	Effect on plant growth	Effect on secondary metabolite content	Reference
<i>Ocimum basilicum</i> L.	4.61 (80 PPFD; 16 h) 6.34 (110 PPFD; 16 h) 8.06 (140 PPFD; 16 h) 9.79 (170 PPFD; 16 h)	Highest yield with DLI = 6.34, 8.06 and 9.79, depending on the basil cultivar	Not studied	Kondrat'Ev et al. (2021)
<i>Ocimum basilicum</i> L.	9.3 (160 PPFD; 16 h) 11.5 (200 PPFD; 16 h) 12.9 (224 PPFD; 16 h) 16.5 (290 PPFD; 16 h) 17.8 (310 PPFD; 16 h)	Higher DLIs increased yield, but no significant differences in yield between DLIs of 12.9, 16.5 and 17.8	Higher DLIs increased the total anthocyanin, phenolic and flavonoid contents <i>per</i> plant	Dou et al. (2018)
<i>Ocimum basilicum</i> L.	12.9 ((298 PPFD; 12 h) 12.9 (256 PPFD; 14 h) 12.9 (224 PPFD; 16 h) 12.9 (199 PPFD; 14 h) 12.9 (179 PPFD; 20 h)	No yield differences between photoperiod and PPFD variation with a fixed DLI of 12.9	Not studied	Dou and Niu (2020)
<i>Ocimum basilicum</i> L. <i>Lactuca sativa</i> L.	5.8 (100 PPFD; 16 h) 8.6 (150 PPFD; 16 h) 11.5 (200 PPFD; 16 h) 14.4 (250 PPFD; 16 h) 17.3 (300 PPFD; 16 h)	Highest yield with DLI = 14.4	Higher antioxidant capacity, phenolics and flavonoids in <i>L. sativa</i> at DLI = 14.4	Pennisi et al. (2020)
<i>Lactuca sativa</i> L.	8.64 (150 PPFD; 16 h) 8.64 (200 PPFD; 12 h) 9.04 (2x3h at 100 PPFD and 6 h at 300 PPFD)	Better yield obtained with longer photoperiod and multi-segment light intensity	Not studied	Mao et al. (2019)

(continued)

Table 3 (continued)

Plant species	Daily light integral (mol m ⁻² d ⁻¹)	Effect on plant growth	Effect on secondary metabolite content	Reference
<i>Perilla frutescens</i> L.	2.88 (50 PPFD; 16 h) 5.76 (100 PPFD; 16 h) 11.52 (200 PPFD; 16 h) 23.04 (400 PPFD; 16 h)	Increased yield with increased DLI	Perillaldehyde content <i>per</i> unit of dry weight similar whatever the DLI. Anthocyanin content <i>per</i> unit of dry weight increased with DLI	Yoshida et al. (2022)
<i>Catharanthus roseus</i> (L.)	4.32 (75 PPFD; 16 h) 8.64 (150 PPFD; 16 h) 17.28 (300 PPFD; 16 h) 34.56 (600 PPFD; 16 h)	Best fresh total leaf weight obtained with DLI = 17.28	Highest vindoline and catharanthine contents with DLI = 8.64	Fukuyama et al. (2015)
<i>Ophiorrhiza pumila</i>	2.16 (50 PPFD; 12 h) 2.9 (100 PPFD; 8 h) 4.32 (100 PPFD; 12 h) 5.8 (100 PPFD; 16 h) 6.48 (150 PPFD; 12 h)	Best yield with DLI = 5.8	Highest camptothecin content with DLI = 5.8	Lee et al. (2020)
<i>Tropaeolum majus</i> L.	17.3 (300 PPFD; 16 h) 17.3 (200 PPFD; 24 h) 25.9 (300 PPFD; 24 h) 34.6 (400 PPFD; 24 h)	Linear increase in total biomass with DLI. At same DLI (17.3), better shoot yield with increased photoperiod.	Antioxidant capacity and total phenolic content increased with increased DLI	Xu et al. (2021)
<i>Stevia rebaudiana</i>	7.2 (249 PPFD; 8 h) 7.2 (165 PPFD; 12 h) 7.2 (125 PPFD; 16 h) 7.2 (125 PPFD; 16 h intermittent)	Highest yield with constant longer photoperiod	Highest yield of stevioside and rebaudioside A <i>per</i> plant under 16 h photoperiod but higher rebaudioside A concentration under 8 h photoperiod	Rengasamy et al. (2022)

(continued)

Table 3 (continued)

Plant species	Daily light integral (mol m ⁻² d ⁻¹)	Effect on plant growth	Effect on secondary metabolite content	Reference
<i>Nasturtium officinale</i> L	11.52 (266 PPFd; 12 h) 11.52 (200 PPFd; 16 h) 11.52 (160 PPFd; 20 h) 11.52 (133 PPFd; 24 h)	Highest yield under 20 h photoperiod	Highest total glucosinolate content <i>per</i> plant shoot under 20 h photoperiod	Lam et al. (2021)
<i>Amaranthus tricolor</i> , <i>Brassica oleracea</i> var. <i>viridis</i> , <i>Ocimum basilicum</i>	14 (250.8 PPFd; 16 h) 14 (166.6 PPFd; 24 h) 21 (376.9 PPFd; 16 h) 21 (247.6 PPFd; 24 h)	Highest yield under DLI = 21 with constant lighting	High DLI with constant lighting and high DLI increased <i>A. tricolor</i> and <i>B. oleracea</i> var. <i>viridis</i> phenolic, anthocyanin and antioxidant contents. Unaffected secondary metabolite concentrations in basil	Lanoue et al. (2022)

water, energy, and light use efficiencies (Pennisi et al. 2020). Secondary metabolites also accumulated in lettuce at a DLI of 14.4 (Pennisi et al. 2020). An extended photoperiod (16 h) under a low light intensity (PPFD = 100 $\mu\text{mol m}^{-2} \text{s}^{-1}$) promoted chlorophyll accumulation and improved the root/shoot ratio, helping lettuce to absorb enough light energy and improve its growth under low light conditions (Mao et al. 2019). Lettuce increased its photosynthetic capacity significantly under multi-segment lighting, which simulated circadian rhythms and resulted in an increased yield (Mao et al. 2019).

Shade plants such as *Ophiorrhiza pumila* have a low saturation point and showed better biomass yield and camptothecin accumulation under a low PPFD (100 $\mu\text{mol m}^{-2} \text{s}^{-1}$) and a long photoperiod (16 h) (Lee et al. 2020a, b). Mid-shade plants such as *Catharanthus roseus* showed an increased yield up to a certain level of DLI (17.28), but a higher DLI led to the inhibition of growth (Fukuyama et al. 2015). In the same plant, vindoline and catharanthine accumulation were greatest under a lower DLI (8.64) (Fukuyama et al. 2015). An extended photoperiod strategy can also be well adapted to tropical countries, where natural weather conditions and the day-neutral photoperiod restrict field growth of some plants. For example, stevia plant productivity and quality were enhanced under a long and constant photoperiod (16 h) at a low light intensity (PPFD = 125 $\mu\text{mol m}^{-2} \text{s}^{-1}$) (Rengasamy et al. 2022).

The effect of *continuous lighting* (24 h) has also been studied. *Tropaeolum majus* L. showed a linear increase in dry weight with the DLI under continuous lighting with DLIs ranging from 17.3 (PPFD = 200 $\mu\text{mol m}^{-2} \text{s}^{-1}$) to 34.6 $\text{mol m}^{-2} \text{d}^{-1}$ (PPFD = 400 $\mu\text{mol m}^{-2} \text{s}^{-1}$) (Xu et al. 2021). The increased yield resulted in reversible photoinhibition during plant growth and in an adaptive process to protect the photosynthetic apparatus from light stress (Xu et al. 2021). With a fixed DLI of 17.3, secondary metabolite production was increased under continuous lighting compared to a higher light intensity and a shorter photoperiod (Xu et al. 2021). Continuous lighting and a higher DLI – hence higher light intensities – maintained the secondary metabolite content (Xu et al. 2021). The productivity and quality of four microgreens were tested under two DLIs and constant lighting or a long photoperiod (16 h) (Lanoué et al. 2022). For each fixed DLI, the yield was better under constant lighting and maximized at the highest DLI (Lanoué et al. 2022). Interestingly, higher energy-use-efficiencies of lighting were observed under constant light, and a reduced electricity cost *per* unit of fresh biomass was measured (Lanoué et al. 2022). The nutritional quality of amaranth and collard greens was also improved at high DLIs, without or with constant lighting, and unchanged in basil (Lanoué et al. 2022). However, constant lighting and a low DLI – i.e., a low light intensity – can impact plant growth negatively. *Nasturtium officinale* L. growth was decreased under constant lighting and a low light intensity (133 $\mu\text{mol m}^{-2} \text{s}^{-1}$) because of reduced net photosynthesis and stomatal conductance (Lam et al. 2021). On the contrary, the total glucosinolate concentrations were highest in those conditions, but the total glucosinolate content *per* shoot dry weight was reduced, because of the markedly reduced biomass (Lam et al. 2021). Continuous lighting can also induce negative effects on sensitive plants, e.g., leaf chlorosis, growth inhibition, and leaf necrosis that may result from photo-oxidative damage (Xu et al. 2021). The hypothesis is that continuous-lighting-tolerant plants have high antioxidant contents that protect them (Xu et al. 2021). For example, continuous lighting induced higher chlorogenic acid content in lettuce plants that could protect them against high levels of reactive oxidative species generated by physiological stresses (Shimomura et al. 2020). On the contrary, basil growth under continuous lighting induced physiological stress, such as chlorosis, stunting, and leaf necrosis (Sipos et al. 2021).

