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Review Article

A Comprehensive Review of the Key Characteristics of the Genus *Mentha*, Natural Compounds and Biotechnological Approaches for the Production of Secondary Metabolites

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Context: The genus *Mentha* is one of the most aromatic and well-known members of the Lamiaceae family. A wide range of bioactive compounds has been reported in mints. Regarding the high economic importance of *Mentha* plants due to the presence of valuable metabolites, the demand for their products is growing exponentially. Therefore, to supply such demand, new strategies should be adopted to improve the yield and medicinal quality of the products.

Evidence Acquisition: The current review is written based on scientific literature obtained from online databases, including Google Scholar, PubMed, Scopus, and Web of Science regarding the characteristic features of some species of the genus *Mentha*, their distribution and cultivation, main uses and benefits, phytochemical composition, biotechnological approaches for the production of secondary metabolites, and strategies for enhanced production of mints secondary metabolites.

Results: In this article, we offer an overview of the key characteristics, natural compounds, biological properties, and medicinal uses of the genus *Mentha*. Current research describes biotechnological techniques such as *in vitro* culture methods for the production of high-value secondary metabolites. This review also highlights the strategies such as elicitation, genetic, and metabolic engineering to improve the secondary compounds production level in mint plants. Overall, it can be concluded that identifying the biosynthetic pathways, leading to the accumulation of pharmaceutically important bioactive compounds, has paved the way for developing highly productive mint plants with improved phytochemical profiles.

Keywords: Mentha; Lamiaceae; Bioactive compound; Secondary metabolite

1. Background

The genus *Mentha* is one of the well-known genera of the Lamiaceae family, which is named after the legendary Greek character "Minthe" (1, 2). Mint with a long history of use (more than 2000 years), is a symbol of hospitality in many cultures. This plant had been used extensively in ancient civilizations, from folk medicinal purposes to non-medicinal uses such as aromatherapy and cooking (3). In traditional Chinese medicine, mint due to its medicinal properties and health effects has been at the forefront of medical treatments (4, 5). Today, the metabolites in this plant are widely used in the preparation of cosmetics (6), painkillers, fever treatment, headache, colds (7), and as a flavoring for foods and sweets in food industries (6). As mentioned, mints represent a great economic and industrial plant due to the presence of highly commercially valuable metabolites. Moreover, the ease of propagation by seed or vegetative means, and the tolerance of the plants to grow under a broad range of

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agroclimatic conditions resulted in the cultivation and domestication of mints throughout the world (2).

Essential oils of the mints are promoted due to their commercial, economic, and health benefits. These substances are composed of a wide range of chemotypes. The essential oil composition varies remarkably depending on numerous factors including the genetic background, the growing location, weather conditions, harvest period, and the extraction method (8).

In species of the genus *Mentha* aromatic essential oils are produced by glandular trichomes that occur especially on the leaf surface. Essential oils can be extracted in a physical process by crushing the leaves or steam distillation as the most popular method (2).

Extraction of plant active ingredients from the tissues of intact plants by humans causes many problems such as: rapid genetic erosion, allocation of a large part of agricultural resources and inputs to the cultivation of medicinal plants, time-consuming production of medicinal plants with acceptable content of secondary metabolites, dependence of particular metabolites production on specific plant growth stage, necessity of using agricultural chemicals such as chemical fertilizers, herbicides, insecticides and fungicides in the cultivation process, severe impact of biotic and abiotic environmental stresses on the production, harvesting processes, and the preservation of harvested plant materials. Therefore, application of new alternative biotechnological methods for the production of secondary metabolites seems reasonable. To achieve this goal, it is necessary to understand the molecular mechanisms controlling the production of secondary metabolites and their utilization in metabolic engineering. Moreover, elicitor application, induction of hairy roots, and optimization of culture medium are several approaches to increase the production level of secondary compounds in *in vitro* cultures. Regarding the high importance of mints in pharmaceutical, food, flavoring, and other industries due to the presence of valuable metabolites with diverse biological activities described in this review, it appears that the only use of traditional approaches for secondary metabolites production in this plant is not sufficient and the implementation of new advanced techniques, can help in more vigorous, purposeful and targeted production of these compounds. The aim of the current review is to appraise scientific literature regarding the characteristic features of some main species of the genus *Mentha*, their distribution and cultivation, uses and benefits, phytochemical composition, and biotechnological approaches for the production of secondary metabolites.

2. Mentha's Taxonomic Classification

The Lamiaceae (Labiatae) family is a flowering plant family which was first described and named by the French botanist, Jussieu, in 1789. This family contains more than 7000 species in about 260 genera (9). According to Li *et al*. (2016), the Lamiaceae comprises 10 subfamilies: Lamioideae, Nepetoideae (the largest subfamily), Ajugoideae, Symphorematoideae, Prostantheroideae, Scutellarioideae, Viticoideae, Cymarioideae, Peronematoideae, and Premnoideae (10). The genus *Mentha* L. (mint) is one of the most aromatic members of the Nepetoideae subfamily which its taxonomy is highly complex and has been always in a state of flux. On the basis of cytological, morphological, and genetic characteristics, the genus *Mentha* is defined to include 18-30 species (11) and about 100 varieties and cultivars (9), placed in five sections: *Mentha*, *Preslia*, *Audibertia*, *Eriodontes*, and *Pulegium* (12). It has a complicated systematic due to diverse basic chromosome numbers, intra- and interspecific hybridization, and the incidence of polyploidy (11, 13).

The *Mentha* section includes 5 basic species: *Mentha spicata* L. (Spearmint), *Mentha aquatica* L. (Water mint), *Mentha arvensis* L. (Corn mint, Wild mint), *Mentha longifolia* (L.) Huds (Horse mint), and *Mentha suaveolens* Ehrh (Apple mint). It has been suggested that the frequent interspecific hybridization between these species has given rise to 11 naturally occurring hybrids (14). *Mentha* × *piperita* L. (peppermint) is a sterile hybrid plant, from the crossing between *M. spicata* and *M. aquatic*. This perennial herbaceous herb is native to the Mediterranean region and is cultivated as an important hybrid in Iran (15).

In Iran, various species and subspecies of the genus *Mentha* such as *M. suaveolens*, *M. spicata*, *M. longifolia*, *M. arvensis*, *M. Piperita*, M. *aquatica,* and *M. Mozaffarianii* Jamzad are found (**Fig. 1**) (16). *Mentha Mozaffarianii* Jamzad is an Iranian native species that is rare and growing wild in a limited geographical area in the south and southeast of Iran (16-18).

The scientific classification and hybrids of the genus *Mentha* are presented in **Table 1**.

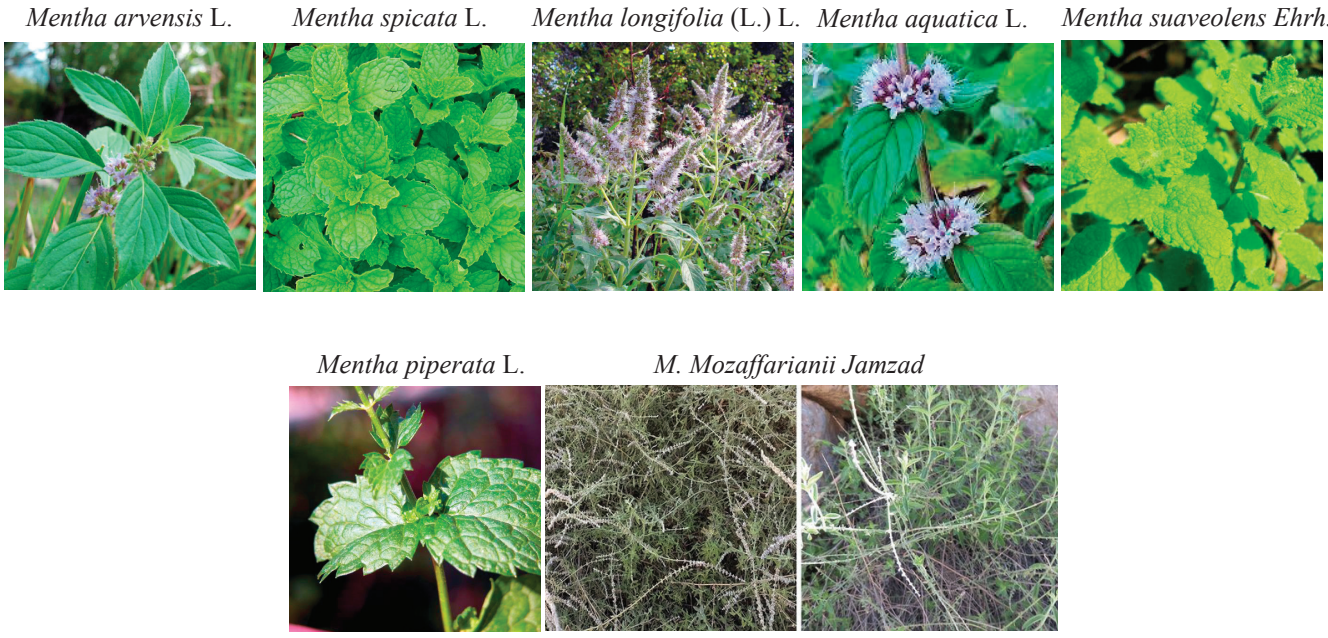

Figure 1. The main basic species of the genus *Mentha* (*M. arvensis* L. (www.actaplantarum.org); *M. spicata* L. (https://botanyphoto.botanicalgarden.ubc.ca/); *M. longifolia* (L.) L. (www.actaplantarum.org); *M. aquatica* L. (www.marylandbiodiversity.com); *M. suaveolens* Ehrh. (www.nparks.gov.sg); *M. piperita* L. (www.actaplantarum.org); *M. Mozaffarianii* Jamzad (21)).

