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Review

Aromatic Plants Metabolic Engineering: A Review

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Abstract: Secondary metabolites of aromatic plants are used in many health applications as drugs, pheromones, insecticides, fragrances, and antioxidants. Due to the huge commercial demand for these secondary metabolites, the need to overcome the insufficient productivity of aromatic plants has become a significant challenge. Plant breeding is a traditional, labor-intensive, and limited method to improve the ability of aromatic plants to produce secondary metabolites. Modern methods of biotechnology, including genetic engineering and genome editing, can be useful and cost-effective in improving aromatic plants, as they can increase the efficiency of obtaining plants with high productivity and the creation of resistant forms and breeding lines. This review illustrates the importance of developing methods for the modification of aromatic plants belonging to different families, with a predictable quality, resistance to adverse factors and pests, and intensive growth and high yields and productivity of valuable essential oils. Particular attention is paid to successful examples of the modification of aromatic plants, applied methods, and principal approaches

Keywords: essential oil; transgenic plants; metabolic engineering; plant protection; abiotic stresses; pathogen resistance

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1. Introduction

Plants produce thousands of different terpenes and terpenoids, which are the largest and most structurally diverse classes of secondary metabolites. These compounds are present in the essential oils (EOs) produced by plants. EOs are obtained from plants by steam distillation or extraction with organic solvents [1]. However, most terpene compounds are present in plant tissues in limited quantities. Plant seeds, flowers, stems, and roots most often contain 0.1–10% EOs in fresh weight [2]. Approximately 3000 different plant species are known, from which various EOs have been isolated. EOs have been widely studied in only 300 plant species, and only approximately 20 plant species have been recognized as valuable for commercial use as sources of EOs that are used regularly and in large volume [3,4]. In nature, EOs play an important role in plant protection as antibacterial, antiviral, and antifungal agents and insecticides. At the same time, they protect plants from herbivores, reducing their appetite for such plants [5,6]. They can also

attract certain insects by scattering pollen and seeds, while they repel others. In addition, they are known for their antiseptic, antiviral, fungicidal, and medicinal properties. EOs isolated from plants are also used in embalming and food preservation, and as antimicrobial, analgesic, sedative, anti-inflammatory, antispasmodic, and local anesthetic agents [7].

In most cases, EO compounds are formed only in certain plant tissues, such as inflorescences or seeds, which constitute a small percentage of the entire plant biomass in one harvesting season [8]. Therefore, the extraction of useful compounds from the EOs of aromatic plants can be an expensive procedure. Although the chemical synthesis of individual organic compounds is often cheaper, and the natural product has a small market share, consumer preference for natural essential oils over synthetic compounds is becoming increasingly widespread. This is mainly due to people's opinions that natural EOs do not contain harmful industrial impurities and often have higher natural taste quality that cannot be achieved via the chemical synthesis of these compounds [9]. The EO industry generates billions of dollars in revenue each year, as they have a wide range of applications in various fields, such as pharmaceuticals, aromatherapy, healthcare, cosmetics, food flavoring, food preservation, and perfumery [10,11]. Therefore, there is a need to reduce the costs of natural products so that they become available to a wider range of consumers. From an ecological point of view, the production of useful compounds by non-chemical environmentally friendly methods is always the preferred and necessary alternative.

Modern biotechnological techniques make it possible to facilitate production and therefore reduce the market value of natural EOs through the use of various environmentally friendly methods. The development of genetic engineering has led to the development of large-scale biosynthesis of natural products, and advances in tissue culture of aromatic plants have opened up new avenues for the large-scale and high-efficiency production of desirable bioactive compounds. Plant tissue culture (including suspension cell cultures and "hairy root" cultures) is a promising alternative for the production of rare and high-value secondary metabolites to traditional approaches (e.g., harvesting wild plants), and is more cost-effective for mass production of plant-derived substances due to a number of advantages [12,13]. Firstly, such a bioprocess is completely independent of any seasonal and geographical conditions. Second, genetic modifications including gene overexpression, RNA interference, and the gene/genome editing due to CRISPR/Cas technique can be easily applied without encountering the regulatory barriers associated with plants growing in the field [14].

Another example of an increase in the productivity of the EOs synthesis by aromatic plants can be an increase in the number or size of cells and groups of cells in which these compounds are produced, or by regulating ploidy, increasing division, and rising the proportion of specialized cells in the tissue [15] (Supplementary Materials Figure S1). In the last decade, more and more efforts have been invested in genetic and metabolic engineering in order to increase the production of key metabolites in plants. However, as attempts to increase the production of individual metabolites progress, it becomes clear that this effect cannot be achieved by direct gene overexpression. To improve the control over the accumulation of natural products, a deep understanding of the genetic, molecular, and biochemical processes occurring in situ and leading to the synthesis of desired compounds is required [16]. Knowledge of the complex network of metabolic pathways for the synthesis of secondary compounds is a crucial initial step.