2.1.2 Effect of the Quality of Light: Spectral Quality and UV Radiation

Spectral Quality The quality of light is perceived by photoreceptors, whose reaction to light quality is species-specific. Therefore, the effect of light quality should be considered separately for each plant species (Dou and Niu 2020; Karimi et al. 2022). Light quality influences plant growth and the synthesis of bioactive compounds (Yang et al. 2018; Dou and Niu 2020).

In general, *red (R)* and *blue (B) lights* are the most commonly used spectra in indoor cultivation, because they correspond to the absorption peaks of chlorophylls

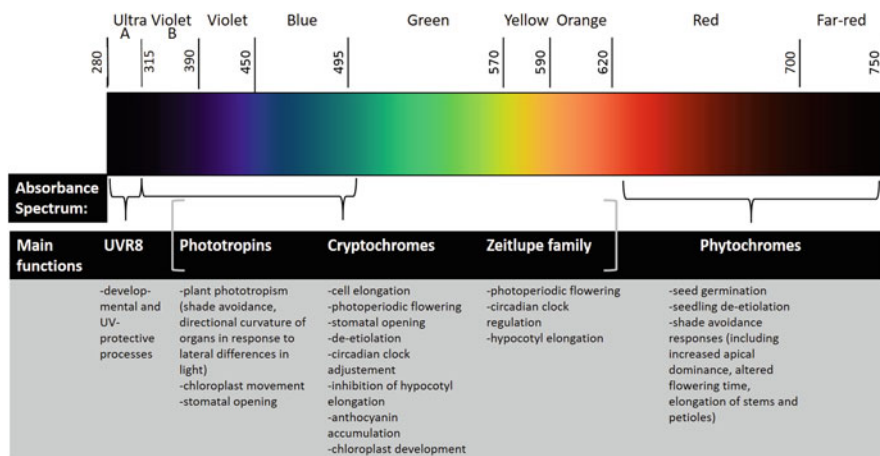


Fig. 8 Representation of the main absorbance spectra and main functions of the five photoreceptor classes. (From Christie et al., 2015; Dou, Niu and Gu, 2019; Appolloni et al. 2022; Paradiso and Proietti 2022). *UVR8* UV resistance locus 8

and to the main plant functions, as showed in Fig. 8 (Dou and Niu 2020; Appolloni et al. 2022). Combined R&B lights are more efficient than monochromatic blue or red lights for plant growth, which can induce physiological disorders in some plant species (Dou and Niu 2020). Full-spectrum *white light-emitting diodes (LEDs)* have recently been found efficient in indoor culture; they supply a full spectrum that optimizes plant growth (Dou and Niu 2020). *Green light* is not fully absorbed by chlorophyll and has long been considered less effective than red and blue lights in promoting plant growth (Paradiso and Proietti 2022). Nowadays, it is admitted that green light penetrates deeper into the plant canopy and may promote better photosynthesis in the whole canopy (Paradiso and Proietti 2022). Inclusion of green light in dichromatic red and blue LEDs impacted plant growth differently depending on its proportion (Orlando et al., 2022a, b). A high proportion of green light (25–44%) generated opposite responses to blue- or red-light-induced effects and negatively affected sweet basil and microgreen quality (Kim et al. 2005; Zhang and Folta 2012; Dou et al. 2019, 2020a, b). A low proportion of supplemental green light – under 10% – to red and blue spectra did not affect the fresh or dried biomass of several microgreens (Ying et al. 2020; Orlando et al. 2022a, b). However, 12–24% green light addition to red and blue lights positively affected the biomass of lettuce and kale and induced secondary metabolite accumulation in *Crocus sativus* and lettuce plants (Kim et al. 2005; Bian et al. 2016; Meng et al. 2019; Orlando et al. 2022a, b).

The effect of light spectra on the accumulation of *phenol* metabolites in medicinal plants has been investigated. Combined blue (38%) + red (62%) lights and combined blue (38%) + green (12%) + red (50%) lights have been tested on *C. sativus* tepal biomass and bioactive metabolite accumulation and compared with

those obtained under greenhouse cultivation (Orlando et al. 2022a, b). The inclusion of green light increased the total flavonoid content and the biomass remained unaffected as compared to the greenhouse production. Therefore, cultivation under LEDs may positively valorize *C. sativus* by-products. Blue LEDs, red LEDs, combined blue (70%) + red (30%) LEDs, and white LEDs have been tested on the growth and the phenolic compound production of *Dracocephalum forrestii* shoots (Weremczuk-Jeżyna et al. 2021). The best biomass values, shoot propagation, and secondary metabolite production were obtained under blue LEDs. The enhancement of the antioxidant capacity was positively correlated with the maximum total polyphenolic acid content. Blue, red, and white LEDs were tested on the roots, stems, and leaves of *Scutellaria baicalensis* seedlings for 2 weeks (Yeo et al. 2021). The roots treated with white LEDs showed increased concentrations of the flavonoids baicalin, baicalein, and wogonin and reduced concentrations of carbohydrates, suggesting the need for energy to enhance the biosynthesis of phenolic compounds. The effects of monochromatic red, blue, and green LEDs, several dichromatic red (60–90%) and blue (40–10%) LEDs, and several trichromatic red (50–90%), green (10%), and blue (40–0%) LEDs were tested on the growth and bioactive compound biosynthesis of *Crepidiastrum denticulatum* (Park et al. 2020a, b). The total phenolic content was similar among all treatments, but the antioxidant capacity and dry weight *per* shoot were increased under the trichromatic red (80%) + green (10%) + blue (10%) LEDs. The addition of far-red light to dichromatic blue (20%) and red (80%) LEDs was tested on the growth and phenolic content of *C. denticulatum* (Bae et al. 2017). Growth was increased under supplemental far-red irradiation, while the phenolic content *per* unit dry weight remained unaffected by the different light treatments.

Several light combinations have been tested on the accumulation of bioactive *terpene/terpenoid* compounds produced by medicinal plants. Six light treatments – monochromatic red and blue LEDs and dichromatic red (80–20%) and blue (20–80%) LEDs – were tested on *Hypericum perforatum* (Karimi et al. 2022). The plants under the monochromatic red light showed an increased accumulation of foliage, higher flower and root fresh and dry weights, and an increased percentage of hypericin, pseudohypericin, and hyperforin in their flowers *per* square meter. Red light stimulated the expression of genes related to *H. perforatum* flowering. Enhanced accumulation of artemisinin and artemisinic acid and other terpenoids in *Artemisia annua* and increased fresh leaf weight were measured under white and blue spectra (Sankhuan et al. 2022). Moreover, crude extracts under the same light treatment showed improved antimalarial anti-*Plasmodium falciparum* activity compared to crude extract under monochromatic red light treatment and greenhouse cultivation. Red light treatment decreased the level of terpenoid production and induced distinct phytochemical profiles.

The effect of the light spectrum on *alkaloid* accumulation has been studied in medicinal plants. Several light spectra were applied on embryogenic *Fritillaria cirrhosa* D. Don calluses for 3 months to measure their effect on growth and alkaloid production (Chen et al. 2020). Monochromatic red, blue, and far-red, warm, and cold white lights and various combinations of red, blue, green, and far-red treatments induced differential development and growth of *F. cirrhosa*. The maximum fresh

weight was obtained under monochromatic red light, and the highest contents in peimisine, peiminine, and peimine were recorded under the monochromatic red light and infrared light. *Picea abies* seedlings were exposed to white light with 12% or 45% added blue light (Kivimäenpää et al. 2021). The spectra with the highest blue light content decreased the alkaloid, terpene, and terpenoid concentrations in needles, although the contents in total flavonoids and acetophenones were increased. Growth and the carbohydrate and pigment contents were unaffected, suggesting carbon reallocation from alkaloid and terpenoid synthesis to flavonoid synthesis as a response to increased blue light.

UV Radiation UV radiation induced multiple responses ranging from slowed down photosynthesis to increased DNA repair, defense mechanisms, and specialized metabolite production (Vanhaelewyn et al. 2020). Reactive species (ROS) in response to UV-B radiation cause DNA damage, affect the plant metabolism, and generate defense mechanisms such as the production of ROS-scavenging enzymes and antioxidant compounds (Park et al., 2020a, b). Specialized metabolites are synthesized, thanks to the reallocation of carbon toward the production of phenolics (e.g., flavones, flavonols, anthocyanins), alkaloids, carotenoids, and glucosinolates (Vanhaelewyn et al. 2020). Supplemental UV-B radiation typically decreases biomass; therefore, using this light stress needs fine-tuning to achieve both good yield and enhanced bioactive metabolites (Dou and Niu 2020).

UV-B radiation has been tested on *C. denticulatum* growth and its biosynthesis of total carotenoids, phenolics, and terpenes (Park et al. 2020a, b). High-energy UV-B light reduced the chlorophyll content and several sesquiterpene contents and increased the total carotenoid, phenolic, and hydroxycinnamic acid contents, while it decreased *C. denticulatum* growth. Moderate energy levels of UV-B radiation (0.1 and 0.25 W m^{-2}) increased the antioxidant capacity, the total hydroxycinnamic acid content, and several sesquiterpenes without inhibiting growth and were considered as a eustress (Park et al. 2020a, b). The effect UV-B light on the terpene content of *Panax ginseng* C.A. Meyer has been tested (Choi et al. 2022). A low-energy dose of 0.1 W m^{-2} for 1, 2, or 3 hours during the preharvest days did not modify the total ginsenoside content. Several spectra – monochromatic blue and red and red with high energy (5 W m^{-2}) UV-A – were tested on the growth and the alkaloid vinblastine content of *C. roseus* for 7 days (Fukuyama et al. 2017). The total leaf dry weight was unaffected whatever the spectrum, while the vinblastine content *per* dry weight unit was significantly increased after 3 days of UV-A treatment and highest after 7 days of UV-A treatment. The effect of several UV-A energy levels combined with red light revealed a positive correlation with the UV-A energy levels on the leaf vinblastine content and a negative correlation on the leaf vindoline and catharanthine contents (Fukuyama et al. 2017).

