Chapter 17
Molecular Biology of Glandular Trichomes and Their Functions in Environmental Stresses

Maridul Kundan, Umar Gani, Abhishek Kumar Nautiyal and Prashant Misra

Abstract Glandular trichomes, the epidermal projections over aerial plant parts primarily function in defense against stresses including protection from insects and microbes. These structures are characterized by dedicated genetic machinery for overproduction of structurally diverse secondary metabolites. Certain secondary metabolites of trichome origin display interesting pharmacological activities, and therefore are of immense economical interest as drug, aroma and allelochemicals. For obvious reasons, glandular trichomes have been focus of 'omics' studies, particularly for elucidating molecular basis of such a large scale production of secondary metabolites. In the last decade, next generation sequencing has fueled the development of transcriptome landscapes of glandular trichomes of several medicinal and aromatic plants. Taken together, these studies have started to unravel gene and metabolic networks operating in glandular trichomes, and therefore are potentially useful for identification of novel molecular targets for strategic metabolic engineering of economically important secondary metabolites as well as for development of stress tolerant plant varieties. The present book chapter will update our current knowledge about aspects of glandular trichome biology including its applied value in plant biology.

Keywords Glandular trichomes · Biotic and abiotic stresses · Plant secondary metabolites · Transcriptomics

---

Authors Maridul Kundan, Umar Gani, and Abhishek Kumar Nautiyal are equally contributed.

M. Kundan · U. Gani · A. K. Nautiyal · P. Misra (✉)
Plant Biotechnology Division, CSIR—Indian Institute of Integrative Medicine, Canal Road, Jammu 180001, India
e-mail: pmisra@iiim.ac.in

Academy of Scientific and Innovative Research (AcSIR), New Delhi, India

S. P. Singh et al. (eds.), *Molecular Approaches in Plant Biology and Environmental Challenges*, Energy, Environment, and Sustainability,
https://doi.org/10.1007/978-981-15-0690-1_17

17.1 Introduction

A vast number of Angiosperms possess hair-like epidermal structures which are termed as trichomes. Sometimes, similar structures have also been reported in gymnosperms, bryophytes (Uphof 1962), lichens and algae (Engene et al. 2012). Trichomes are primarily present on surface of leaves and stem, but they are also found on petals, petioles, peduncles and seeds, depending upon the species. Trichomes display tremendous diversity in terms of cellular organization, structure and chemistry. These structures can be broadly divided into two categories—glandular and non glandular, depending upon their morphology and secretion ability (Fahn 2000; Kolb and Muller 2004). Irrespective of the types, all the trichomes originate from epidermal cells. Some of the epidermal cells elongate and modify into unicellular trichomes or may undergo division and specialization to develop into multicellular trichomes. Glandular trichomes, characterized by presence of gland cell(s) or secretory cell(s) have been reported in approximately 30% of all vascular plant species (Fahn 2000) and in a single plant species several types of trichomes (both glandular and non-glandular) have been reported to be present together. Owing to their remarkable ability to biosynthesize, store and secrete a range of secondary metabolites, the glandular trichomes are often referred to as biofactories of specialized metabolites. They secrete a mixture of chemicals that often offer a vast array of uses in the pharmaceutical, pesticides and flavour & fragrance industries, besides playing important role in plant biology. These structures are regarded as suitable systems for studying molecular basis of cellular differentiation and biosynthesis of specialized plant metabolites. For obvious reasons, there have been emerging interests to study the gene expression and metabolism in these structures with main focus on identification of genes involved in biosynthesis of trichome specific natural products. Thus, due to their wide occurrence, usage as development model and many other important functions, glandular trichomes have been of academic and applied significance.