This review discusses recent biotechnological approaches that have received special attention in the last 12 years (2010–2022) and whose main goal was to increase the productivity and resistance of aromatic plants to abiotic and biotic stresses.

2. The Specifics of Biotechnology Application in Improving the Quality of Aromatic Plants

The use of biotechnological methods, of course, can significantly increase the production of EOs and improve their quality and the predictability of a given composition in specialized cells in aromatic plants, by changing or regulating the biogenesis of related

compounds, introducing missing enzymes, creating optimal conditions for cultivation, or increasing the biomass of valuable plant organs. (Figure 1).

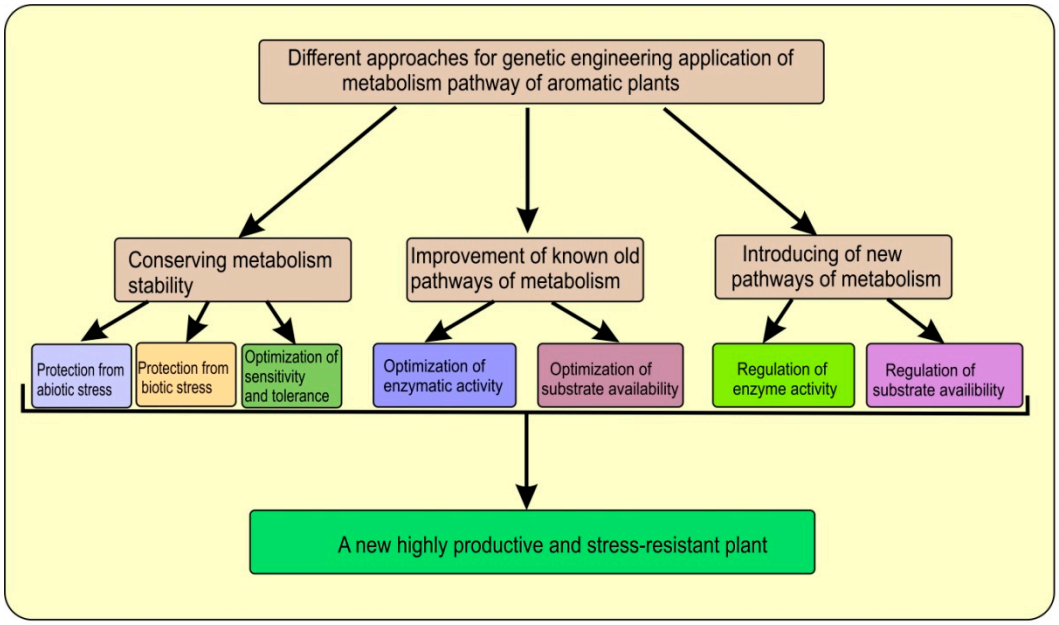

Figure 1. The scheme illustrates those physiological processes in aromatic plants that could be modified (improved) through the application of genetic engineering.

However, even those technologies that are currently well known and repeatedly utilized have significant limitations when dealing with aromatic plants. One such obstacle may be that a number of valuable aromatic plants are perennials and woody plants. This complicates the evaluation of newly modified plants, since the production of complex compounds, where various metabolic enzymes are involved in sequential stages, requires a rather long period [17]. In addition, in such plants, flowering occurs only when a certain stage of development is reached, and often flowers are the main source of EOs [18]. In this case, to assess the potential properties of such plants, the technology of grafting the obtained modified regenerants onto a rootstock of the same species can be used, followed by an assessment of the qualitative and quantitative yield of the product [19].

It is known that regenerants obtained in vitro are often tender plants, poorly adapted to ex vitro conditions, especially in the presence of difficulties with rhizogenesis; the regenerant is first grafted onto a stable root system in vitro, after which acclimatization and plant cultivation take place. Another significant problem when working with aromatic plants is their ability to accumulate a significant amount of phenols, the presence of which greatly complicates the purification of the product of interest. This creates the problem of limiting the availability of explants for transformation, since the protocols for the maceration, cultivation, and transformation of cells or tissues of such plants, produced from mature tissues, are problematic and inefficient [20]. Varietal specificity may even limit the possibility of obtaining the required modifications of especially valuable screeds of various cultivars. To solve such problems, various methods are used to achieve a higher yield of regenerated products using complex protocols for multicomponent nutrient media, a special lighting regime, drugs that reduce the rapid "aging" of cells and the excessive accumulation of harmful secondary metabolites that affect the production of regenerated shoots (roots), and the release of protoplasts, depending on the chosen method. The most commonly used are various phytohormones, synthetic regulators, osmotically active substances, altered temperature conditions (usually lower temperatures), amino acids, and peptides, as well as vitamins, activated charcoal, and antioxidants [21].