2.1.3 Light Combined with Others Factors

The growth of a plant depends on many abiotic factors. The plant's response may differ when a single factor or several additional environmental factors are studied. Therefore, checking the effects of multiple factors is an interesting approach. A classic approach is the one-factor-at-a-time (OFAT) design, which makes only one factor vary while the other variables are kept constant. Some limitations are that the interactions between factors cannot be estimated, and the risk of obtaining a false optimum is high when more than two factors are considered (Czitrom 1999). Another method is the design of experiments (DOE), for example, the response surface methodology or the Box-Behnken experimental design, which search for the factor level combination that gives the best answer (i.e., yield, content in phytochemicals). In this case, multiple factors can be modified together, the interactions among factors are estimated, and the response is optimized (Czitrom 1999).

Several studies have addressed the effect of multiple factors on plant growth and phytochemical production. Growth and bioactive metabolite production by red and green *Perilla* were tested by making three levels of electrical conductivity (EC) and three levels of PPFD vary (Lu et al. 2017). The concentration of perillaldehyde – a terpene – was not affected by EC or light intensity in red perilla, but the content in rosmarinic acid – a phenol – was highest under the highest light intensity and the lowest EC and decreased significantly when EC was increased. The shoot dry weight was promoted by higher light intensities under mid and high EC. In green perilla, the shoot dry weight increased with PPFD and EC, the perillaldehyde and rosmarinic acid concentrations decreased with increased EC, and rosmarinic acid was promoted by higher PPFD. Yield, anthocyanins, and soluble sugars were measured in *Brassica rapa* var. *Chinensis* under several light intensities and nitrogen concentrations (Hao et al. 2020). The yield was enhanced by the combination of a moderate PPFD and a moderate nitrogen concentration, but anthocyanins were optimized under high PPFD and nitrogen, and soluble sugars were promoted by the lowest nitrogen concentration. This shows how difficult it is to obtain a unique optimum for all parameters taken together. The optimal light intensity, temperature, and nutrients for *H. perforatum* L. accumulation of bioactive compounds were investigated (Kuo et al. 2020). Hyperforin and rutin were significantly affected by the light intensity and temperature, but the nutrient concentration had little effect. Melatonin seemed to be unaffected by the environmental factors considered in the study. The leaf biomass was enhanced with light intensity, temperature, and nutrients. Based on the response surface methodology, the optimal conditions for the yield of each specific metabolite were calculated.

2.1.4 Toward Sustainability of the Use of the Light Resource

The need for more sustainable agriculture is important in indoor cultivation systems where energy consumption is one of the major drawbacks. Artificial lighting

represents a major share of the energy requirements. The energy and light use efficiencies are two ways of measuring the energy costs of crop production in indoor systems. Energy use efficiency (EUE) is expressed in grams of biomass produced *per* kWh, and light use efficiency (LUE) is expressed in grams of biomass produced by light integral. Both units are useful to find the optimal response of plant growth to light intensity, and using them can show if higher light intensity – and higher energy requirements – can bring enough yield gain to be expressed as increased light and energy use efficiencies. The technological evolution of artificial lights has already improved the EUE of lettuce cultivated under LED light (EUE = 40.6 g kWh⁻¹) compared with lettuce cultivated under fluorescent lamps (EUE = 15.9 g kWh⁻¹) (Zhang et al. 2018). With further technological developments and societal demand, next-generation LEDs will improve energy supply and will allow for improved sustainability. Moreover, the use of the right spectral composition can improve EUE, as showed for indoor lettuce and basil cultivation (Pennisi et al. 2019a, b).

2.2 Nutrient Solutions

Nutrient solutions in soilless crop cultivation have to bring all the nutrients necessary for plant growth. Nutrients are described as essential macroelements and microelements, i.e., nutrients that cannot be replaced by another element, whose absence induces deficiency symptoms. They are directly involved in the plant metabolism (Tsukagoshi and Shinohara 2020). The nine macroelements are used in relatively large amounts, and the eight microelements are required in small amounts. Three macro-nutrients – carbon, oxygen, and hydrogen – are supplied from atmospheric carbon dioxide and water and are not included in fertilizers. However, enough dissolved oxygen has to be present in water for root respiration, generally brought by air pumps or agitation of the nutrient solution. The remaining macro-nutrients are nitrogen, phosphorous, potassium, calcium, magnesium, and sulfur. Micronutrients are iron, boron, manganese, copper, zinc, molybdenum, chlorine, and nickel. The main functions of each element are well-known and summarized in Fig. 9 (Tsukagoshi and Shinohara 2020).

Typical formulas have been developed and commercialized for soilless application and exist in a ready-to-use form. However, nutrient compositions should be ideally tested according to the plant type, its growth stage, the substrate type, and the targeted quality (Tsukagoshi and Shinohara 2020). Several ways of studying the effect of nutrition on plant growth and secondary metabolite accumulation are available. We selected four methodologies among them.

1. *Tailor-made nutrient recipes* have been developed and tested. Nitrogen, potassium, and phosphorous supplies were modulated on two medicinal plants – *Lavandula angustifolia* and *Mentha spicata* – to assess the yield and quality of essential oils (Chrysargyris and Tzortzakis 2021). Lower camphor and higher carvone contents were measured in *L. angustifolia* under nitrogen levels above

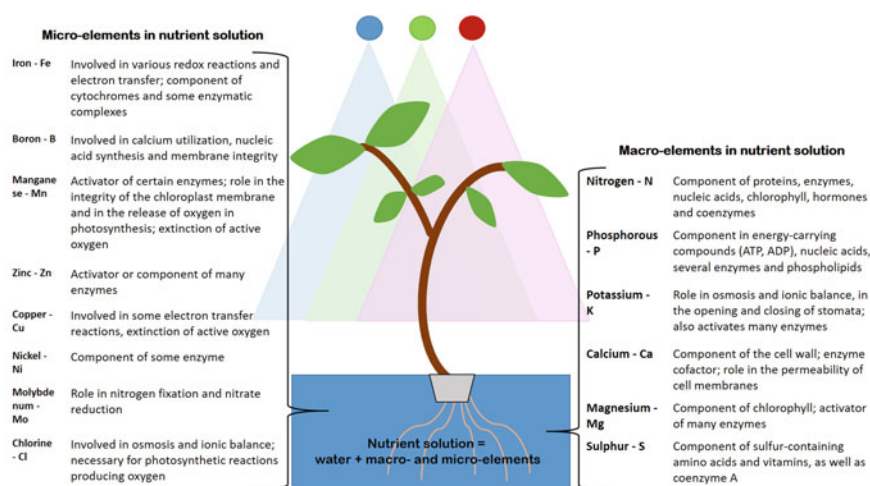


Fig. 9 Schematic representation of an indoor soilless plant and the macro- and microelements to be added to water to form a nutrient solution. The main functions of the nutrients are indicated (Tsukagoshi and Shinohara 2020). The macronutrients carbon, hydrogen, and oxygen are supplied by atmospheric carbon dioxide and water

200 mg L⁻¹, both indicating increased oil quality. The carvone and limonene contents of *M. spicata* were more sensitive to the nitrogen and potassium contents than to the phosphorous content. A home-made nutrient solution was tested on the growth, antioxidant level, and chicoric acid contents of *C. denticulatum* (Park et al. 2016). Increased EC increased *C. denticulatum* biomass, total phenolic content, chicoric acid content, and antioxidant capacity.

2. *Testing several concentrations of typical formulas* (e.g., Hoagland, Otsuka composition, commercial fertilizers) by making EC or application rates vary. Several concentrations of a ready-to-use fertilizer solution were tested on the growth and alkaloid content of *Mitragyna speciosa* (Zhang et al. 2020). Growth was promoted by increasing amounts of fertilizer, while the alkaloid concentrations were highly variable. Lower and medium fertilizer rates promoted the accumulation of several alkaloids, suggesting that nitrogen was reallocated to secondary metabolite synthesis. The yield, total phenolic content, and antioxidant capacity of *O. basilicum* L. were measured under several EC levels (Ren et al. 2022). Biomass was increased by medium to high EC, while the total phenolic content and antioxidant capacity were increased at low EC. Two-step cultivation was successfully applied, consisting in a first, long step under medium-high EC that promoted a good yield of sweet basil, followed by a second, short step just before harvest, when water (no fertilizer) or a low EC promoted total phenolic accumulation and the antioxidant capacity. The effects of the nutrient formula concentration and root temperature were tested on *Ophiorrhiza pumila* growth and camptothecin accumulation (Lee et al. 2020a, b). Growth and the

camptothecin content were best at a mid-high nutrient solution concentration. Several root temperatures were applied at the best nutrient concentration, among which 20 °C gave the optimum in yield and camptothecin content.