3. Characteristic Features of Some Main *Mentha* Species

Mint species are aromatic, herbaceous perennial plants that are characterized by wide-spreading underground and overground stolons (19). The branched stems are square-shaped in cross-section and the aromatic leaves are arranged in opposite with serrated or entire margins (9) and oblong-elliptical to lanceolate in shape (20). The other characteristic features of the *Mentha* species include the white or purple zygomorphic bilaterally flowers that are produced in dense clusters known as verticillasters and the small, dry, and woody fruit containing 1 to 4 seeds (9, 20).The morphology of the main species of *Mentha* is given in **Table 2**.

4. The Genus *Mentha* Distribution and Cultivation

Mints are widely distributed and commercially cultivated in regions with tropical and temperate climates in different parts of the world (22). The genus *Mentha* is believed to be primarily originated in the Mediterranean basin (9, 12) and has a cosmopolitan distribution across Asia, Europe, Australia, North America, and North Africa (22, 23).

The members of the genus *Mentha* generally tolerate a broad range of climatic conditions, although most of them prefer moist habitats and thrive in, cool spots with partial shade (9, 14, 19, 20). Mints as vigorous spreaders and fast-growing herbs, extend a network of underground and overground runners (rhizomes) (20).

4.1. Agro-Climatic Conditions

Climatic conditions play a significant role in the effective management, successful cultivation, and higher productivity of mints. *M. arvensis* prefers tropical and subtropical areas (24) whereas temperate and subtemperate regions are more suitable for *M. piperita* (Peppermint) and *M. spicata* (Spearmint) (20). Peppermint is able to withstand cooler temperatures. The climatic requirements for cultivation of this plant include temperature in the range of 15-25 ^{0}C and rainfall between 90 and 105 cm (25). An investigation by Devi and Sharma (2021) indicated that *M. longifolia* (L.) L. and *M. spicata* L. which are growing in subtropical zones, produce more herbage than other climatic zones, which is considered a desirable trait for breeders (26).

Table 1. Scientific classification and hybrids of the genus *Mentha* L. (14)

Scientific classification of the genus *Mentha* L.	
Kingdom: Plantae – Plants Subkingdom: Tracheobionta – Vascular plants Superdivision: Spermatophyta – Seed plants Division: Magnoliophyta – Flowering plants Class: Magnoliopsida – Dicotyledons Subclass: Asteridae Order: Lamiales Family: Lamiaceae – Mint family Genus: *Mentha* L. – Mint	
Hybrid	**Parent species**
Mentha × *carinthiaca* Host	*M. arvensis* L. × *M. suaveolens* Ehrh.
Mentha × *dalmatica* Tausch	*M. arvensis* L. × *M. longifolia* (L.) L.
Mentha × *dumetorum* Schultes	*M. aquatica* L. × *M. longifolia* (L.) L.
Mentha × *gracilis* Sole	*M. arvensis* L. × *M. spicata* L.
Mentha × *maximilianea* F. W. Schults	*M. aquatic* L. × *M. suaveolens* Ehrh.
Mentha × *piperita* L.	*M. aquatica* L. × *M. spicata* L.
Mentha × *rotundifolia* (L.) Huds.	*M. longifolia* (L.) L. × *M. suaveolens* Ehrh.
Mentha × *smithiana* R. Graham	*M. aquatic* L. × *M. arvensis* L. × *M. spicata*
Mentha × *verticillata* L.	*M. aquatica* L. × *M. arvensis* L.
Mentha × *villosa* Huds.	*M. spicata* L. × *M. suaveolens* Ehrh.
Mentha × *villosa-nervata* Opiz	*M. longifolia* (L.) L. × *M. spicata* L.

It is reported that the yield and composition of *Mentha* essential oils are related to climatic conditions (27). In a study by Heydari *et al*. (2018), it was suggested that heat stress strongly affects essential oil yield, chemical composition, and antibacterial activities in *M. piperita* and *M. arvensis* L (28). Moreover, Mollaei *et al*. (2020) recorded the variability of the composition and content of essential oils among 12 *M. pulegium* L. populations in Iran. Their results indicated the significant effect of environmental factors including average rainfall, temperature, and altitude on antioxidant activity and phytochemical constituents (29).

4.2. Soil

Mints do best in well-drained soils rich in organic matter with high levels of nutrients (20). Fertile loam to sandy loam soil with a slightly acidic pH between 6 and 7.5 is favorable for the cultivation of mints (12). It is reported that the soil composition and bioactive compounds of essential oil are certainly correlated. Therefore, substantial soil parameters such as pH, organic content, and drain capacity should be optimized for mint cultivation (27). Salehi *et al*. (2018) reported that the essential oil yield of *M. piperita* is affected by the pH of the soil (12).

4.3. Land Preparation Before Propagation

The land must be repeatedly (3-4 times) ploughed and harrowed twice to make a weed-free and fine seedbed before planting the crop (12, 20). Farmyard manure (compost) of about 25-30 tons per hectare has to be applied as part of land preparation (12).

4.4. Propagation

Mints can be propagated either by seed or vegetative means; however, vegetative propagation through stolons and runners (rhizomes) is the main reliable method for raising mints (12).

Table 2. Characteristic features of some of the main *Mentha* species (Fig. 1)

***Mentha* species**	**Morphology**
Mentha arvensis L.	**Stem:** Erect–ascending branched stem (19, 20) **Leaves:** Arranged in opposite pairs, sparsely hairy, shortly petiole or sessile, oblong-ovate or lanceolate in shape and shiny dark green in color, serrated margins (19, 20, 32) **Flowers:** Mauve in color, occur in whorls and borne on leaf axils (20, 32)
Mentha spicata L.	**Stem:** Square-shaped and may be hairless or hairy (33) **Rhizome:** Wide-spreading and creeping underground rhizome **Leaves:** Arranged in opposite pairs, ovate to lanceolate in shape and light green in color, often hairless on both sides, serrated margins (20) **Flowers:** Pink or white in color, arranged in a spike inflorescence (20)
Mentha longifolia (L.) Huds.	**Stems:** Whitish and branched stems, the stems are erect to creeping 0.5–1 m tall and covered with short and soft hairs **Rhizome:** Creeping rhizome (19) **Leaves:** The leaves are covered by whitish long hairs, oblong-elliptical to lanceolate in shape with toothed margins and green to greyish-green in color (19, 20, 33) **Flowers:** White to mauve in color, densely arranged into tapering spikes (20, 33)
Mentha aquatica L.	**Stems:** Square-shaped in cross-section, green or purple in color and hairy to almost hairless (19, 33) **Rhizome:** Wide-spreading rhizomes with fibrous roots **Leaves:** Opposite, finely toothed, ovate to ovate-lanceolate in shape, green and sometimes purplish in color, hairy to almost hairless **Flowers:** The flowers are very small, densely crowded and the inflorescences are near-spherical, pinkish to purple in color (19, 33)
Mentha suaveolens Ehrh.	**Stems:** Erect, square-shaped stems with short internodes, sparsely hairy (34) **Leaves:** Opposite, toothed margins, shortly petiole or sessile, ovate-oblong to suborbicular in shape and bright green in color, the leaves are wrinkled with sunken venation and hairy above (34) **Flowers:** Tubular flowers arranged on spike inflorescence and their color is white, pinkish or violet (34)
Mentha piperita	**Stems:** Four-angled, purplish, branching towards the top, slightly hairy **Leaves:** Opposite, petiolate, sharply seriate, pointed, dark green color **Flowers:** Purple, small, four-lobed corolla (20-mint/peppermint p.pushpangadan,S.K. Tewari handbook of herbs and spices)
M. Mozaffarianii Jamzad	**Stems:** Quadrangular, epidermis covered of hairs **Leaves:** Leaf surface covered of hairs (21, 35)

Peppermint (*Mentha* × *piperita* L.) is one of the most common and popular hybrid mints that rarely produces viable and germinating seeds, therefore vegetative plant parts such as stem cuttings, green shoots, rooty turions, and underground stolons are commonly used for its propagation (30, 31).

4.5. Planting

Two different planting methods are developed for mints (20):

1) Traditional farming: In this method, small pieces of cuttings from the runners or healthy roots with at least one growth bud are placed in shallow furrows (7-10 cm deep). The distance between adjacent rows should be 45-60 cm and after covering the furrow with soil, the plot is irrigated immediately (12). It has been reported that optimization of cultivation factors such as planting time, methods, and plant density play significant roles in improved productivity and maximum yield of crops like *Mentha arvensis* and *Mentha piperita* (24, 36, 37).

2) Micropropagation by using modern plant tissue culture methods: This technique provides an excellent alternative for the mass production of high-quality plantlets in a short period of time. Production of disease-free plants in small spaces, at any time of the year, is the other advantage of this method, in comparison to conventional propagation methods (38, 39).

Hydroponics and aquaponics as soilless growth systems have been successfully utilized for the cultivation of several *Mentha* species like *Mentha spicata* (40, 41), and *Mentha piperita* var. citrata (Ehrh.) Briq. (42). Aquaponics system is a relatively new method of mint cultivation that offers many benefits such as environmental compatibility, energy efficiency, minimal maintenance requirement, and increased biomass. Also, it is believed that the flavor and taste of mints might be stronger than those grown in soil (40).

4.6. Irrigation

As mints are high water-demanding crops, the plants require frequent irrigation (at least three times a week, when the plants are fully developed) (12) for optimum productivity, growth, maximum yield, high-quality crop, and higher quantities of secondary metabolites (43, 44). Water stress can reduce vegetative growth and productivity (45). Several studies have reported the negative effects of water stress on some growth parameters and biomass production of peppermint and spearmint (12, 45). However, the published data regarding the effect of irrigation on essential oil content are conflicting (27). In a study by Chiappero *et al*. (2019) drought-stressed *M. piperita* showed an improvement in total phenolic content (46). By contrast, a negative impact of drought stress on the flavonoid content, total phenolic content, and the radical scavenging activity of *M. piperita* extracts was reported by Rahimi *et al.* (2018) (47).