17.2 Morphology and Classification of Glandular Trichomes

Glandular trichomes have a multicellular structure, consisting of a stalk, which is terminated by a glandular head (Turner et al. 2000). They are developed from a single protodermal cell, which following vertical enlargement and multiple divisions develop into a trichome structure. On the basis of structure and cellular organization, glandular trichomes can be subdivided into two major classes, namely peltate and capitate trichomes (Fig. 17.1) (Werker 2000). The peltate trichomes are generally characterized by presence of a short stalk, composed of one or two cells, and large head, comprising of four to eight secretory cells, having a large sub-cuticular space (Turner et al. 2000; Werker 2000). The secretory cells are remarkably active in biosynthesizing metabolites that along with other molecules are transported out

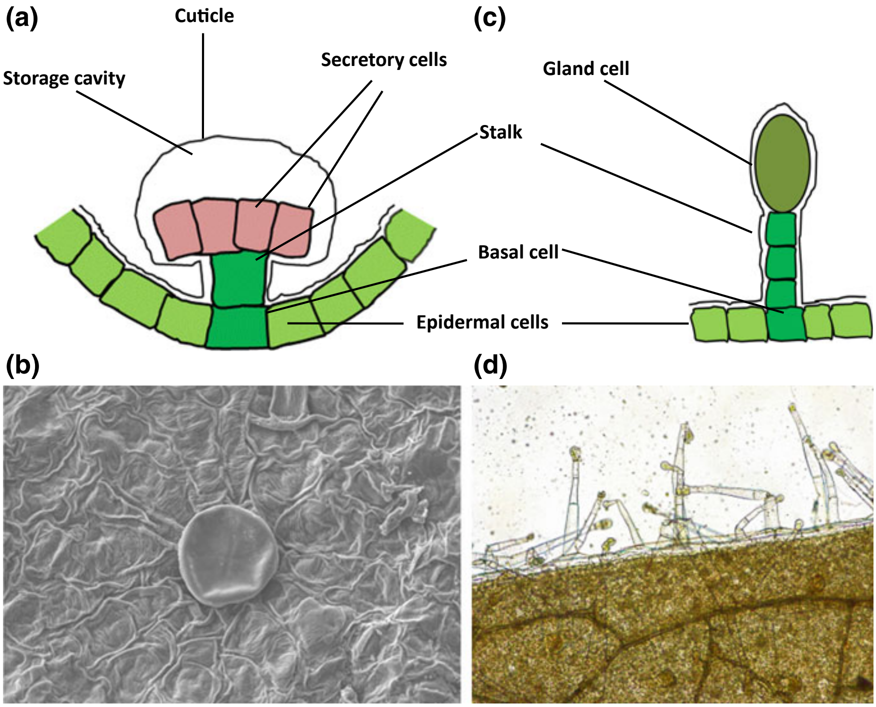

Fig. 17.1 Types of glandular trichomes. **a** and **c** Schematic diagrams showing peltate and capiate trichomes, respectively. **b** Scanning electron microscopic view of leaf surface of a member of family lamiaceae showing peltate trichome (Author's own lab, unpublished picture). **d** Light microscopic view of leaf surface of *N. tabacum* showing glandular trichomes

and stored in a prominent sub-cuticular space. Capitate trichomes are characterized by presence of a single basal cell, which is embedded within the epidermal layer, one or two stalk cells and one or two spherical secretory heads (Werker 2000; Bisio et al. 1999). The *Solanum* sp., for example are characterized by presence of eight types of trichomes. Out of them, four (i.e., type I, IV, VI and VII) are glandular capitate trichomes and the rest (i.e., type II, III, V and VIII) are non-glandular (Glas et al. 2012). The type I and IV glandular trichomes are capitate, whereas type VI and VII appear to display a peltate structure. These types differ in number of stalk and secretory cells. In *S. lycopersicum*, Type I and Type VI are the two abundant types of glandular trichomes (McDowell et al. 2011). Type I trichomes consist of a multicellular stalk with a single, small gland cell at the tip where as Type VI trichomes have a unicellular stalk with a four-cell glandular head. The glandular trichomes of *Nicotiana tabacum, N. sylvestris* and *N. rustica* exhibit very similar features, characterized by presence of 4 to 6 stalk cells and 1 to 6 head cells. In *N. tabacum*, usually, two types of capitate glandular trichomes are found (Shepherd et al. 2005); the larger ones with a long stalk and a chlorophyllous head due to presence of chloroplast, and the smaller ones with a short stalk and non- chlorophyllous head. In contrast to the long trichomes, short trichomes do not possess chloroplasts in their head cells. In the members of Lamiaceae, for example, *Ocimum* sp. and *Mentha piperita* (mint), both types of glandular trichomes are present together. The *Mentha* species has non-glandular trichomes, peltate glandular trichomes and capitate glandular trichomes, present on abaxial and adaxial surfaces of the leaf.