3. *Applying NaCl stress.* Salinity and nutritional stresses have been largely described to modulate the biosynthesis of secondary metabolites. The impact of salinity and the ammonium-to-total-nitrogen ratio were tested in closed hydroponic cultivation of *Solanum lycopersicum* (Tzortzakis et al. 2022). Salinity decreased plant growth and fruit yield but enhanced fruit quality, and increased lycopene, β -carotene, and vitamin C at harvesting or during storage. An appropriate ammonium-to-total-nitrogen ratio was suggested to reduce the negative effects of NaCl on the nutritional status of plants by regulating the pH in hydroponic systems. Several NaCl concentrations – 1.7, 25, 50, and 100 mM – were applied on *Reichardia picroides* (L.) Roth in hydroponic cultivation (Maggini et al. 2021). After 6 weeks, salinity above 1.7 mM induced a decreased yield but accumulation of anthocyanins, flavonol glycosides, and total phenols and improved the antioxidant capacity. The effects of increasing NaCl concentrations (1–40 mM) were tested in hydroponic and aquaponic cultivation systems of the drug-type *Cannabis sativa* L. during the flowering period (Yep et al. 2020). The cannabinoid contents decreased linearly with increasing NaCl concentrations in both systems. Decreased yields in hydroponic systems have been observed from NaCl concentrations above 5 mM. Forty mM was phytotoxic in hydroponics, but not in aquaponics, suggesting a potential NaCl tolerance induced by aquaponics. The impacts of salinity, calcium chloride – that may alleviate salt stress – and successive harvests were tested on two *O. basilicum* L. cultivars (Ciriello et al. 2022). Moderate salinity in the presence or absence of calcium chloride and high salinity in the presence of calcium chloride showed improved nutritional quality with improved phenol concentrations and reduced nitrate levels without affecting the eucalyptol content. In the green cultivar, the yield decreased with increased salinity. Successive harvests increased the phenol and vitamin C concentrations but reduced the eucalyptol content. The impact of nutrient deficiency and salinity was tested on the soilless greenhouse cultivation of the halophyte *Crithmum maritimum* (Castillo et al. 2022). Increasing salinity induced reduced foliar accumulation of several terpenes and total lipids, while nutrient deficiency increased the concentrations of some polyphenols. Salt stresses were applied in soilless greenhouse cultivation of *Schizonepeta tenuifolia* Briq. (Zhou et al. 2018). Salt treatments positively modulated the density of total glandular trichomes on both leaf sides, while their relative contents in pulegone, other monoterpenes, and sesquiterpene decreased significantly. On the other hand, ketones, alkanes, and esters increased significantly in glandular trichomes with increasing salt stress.
4. *Adding a plant-growth-promoting rhizobacterium or a natural bioactive compound.* The impact of mineral nutrient supply (S or N) and rhizobacterium inoculation on two *O. basilicum* L. cultivars was investigated (Kolega et al. 2020). Fortified nutrient solutions positively impacted the fresh biomass of both cultivars, while inoculation with *Azospirillum brasilense* did not promote growth.

Metabolomics analyses revealed that rhizobacterium inoculation modulated the accumulation of more than 400 secondary metabolites, e.g., terpenoids, phenols, alkaloids, and phenylpropanoids. The primary metabolism was also influenced, with changes in the metabolism of fatty acids, carbohydrates, and amino acids. However, the observed responses were rather cultivar-dependent than following a generalized modification of the phytochemical profile. The effects of natural bioactive products (NBP) – two from fermented plant extracts and microorganisms; bioactive substances extracted from *Ecklonia maxima* – on the growth and ginsenoside content of vertically and aeroponically cultivated *P. ginseng* were tested (Kim et al. 2012). The effects on the root and leaf ginsenoside content were treatment- and location- (upper or lower layer) dependent. A biostimulant made of a plant-derived protein hydrolysate and saline conditions were tested on soilless greenhouse production of *L. sativa* L. (Lucini et al. 2015). Salt stress decreased the shoot and root dry biomass of lettuce, but application of a biostimulant under salt stress increased fresh yield, dry biomass, improved the plant nitrogen metabolism, and delayed photoinhibition as compared to plants under salinity stress. Root and leaf application of the biostimulant under salt stress induced changes in sterol and terpene composition.

Sustainable Nutrients in Vertical Farming

Mineral fertilizers are mainly used in hydroponics nutrient solutions. However, exploiting these resources contributes to land degradation, water contamination, excessive energy consumption, and air pollution (Szekely and Jijakli 2022). In a perspective of sustainability and to meet the challenges of agriculture and climate change worldwide, alternatives should be developed. The organic form of hydroponics (called bioponics) recycles organic waste into a nutrient solution. Several studies have showed positive effects on plant disease mitigation and crop quality, notably with higher health-promoting compounds and/or lower nitrate levels in leafy vegetables (Szekely and Jijakli 2022).

2.3 Temperature

Temperature stress induces many changes in the physiological, biochemical, and metabolic processes and alters the production of bioactive compounds (Fig. 10). Crops with cold or heat tolerance mechanisms better cope with temperature stress (Hasanuzzaman et al. 2013). At low chilling temperature, enzymatic activities are slowed down. In leaves, the balance between light harvesting by photosystem II (PSII) and light utilization through metabolic enzymatic activity is disrupted, leading to photoinhibition and decreased photosynthetic activity (Miura and Furumoto 2013). The reduced activities of antioxidant enzymes result in the accumulation of reactive oxygen species (ROS) (Hasanuzzaman et al. 2013). Adaptive mechanisms have been described, such as promotion of the cyclic electron flow, regulation of energy distribution, antioxidant activity initiation, and accumulation of osmotic

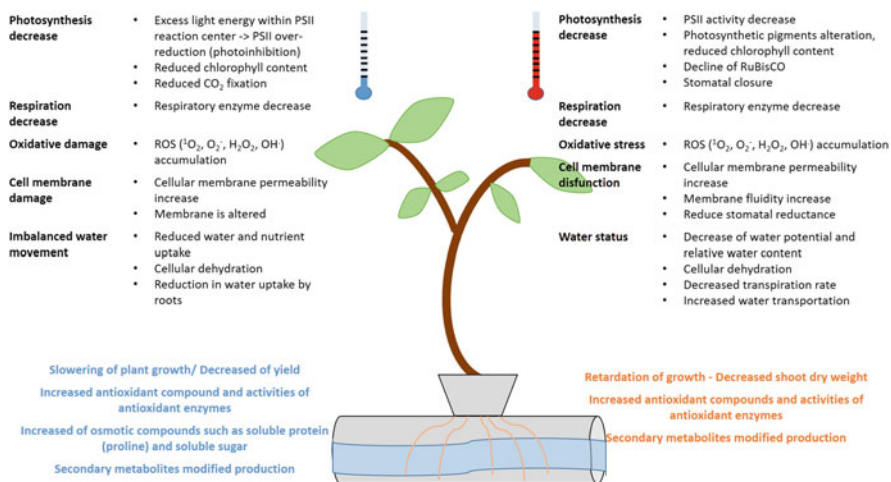


Fig. 10 Representation of the main physiological modifications induced by cold or heat stress in a hydroponically cultivated plant

regulators (soluble sugars and soluble proteins such like proline and betaine) (Li et al. 2022). Under heat stress, the efficiency of photosynthesis declines, because PSII activity, Rubisco activity, the photosynthetic pigment content, and the carbon fixation capacity are reduced (Zhao et al. 2020). Other physiological changes occur like altered cell membrane thermostability or oxidative damage (Zhao et al. 2020). Plants accumulate antioxidants (proline, glutathione, ascorbate, carotenoids), and the activity of antioxidant enzymes is increased (Hasanuzzaman et al. 2013). Another adaptive response may be a reduced chlorophyll content, as this decreases the energy absorption linked to chlorophyll energy absorption and lowers leaf heating (Mesa et al. 2022).

The response of *Paspalum wettsteinii* under heat stress treatments has been investigated (Zhao et al. 2022). A metabolic analysis revealed that biosynthesis of flavonoids and anthocyanins was both up- and downregulated under heat stress. Heat and cold stresses were applied on *S. lycopersicum* L. (Mesa et al. 2022). Heat stress decreased plant productivity and increased tocochromanols in the leaves and ascorbic acid in the fruit. The effect of short low/high temperature treatments on the root zone of *Coriandrum sativum* L. have been studied (Nguyen et al. 2020). Short temperature treatments reduced fresh biomass, while carotenoids, phenolics, chlorogenic acid, ascorbic acid, and the antioxidant capacity of the plants were enhanced under the extreme temperature treatments (15 °C or 35 °C) for 6 days.

Terpene emission is generally controlled by temperature (Staudt and Bertin 1998; Tarvainen et al. 2005; Ibrahim et al. 2010; Yang et al. 2018). Augmenting night temperature increased the terpene content of *Betula pendula* and *Populus tremula* (Ibrahim et al. 2010). The influence of antagonistic successive stresses – cold (4 °C, 30 min)/heat (from 25 °C to 60 °C within 5 min) and heat (from

25 °C to 60 °C within 5 min)/cold (4 °C, 30 min) – on *O. basilicum* L. and *Salvia officinalis* L. was tested (Copolovici et al. 2022). Terpene emissions were enhanced in plants under successive stresses as compared to the control plants, while the phenolic and flavonoid contents remained unaffected. The impact of temperature stress on *H. perforatum* was investigated (Zobayed et al. 2005). The shoot contents in hypericin, pseudohypericin, and hyperforin increased with high temperature (35 °C). The effects of temperature on the growth and terpene production of *Platycodon grandiflorum* A. DC in soil and soilless culture systems were measured (Nguyen et al. 2022). Fresh weight was highest under soilless cultivation conditions at 20 °C, and the shoot contents in platycodin D3, polygalcin D, and total saponin were optimized at 20 °C and 25 °C.

The increase in metabolite production should be calculated along with CO₂ emissions if temperature is increased or decreased in order to improve sustainability and lower environmental costs.