2.1. Specialized Metabolites of EOs and Their Biosynthesis

Today, terpenes or terpenoids, which are components of essential oils, represent a large and structurally diverse class of compounds, numbering more than 80,000 names [22]. The basic structures of all terpenes are synthesized as a result of two alternative and independent biosynthetic pathways located in different subcellular compartments from the universal five-carbon precursors, isopentenyl diphosphate (IPP) and its dimethylallyl diphosphate (DMAPP) all isomer (Figure S2) [23]. The classic mevalonic acid pathway includes six enzymatic steps, starting with acetyl-CoA and ending with the formation of IPP. The MVA pathway is commonly known as the cytosolic one, where the enzymes are located in the cytosol [24]. The second pathway, which includes seven enzymatic steps, also results in the formation of IPP and DMAPP from pyruvate and glyceraldehyde-3-phosphate in plastids [23]. It is known that the enzymes of the MEP pathway are encoded by the nuclear genome and imported into plastids, where certain types of terpenoids are produced [25].

Recent studies have shown that in addition to the classical synthesis of IPP and DMAPP using enzymes in cytosol (MVA pathway) and plastids (MEP pathway), their synthesis is possible in both locations. Plant genomes contain the isopentenyl phosphate kinase (IPK) gene, which expresses the IPK protein found in the cytoplasm, where it converts isopentenyl phosphate (IP) and possibly dimethyl allyl phosphate (DMAP) into IPP and DMAPP via ATP-dependent phosphorylation [26].

In a number of aromatic plants, the gene clusters involved in the biosynthesis of specialized terpenoids have been studied and have provided the means to enhance the biosynthesis of some specialized terpenoids (Table 1) [27–35].

Table 1. The genes encoding some of the enzymes involved in the synthesis of EOs.

Artemisia annua L.	AaβFS1 (an EβF synthase gene)	The CTP + AaβFS1 transgenic tobacco plants could emit EβF what enhanced repellence to green peach aphid (*Myzus persicae*)	[27]
Citrus sinensis L. Osbeck	Linalool synthase (CuSTS3-1)	Transgenic sweet orange plants showing the highest linalool content, demonstrated strong resistance to cancer in citrus (*Xanthomonas citri* subsp. *citri*)	[28]
Eucalyptus Camaldulensis Dehnh.	"Mangrin" gene-homolog of the allene oxide cyclase (AOC) gene	The mangrin gene is one approach to safely enhance salt tolerance in *Eucalyptus camaldulensis*. Salt-tolerant transgenic eucalyptus plants had somewhat less α-pinene in their essential oil and in the case of 1,8-cineole no differences were observed between transgenic and non-transgenic genotypes.	[29]
Lavandula spp.	AG-like and SEP3-like genes	Study of genes regulating flowering time in commercial lavender species	[30]
Matricaria recutita	(E)-β-farnesene synthase gene	The expression pattern of the gene encoding βFS, which is involved in chemical communication, has been studied, which provides the basis for the subsequent increase in crop resistance to aphids.	[31]
Mentha piperita L.	Mitogen-activated protein kinase (MAPK)	Data demonstrated the MAPK-dependent regulation mechanism of EOs biosynthesis in the salt-tolerant peppermint	[32]
Ocimum basilicum L.	ObDMR1	Editing of the ObDMR1 gene was tested, the mutation of which gives resistance to the causative agent of downy mildew	[33]
	β-glucuronidase (GUS)	The GUS expression is induced and up-regulated by increasing of water deficit stress.	[34]
Pelargonium graveolens cv. Hemanti	ACC deaminase	Transgenic *P. graveolens* expressing ACC deaminase showed immense tolerance to salinity and drought stress. Additionally, expression of ACC deaminase enhanced the total biomass under normal conditions, important in increasing the productivity of the rose-scented geranium oil.	[35]

Studies conducted in the last few years in the field of genomics and metabolomics were reflected in a series of review papers [36–40]. Some studies have shown the presence of non-canonical pathways and gene clusters involved in the formation of precursors, as well as the following terpenoid compounds in certain plant species [39]. Regulatory factors and gene clusters involved in the biosynthesis of specialized terpenoids in various plant species have been identified. It has been shown that the subcellular localization of the precursors pool and introduced enzymes are the crucial factors for increasing the specific terpenoid production in plants [40]. Additionally, if at present, the enhanced synthesis of a particular terpene compound was due to the overexpression of a single introduced gene, then future studies may focus on the delivery of several genes comprising several stages in the metabolic pathway of the biosynthesis of the target compound (Figure 2). Further understanding of the fine regulation of already known and lesser understood biosynthetic pathways, identification of new genes or gene clusters in selected species of industrially important aromatic plants, may lead to the production of commercially significant amounts of valuable terpene compounds in host plants.