17.3 Glandular Trichomes as Source of Economically Important Natural Products

The glandular trichomes have the ability to synthesise, store and secrete diverse secondary metabolites such as terpenoids (Gershenzon and Dudareva 2007), flavonoids (Treutter 2006), phenylpropenes (Gang et al. 2002), methyl ketones (Fridman et al. 2005) and acyl sugars (Kroumova and Wagner 2003). Many of these secondary metabolites are of human interest and utilized as pharmaceuticals and neutraceuticals (Table 17.1) (Mahmoud and Croteau 2002; Schilmiller et al. 2008). For instance, Lamiaceae, an important aromatic plant family with species such as Basil (*Ocimum basilicum*), lavender (*Lavandula spica*), mint (*Mentha* × *piperita*), oregano (*Origanum vulgare*) and thyme (*Thymus vulgaris*), is renowned for its essential oil, which is produced exclusively in glandular trichomes (Schilmiller et al. 2008). Artemisinin, a sesquiterpene lactone, produced in the glandular trichomes of *Artemisia annua* (a member of Asteraceae family), is used as an effective drug for the treatment of malaria (Duke et al. 1994; Weathers et al. 2011). The glandular trichomes of *Cannabis*

Table 17.1 A list of plants with economically important natural products produced primarily by glandular trichomes

Plant species	Metabolite	Important compound	References
Mentha piperita	Monoterpene	Menthol	Gang et al. (2002)
Salvia sclarea	Diterpene	Sclareol	Moulines et al. (2004), Frija et al. (2011)
Cannabis sativa	Cannabinoids	Tetrahydrocannabinol (THC); Cannabidiol (CBD)	Sirikantaramas et al. (2005), Pellati et al. (2008), Taura et al. (2007)
Humulus lupulus	Terpenes	Humulone	Wang et al. (2008)
Gossypium hirsutum	Sesquiterpene	Gossypol	Mellon et al. (2014)
Artemisia annua	Sesquiterpene	Artemisinin	(Weathers et al. 2011)
Cistus creticus	Diterpene	Labdanum	Attaguile et al. (1995), Demetzos et al. (1997, 2001)
Thymus vulgaris	Monoterpene	Thymol and Carvacrol	Dauqan and Abdullah (2017)
Origanum vulgare	Monoterpene	Carvacrol and Thymol	Sivropoulou et al. (1996)