2.4 CO₂ Level

Increased levels of CO₂ induced increased photosynthesis, mainly due to increased Rubisco activity, which is not saturated at current atmospheric CO₂ concentrations. Increased photosynthesis results in better growth and yield. The photosynthetic rate, the transpiration rate, stomatal conductance, and the leaf, stem, and root carbon contents of *Withania somnifera* (a medicinal plant native to India) increased significantly in elevated CO₂ conditions, and dry weight increased too (Sharma et al. 2018). Elevated CO₂ levels improve water use efficiency and mitigate the negative effects of drought stress (Li et al. 2018). Cucumber seedlings under drought stress conditions and increased CO₂ levels had a higher leaf water content, regulated the cell osmotic pressure by accumulating carbohydrates, and accumulated secondary metabolites (Li et al. 2018). Several studies were conducted under CO₂ enrichment to increase the medicinal properties of *Labisia pumila*, a medicinal plant found in the Indochinese Peninsula. The total phenolic and flavonoid contents increased under high CO₂, together with a reduced chlorophyll content (Ibrahim and Jaafar 2011a). The enhanced secondary metabolite content could be due to reallocation of phenylalanine from protein synthesis to secondary metabolite production (Ibrahim and Jaafar 2011b). Under 1200 μmol mol⁻¹ of CO₂ enrichment, increased nitrogen fertilization reduced the total phenolic and flavonoid contents (Ibrahim and Jaafar 2011b, 2017).

Combined light intensities and CO₂ levels have been investigated. The cumulated values of secondary metabolites and antioxidant activity were observed at the lowest light intensity (PPFD = 225 μmol m⁻² s⁻¹) and the highest CO₂ level (1200 μmol mol⁻¹) (Ibrahim et al. 2014). The cytotoxicity of *L. pumila* variety *alata* leaf extract toward cancer cells was strongest under elevated CO₂ (1200 μmol mol⁻¹) and low light intensity (PPFD = 300 μmol m⁻² s⁻¹), and the concentrations of different phenolics and flavonoids, the total phenolic, flavonoid,

and saponin contents were highest (Karimi et al. 2016). Some medicinal plants showed a positive correlation of their secondary metabolite content with light intensity and the CO₂ concentration. For example, *H. perforatum* L. (a herb native to Europe and West Asia) showed increased hypericin and pseudohypericin contents under a high CO₂ level and increased light intensity (Mosaleeyanon et al. 2005).

The combination of temperature and CO₂ concentrations has been investigated. *Gynostemma pentaphyllum* (a herbal drug that grows in Asian countries) showed increased biomass but a reduced total antioxidant capacity and reduced levels of antioxidant compounds when cultivated under elevated CO₂ and increased temperature (Chang et al. 2016).

The impact of CO₂ enrichment seems to be species- as well as growth-stage-specific. If CO₂ is increased, one should check that it is well absorbed by the plants and that all the other conditions are optimal for the growth of the plant.

3 Economic Approach of Vertical Farming of Medicinal Plants

Vertical farms are shortly defined as multilayer soilless crop production systems including various ways of producing vegetables. “Vertical” refers to layers that can be vertically or horizontally mounted and to crop production systems that can be installed in closed or semi-closed structures. Semi-closed systems are typically greenhouses with sunlight that can be supplemented with artificial light. Indoor vertical farms are closed systems defined as plant factories using artificial lighting (PFALs), e.g., a container or a closed building. PFALs are controlled systems and are ideal for producing medicinal plants because the system ensures stable high standards, constant quality, and constant quantity. However, PFALs use intensive technology and are expensive because of expensive facilities and high energy and labor costs. As discussed previously, vertical farming of leafy greens is economically tricky in Europe, mainly due to high investment, energy, and labor costs combined with low market prices for such commodities. Economic studies on vertical farm construction, operation, and viability are lacking (Baumont de Oliveira et al. 2022). Most economic feasibility studies are based on hypothetical case studies and horticultural crop predictions, and none of them deals with medicinal plants. Cultivating high-added-value plants is assumed to be less economically challenging. However, no studies have been carried out on the whole process of making medicinal plant, from the indoor growing to the final product. The complete production scheme of medicinal plants depends on the form and application of the final product (Figs. 11 and 12). A medicinal plant product can be under various forms depending on its use, e.g., infusion, decoction, paste, poultice, multi-metabolites extract, or powder. The end-user’s choice involves a more or less complex production pattern. The cultivation process has to target the yield and the metabolite content through a fine-tuning of abiotic factors. If the final product is used fresh, the postharvest

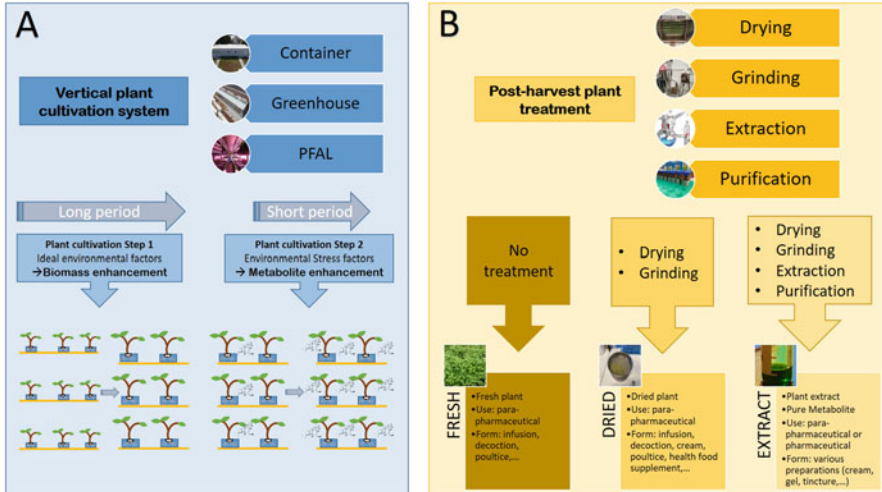


Fig. 11 Schematic representation of the two-step cultivation process of vertical medicinal plant farming (a) and the possible postharvest plant treatments (b)

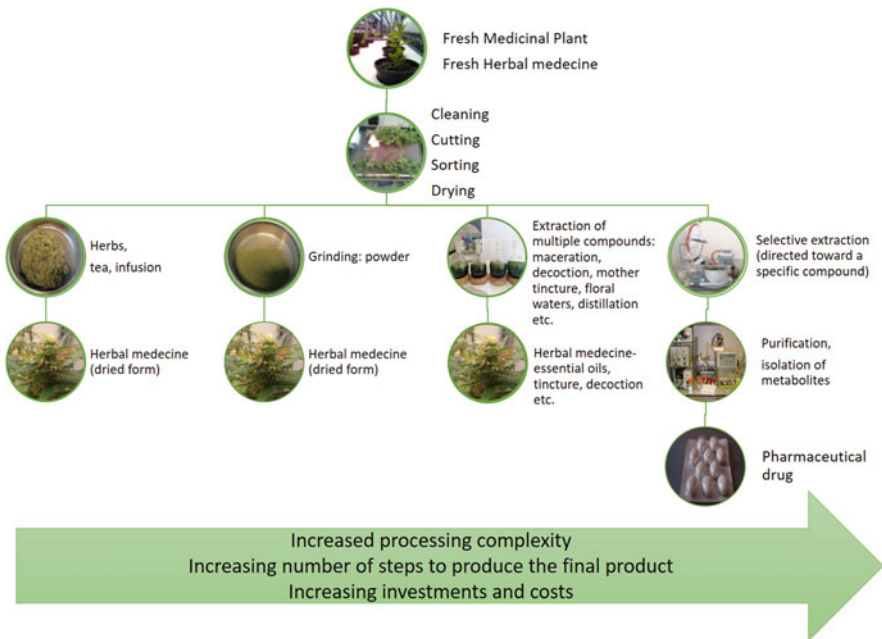


Fig. 12 Schematic representation of the various forms of herbal medicine

treatments and cost will be limited, but shelf-life could also be limited. For a powder formulation, a grinding and drying device will be necessary and can be acquired at a limited cost. In the case of plant extracts, more equipment is necessary, from an extraction device to a purification equipment, depending on the extract type and purity. After extraction and/or purification, a new treatment (drying, freeze-drying or dielectric drying) is often necessary to obtain a stable extract. Each supplementary step adds cost and makes the economic balance more difficult to achieve. This chapter analyzes the different steps of the production of a herbal medicine, from vertical indoor cultivation to extraction, including the pharmaceutical process. It is based on a case study on the agro-economic feasibility of cultivating a medicinal plant – *E. peplus* – in a vertical container farm and extracting ingenol-mebutate. The cultivation and extraction costs were based on experimental results, while the development, gel production, and flat fees costs were hypotheses based on the literature and consultation (Bafort et al. 2022). The economic feasibility of producing an ingenol-mebutate-based pharmaceutical product was calculated with Picato[®] gel, a prescription medicine containing ingenol-mebutate and used to treat skin actinic keratosis. Data on another medicinal plant – *Artemisia annua* – is also discussed (Bafort et al. 2023). The cost price is an economic term that refers to all the costs supported by a company to produce goods or a service. The sum has to include direct costs and indirect costs. Indirect costs are expenses that are not directly linked to the production of the product or service (advertising, rental of premises, salaries, etc.). Different calculation approaches exist, based on variable cost prices, direct cost prices, coefficient methods, and activity-based costing (Niessen and Chanteux 2005). Therefore, a company that offers different products and services has to choose the right analysis in order to understand how much a service or a product costs. In the paper, all the costs are related directly to production. The case-study is useful to forecast an economical evaluation of (i) cultivation and extraction process and (ii) pharmaceutical drug production. The forecast calculation for the pharmaceutical market is based on assumptions and general costs. The objective is to verify the economic viability of this type of model.