Currently, there are only a few examples of the production of specialized terpenoids in host plants due to advances in metabolic engineering. Thus, the development of a pathway for the biosynthesis of menthol in peppermint (*Mentha* x *piperita* L.) made it possible, as a result of the suppression of the menthofuran synthase gene, to increase the yield of EO with a reduced amount of undesirable (+)-menthofuran in the MFS7A transgenic line [41]. Moreover, the overexpression of DXR led to an increase in the yield of EO in transgenic plants grown in a greenhouse by more than 50% at a low level of (+)-menthofuran (≤1.9% in EO) and (+)-pulegone (approximately 0.2% in essential oil) [42]. Field trials of these transgenic peppermint lines showed similar results in terms of EO yield and composition to those observed in greenhouse-grown lines [41]. Another example of the successful metabolic engineering of specialized terpenoids is the genetic engineering of sweet wormwood (*Artemisia annua* L.), in which the combined expression of the HMGR, FPPS, and DBR2 genes resulted in the more than three-fold higher accumulation of artemisinin [43].

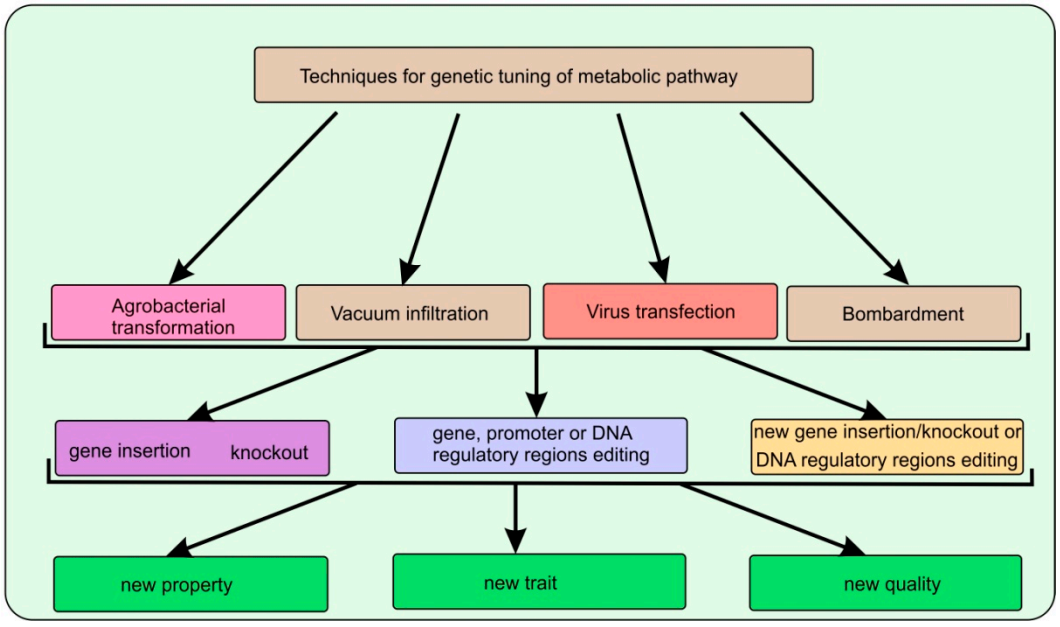

Figure 2. The scheme illustrates the genetic engineering methods used to modify aromatic plants: methods for delivering genetic material into the germplasm of plant cells; molecular genetic targets exposed to directed action; and the end result to be achieved.

However, so far, engineering with the introduction of foreign genes for the biosynthesis of specialized terpenoids using a transgenic approach has been successful in producing

commercially advantageous amounts of specialized terpenoids in only a few plant species. It involves manipulation via the relevant pathways for the synthesis of many metabolites; although it requires great effort, it would allow us, in the future, to better understand both already known and less studied pathways and regulatory mechanisms, and to identify new genes or gene clusters involved in the biosynthesis of specialized terpenoids. The understanding of biosynthesis and its regulation can be used to develop homologous or heterologous transgenic systems to obtain higher amounts of commercially valuable terpenoids, as well as to increase plant yields and improve the quality of their EOs in industrial production.

2.2. Diseases of Aromatic Plants

Thus far, the focus has been on diseases affecting agricultural plants, and diseases affecting aromatic plants have been largely ignored. The cultivation of aromatic plants faces serious threats from various groups of phytopathogens (bacteria, fungi, viruses, phytoplasmas, nematodes), which reduce the yields of these crops and the quality of the crude materials obtained [44].

The main pests that cause serious damage to aromatic plants are various types of nematodes, they damage the roots of the host plant and reduce their productivity and yield [45–48]. Some of them are carriers of viruses for these plants, such as Arabis mosaic virus, Strawberry latent ring spot virus and Tobacco ring spot virus). Other pests also carry viruses. So, aphids are intermediate hosts of such viruses as Alfalfa mosaic virus, Cucumber mosaic virus and Mint vein banding associated virus, thrips carry Impatiens necrotic spot virus and Tomato spotted wilt virus, whitefly-Tomato leaf curl Pakistan virus, and unknown vectors-Tobacco mosaic virus and Lychnis ringspot virus [49,50]. Various fungal pathogenic invasions of these species are also observed in aromatic plants: *Puccinia menthae* (rust), *Rhizoctonia solani* (air rot), *Rhizoctonia solani/bataticola* (root and stolon rot), *Verticillium dahliae* (wilt), *Phoma stasseri* (stem rot), *Alternaria alternata* (leaf rot or leaf spot) and *Erysiphe cischoracearum* (powdery mildew) [51,52].