4.7. Mint Diseases and Pests

Mints are attacked by a wide variety of diseases and pests, causing serious crop loss and reducing the yield and mint oil quality. Several organisms such as fungi, nematodes, viruses and phytoplasma, bacteria (48, 49), and insects (12) have been reported as causal agents that threaten mint cultivation. The major fungal pathogens that have been reported to cause significant economic loss are *Erysiphe cischoracearum* (powdery mildew), *Puccinia menthae* (rust), *Alternaria alternata* (leaf spot), *Rhizoctonia solani* (aerial blight), *Phoma stasseri* (stem rot), *Verticillium dahliae* (wilt) and *Rhizoctonia solani/bataticola* (root and stolon rot) (12, 48). Mints are susceptible to various viruses, some of them include Cucumber Mosaic Virus (CMV), Mint Vein Banding associated Virus (MVBaV), Peppermint Latent Virus (PeLV), Peppermint Stunt Virus (PmSV), Tobacco Ringspot Virus (TRSV), Tomato Aspermy Virus (TAV), and Tobacco Mosaic Virus (TMV) (48, 50). Despite the fast-acting and easy application of chemical control of pests and diseases, the continual application of synthetic pesticides threatens the animals and human health due to environmental pollution and residual toxicity (51). Therefore, non-chemical disease control strategies such as crop rotation, biological control, use of biopesticides, and producing disease resistance lines through breeding programs, should be developed (48, 49).

4.8. Harvesting mint plants

Two important factors that greatly influence forage yield, essential oil quality, and composition are the harvest time and the number of harvests per year (52). Harvesting the crop too early results in an immature crop and a reduction in essential oil quality (12), whereas delayed harvesting results in decreased essential oil contents. The proper time for harvesting is when the mint plant is in the full-bloom stage (80%), on dry sunny days (20, 52). Based on different species,

mints are harvested once or twice a year, and it has been reported that the essential oil quality and content differ between the first and second harvests (12). Harvesting can be done either manually by hand or mechanically with green-crop loaders and combine harvesters (53).

4.9. Postharvest Handling

After harvesting, plants may be sold in a fresh or dried form. Due to the rapid senescence of fresh herbs like mints, the postharvest process is considered as a substantial stage to maintain the quality and improve the shelf-life of the fresh plant product. In a study on postharvest quality maintenance of *Mentha Piperita* by Barbosa, hydroocoling and non-perforated plastic packages were reported as an effective method (54). Drying as a common method of mint preservation, reduce the moisture content and expand the shelf-life (55). Different drying approaches like hot air drying, solar drying, open sun drying, freeze drying, and vacuum drying have been used for dehydrating mint leaves. Moreover, desiccant based dehumidified air-drying system has been reported as an effective low-temperature drying option for heat-sensitive leafy vegetables, especially mints (56, 57).

Consequently, due to the influence of different growing conditions and cultivation systems on the yield and quality of mints; they should be carefully selected for the cultivation of these valuable plants to achieve a higher concentration of useful phytochemical constituents.

5. Main Uses and Benefits of Mint

Since ancient times, mints as aromatic plants have been used in a wide variety of applications both in Eastern and Western cultures (58). Members of the genus *Mentha* are used in the pharmaceutical, cosmetic, and food industries due to their volatile oil compositions (23).

5.1. Culinary Uses

Mint can be used fresh and dried as a seasoning herb to improve the flavor of foods, confections, and beverages (14, 59). *Mentha* species have traditionally been used as flavoring and aromatic agents in food preparation (12). The fragrant leaves have a wonderful fresh, sweet, warm flavour with a cool, refreshing aftertaste and are valued as a wonderful appetizer. Species such as *M. piperita* and *M. arvensis* are used as popular flavouring in food products such as ice creams, syrups, mint sauces, and drinks (20, 60). The most popular mints, peppermint (*M. piperita*) and spearmint (*M. spicata*) are commonly used for tea preparation. *Mentha* essential oil and menthol are often associated with breath fresheners, toothpaste, mint tablets, and chewing gums (14, 19).

5.2. Therapeutic Uses

In addition to their culinary uses, *Mentha* species have been used in traditional medicines since ancient times. Although mint as a calming herb has been used for centuries to cure gastrointestinal ailments, it has a wide spectrum of medical activities (9). In folkloric remedies, mint is considered a treatment for stomachache, biliary disorders, enteritis (9), respiratory problems (59), bronchitis, nausea, coughs (61), colds, flu, and hemorrhoids (54). Mint leaves are generally taken as a tea which is a strong diuretic (9) and aids digestion with its carminative properties (58). Herbal tea made from this plant has traditionally been used in the treatment of fever, headaches, and different minor health disorders such as indigestion (12). Different parts of *M. longifolia* have been used in traditional folk medicine in the treatment of gallstones, jaundice, flatulence, and bladder stone in Iran (62). Spearmint leaves have been recommended by traditional Iranian medical practitioners to treat digestive disorders (63). It is reported that peppermint essential oil acts as a smooth muscle relaxant, decreases visceral pain, small bowel contractility, colonic spasm, and modulates psychosocial distress (64). In terms of biological activities, mint oil act as a low-risk insecticide against several grain pests (65, 66). Moreover, antimicrobial (64), antiviral, antifungal, antioxidant (22, 67), and anti-inflammatory (14, 64) properties of mints have been frequently reported.

5.2.1. Antioxidant Properties

Mentha species are found to contain high levels of antioxidant compounds such as phenolic acids, flavonoids, ascorbic acid, and carotenoids which act as free radical scavengers. In a study by Park *et al*. (2019), the extracts of nine *Mentha* species were investigated for antioxidant and free radical scavenging activities. They reported a range of antioxidant activities among the different *Mentha* species. According to their results, *M. longifolia* showed the highest antioxidant activity among the other investigated species (68). In another study (69), Nickavar *et al*. reported that out of five *Mentha* species (*M. longifolia*, *M. spicata*, *M. piperita*,

M. pulegium, and *M. rotundifolia*) M. piperita showed the highest total phenolic content and the strongest DPPH scavenging activity. As mentioned before, several factors such as cultivation, harvesting, and extraction methods are implicated in these different results.

5.2.2. Antibacterial Properties

Mentha essential oils and extracts are found to demonstrate a wide spectrum of antibacterial activity against bacterial strains. Anwar *et al*. (2017) reported that the antimicrobial activities of *Mentha* essential oils are correlated with oxygenated monoterpenoids and monoterpene hydrocarbon contents (70). It is believed that the presence of the hydroxyl group in phenolic compounds plays a significant role in the antimicrobial properties of essential oils (71).

5.2.3. Anticancer Properties

Research has developed into an investigation of plant species for their anticancer potential (72). The cytotoxic effects of some *Mentha* species have been reported in numerous studies (73-75). Polyphenolic compounds such as flavonoids are considered as anticancer compounds and their cytotoxicity and antioxidant properties have been demonstrated. It has been suggested that polyphenols can induce apoptosis and suppress the proliferation of cancer cells (72).

Various therapeutic effects reported for *Mentha* species are summarized in **Table 3**.

5.3. The genus Mentha Essential Oils as Biopesticides

Some *Mentha* species have long been known for their insecticidal and antimicrobial efficacies against plant pathogens (fungi, bacteria) and stored products insects. Biopesticides based on mint essential oils may present efficient alternatives and less harmful crop protectants than commercial pesticides (76). Essential oil-based botanical insecticides are very effective in controlling the stored product pests and plant pathogens responsible for preharvest and postharvest diseases. Diverse mechanisms of action on insect pests have been reported for essential oils. Many studies have demonstrated the neurotoxic action of essential oils. One of the most reported mechanisms of action in essential oils and constituents is the inhibition of acetylcholinesterase enzyme activity which cause paralysis and final death of the insects occurs (77). In insects, the octopaminergic system is also the main target site of essential oils activity. It has been reported that *Mentha* essential oils constituents affect the octopamine receptor which leads to the killing of the larvae and pupae in insects (76). The insecticidal, antifungal, and antibacterial properties of essential oils from different *Mentha* species are presented in **Table 4**.

6. Phytochemical Composition of *Mentha* Species

The biological properties and medicinal uses of mints are ascribed to essential oils and polyphenolic compounds that have been extensively investigated in literatures.

6.1. Volatile Compounds

Essential oils of mints are highly complex mixtures of volatile compounds characterized by a pleasant and strong odor (9). They are usually liquid and rarely colored (pale yellow or greenish-yellow) at room temperature. Essential oils are isolated by steam or hydro-distillation (9) and are freely soluble in organic solvents and lipids (12). Specialized secreting tissues called glandular trichomes are responsible for the biosynthesis of mint odorous secondary metabolites and are considered important sources of essential oils (78).

Mint essential oils are largely utilized in perfumery, cosmetics, pharmaceutical industries, and aroma-therapy (19, 79). Moreover, thanks to their active constituents, they possess antimicrobial and repellent effects that can be used as safe and potential alternatives for chemical pesticides (80). The most economically important essential oils belong to *Mentha* species including, *M. piperita* L., *M. spicata* L., *M. canadensis* L., and *M. gracilis* sole. In addition, *M. citrata* and *M. pulegium* L. oils also have commercial value, but to a lesser extent (14).

The essential oils of mints are mainly composed of terpenes (monoterpenes and sesquiterpenes) (9), hydrocarbons, alcohols, ketones, esters, and ethers (14). Terpenes are characterized as aromatic compounds which are the major constituents found in essential oils and responsible for the unique fragrance of the mints. It has been reported that terpenes exert antimicrobial activities (81). In addition, terpenoids are derivatives of terpenes containing oxygen molecules and play an important role in disease resistance (82).