3.1 Cultivation Cost

Cultivation characteristics, such as the plant species, plant biomass, culture length, plant density, surface area, and specific environmental factors, have a direct influence on production costs. Several factors have been tested recently, such as the surface area, the cultivation cycle length, and the light intensity (Bafort et al. 2022). The production cost is strongly related to the productivity of the cultivation system, which can be described in different ways. Annual biomass – fresh or dried – is one of them and can also be described partly by the mean fresh or dried biomass *per* plant. The productivity of a cultivation system varies according to the following factors:

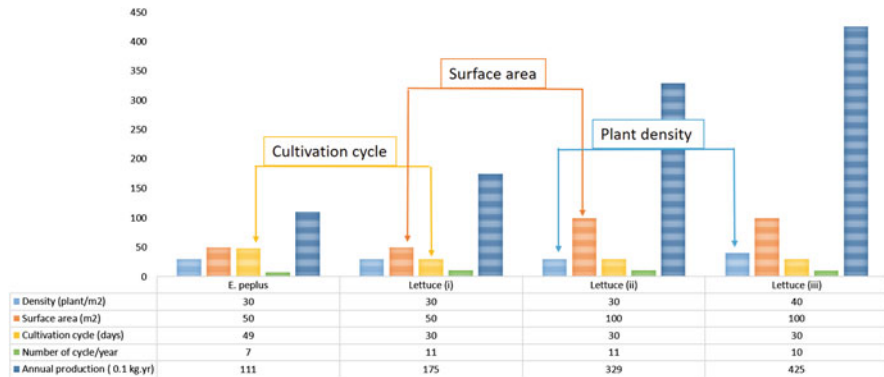


Fig. 13 Influence of plant density, surface area, and the length of the cultivation cycle on the annual production yield. First column and bars, typical cultivation conditions of *E. peplus* in a vertical container. Second to fourth columns and bars, simulation of Romaine lettuce cultivation in a vertical container with a shorter cultivation cycle (i), an increased surface area (ii), and an increased density of plants (iii)

- (i) The *cultivation cycle*. For a fixed biomass *per plant*, Fig. 13 shows how the annual biomass output depends on the cultivation cycle. If the cycle is short, more cycles can be achieved *per year* and productivity is increased. The cycle can be shortened by modifying abiotic factors. For example, reducing vegetative growth of hemp (*C. sativa*) by modifying the photoperiod shortens the cultivation cycle. Working with cuttings or in-vitro propagated plants instead of seeds can also make the cycle shorter. Container farming of the medicinal plant *E. peplus*, which has a cycle of 48.5 days, allows 7.2 cycles *per year*, taking the time needed for harvesting and cleaning into account, and gives an output of 1106 kg *per year*. Cultivating Romaine lettuce – a crop with a shorter culture cycle (30 days) – increased the number of cycles *per year* and increased annual biomass to 1745 kg.
- (ii) The *surface area*. Small cultivation surface units decrease productivity. Figure 1 shows that for a same crop and under identical environmental conditions, doubling the cultivating area enhanced annual productivity by 88.5%, from 1745 kg to 3285 kg.
- (iii) The *plant density*. The plant density is a way of increasing the productivity of a crop system. It can be improved by a specific design/improvement of the production area. For example, cultivation on vertically stacked layers can improve the plant density for some species, especially small plant. It will also need light to be placed not only above the cultivation tray but also surrounding the crop production layer. A greater plant density of lettuce from 30 to 40 plants *per m²* resulted in a 29.5% increase to reach 4255 kg of lettuce *per year* (Fig. 13).
- (iv) The *biomass per plant*. Higher biomass results in higher annual productivity and higher output of the medicinal product (dried leaves, infusion bags,

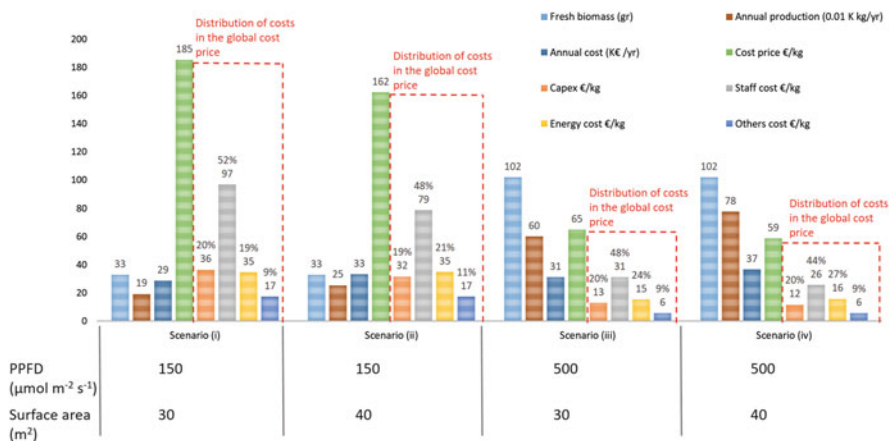


Fig. 14 Fresh shoot biomass *per plant*, annual output, CapEx, OpEx (subdivided in staff cost, energy cost, and other costs), total cost (CapEx + OpEx), and cost price of *Euphorbia peplus* cultivation in a vertical container farm following several scenarios. The dotted box includes CapEx and OpEx, the sum of which corresponds to the production cost price; the relative percentage of each cost in the cost price is indicated above each bar. Scenario (i), cultivation under a PPF of $150 \mu\text{mol}^{-2} \text{s}^{-1}$ with a surface area of 30 m^2 ; scenario (ii), cultivation under a PPF of $150 \mu\text{mol}^{-2} \text{s}^{-1}$ with a surface area of 40 m^2 ; scenario (iii), cultivation under a PPF of $500 \mu\text{mol}^{-2} \text{s}^{-1}$ with a surface area of 30 m^2 ; and scenario (iv), cultivation under a PPF of $500 \mu\text{mol}^{-2} \text{s}^{-1}$ with a surface area of 40 m^2 . (Bafort et al. 2022)

poultice, etc.). The biomass *per plant* can be optimized by cultivation under optimized environmental factors (Fig. 14) or by breeding or selecting high-biomass varieties.

If all three factors – cultivation cycle length, surface area, and plant density – are upgraded from the initial crop system, the annual production could sharply rise by 284% as the yield could increase from 1106 to 4255 kg (Fig. 13).

Production costs are influenced by several parameters, among others the productivity of the cultivation system. Costs are divided in two items: (1) capital expenditures (CapEx), long-term investment (e.g., equipment, property, buildings), and (2) operating expenditures (OpEx), daily expenses necessary to keep the business operational (e.g., labor, energy, water consumption, nutrients, seeds). Figure 14 represents the production cost of the medicinal weed *E. peplus* in a vertical indoor hydroponic container and shows the relationship between productivity and the production cost (Bafort et al. 2022). At a low light intensity, *E. peplus* growth was not optimized, and the mean biomass *per plant* reached 33 g. This resulted in a low annual productivity, and costs were distributed across a small volume of production. When the mean biomass *per plant* and the surface area increased, through modification of the cultivation process, productivity increased too. If the induced costs (e.g., for structural modifications, more powerful LEDs) increased moderately, the production cost *per kg* of plant decreased. Figure 14 shows that if

the surface area is increased by 33% by placing an additional layer in the container under the same light intensity (scenarios (i) and (ii)), CapEx and OpEx increase by 14%. As productivity is increased by 31.2%, the production cost is cut by 23€ per kg. In scenario (iii), the environmental factors have been modified: an increased light intensity results in a significant 209% rise of the mean biomass per plant as compared with scenario (i). Although the total cost is higher due to increased energy consumption and investment in upgraded LEDs, the total costs increase by only 9%, whereas annual production is increased by 212%, hence a 65% decrease of the production cost. In this optimized plant environment, if the surface area dedicated to production is increased by 10 m² (scenario iv), the production cost is reduced by 68% as compared to scenario (i). This shows the importance of optimizing the technical cultural itinerary to maximize productivity, as investment, labor, and energy costs are important.

The production cost of the vertical farming of another medicinal plant – *Artemisia annua* L. – in a modified shipping container has been calculated (Fig. 15) (Bafort et al. 2023). *A. annua* is an annual herb native to Asia. It has been used in traditional Asian medicine for treating and preventing fever and chills for many centuries and has been widely used for treating malaria (Kim et al. 2015). Again, the production cost of 1 kg of *A. annua* is closely related to the productivity of the horticultural process, and the production cost can be significantly reduced if the optimization of productivity does not increase costs too much. Higher-intensity LED