sativa are source of unique terpeno-phenolic compounds, known as cannabinoids. The Tetrahydrocannabinol (THC)-a psychoactive cannabinoid displays anti-nausea and anti-cancer activities (Sirikantaramas et al. 2005; Pellati et al. 2008) whereas Cannabidiol (CBD)—a non psychoactive cannabinoid has been found to be effective in prevention of neurodegenerative and cardiovascular diseases (Pellati et al. 2008; Taura et al. 2007). Gossypol and other related disesquiterpene produced by the trichomes of *Gossypium hirsutum* (cotton), possessing anti-fungal activities are potential natural pesticides (Mellon et al. 2014; Dayan and Duke 2003). The labdane-type diterpenes, produced in trichomes of *Cistus creticus* (Pink Rock-Rose) trichomes exhibit gastric antiulcer (Attaguile et al. 1995), antifungal, antibacterial and anti-inflammatory activities (Demetzos et al. 1997; Demetzos et al. 2001). *M. piperita* trichomes produce monoterpenes including menthone and menthol (Lange et al. 2000) where as *M. spicata* (spearmint) produces carvone, that gives attribute like odour and taste to the plant and have been used as flavouring agent in food and pharmaceutical preparations (Chauhan et al. 2009). Several species from Solanaceae family like *Solanum lycopersicum*, *S. habrochaites* and *S. pennellii* contain diverse metabolites in their glandular trichomes such as monoterpenes, sesquiterpenes, methylketones, diterpenes and acyl sugars (Antonious 2001; Besser et al. 2009); The glandular trichomes of *Ocimum basilicum* (Basil) secrete phenylpropanoids (Gang et al. 2002); gland exudates of *Medicago sativa* (alfa alfa) contain lipophilic amides (Ranger et al. 2005) and accumulate flavonoids that contributes to the plant's antioxidant properties (Aziz et al. 2005). The glandular trichomes of *Salvia sclarea* (clary sage) trichomes accumulates sclareol—a labdane diterpene, that is used as precursor for Ambrox or Ambroxane, which finds application in flavour and fragrance industry (Moulines et al. 2004; Frija et al. 2011).

17.4 Role of Glandular Trichomes in Plant Biology

Trichomes cover the outermost layer of plant organs such as leaf and stem and thereby are directly exposed to the surroundings to encounter prevailing, changing and often challenging growth conditions. In this regard, these structures can act as a component of physical defense system of plants against insects, pathogens and some abiotic stresses (Fig. 17.2). In addition, owing to the appreciable biosynthetic capabilities for producing secondary metabolites, the glandular trichomes are involved in ecological interactions, including chemical defense against invading pathogens and insects (Runyon et al. 2010; Tian et al. 2012).

17.4.1 Role in Abiotic Stress Tolerance

Abiotic stress conditions trigger an array of morphological, physiological, molecular and biochemical changes that drastically affect plant growth and development and

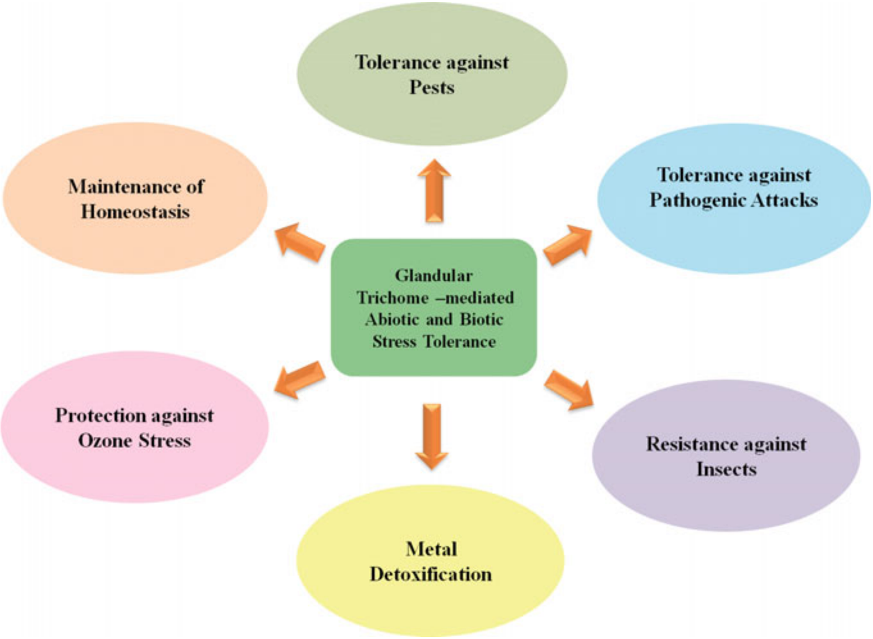

Fig. 17.2 Schematic representation summarizing role of trichomes in stress

remains the major constraint to crop yield. In the recent past, several studies have demonstrated that trichomes under adverse abiotic environmental conditions play a vital role in the plant survival.