At present, the use of the possibilities of bioengineering of aromatic plants makes it possible to increase plant resistance to diseases [53,54]. For example, genes encoding proteins capable of degrading mycotoxins can be introduced into plants [55]. Plant protein baits that serve to capture pathogens can be modified to avoid the specificity of pathogen recognition [56,57]. The mechanism of RNA interference to provide robust viral immunity by targeting the degradation of viral RNA can also be used [58]. Natural or engineered immune receptors that recognize different pathogen strains can be introduced singly or in combination to provide reliable resistance to broad-spectrum diseases [59].

Phytoplasmas are a fairly large group of pathogens of aromatic plants. They cause changes in the amount and composition of secondary metabolites in diseased plants, which greatly affects the concentration of valuable phytochemicals [60,61]. Thus, in St. John's wort (*Hypericum perforatum*) infected with phytoplasma 16SrVII, the EO yield significantly decreased (0.11 vs. 0.75% in healthy plants), and the content of sesquiterpenes increased in their composition, while the content of monoterpene hydrocarbons (and aliphatic compounds) decreased [61]. As one of the mechanisms by which phytoplasma spreads, several proteins secreted by phytoplasma in host plants have been identified and named as effector molecules, namely SAP54, SAP11, TENGU, SAP21, etc., which ensure its colonization and survival in the host plant [62]. Recent molecular studies of phytoplasma effector proteins and host plant microRNAs have shed light on the complex mechanisms underlying the development of phytoplasma infection symptoms. TENGU-induced dwarfism and infertility in plants are associated with the altered biosynthesis of auxin and jasmonic acid. SAP 54 plays a significant negative role in the degradation of transcription factors involved in flower development. The role of another effector molecule, SAP11, is manifested in the proliferation of axillary shoots and symptoms of hairy root [62]. Although the mechanisms by which phytoplasma infections spread remain a complex issue, studying the processes involved will provide a platform for developing measures to control phytoplasma-related diseases.

Despite the fact that biotic stress entails an increase in the production of secondary metabolic products, since they perform protective functions in plant organisms, the penetration of pathogens into the host plant is nevertheless a major obstacle to obtaining high-quality products. The development of the resistance of the main plants to unfavorable conditions of cultivation, and to diseases and pests, also makes it possible to increase the yield of the final product and increase their commercial value.

2.3. The Biotransformation of Aromatic Plants

Genetic engineering of aromatic plants has continued to develop over the past decade, both in the biotransformation of secondary metabolic pathways in general and in individual terpene pathways.

Microorganisms, particularly *E. coli*, continue to be the main objects of metabolic and combinatorial engineering experiments. Advances in genome sequencing and transcriptome and proteome analysis have created more suitable starting platforms for the development of secondary metabolite production. Genetic manipulation of bacteria and yeast makes it possible to use them as an alternative host for the production of plant EO components and to obtain valuable substances in commercially viable quantities. One such example is the production of *cis*-abienol, a bicyclic tertiary labdanoid diterpene alcohol, which is obtained by extraction from *Abies balsamea* and *Nicotiana tabacumum* [63]. This compound is the flavor precursor of most oriental tobaccos and is commonly used in cigarette extracts. In addition, *cis*-abienol is used as a precursor for the semi-synthesis of succinic compounds, which is a substitute for natural ambergris and is widely used in industry. However, the existing method of isolating *cis*-abienol from a plant is inefficient, and it requires a significant amount of natural resources and many chemicals that are hazardous to the environment; meanwhile, microorganisms provide a sustainable and environmentally friendly alternative to *cis*-abienol production [64]. Another example is the large-scale cultivation in bioreactors of geraniol, an acyclic monoterpene alcohol, which is the main component of the EOs of plants such as geranium, lemongrass, and rose [65–67]. Recently, it has become possible to obtain, in cell cultures, the compounds that are present in the EOs of especially valuable and endangered plants, such as *Ajuga bracteosa*, *Nepenthes khasiana*, and *Zataria multiflora* [68,69].

Another popular strategy for obtaining biologically active compounds continues to be the cultivation of specialized organs, such as shoots or hairy roots [70,71]. Along with a high growth rate, genetically transformed roots (hairy roots) can be cultivated on hormone-free media while maintaining their genetic stability. Therefore, hairy root cultures have a significant advantage in obtaining these metabolites in significant amounts, comparable to their amounts in intact plants [72–74].