Table 3. Various therapeutic effects reported for *Mentha* species

Therapeutic effects	Mentha species	Preparation used	Reference
Antioxidant	*M. spicata*	Diethyl ether extract	(85)
		Methanolic extract	(86-88)
		Ethanolic extract	(88)
	M. arvensis	Water extract	(89)
	M. pulegium	Ethanolic extract	(90)
	M. piperita L.	Essential oil	(91)
		Water extract	(92)
		Water extract	(9)
	M. longifolia L.	Essential oil	(93)
		Methanolic extract	(94)
			(95)
Antidiabetic	*M. piperita* (chocolate mint)	Water extract	(96, 97)
	M. spicata	Water extract	(98)
		Ethanolic extract	(88)
	M. arvensis	Methanolic extract	(99)
Antifungal	*M. spicata*	Volatile oil	(61)
	M. spicata	Ethanolic extract	(88)
		Methanolic extract	(88)
	M. piperita	Essential oil	(100, 101)
	M. longifolia L.	Essential oil	(102)
	M. Mozaffarianii	Essential oil	(103)
Antibacterial	*M. spicata*	Volatile oil	(61, 88)
	M. arvensis	Ethanolic extract	(90)
	M. pulegium	Essential oil	(91)
		Essential oil	(104)
	M. piperita	Essential oil	(93)
	M. aquatica	Essential oil	(105, 106)
	M. longifolia	Essential oil	(106, 107)
	M. Mozaffarianii	Essential oil	(103)
Analgesic	M. arvensis	Ethanolic extract	(90)
	M. piperita	Methanolic extract	(108)
	M. suaveolens	Methanolic extract	(109)
		Essential oil	(34)
	M. spicata	Methanolic extract	(88)
	M. Mozaffarianii	Essential oil	(16)
Anti-inflammatory	*M. piperita*	Methanolic extract	(108)
		Essential oil	(73, 110)
		Ethanolic extract	(111)
	M. spicata	Water extract	(89)
		Methanolic extract	(88)
	M. Mozaffarianii	Essential oil	(16)
Cytotoxic Anticancer	*M. piperita*	Essential oil	(73)
	M. arvensis	Methanolic extract	(74)
	M. longifolia	Methanolic extract	(74, 95)
	M. spicata	Methanolic extract	(74)
	M. viridis	Methanolic extract	(74)
	M. villosa	Essential oil	(75)
Antiviral	*M. suaveolens*	Essential oil	(112)
	M. spicata	Essential oil	(113)
	M. piperita	Essential oil	(113)
Antiallergic	*M. arvensis*	Water extract	(114)
	M. piperita	Water extract	(115)
	M. spicata	Methanolic extract	(116)

Table 4. The insecticidal, antifungal, and antibacterial properties of essential oils from different *Mentha* species (76, 117, 118)

Species	Antibacterial activity	Antifungal activity	Insecticidal activity
M. piperita	*Pseudomonas syringae pv. syringae*	*Penicillium digitatum*	Callosobruchusmaculatus Phthorimaea absoluta
	P. syringae pv. tomato	*Aspergillus. flavus*	
	P. syringae pv. phaseolicola	*A. niger*	
	Xanthomonas campestris pv. campestris	*Mucor* spp	
	X. campestris pv. phaseoli	*Fusarium oxysporum*	
	X. campestris pv.juglandis	*A. niger*	
	Erwinia carotovora subsp. *carotovora*	*Rhizopus solani*	
	X. vesicatoria	*Alternaria alternata*	
		A. flavus	
		F. oxysporum f.sp. *lycopersici*	
		Drechslera spicifera	
		F. oxysporum f.sp. *ciceris*	
		Macrophomina phaseolina	
		Verticillium fungicola	
		T. harzianum	
M. spicata	*X. campestris pv .juglandis*	*Rhizopus solani*	*Rhyzopertha dominica* *Callosobruchus chinensis* *Ephestia kuehniella* *Plodia interpunctella* *Leptinotarsa decemlineata*
		A. niger	
		Alternaria alternata	
		Geotrichum citri-aurantii	
		P. digitatum	
		P. italicum	
		A. ochraceus	
		A. versicolor	
		A. flavus	
		A. terreus	
		A. alternata	
		P. ochrochloron	
		P. funiculosum	
		C. cladosporioides	
		T. viride	
		F. tricinctum	
		Phomopsis helianthi	
		Verticillium fungicola	
		T. harzianum	
		A. terreus	
		F. oxysporum	
		P. expansum	
		V. dahliae	
M. arvensis	*Pantoea agglomerans*	*Aspergillus* spp	*Tribolium castaneum*
	Erwinia amylovora	*Fusarium spp*	
	Pantoea dispersa		
	P. fluorescens		
	Ps. syringae pv. syringae		
M. longifolia		*A. niger*	*T. castaneum* *C. maculates* *Sitophilus zeamais*
		A. versicolor	
		Cladosporium fulvum	
		F. tricinctum	
		F. sporotrichioides	
		P. funiculosum	
		P. ochrochloron	
		C. cladosporioides	
		Aspergillus spp	
		Fusarium spp	
		P. funiculosum	
		Trichoderma viride	
		C. fulvum	
		C. cladosporioides	
		P. ochrochloron	
		Rhizopus solani	
		A. niger	
		Alternaria alternata	

The terpenoid profile of mint essential oils is highly valued. Menthol as a dominant constituent of the essential oil in *Mentha* is a cyclic monoterpene alcohol that is used widely in medicinal preparation and cosmetics (83). The chemical composition of essential oils is reported to be affected by different factors, such as geographical site (84), environmental conditions, phonological phases of the plant, the part of the plant used, and the essential oil analysis methods (12).

6.2. Non-Volatile Compounds

A wide range of other bioactive compounds have been reported in mints, including phenolic compounds which comprise the largest group among the different classes of plant secondary metabolites (22). Phenolics can be classified based on their structures into phenolic acids, tannins, coumarins, flavonoids, stilbenes, and lignans (119). *Mentha* plants are potential sources of phenolic compounds, especially flavonoids and phenolic acids as one of the most important groups of mint phenolics (120). **Table 5** and **Table 6** present the major polyphenolic compounds and the main components of some prevalent *Mentha* species essential oils.

6.2.1. Phenolic Acids

Phenolic acids are ubiquitous compounds with a wide range of pharmacological activities, which are present abundantly in plants belonging to the Lamiaceae family, especially *Mentha* species. They are divided into two subgroups: Hydroxycinnamic acids (HCAs) with a chemical backbone of C6-C3, and hydroxybenzoic acids (HBAs) with a common structure of C_6-C_1 (119, 121). *Mentha* species are considered a rich source of caffeic acid and its derivatives, rosmarinic acid and chlorogenic acid (9, 14). Caffeic acid as a hydroxycinnamic acid has been found in *M. spicata* L. (22, 23, 122, 123), *M. rotundifolia* Huds. (122), *M. australis* R. Br. (124), *M. pulegium* L. (122), *M. piperita* L. (125), and *M. aquatica* L. (126). Hydroxycinnamic acid esters are widely present in plants and are often bound to sugar units in the form of glycosides such as chlorogenic acid that is formed between caffeic acid and quinic acid as a soluble ester and its presence has been reported in several *Mentha* species such as *M. spicata* L. (22, 23, 122), *M. piperita* L. (125), *M. australis* R. Br. (124), and *M. longifolia* (L.) L. (127). Rosmarinic acid is a highly valued hydroxycinnamoyl ester that has been abundantly found in a wide variety of *Mentha* species (122-124, 128). Moreover, seven salvianolic acids have been detected in mints, such as salvianolic acid B (lithospermic acid B), a dimer of rosmarinic acid (22, 23, 129).

The genus *Mentha* is a rich source of flavonoids, especially flavones and flavanones (9, 14). Luteolin-7-O-glucoside, eriocitrin, and hesperidin have been reported to be the major flavonoids in *Mentha* species (12). The content of phenolic compounds within the methanolic extract of *M. spicata* subsp. spicata is reported to be caffeic acid, rosmarinic acid and luteolin (130). The main extracted phenolic compounds from *M. aquatic*a L. are rosmarinic acid, eriocitrin, and luteolin-7-O-glucoside (6), whereas eriocitrin (the dominant flavonoid glycoside), luteolin-7-*O*-rutinoside, rosmarinic acid, luteolin-7-*O*-glucoside, and hesperidin are the main polyphenolic components of the peppermint (6, 131).

7. Phytochemical Analysis Methods

As mentioned before, secondary metabolites are high-value chemicals that are used as medicines, food supplements, dyes, flavors and fragrances, pigments, and insecticides (132). Therefore, metabolomic profiling to identify compounds with putative biological activity is highly crucial. In *Mentha* plants, the gas chromatography-mass spectrometry (GC-MS) method is generally used to identify the chemical compounds in the essential oil, and the spectrophotometry method is performed to measure the amount of metabolites. Identification of compounds present in the extracts of *Mentha* plants such as phenolic acids, flavonoids, and carotenoids is accomplished using High-Performance Liquid Chromatography (HPLC) and Liquid Chromatography–mass spectrometry (LC-mass) methods (12).

8. Breeding Efforts of the Genus Mentha

From a commercial point of view, breeding efforts are focused on improving the essential oil quality and verticillium wilt disease resistance of new mint cultivars (2). Clonal propagation in cultivated commercial mints such as peppermint and spearmint as the main producers of essential oils, leads to unusual ploidy levels (2). Peppermint and spearmint have complex polyploidy genomes and conventional breeding is not amenable to improving crops due to sterility. The complex polyploidy genome of the cultivated mints, disease sensitivity, and sterility all threaten the sustainability of mint farming (133).