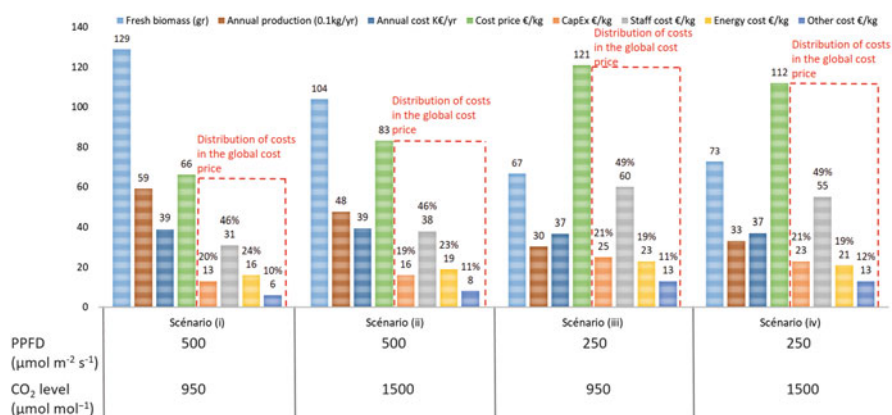


Fig. 15 Fresh shoot biomass per plant, CapEx, OpEx (subdivided in staff cost, energy cost, and other costs), annual fresh shoot biomass output, total cost (CapEx + OpEx), and cost price of *Artemisia annua* cultivation in a vertical container farm following several scenarios. The dotted box includes CapEx and OpEx, the sum of which corresponds to the production cost price; the relative percentage of each cost in the cost price is indicated above each bar. Scenario (i), cultivation under a PPFD of 500 μmol⁻² s⁻¹ with a CO₂ concentration of 950 μmol⁻² s⁻¹; scenario (ii), cultivation under a PPFD of 500 μmol⁻² s⁻¹ with a CO₂ concentration of 1500 μmol⁻² s⁻¹; scenario (iii), cultivation under a PPFD of 250 μmol⁻² s⁻¹ with a CO₂ concentration of 950 μmol⁻² s⁻¹; and scenario (iv), cultivation under a PPFD of 500 μmol⁻² s⁻¹ with a CO₂ concentration of 1500 μmol⁻² s⁻¹

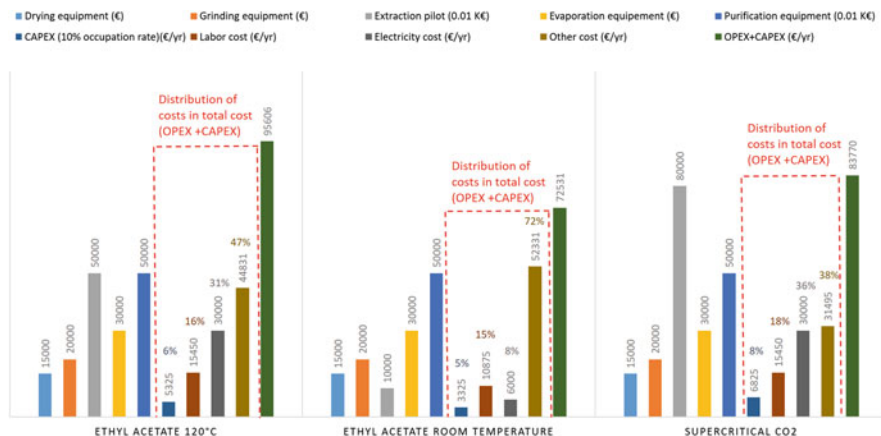


Fig. 16 Evaluation of the costs of extracting a diterpene from *Euphorbia peplus*. Estimated costs of various facilities (drying, grinding, extraction pilot, evaporation, and purification), CapEx per year at a 10% occupation rate and on a 20-year depreciation basis, OpEx per year (labor cost, electricity cost, and other costs), and total expenses per year (CapEx + OpEx). The dotted box includes CapEx and OpEx, the sum of which corresponds to the total cost (CapEx + OpEx); the relative percentage of each cost in the total cost is indicated above each bar. (Bafort et al. 2022)

lamps increased the total cost by 7%, but their use increased productivity by 56.4% so that the production cost per kg decreased significantly. Under the same light intensity ($PPFD = 500 \mu\text{mol}^{-2} \text{s}^{-1}$), increasing the CO_2 concentration induced a negative stress on *A. annua* and the mean fresh shoot biomass decreased, hence a higher production cost per kg (Fig. 16).

The cultivation cost is a vital economic piece of data, and its calculation is a key step for establishing the breakeven point of a product and a coherent selling price. It does not include distribution, marketing, or storage costs. If the medicinal plant is used fresh, such costs have to be added to calculate the cost price of the product and evaluate profitability. If the plant has to be dried, the drying and grinding process, or any necessary additional step (e.g., cleaning, cutting, sorting), have to be calculated in the same manner as for the cultivation cost (OpEx and CapEx).

3.2 Extraction Cost

The cultivation of a medicinal plant is the first step of its production. Depending on the final use of the plant (Fig. 11), the next steps after harvest can range from drying to the manufacturing of a pharmaceutical specialty. The cost of terpene extraction from the shoot biomass of a medicinal plant after vertical container cultivation has been studied recently (Bafort et al. 2022). Cultivation of *E. peplus* in a container farm resulted in a yearly output of 776 kg of fresh shoot biomass (Fig. 14). This

output was divided into several batches of 103 kg each, representing a very low load for industrial drying, grinding, extraction, evaporation, and purification devices, which can handle much more biomass. To take the low level of occupation of the devices into account, the occupation rate of the drying, extraction, and purification devices was set to 10% with a depreciation rate of 20 years. Three extraction methods were evaluated (ethyl acetate at 120 °C, ethyl acetate at room temperature, and supercritical CO₂), and their respective costs were calculated (Fig. 14). The investment costs were similar for the drying, grinding, evaporation, and purification facilities. However, the extraction method represented different investment costs depending on the extraction technique. The cost was higher for supercritical CO₂ extraction, and lower for ethyl acetate extraction at room temperature, which induced the highest and lowest CapEx, respectively. The OpEx differed depending on the extraction method. The method generating the highest operational cost was the “ethyl acetate at 120 °C” method, followed by the “supercritical CO₂” method, and finally the “ethyl acetate at room temperature” method. The distribution of costs differed between the extraction methods. With ethyl acetate at 120 °C, the largest contributor to annual cost was the operating and maintenance cost of equipment (“other costs” – 47%), followed by energy cost (31%) and labor cost (16%), while CapEx only represented 6%. With supercritical CO₂, the main costs were the “other costs” (38%) together with electricity cost (36%), and with ethyl acetate at room temperature, the major cost was “other costs” (72%), while electricity and labor costs and CapEx were much lower (15–5%).

The production cost of a metabolite depends on the CapEx and OpEx of the cultivation and extraction processes, but it is also strongly dependent on the extraction yield (Fig. 17). Although extraction by ethyl acetate at 120 °C generated the highest OpEx and CapEx, it also gave a significantly higher yield; as a result, this diterpene extraction method was the cheapest, with a cost of 37.8 € per mg. The increased yield allowed reducing production costs by 34% and 19.5% as compared to the “ethyl acetate at room temperature” and “supercritical CO₂” methods, respectively. This shows that production costs are related to multiple factors and how important it is to evaluate the expenses and yield of each step when producing medicinal plants and extracts. In the case study of ingenol-mebutate production from *E. peplus*, the concentration of this metabolite in the plant was low (about 60–70 mg per kg of plant shoot) (Bafort et al. 2022). The selection of the appropriate cultivation method (i.e., a high light intensity and an increased surface area) increased the extraction yield as compared to other studies (Hohmann et al. 2000). However, the plant content in ingenol-mebutate is constitutively low, so that the extraction yield remained low too. Increasing the content in a specific metabolite by appropriate abiotic factors such as high-temperature stress during the cultivation process could increase the content in terpene and ultimately the extraction yield (see also Chap. 2). Another possible way of reducing the cost of the production process of a metabolite is to increase the surface area to augment the cultivation yield or productivity.

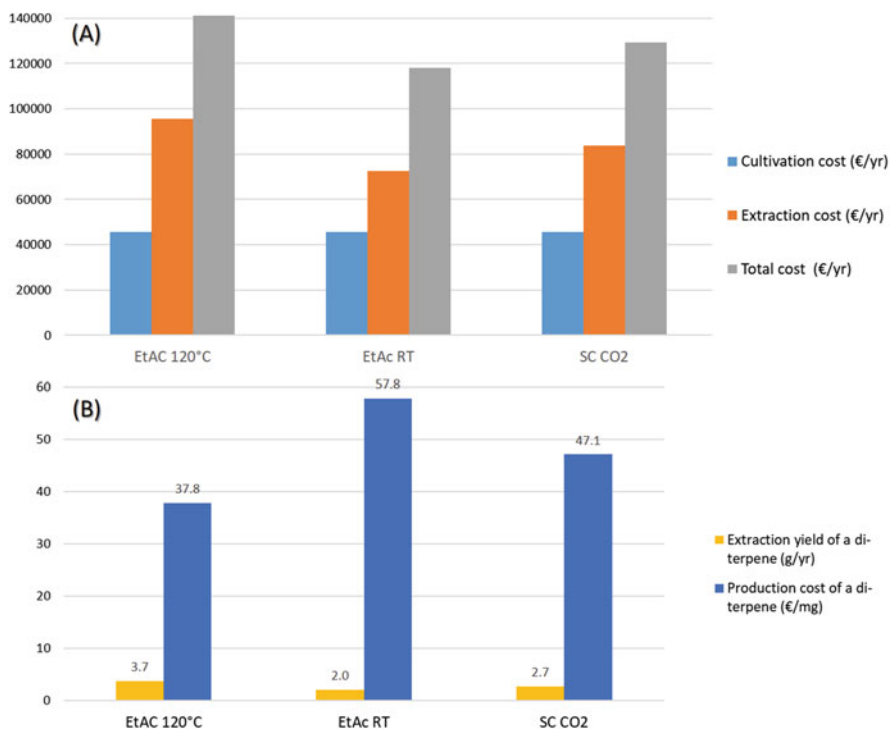


Fig. 17 Evaluation of the production cost of a diterpene extracted from a medicinal plant cultivated in a vertical container farm following three extraction methods. (A) Cultivation, extraction, and total cost following three extraction methods. EtAc 120 °C, ethyl acetate at 120 °C; EtAc RT, ethyl acetate at room temperature; SC CO₂, supercritical CO₂. (B) Extraction yield and production cost *per mg* of a diterpene following three extraction methods: EtAc 120 °C, ethyl acetate at 120 °C; EtAc RT, ethyl acetate at room temperature; SC CO₂, supercritical CO₂. (Bafort et al. 2022)