In addition, hairy roots are used as an important research tool to elucidate pathways for the biosynthesis of secondary metabolites, as well as the expression, function, and regulation of key genes. In recent years, studies in this direction have been carried out on a number of aromatic crops, such as *Mentha spicata* L. [75], *Artemisia* spp., *Salvia* spp. [72,76].

Recent progress in transgenic research has offered the possibility of metabolic engineering to study biosynthetic pathways to produce valuable secondary metabolites. Identification of metabolic genes/pathways and their engineering has become common practice. Some results of EOs metabolic engineering in aromatic plants is presented in Table 2.

Metabolic engineering offers a promising tool to increase yields. In addition, a transgenic approach can be used to increase the production of endogenous secondary metabolites in the plant system. The isolation and expression of such genes using transgenic approaches in intact and cultivated aromatic plants can lead to the synthesis of these secondary metabolites. For example, overexpression of the *AaWRKY1* and *TfGA20ox2* genes in *Artemisia annua* resulted in the increased yield and accumulation of artemisinin (an important antimalarial drug) in this plant [79,81]. Manipulations with the expression (reduced/over-) of the *MsYABBY5* and *R2R3-MYB*, *MsMYB* genes in *Mentha spicata* lead to an increase/decrease in the level of monoterpenes in the composition of mint EO [99,100].

In addition, transgenic *ObCAAT1-RNAi Ocimum basilicum* lines with suppressed expression of the BACDH acyltransferase gene, which is involved in the synthesis of eugenol, showed a decrease in the level of volatile organic compounds, eugenol, and the accumulation of coniferous alcohol [102].

Another direction of molecular research is the identification of genes that regulate the size and density of glandular trichomes responsible for the biosynthesis and secretion of plant EOs. The overexpression of genes under the control of trichomospecific promoters in most cases leads to an increase in the size and density of trichomes in transgenic species such as *Artemisia annua* [77], *Mentha piperita* L. [98], and *Salvia fruticosa* [110].

Table 2. Results of experiments on transgenesis with aromatic plants.

Species	Gene	Result of Transgenesis	Reference
Artemisia annua L.	trichome-specific LTP genes (AaLTP3 and AaLTP4)	Overexpression of AaLTP3 or AaLTP4 in transgenic *A. annua* plants resulted in enhanced production of sesquiterpene lactones (arteannuin B, artemisinin, dihydroartemisinic acid and artemisinic acid)	[77]
	TLR1 and TLR2	TLR1 and TLR2 negatively regulate trichome density and reduces production of sesquiterpene (artemisinin)	[78]
	TfGA20ox2	enhances production of essential oil yields and sesquiterpene (artemisinin)	[79]
	Five sesquiterpene synthases (ADS, GAS, CPS, ECS and FS	GAS, ECS or CPS genes not improve artemisinin production; ADS and FS genes have an effect on the yield of artemisinin.	[80]
	AaWRKY1 (expression of ADS)	The regulation (increase) of artemisinin production	[81]
	Monoterpene synthase linalool synthase (LIS)	The expression of LIS not influence artemisinin production	[82]
	cyp71av1 and cpr genes	Overexpressing cyp71av1 and cpr is an effective means for increasing artemisinin content	[83]
	valencene synthase (VS) valencene oxidase (VO)	Transgenic *Artemisia annua* coexpressing VS and VO in the cytosol ans farnesyl diphosphate synthase (FPS), VS, and VO in plastids produced a valuable sesquiterpene noocatone	[84]
Cinnamomum osmophloeum Kaneh	CoPAL, Co4CL1, Co4CL4 and CoCCR	Identification of four genes (CoPAL, Co4CL1, Co4CL4 and CoCCR) involved in the cinnamaldehyde biosynthesis pathway.	[85]
Cuminum cyminum L.	GUS	The first report on *Agrobacterium*-mediated genetic transformation in cumin.	[86]
Eucalyptus grandis × *E. urophylla*	GFP and GUS	There were no significant differences in leaf essential oil content or chemistry between transgenic (to improve wood production, wood quality and disease resistance) and non-transgenic eucalyptus trees.	[87]
Eucalyptus polybractea R.T. Baker	*mgfp6* and *hpt* genes	Developed a system that can be used as an efficient protocol for the genetic transformation of *E. polybractea*.	[88]
Lavandula spp.	Linalool synthase (*LIS*)	Increased linalool synthesis and EO yield	[89]
	LiGPPS, LiGGPPS, LiFPPS	The work functionally characterized cDNAs encoding the main short-chain trans-IDS genes of *Lavandula x intermedia*.	[90]
	HMGR	Overexpression of HMGR did not have significant impact upon the crosstalk between the MVA and MEP pathways for the synthesis of C5 monoterpene precursors in lavender.	[91]
	DXR	Characteristics of the lavender DXR gene and assessment of its effect on EO biosynthesis are presented	[92]
	CINS and LIMS	The composition of the EO of transgenic regenerants has been changed.	[93,94]
	GFP and GUS	Transformation protocol developed *L. iberica*	[95]