Table 5. Major chemical constituents of some *Mentha* species essential oils

Compounds	Species	Biological activity	Reference
Terpenoid			
Geranyl acetate	*M. arvensis*	-----	(60)
	M. piperita L.		(60)
Pulegone/ Isopulegone	*M. arvensis*	-----	(60)
Menthonel lsomenthone	*M. arvensis*	-----	(60)
Sabinene	*M. piperita* L.	-----	(60)
β- Pinene	*M. piperita* L.	-----	(60)
β-Mircene	*M. piperita* L.	-----	(60)
α-Terpinene	*M. piperita* L.	Antioxidant	(60, 134)
Elixene	*M. piperita* L.	-----	(60)
Monoterpene	*M. piperita* L.	-----	(60)
Hydrocarbons			
β-caryophyllene	*M. piperita* L.	Anticancer	(84, 135)
	M. spicata L.		(136, 137)
	M. rotundifolia		(138)
	M. aquatica L.		(139, 140)
Germacrene D	*M. piperita* L.	-----	(84)
	M. rotundifolia		(138, 141)
	M. spicata L.		(136)
Limonene	*M. spicata* L.	Antibacterial Antifugal Antiyeast	(73, 84, 142)
	M. gracilis		(84, 135)
	M. piperita L.		(84)
	M. pulegium L.		(136)
	M. rotundifolia		(143)
	M. aquatica L.		(140, 144)
	M. arvensis		(60)
Alcohols			
Elemol	*M. aquatica* L.	-----	(144)
Geraniol	*M. rotundifolia* *M. suaveolens* Ehrh. *M. longifolia*	-----	(143) (12) (102)
Linalool	*M. gentilis* L.	-----	(142)
	M. rotundifolia *M. spicata* subsp. *condensata*	-----	(143) (12)
	M. piperita L.		(60)
	M. Mozaffarianii		(103)

Menthol	*M. piperita* L.	Antifugal Antiyeast Antiviral	(84, 135)
	M. rotundifolia		(143)
	M. spicata L.		(145)
	M. arvensis L.		(135, 146, 147)
Neomenthol	*M. piperita* L.	-----	(84)
	M. pulegium L.		(141, 148)
	M. rotundifolia		(143)
	M. arvensis L.		(147)
3-octanol	*M. gracilis*	-----	(84)
	M. arvensis L.		(147)
cis/trans-sabinene hydrate	*M. rotundifolia*	-----	(12, 149)
	M. piperita L.		(60)
α-terpineol	*M. spicata* L.	-----	(12)
	M. suaveolens Ehrh.		(12)
terpinen-4-ol	*M. spicata* L.	-----	(12)
	M. longifolia subsp. *longifolia*		(150)
	M. piperita L.	-----	(60)
viridoflorol	*M. aquatica* L.		(14, 151)
	M. piperita L.		(60)
Esters			
Decyl acetate	*M. verticillata* L.	-----	(14)
Dihydrocarvyl acetate	*M. smithiana* R. Graham	-----	(14)
	M. villosa Huds.		(14)
1,2-epoxyneomenthyl acetate,	*M. suaveolens* Ehrh.	-----	(14)
Menthyl acetate	*M. piperita* L.	-----	(84)
	M. rotundifolia		(143)
	M. spicata L.		(145)
	M. piperita L.		(12)
	M. arvensis		(60)
Neoisomenthyl acetate	*M. pulegium* L.	-----	(14)
Neomenthyl acetate	*M. diemenica* Spreng.	-----	(14)
	M. arvensis L.		(146)
3-octyl acetate	*M. arvensis* L.	-----	(14)
α-terpinyl acetate	*M. longifolia* subsp. *longifolia*	-----	(150)
Ketones			
Carvone	*M. spicata* L.	Antioxidant Antibacterial Antifugal Antiyeast	(73, 84, 135, 152)
	M. gracilis		(9)
cis-/trans-dihydrocarvone	*M. spicata* L.	-----	(12)
Isomenthone	*M. pulegium* L.	Antibacterial	(135, 136)
	M. piperita L.		(9)
	M. rotundifolia		(143)
	M. arvensis L.		(146, 147)

Menthone	*M. piperita* L.	Antibacterial Antifugal Antiyeast Anticancer	(84, 135)
	M. pulegium L.		(136, 141)
	M. rotundifolia		(143)
	M. spicata L.		(145)
	M. arvensis L.		(146, 147)
	M. Mozaffarianii		(103)
3-octanone	*M. arvensis* L.	-----	(14)
	M. verticillata L.		(14)
Pulegone	*M. pulegium* L.	-----	(141, 149)
	M. spicata L.		(142, 153)
	M. rotundifolia		(138)
	M. longifolia		(154)
	M. Mozaffarianii		(103)
	M. piperita L.		(60)
Piperitenone	*M. pulegium* L.	-----	(136)
	M. Mozaffarianii		(103)
Piperitone	*M. spicata* L.	Antifugal Antiyeast	(135, 153)
	M. pulegium L.		(136)
	M. piperita L.		(60)
	M. Mozaffarianii		(103)
Ethers			
1,8-cineole,	*M. piperita* L.	Antioxidant	(84, 135)
	M. spicata L.		(73, 84, 142, 155)
	M. longifolia		(155)
	M. rotundifolia		(143)
	M. aquatica L.		(140)
	M. arvensis		(60)
	M. Mozaffarianii		(103)
Menthofuran	*M. piperita* L.	-----	(9, 84)
	M. rotundifolia		(143)
	M. spicata L.		(145)
	M. aquatica L.		(140)
Oxides			
Caryophyllene oxide	*M. aquatica* L.		(14)
Piperitenone oxide	*M. suaveolens*	-----	(155)
	M. spicata L.		(155)
	M. longifolia		(154, 155)
	M. rotundifolia		(138, 156)
	M. spicata L.		(12)
	M. Mozaffarianii		(103)
Piperitone oxide	*M. rotundifolia*	-----	(141)
	M. spicata L.		(12)
	M. longifolia subsp. *longifolia*		(150)

Therefore, genetic improvement of this economically important crop is needed for its long-term sustainability. Since the advent of genome sequencing technology and the development of molecular markers, marker-assisted selection to improve verticillium wilt disease resistance and desirable essential oil characteristics has increased the importance of breeding programs in mints (2).

9. Biotechnological Techniques for the Production of High-Value Secondary Metabolites

Extraction of plant active ingredients from the tissues of intact plants results in biodiversity loss. In addition, production of valuable secondary metabolites by plants is often less than 1% of dry weight and is dependent on the physiological and developmental stage of the plant. To overcome these problems alternative methods such as *in vitro* culture techniques should be applied for secondary metabolites production (157).

9.1. Production of Mints Secondary Metabolites by Plant Cell and Tissue Culture Techniques

Plant cell and tissue culture techniques are considered as alternative methods for the production of important secondary metabolites when the supply of these compounds from nature is limited and traditional methods are not practical. Some advantages of the *in vitro* techniques are including the mass propagation of *Mentha* plants in an aseptic environment under controlled nutritional and environmental conditions, and the production of bioactive secondary metabolites on a large scale throughout the year without seasonal restrictions. Plant cell and tissue culture is a reliable and novel approach for high-efficient secondary metabolite isolation within a short span of time (158).

9.1.1. Hairy Root Culture System

Since secondary metabolites are often produced in limited quantities in differentiated tissues of medicinal plants, the extraction, isolation, and purification of these metabolites is generally a major problem. It is advantageous to use an efficient biotechnological method to produce these metabolites in less time and higher yield. Hairy root cultures offer many great features as a persistent source for the production of beneficial secondary metabolites due to their high growth rate, easy preservation, biochemical and genetic stability, and potential to synthesize higher quantities of secondary metabolites relative to natural plant roots. Hairy root disease which is induced by the gram-negative bacterium *Agrobacterium rhizogenes*, has gained attention as an effective biotechnological method for the production of active plant ingredients (23). Induction of hairy root and the production of secondary metabolites such as phenolic acids from some species of *Mentha* plants have been reported (22, 23, 159). In a recent study by Yousefian *et al*. (2020) the phenolic acids (caffeic acid, rosmarinic acid, chlorogenic acid, lithospermic acid, and cinnamic acid) production was carried out in hairy root cultures of *M. spicata* using five different *A. rhizogenes* strains (23).

10. Strategies for Enhanced Production of Mints Secondary Metabolites

Biotechnology has made it possible to apply several approaches such as metabolic engineering, elicitation, strain improvement, and optimization of culture medium to improve the *in vitro* secondary compounds production level (160). A better understanding of the mechanisms stimulated by external signals that can improve the secondary metabolites levels can be valuable for biotechnologists to increase the production of these compounds (161).

10.1. Optimization of Culture Medium

There are numerous parameters that can be optimized to enhance the secondary metabolite content of *Mentha* plants, including the medium pH, nutrient composition, nitrate, and phosphate levels, carbon source, and plant growth regulators type and concentration (158). The effect of phosphate, nitrogen, and pH on the rosmarinic acid content of *M. aquatica* hairy roots was evaluated by Yousefian *et al*. (2020). The results indicated that phosphate deficiency, increased phosphate levels, and acidic pH (phosphate 2.5 mM (+P), 0.6 mM (-P), and pH=5.5) significantly increased the rosmarinic acid content of hairy roots in comparison to the control medium (1.25 mM phosphate and pH= 5.8), whereas increasing the amount of nitrogen did not affect its level (159).

10.2. Elicitation

Stress as an important factor regulates the formation of many secondary metabolites (22). High-value plant secondary metabolites play a key role in plant responses to biotic and abiotic stresses to protect them against any threats. Stimulating the plant defense response by using substances to improve the production of these secondary metabolites is called elicitation.