3.3 Pharmaceutical Drug Production Cost

Medicinal plants have secondary metabolites that can be of interest for pharmaceutical applications as purified molecules. In this case, the use of the metabolite in a pharmaceutical drug has to be approved by an official agency like the European Medicines Agency. Approval requires significant development costs showing the safety and efficacy of the drug and includes preclinical and clinical studies. Estimating the average cost of developing a drug is difficult. It largely varies according to studies, from US\$ 92.0 million to US\$ 884 million and even US\$ 1395 million (Morgan et al. 2011; DiMasi et al. 2016). Moreover, the clinical costs of drug development vary, depending on the treatment category. They range from US\$ 312 million for analgesics/anesthetics to US\$ 448 million for anti-infective drugs (Morgan et al. 2011). Therefore, pharmaceutical use requires far more invest-

ment than traditional para-pharmaceutical use (e.g., extracts (decoction, infusion, poultice, etc.)). The extract will also need a pharmaceutical-grade certification and will have to be manufactured in a “Good Manufactory Practices”-certified factory. Cultivating a medicinal plant in a vertical indoor farm is particularly suited for pharmaceutical or high-grade standard quality, because the process is completely controlled and ensures large, regular, and predictable quantities and constant high-quality metabolites. Moreover, the pharmaceutical use of the crop will give a higher added value to the metabolite. Few studies have investigated the entire cost of processing a medicinal plant from cultivation to the final pharmaceutical drug. The economic feasibility of producing a medicinal molecule was calculated from *E. peplus* annual biomass yield and ingenol-mebutate extraction yield (Bafort et al. 2022), based on a prescription medicine containing ingenol-mebutate and used to treat precancerous skin lesions. Figure 18 shows the output, CapEx and OpEx of *E. peplus* cultivation in a 40-m² vertical container farm under high light intensity producing 776 kg of fresh shoot crop *per* year, from which 3.73 gr of ingenol-mebutate *per* year are extracted with ethyl acetate at 120 °C. This process gave an output of 0.56 M€ with the selling of pharmaceutical gels containing 0.015% and 0.05% of the metabolite. The development costs were estimated to be 300 M€ (15 M€ *per* year) allocated over the term of a 20-year patent. Compared with this very high investment cost, other OpEx appeared as a very low load: 0.14 M€ for the cultivation and extraction costs and 0.12 M€ for gel manufacturing and flat

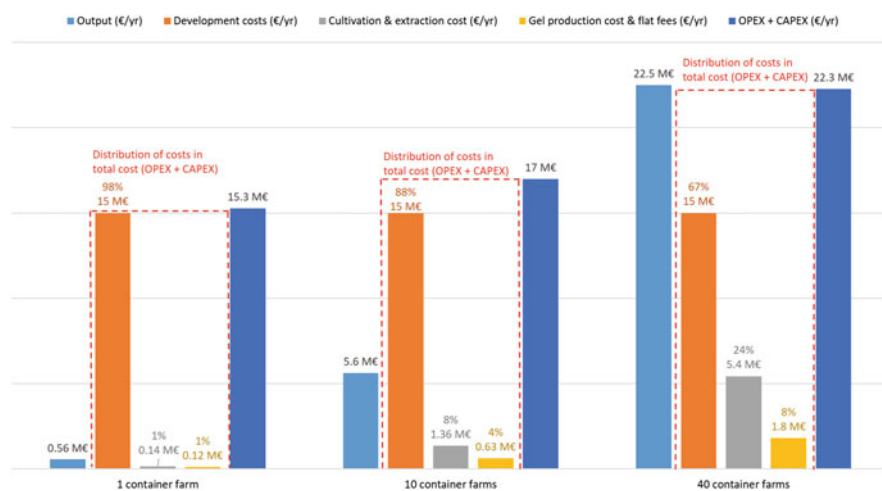


Fig. 18 Simulation of the production costs of a pharmaceutical gel based on ingenol-mebutate extracted from vertical container farming of *Euphorbia peplus*. Vertical cultivation in one container, 10 containers, or 40 containers and generated outputs, OpEx and CapEx. OpEx are subdivided in development costs, cultivation and extraction costs, gel production costs, and flat fees. The dotted box includes CapEx and OpEx, the sum of which corresponds to the total production cost; the relative percentage of each cost in the total cost is indicated above each bar. (Bafort et al. 2022)

fees. The total cost – the sum of CapEx (pharmaceutical manufacturing building) and OpEx – reached 15.3 M€ for 0.56 M€ of output. Therefore, the return time on investment for a total annual cost was 27 years. By multiplying the cultivation yield by 10 (by acquiring 10 vertical container farms), the extraction yield would be multiplied by 10, with a total of 37.3 g of ingenol-mebutate manufactured *per* year. This would raise the output to 5.6 M€ *per* year. The CapEx and OpEx costs, except the development costs, would also be increased and would reach an annual total of 17 M€. Therefore, the return time on investment for a total annual cost would be 3 years. Forty vertical container farms would be needed to reach a return time on investment of 1 year, with an output of 22.5 M€ and a total annual cost of about 22.3 M€, without being sure that the demand would absorb such a production. When looking at the distribution of costs of the whole plant-based drug production process from plant cultivation to drug production, the largest contributor is the R&D cost (98–67%), followed by cultivation and extraction costs (1–24%) and drug manufacturing costs (1–8%), depending on the number of containers, i.e., on the productivity of the cultivation and extraction steps.

Although the simulation of the profitability of the pharmaceutical gel showed that economic feasibility was difficult to reach, some factors could rapidly increase the profitability of ingenol-mebutate production. The improvement of the ingenol-mebutate content in the plant by a more specific and adapted cultivation process would increase the extraction yield rapidly. Furthermore, upcoming new plant factory designs with increased growing surfaces and planting densities together with digital agriculture will reduce the CapEx and OpEx and the cost *per* kg of crop, and profitability will be less challenging.

4 Conclusion

The sector of medicinal plants is complex because many forms exist, from freshly cut plants to dried preparations through essential oils, macerates, creams, or poultice, and various stakeholders are involved among whom consumers, herbalists, retailers, funding agencies, processors, policymakers, and growers (WildMapsFit 2020). Production of medicinal plants includes various steps, depending on the final use of the plant (Fig. 19) that make processing more or less complex. The complexity of the process increases with the number of steps, and so does the cost, but the added value of the product increases too.

The production of medicinal plants under a controlled environment offers new opportunities (WildMapsFit 2020; Zobayed 2020):

- A greater number of botanically reliable products free of misidentified plants.
- A product uncontaminated by pollutants, pesticides, and microbes.
- A stable source of guaranteed raw material.
- Uniform and optimized biochemical profiles.
- Quantity and quality are predictable and guaranteed.

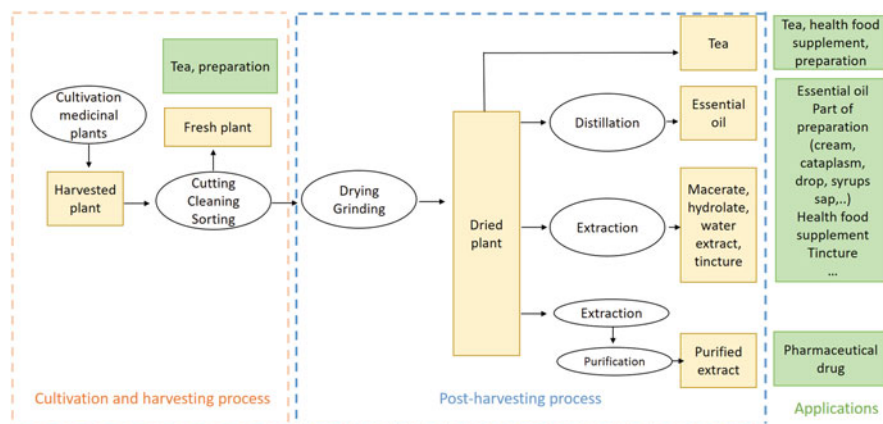


Fig. 19 Manufacturing processes of medicinal plants. (Adapted from EIP-AGRI 2020)

- Relationships between producers and purchasers are enhanced, based on stable and predictable production.
- Controlled postharvest handling.
- Quality control can be more easily implemented in such structures.
- Product certification or labeling.

Growers may in turn consider medicinal plant cultivation safer and more profitable than traditional crops. However, growers need to carefully calculate the economic viability of these production systems.

The demand for sustainability from consumers and regulators is increasing. Actors in the value chain must respond to consumer expectations, e.g., raw material sourcing, traceability, quality regulation, efficiency, and safety, while considering sustainability in the cultivation process (WildMapsFit 2020).

Five factors of the crop cultivation process under a controlled environment need to be optimized: (1) productivity (fresh or dried biomass *per year*) has to be maximized, (2) the plant content in metabolites of interest has to be maximized, (3) yields of postharvest processes (drying, extraction, purification, etc.) have to be maximized, (4) the sustainability of the process (life cycle assessment, energy use efficiency, light use efficiency, water use efficiency) has to be maximized, and (5) costs have to be minimized. The cultivation practices need a fine-tuning of environmental factors that should be specific to the crop and the metabolite of interest as plant responses to abiotic factors are mainly species-specific. The use of controlled environment cultivation systems can facilitate the development of safe, steady cultures in quality and quantity and high-quality (para)pharmaceutical plant products extracted from medicinal plants.

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