Table 2. *Cont.*

Species	Gene	Result of Transgenesis	Reference
Lallemantia iberica (M.Bieb.) Fisch.& C.A. Mey.	NtLTP1	Overexpression of NtLTP1 gene in transgenic orange mint resulted in enhanced accumulation of monoterpenes in the glandular trichomes	[96]
Mentha citrata L.(*Mentha* × *piperita* f. *citrata*)	IPP, DMAPP	Data on the development of pathways for the biosynthesis of isoprenoids in glandular trichomes are presented	[97]
Mentha piperita L.	DXPS, IPPI, GPPS, MFS	The overexpression of DXR led to oil yield increases, the expression of MFS in transgenic peppermint plants (elite line MFS7A) resulted in desired decreases in the relative amounts of (+)-menthofuran and (+)-pulegone.	[98]
	MsYABBY5 MsMYB	The reduced expression of MsYABBY5 led to increased levels of terpenes and that overexpression decreased terpene levels. MsMYB is a novel negative regulator of monoterpene biosynthesis.	[99,100]
	IPP isomerase, limonene synthase	It was found that overexpression of the IPP isomerase and limonene synthase genes can lead to the synthesis of more terpenoids in transgenic plants.	[101]
Mentha spicata L.	ObCAAT1	The BAHD ObCAAT1 acyltransferase gene has been isolated, which is involved in eugenol synthesis.	[102]
Ocimum basilicum L.	β-glucuronidase (GUS)	The GUS expression is induced and up-regulated by increasing of water deficit stress.	[34]
	β-glucuronidase (GUS)	A protocol for obtaining a transgenic plant has been developed	[103]
	β-glucuronidase (GUS)	An effective protocol for the regeneration and transformation of *P. gravolens* was developed	[104–106]
Pelargonium graveolens cv. Hemanti	GUS	The developed transformation method should provide new opportunities for the genetic improvement of patchouli according to the desired trait	[107]
	RrAADC, RrAAAT, RrPPDC1, RrNUDX1	The overexpression of genes responsible for the synthesis and accumulation of the main components of rose EOs has been studied	[108,109]
Pogostemon cablin (Blanco) Benth	SfCinS1, SfCinS2 and SfBPPS	The analysis of gene expression in trichomes of transgenic *Salvia fruticosa* was carried out according to the glandular trichome library	[110]
Rosa rugosa Thunb.	terpene synthase (TPS)	The identification of genes encoding enzymes involved in the biosynthesis of terpenoids was carried out, a relationship was found between the levels of expression of TPS genes and end products.	[111]
Salvia fruticosa Mill.	SaDXR	The role of SaDXR in the biosynthesis of photosynthetic pigments has been studied. SaDXR expression has been shown to enhance the biosynthesis of sandalwood-specific sesquiterpenoids.	[112]
Salvia guaranitica A.St.-Hill ex Benth.	Bisabolene synthetase (SaBS)	The mechanism of transcription regulation of the SaBS gene, which is a key enzyme in the synthesis of bisabolene in the EOs of *S. album*, was studied.	[113]
Santalum album L.	Terpene synthase (TPS)	Increase in thymol content	[114–116]
	IPT	The quality of the EOs has been modified by the introduction of the IPT gene. The amount of oxygenated sesquiterpenoid compounds in transgenic lines was 15–21% higher than in wild type plants.	[117]

Metabolic engineering in aromatic plants that synthesize a sufficient amount of secondary metabolites in their organs and tissues makes it possible to develop resistance to a number of diseases and pests. Thus, transgenic lines of *Citrus sinensis* with overexpression of the linalool synthase gene (*CuSTS3-1*) and with the highest content of linalool showed strong resistance to cancer of citrus *Xanthomonas citri* subsp. *citri* [28]. Gene expression

in *Matricaria recutita* resulted in the increased release of (E)-beta-farnesene, a compound that helps the plant to attract natural enemies to repel aphids [31]. In addition, due to the expression of interspecies metabolites, the positive resistance activity of essential oil plants to adverse growing conditions, such as salinity, water deficiency, and temperature, has been developed. Thus, in the EO of salt-tolerant transgenic eucalyptus, the content of most components is at the level of non-transgenic genotypes [29]. Meanwhile, the expression of the β-glucuronidase gene in *Ocimum basilicum* largely induces water deficiency [34].

The production of transgenic citrus trees to improve their properties using ballistic [118] and agrobacterial transformation is currently a widely used, routine procedure [119]. The regulation of fruit development and engineering protection against pathogens showed the promise of this approach [120,121]. Another method for the genetic modification of citrus plants is the method of genome editing [122]. Although significant changes in the timing of development and features of ontogeny can significantly affect the quality of EOs in transgenic citrus plants, neither the composition nor the quality of oils were studied in such research due to the laboriousness and difficulties in testing these parameters in adult woody plants [123,124].