Table 6. Major polyphenolic compounds of some Mentha species

Species	Essential oil main components	Polyphenolic Compounds	Reference
M. piperita L.	cineol (8.69%) menthol (40.47%) menthone (36.58%) menthol acetate (4.33%) sabinene (1.64%) α-pinene (1.11%)	Rosmarinic acid, caffeic acid, lithospermic acids, salvianolic acid, syringic acid, gallic acid, vanillic acid, p-coumaric acid, ferulic acid, protocatechuic acid glucoside, isosalvianolic acid A, prolithospermic acid, salvianolic acid, danshensu, chlorogenic acid, Luteolin 7-O-rutinoside, isorhoifolin, eriodictyol 7-O-glucoside, hesperidin, eriocitrin, narirutin, diosmin, sorbifolin, thymosin, sideritoflavone, ladanein, xanthomicrol, acacetin, salvigenin, 5-O-demethylnobiletin, pebrellin, hesperidin, Catechin, rutin, quercetin, medioresinol, medioresinol sulfate, trans-resveratrol	(3, 122, 163-168)
M. Spicata L.	carvone(42.84%) carveol (34.98%) menthol (40.47%) α-pinene (17.77%)	Rosmarinic acid, veratric acid, vanillic acid, homovanillic acid, hydroxybenzoic acid, syringic acid, 4-hydroxy cinnamic acid, trans-hydroxy cinnamic , 4-hydroxy cinnamic acid, 2-hydroxy cinnamic ,4-hydroxy cinnamic acid, ferulic acid, gallic acid, protocatechuic acid, chlorogenic, caffeic , 4-hydroxy cinnamic acid, p-coumaric, 4-Hydroxy benzoic acid, diosmin, diosmin-7-glucoside, 6,4′-trihydroxy-7,3′-dimethoxflavone, desmethoxynobiletin, 5,6-di-hydroxy-7,8,3′,4′-tetramethoxyflavone, thymonin, sideritiflavone, 5-Hydroxy-3′,4′,6,7-tetramethoxyflavone, thymonin, naringenin, luteolin, apigenin, rutin, catechin, chrysoeriol, 5,6-dihydroxy-7, 8,3′,4′-tetramethoxyflavone, nodifloretin, quercetin, luteolin, scopoletin, catechin, epicatechin, myricetin, apigenin, kaempferol, spicatolignan A, spicatolignan B	(3, 122, 163, 169, 170)
M. rotundifolia L.	cineol (2.4%) limonene (1.8%) menthol (40.50%) menthone (5%) menthofuran (4.2%) isomenthone(2.5%) linalool (2%) linalyl acetate(3.5%) piperitone (3.1%) menthyl acetate (4.5%)	Caffeic acid, p-hydroxybenzoic acid, ferulic acid, p-coumaric acid, chlorogenic acid, rosmarinic acid, apigenin, luteolinidin, elargonidin, cyanidin, delphinidin, petunidin, luteolin, thymonin, thymosin, 5,6-dihydroxy-7,8,3′,4′-tetramethoxyflavone, jaceo-sidin, hispidulin, ladanein, sorbifolin, nodifloretin, Esculetin, diosmin, naringenin, kaempferol	(9, 122, 171)
M. longifolia L.	limonene (4.3%) piperitenone (43.9%) Tripal (14.3%), oxathiane (9.3%) piperitone oxide (5.9%)	Rosmarinic acid, salvianolic acid, Luteolin-glucuronide, eriodi-ctyol- glucopyranosyl-rhamnopyranoside	(167, 172, 173)
M. pulgium L.	limonene (1.2%) menthol(3.28%) menthone (3.09%) menthofuran (2.15%) pulegone (6.45%) isomenthone (1.56%) carvone (1.13%) piperitenone (21.18%) piperitone (35.56%) α-terpineol (10.89%)	Caffeic acid, vanillic acids , ferulic acid, 4-Hydroxy benzoic, p-coumaric acids, chlorogenic acids, rosmarinic acid, Diosmin, Thymonin, jaceosidin, pectolinaringenin, ladanein, sorbifolin, pedalitin, 5,6,4′-trihydroxy-7,3′-dimethoxyflavone; 5,6-dihydroxy-7,3′,4′-trimethoxyflavone; 5-hydroxy-6,7,3′,4′-tetramethoxyflavone, apigenin, luteolin, chrysoeriol, kaemp-ferol, naringenin, catechin	(9, 143, 170)
M. arvenisis L.	limonene (1.47%) menthol (21.33%) menthone (29.41%) isomenthone (10.80%) eucalyptol (6.91%) linalool (2.2%)	rosmarinic acid, chlorogenic acid, caffeic acid, neoponcirin, narirutin, biochanin A, apigenin, hesperetin	(174, 175)
M. suaveolens L.	pulegone (62.3-34.3%) menthone (39.4–10.8%) isomenthone (9.3–7.8%)	4-Hydroxybenzoic acid, vanillic acid, chlorogenic acid, Viola-xanthin, Antheraxanthin, Lutein, Zeaxanthin, 13Z-β Carotene, α-Carotene, E-β-Carotene, 9Z-β-Carotene syringic acid, o-coumaric acid, p-coumaric acid	(9, 176)
M. aquatica L.	menthofuran (66–64%) cineol (7%) limonene (4–9%) menthol (0–2%) menthone (0–1%)	Rutin-O-glc, lavandulifolioside, eriodictyol O-rut, quercetin-3-O-soph, verbascoside, caffeic acid, rosmarinic acid	(3, 177)

The plant tissue cultures can be elicited by biotic or abiotic elicitors (signaling molecules such as phytohormones) (23). The effect of phytohormones as abiotic elicitors on secondary metabolites production has been widely studied. Methyl jasmonate (MeJA) as a signal molecule has a prominent role in plant signal transduction pathways (162). It is considered a potent abiotic elicitor which is applied exogenously in plant cell and tissue cultures to induce the production of desirable secondary compounds (22). Yousefian *et al*. (2020) investigated the effect of MeJA on phenolic acid biosynthesis in hairy root cultures of *M. spicata*. The results implied that MeJA has a significant impact on rosmarinic acid, caffeic acid, chlorogenic acid, and cinnamic acid accumulation, which might be the consequence of gene activation from the phenylpropanoid and tyrosine-derived pathways in the elicitor-treated hairy root cultures (22).

10.3. Genetic and Metabolic Engineering

As mentioned earlier, *Mentha* plants have been recognized as medicinal herbs in the traditional medicine of many countries (178). They are known for a range of various bioactive phytochemicals, especially polyphenols (rosmarinic and salvianolic acids) and monoterpenes (menthol and carvone) (179). Nowadays, due to the economic importance of *Mentha* plants, the demand for their products is growing exponentially. Therefore, to supply such demand, new strategies should be adopted to improve the yield and medicinal quality of the products. The advanced methods of genetic and metabolic engineering are useful to deal with any obstacles which limit the accumulation of bioactive compounds, and thus, to improve the yield of plants. Up to now, few studies have been carried out regarding the genetic modification of *Mentha* spp. This could be due to the lack of sufficient information about *Mentha* genome sequences. For instance, a little information about the number of Coding DNA Sequences (CDS) and Expressed Sequence Tags (EST) of *Mentha* have been submitted to the National Center for Biotechnology Information (NCBI). Additionally, due to the low number of sequence data, the cloning and sequencing process of regulatory genes are restricted to using the sequence of closely related *Mentha* species. However, a draft of *M. longifolia* genome has been recently published that provides a valuable genomic resource for studies aiming to identify novel genes linked to desirable oil characteristics.

In the following paragraphs, we will report and discuss the obtained results about the biosynthetic and regulatory genes that can be used in biotechnological strategies to boost the synthesis of the main class of compounds that have been characterized in *Mentha* ssp.

10.3.1. Metabolic Engineering of Monoterpene Biosynthesis

Terpenoids are the main group of pharmacologically active phytochemicals found in *Mentha* plants (180). By the number of isoprene units (C5H8), terpenes are classified into different groups such as monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes, and polyterpenoids (181). All these terpenoids arise biosynthetically from the cytoplasmic mevalonate pathway or plastidial 2-C-methyl-D-erythritol 4-phosphate (MEP) pathway (**Fig. 2**) (182). Monoterpenes are the main class of mint essential oil, which are generally colorless, lipophilic, and volatile (182). They are frequently used in pharmaceuticals, cosmetic products, fragrance, and flavor industries (183). Carvone and menthol are economically valuable monoterpenes found in *M.spicata* and *M. piperita*, respectively (184). During previous attempts, high-efficiency transformation protocols using *A. tumefaciens/rhizogenes* have been used for transferring genes that are involved in the biosynthesis of monoterpenes in spearmint and peppermint (185,186). The genes were cloned and functionally characterized using metabolic engineering strategies including up-regulation or over-expression of the gene(s)/enzyme(s), down-regulation of the gene(s)/enzyme(s), and engineering of the regulatory gene(s) (184, 187-194).

10.3.1.1. Up-Regulation or Over Expression of Genes

Monoterpenes are mainly derived from the MEP pathway in plastids (**Fig. 3**). One way to potentially elevate the yield of mint oil is overexpression of the key genes involved in the production of precursors in the monoterpene biosynthesis pathway. For example, Mahmoud and Croteau (2001) reported that the oil yield of *Mentha* spp. was increased in transgenic plant lines through the overexpression of the 1-deoxy-D-xylulose 5-phosphate reductoisomerase (*DXR*) gene (189). They generated transgenic lines of *M.piperita* with a homologous sense version of *DXR* cDNA. According to their results, regenerated transgenic

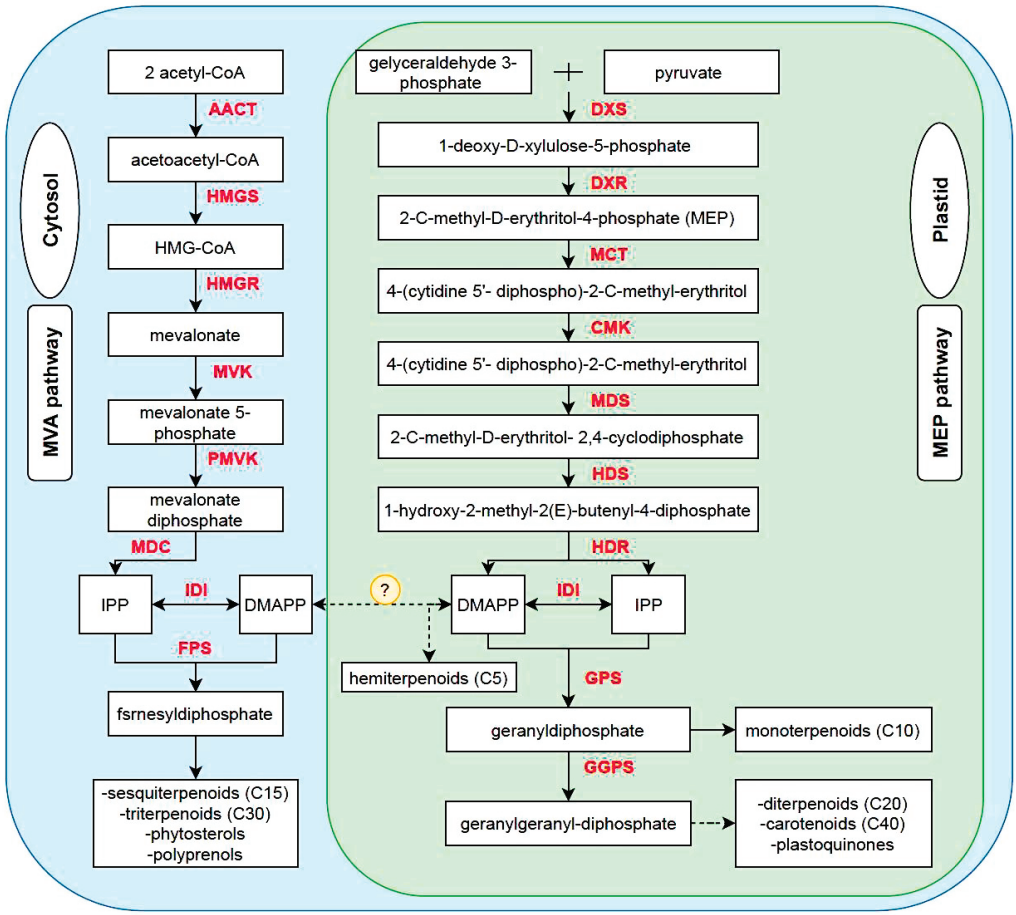

Figure 2. An overview of terpenoids biosynthetic pathway (195)