At present, the possibility of modifying lavender essential oil is being most intensively studied [125]. Switching the attention of researchers to the more difficult-to-produce EOs of tree crops can significantly accelerate progress in the production of these valuable products for perfumery, medicine, and household needs or the use of genes in other plants as biofactories [126].

For aromatic plants, there are additional obstacles in obtaining transgenic and modified plants associated with the difficulties of growing them in an in vitro system, as a result of the rapid accumulation of specialized metabolites, as well as the peculiarities of the interaction of agrobacteria and viruses with plant cells and tissues, in which the effective operation of the antioxidant system and inhibition functions of agrobacteria are a result of the antibacterial action of the metabolites of EOs [20]. For this reason, research with aromatic plants is limited and less common than with typical crops, for which such processes are not typical.

2.4. Prospects for the Development of Biotechnological Approaches for Large-Scale Cultivation of Aromatic Plants

The significant demand for aromatic plants provides great prospects for the further development of biotechnological approaches for the large-scale production of biologically active compounds. Various in vitro cultivation techniques (callus cultivation followed by organogenesis, somatic embryogenesis and cultivation of genetically modified cells/plants, micropropagation, hairy root culture) have proven to be important tools for the rapid propagation of selected plant species and in increasing the yields of secondary metabolites [127]. The most preferred systems for obtaining some secondary metabolites remain the cultivation of tissues with epigenetic changes, such as DNA methylation [128], or the expression of certain miRNAs [129], in suspension cultures, which allows one to regulate the transcription of enzymes of the secondary metabolite biosynthesis pathway. Ultimately, this leads to the accumulation of secondary metabolites in high concentrations in specialized cells or in specific intracellular organelles. At the same time, the development of simpler and faster methods for transforming the culture of hairy roots continues due to their similarity in productivity with intact aromatic plants [130].

Another potential approach to the production of natural bioactive compounds is the modification of aromatic plants in order to increase their yield and increase the content of EOs. The creation of plants with a predominance of one or more components in the EO, allows one to expand the scope of the final product and increase the market potential of aromatic plants. A strong example of such an approach is the development of an environmentally friendly production method for *Artemisia annua* essential oil, which contains, along with artemisin, another commercially valuable compound—sesquiterpene nootkatone [131]. The development of resistance in aromatic plants to unfavorable conditions of

cultivation, and to diseases and pests, also makes it possible to increase the yield of the final product and increase their commercial value (Figure S3) [132].

The use of natural bioactive compounds produced by plants can be a potential solution to reduce the consumption of chemical compounds currently used as substitutes for EOs in various industries. Therefore, their production should be encouraged. However, many issues, especially those related to toxicity, need to be addressed in order to encourage farmers to accept the use of biotechnologically modified aromatic plants.

3. Conclusions

The EOs of aromatic plants are a source of many valuable products, along with traditional uses such as perfumery and cosmetics. EOs have also long been used as safe and effective plant protection products, as well as in food preparation and as an alternative to expensive drugs. With the ever-growing demand for EOs, the industry's limited ability to meet it necessitates a corresponding increase in production. This is due to the complexities of agricultural technologies, low productivity and the lack of an efficient growing model, seasonality, limited available growing areas, and climate change, as well as increasing drought and salinity in traditional growing regions.

Currently, biotechnology offers several options through which the secondary metabolites in aromatic plants can be transformed in innovative ways to produce sufficient quantities of marketable phytochemicals. Previously developed methods of suspension cultures, organ cultures, or transformed hair roots continue to develop; these, in many cases, can successfully increase the production of secondary metabolites. The use of the expression of genes for the biosynthesis of secondary metabolites of aromatic plants in microorganisms continues to help to elucidate their functions in biosynthesis and allows the production of plant metabolites of interest in microbes. One of the major achievements of the last decade can be considered the development of the possibility of modifying the enzymatic pathway for the conversion of metabolites, achieving an improvement in the quality of the EO and neutralization of the undesirable characteristics of its composition, making the EO better and safer, with predictable properties. Significant progress has also been made in obtaining more resistant forms and lines of aromatic plants through the use of various genetic modification approaches that can reduce losses and increase productivity while using the capabilities inherent in plant systems to form protective mechanisms.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/agronomy12123131/s1, Figure S1: An increase in volatile compound productivity can be achieved by increasing the number or size of cells and groups of cells, in which compounds are produced, or due to regulating ploidy, increasing divisions, and increasing the proportion of specialized cells in the tissue. Figure S2: Two independent pathways for the biogenesis of secondary metabolites: precursors and EOs in plant cells. Figure S3: The use of heterologous genes of various organisms in genetic engineering makes it possible to protect the plant from adverse environmental factors of both biotic and biotic nature [133,134]. Epigenetic regulation and genetic modification of the regulatory sequences of cultivated plants allows expanding the range of adaptability and productivity in a wide range [135,136]. Abbreviations: WT-wild type; GMP-genetically modified plant; GEP-genetically edited plant.

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