samples which remained normal in appearance and development, showed a strong expression of reductoisomerase. The yield of oil was also increased up to 50% without any changes in monoterpene composition. On the other hand, the mRNA or enzyme activity of reductoisomerase was not detected in chlorophyll-deficient transgenic lines. These plants yielded less essential oil than wild-type samples, which indicated the co-suppression of the reductoisomerase gene (189). In *Salvia* plants, a close genus to *Mentha*, a complex metabolic engineering push-pull strategy including simultaneously over-expressing three genes (DXS and GGPS from MEP pathway and HMGR from MVA pathway) was conducted for enhancing monoterpenes biosynthesis by transgenic hairy root cultures. The results showed remarkable achievement of tanshinones production (about 4.74 times higher than the control) (196). In another study, the co-introduction of DXS and GGPPS yielded monoterpene levels as high as 12.93 mg/g DW, compared to 0.61 mg/g DW in the controls (196). These findings showed that overexpression of precursor genes involved in monoterpene pathways (alone or in combination) was an appropriate approach to enhance monoterpene production.

Contrary to obtained results from the overexpression of biosynthetic genes, enhancing the expression level of enzymatic genes didn't have any significant effect on increasing mint oil yield. Cyclization of geranyl pyrophosphate to the olefin (-)-4S-limonene is the first committed enzymatic process in the biosynthesis of monoterpenes which is catalyzed via limonene synthase ((−)-LS) (**Fig. 3**). This enzyme is considered as a potentially rate-limiting enzyme because of its relatively low catalytic efficiency (187). The previous results demonstrated that elevating the expression level

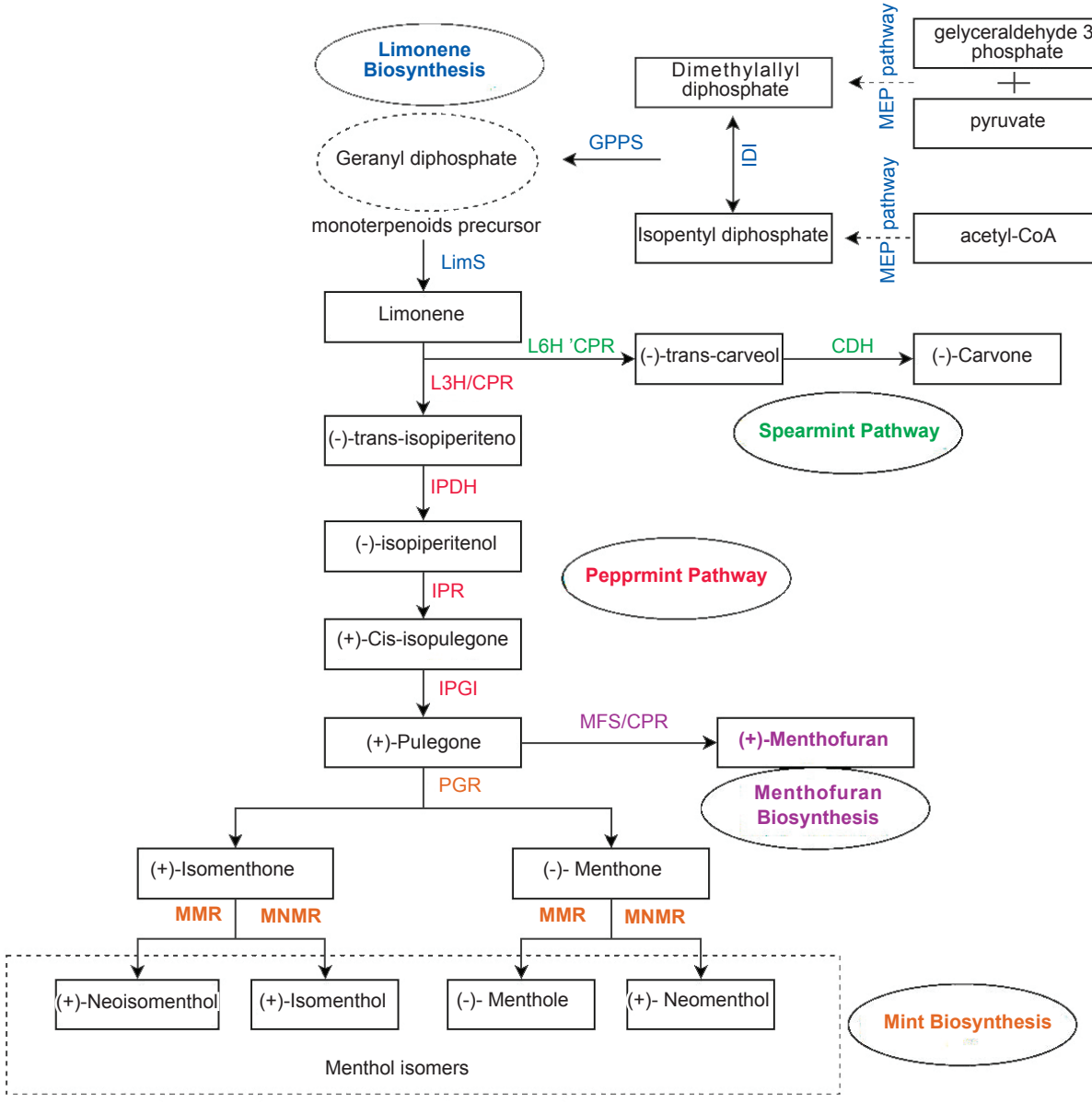

Figure 3. Monoterpenoids biosynthetic pathway in mint species (198)

of the gene encoding (−)-LS (*LimS*) in *M. piperita* led to only a moderate increase in the oil yield (197). Mahmoud *et al*., (2004) transformed cDNA clones of limonene synthase and limonene-3-hydroxylase into *M.piperita*. Despite the constitutive expression of both genes in transgenic plants, the activity of the corresponding enzyme was not significantly increased. Based on their result, overexpression of this enzyme had no effect on oil yield or its composition in the regenerated plants (191).

10.3.1.2. Downregulation or Functional Knockout of Genes

Downregulation or functional knockout of the genes is an effective strategy to decrease the production of certain unwanted compounds and boost the concentration and quality of a desired secondary metabolite. RNA interference (RNAi) and antisense RNA technologies approaches have been used for the inhibition or down-regulation of a gene. The principle of antisense RNA technology is that an antisense nucleic acid sequence

base pairs with its complementary sense RNA strand and prevents its translation into protein. Whereas, RNAi is a gene silencing process by double-strand RNA (dsRNA) in which only the mRNA associated with dsRNA is specifically degraded (181).

The gene silencing approaches have been successfully employed to enhance the quality of mint essential oil. For instance, (+)-menthofuran monoterpenoid and its intermediate (+)-pulegone (common components in several *Mentha* species essential oils) are considered undesirable components in commercial essential oil (**Fig. 3**) (190). Their adverse effects, such as increased liver weight, hepatotoxicity, and cerebellar pathology have been proven in multiple studies (190, 200). Therefore, metabolic engineering efforts aimed at improving oil composition have focused on reducing these ingredients. For example, antisense RNA technology was used to downregulate the expression of the (+)-menthofuran synthase (MFS) in *M. piperita.* Interestingly, the transgenic antisense lines, not only had a reduction in (+)-pulegone and (+)-menthofuran levels but also showed an increased oil yield by roughly 35% (189). This is inconsistent with the study by Mahmoud *et al*., which reported that transformed peppermint with the antisense version of the menthofuran synthase cDNA produced less than half of this unfavorable monoterpene than wild-type mint (190). In another research, Lange *et al*., transformed *M. piperita,* with various gene constructs to improve essential oil yield and composition simultaneously. They achieved transforming plants expressing an antisense version of (+)-menthofuran synthase with a construct for the overexpression of the DXR gene. The results showed significantly enhanced oil content (up to 61% oil yield increase over wild-type controls). Also, the level of undesirable side-products like (+)-menthofuran and (+)-pulegone was decreased (180). The above-mentioned descriptions demonstrated that the reduction of both menthofuran and pulegone levels by metabolic engineering approach has commercial significance in improving the quality of mint's essential oil.

10.3.1.3. Engineering of Regulatory Genes

Although the cloning and functional characterization of genes involved in terpene biosynthesis has been quite successful in *Mentha* species, knowledge about the regulation of these secretory trichome-specific pathways is extremely limited. Studies on spearmint indicate that essential oil biosynthesis is highly controlled at the transcriptional level (194). Hence, recognition of transcription factors (TFs) that regulate metabolic pathways will present an attractive strategy for the engineering of terpenoids biosynthesis. Recently, *MsMYB* (a R2R3-MYB gene) and *MsYABBY5* TFs that are preferentially expressed in the PGTs (peltate glandular trichomes) were isolated from transcriptomic data of spearmint. To investigate the role of these TFs in monoterpene production, transgenic lines were generated in which the *MsMYB* and *MsYABBY5* were either overexpressed or silenced. A High level of monoterpenes was detected in TFs-RNAi transgenic lines, whereas TFs-upregulation transgenic lines showed decreased levels of monoterpenes. These results demonstrated that *MsMYB* and *MsYABBY5* are novel inhibitors of monoterpene biosynthesis in *Mentha* spp. (181, 194). Additionally, according to obtained results from the RNA-seq data of spearmint, *MYB*s, and *WRKY* transcription factors were significantly more abundant in PGTs (183). Therefore, they can be good candidates for engineering the biosynthetic pathway of monoterpenes.

10.3.2. Metabolic Engineering of Phenolic Compounds Biosynthesis Pathway

It has been shown that *Mentha* species especially *M. spicata* contain considerable amounts of phenolic compounds specially Rosmarinic acid (RA) (201). Although progressive genetic improvement was focused on increasing of the *Mentha*'s essential oils, no efforts have yet been made to improve the production of rosmarinic acid or other antioxidant compounds in *Mentha* spp. Therefore, developing mint varieties with high levels of rosmarinic acid provides an economically valuable source of rosmarinic acid or other phenolic acids.

In brief, RA biosynthesis requires the contribution of both the phenylpropanoid branch which leads to the caffeic acid moiety, and the tyrosine-derived branch which drives to the dihydroxyphenyl lactic acid. Conversion of L-phenylalanine to 4-coumaroyl-CoA is done through the phenylpropanoid pathway via multiple reactions catalyzed by phenylalanine ammonia-lyase (*PAL*), cinnamic acid 4-hydroxylase (*C4H*), and 4-coumarate CoA ligase (*4CL*). In the tyrosine-derived pathway, L-tyrosine is converted to 4-hydroxyphenyllactate by two reactions, catalyzed

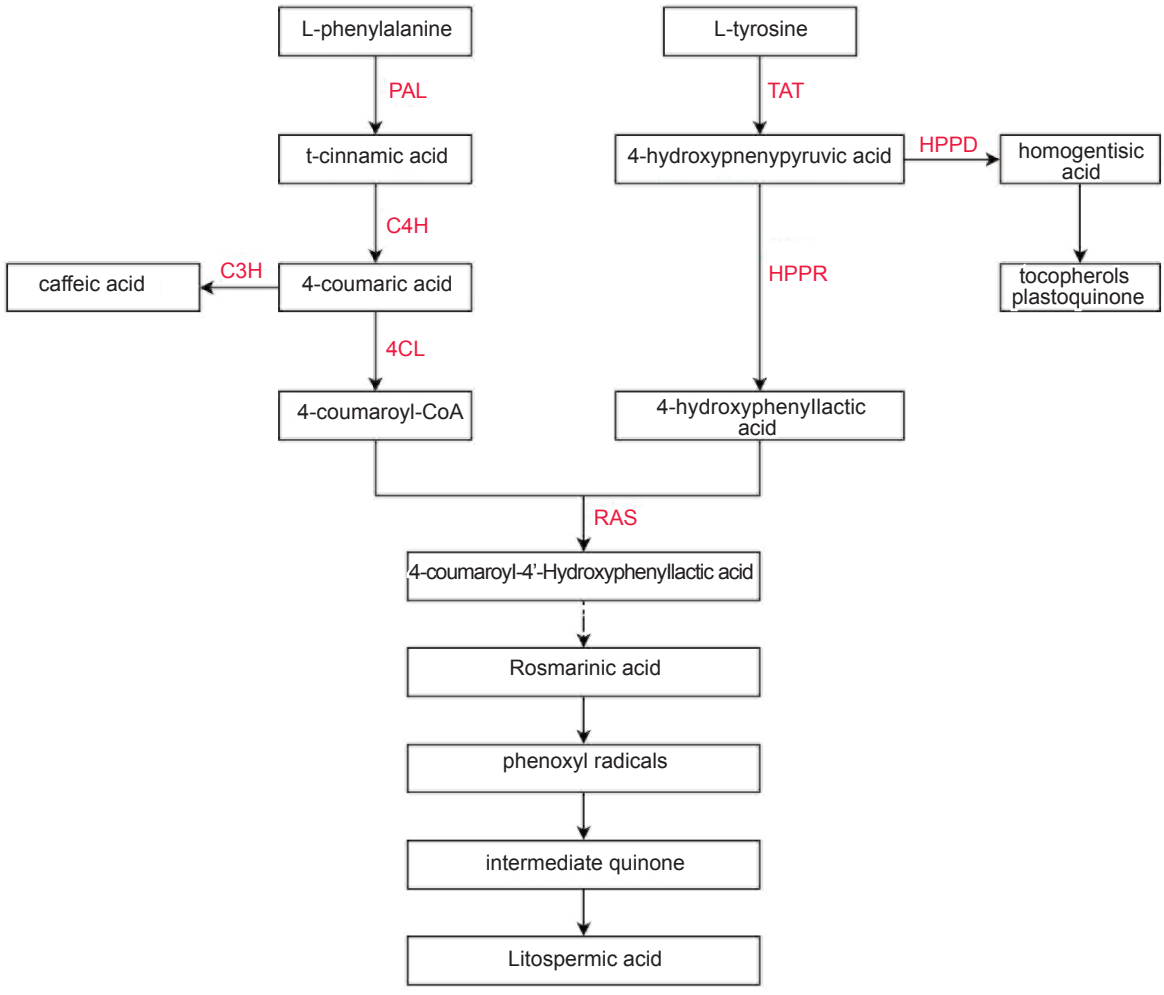

Figure 4. Simplified diagram of enzymes and products involved in rosmarinic acid biosynthesis (22)

by tyrosine aminotransferase (*TAT*) and *HPPR*. Hydroxyphenyllactate is then coupled with 4-coumaroyl CoA by the enzyme rosmarinic acid synthase (RAS) to form rosmarinic acid, and its intermediates (**Fig. 4**). Since there are no studies focusing on the metabolic engineering of rosmarinic acid and other phenolic compounds of mint plants, this section introduces candidate and engineered biosynthetic genes which are used to increase polyphenol biosynthesis in *Salvia* species. According to the results of a study by Xiao *et al*., a strong increment of RA and Salvianolic acid B (SalB) production was observed through overexpression of both *TAT* and *HPPR* in *s. miltiorrhiza* hairy roots (202). Yousefian et *al*. reported that upon MJ-elicitation of *M. spicata* hairy roots, the relative expression levels of phenylpropanoid pathway genes (*PAL*, *C4H*, *4CL*), and *HPPR* in the tyrosine-derived pathway were significantly increased compared to untreated controls. Additionally, based on their results, high-performance liquid chromatography analysis indicated that MeJA had a significant impact on RA, CA (caffeic acid), CGA (chlorogenic acid), and CIA (t-cinnamic acid) accumulation (22). These findings suggested that the overexpression of genes involved in phenylpropanoid and tyrosine-derived pathways can improve the phenolic acid content in *Mentha* spp. Jin *et al*. reported the expression of transcripts encoding enzymes for *PAL*, *C4H*, and *4CL* in the PGT of spearmint (183).

New reports evidenced that the phenylpropanoid pathway is highly controlled at the transcriptional level (203). Moreover, several transcription factors have been identified that control the expression of the essential genes (*PAL*, *C4H*, and *4CL*) in the phenolic acids production process. Different transcriptional

factors (TF) and other protein regulators have been characterized and may be used to enhance the precursor flow of the bioactive *Salvia* phenolic acids (196). For instance, successful technological results for increasing the amount of both RA and SalB have been obtained by constitutively co-expressed *AmDELILA* (belonging to the R2R3 MYB family) and *AmROSEA1* (belonging to the bHLH family) in *S. miltiorrhiza* (204). Genome-wide comparative analysis has identified seven R2R3MYB regulators of *Salvia* phenolic acids including *SmMYB1*, *SmMYB13*, *SmMYB16*, *SmMYB35*, *SmMYB62*, *SmMYB63*, and *SmMYB79*. These TFs were considered theoretically as putative regulators which may be proven to be useful, alone or in combination, for the re-direction of metabolic flux towards the desired phenylpropanoid branches (205). Sequence data and expression values of 4 R2R3-MYBs of spearmint including *MYB1*, *MYB16*, *MYB35*, and *MYB79* have been identified by Reddy *et al*. (194). Overexpression of heterologous *OsMYB4* TF in *S. sclarea* hairy roots and tobacco plants was also proved to be effective for increasing phenolic acids accumulation. The results of this research suggested that several genes involved in the phenylpropanoid pathway were up-regulated by this MYBTF. These findings indicated that the regulatory role of this TF is evolutionarily conserved in phenylpropanoid biosynthesis (196, 206).

11. Conclusion

Identifying the general biosynthetic pathways, leading to the accumulation of pharmaceutically important secondary metabolites, such as terpenoids in *Mentha* species, has paved the way for developing highly productive plants with improved phytochemical profiles. Nowadays, methods, such as metabolite engineering, and -omics technologies, especially functional genomics and mapping can be useful to improve highly productive, economically feasible platforms for the sustainable production of valuable medicinal phytochemicals of *Mentha* origin. Elucidation of regulatory mechanisms and evaluation of the potential rate-limiting steps are fundamental biotechnological strategies in many secondary metabolite synthesis pathways. Sequencing and characterization of the *M. longifolia* genome and the availability of transcriptomic data of *M. spicata* create opportunities for the identification and characterization of key genes involved in the main secondary metabolites of *Mentha* species (207). Such methods could help to a better understanding of the specific biosynthetic and regulatory mechanisms existing in this remarkable genus. On the other hand, an advanced method in metabolic engineering, called genome editing tools, provides a much easier way for engineering secondary metabolites biosynthetic pathways and relevant genes (208).

Declaration of Competing Interest

The authors declare that this article has no conflicts of interest.

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