17.4.1.1 Role in Heavy Metal Detoxification and Homeostasis

The extensive and burgeoning accumulation of heavy metals (HMs) in the biosphere due to anthropogenic disturbances has become a predicament condition for all forms of life including both plants and animals. HMs are non-biodegradable, inorganic chemical constituents which inflict detrimental effects on plants and animals including humans (Cirlakova 2009). HMs at elevated levels can hamper the functions of several important cellular biomolecules such as DNA, nuclear proteins, enzymes and pigments which can lead to excessive generation of reactive oxygen species (ROS) (Zengin and Munzuroglu 2005; Ali et al. 2013). The increased generation of ROS such as superoxide free radicals ($O_2\cdot-$), hydroxyl free radicals ($OH\cdot-$) or non-free radical species such as singlet oxygen ($^1O_2$) and hydrogen peroxide (H_2O_2) due to disturbance of cellular homeostasis cause an imbalance between ROS generation and scavenging, results in oxidative stress (Sytar et al. 2013). This stress condition implicates serious deteriorative anomalies within plant cells such as DNA damage, protein degradation, redox imbalance, leakage of ions, and disruption of cell components and membranes which ultimately can lead to cell death via programmed cell death (PCD) pathways (Sharma et al. 2012).

Plants have evolved a repertoire of defense strategies to cope with heavy metal stress (Kupper and Kroneck 2005). Trichomes have been implicated in ion homeostasis and heavy metal detoxification process either by serving as storage sites for HMs or as secretion sites of a wide array of secondary metabolites that counteract perilous effects of heavy metal contamination (Hauser 2014). The HMs have been found to be accumulated in the trichomes of both hyper (Sarret et al. 2006; Broadhurst et al. 2004) and non-hyper accumulating (Lavid et al. 2001; Dominguez-Solis et al. 2004) plants. The role of trichomes in heavy metal sequestration and detoxification has been studied in details in *N. tabacum*. On exposure of tobacco plant to the toxic level of cadmium (Cd), trichomes were reported to be the primary sites on the leaf surface, which are engaged in exudation of Cd crystals. Also cysteine synthase overexpressing tobacco lines showed Cd tolerance with 20% less endogenous Cd concentration as compared to wild-type plants and its trichome density has been reported to be 25% higher than the wild-type control plants (Harada and Choi 2008). The sequencing of cDNA libraries corresponding to the trichomes of tobacco, with or without Cd treatment revealed that trichomes are the primary sites of expression of genes encoding for stress related proteins such as antipathogenic T-phylloplanin-like proteins, glutathione peroxidase and many other classes of pathogenesis-related (PR) proteins. Furthermore, the glutathione levels were found to be elevated in the tip cells of trichomes as compared to other cells, reflecting the existence of a well developed sulfur-dependent protective system for heavy metal detoxification. Higher expression of genes encoding metallothionins, functioning in metal tolerance has been documented in trichomes of some plants species such as *Vicia faba* (Foley and Singh 1994). These observations clearly indicate that trichomes have well developed molecular machinery for accumulation, sequestration and exudation of heavy metals.

17.4.1.2 Role in Ozone Stress

During the past century, average tropospheric global ozone (O_3) concentration has drastically elevated and is expectedly increasing further (Hartmann et al. 2014; Oltmans et al. 2013). Several reports suggest that elevated level of atmospheric O_3 inhibits plant growth and development and results in decrease in productivity (Ainsworth et al. 2012; Fares et al. 2013). Certain plants show more tolerance to ozone stress than others but the underlying mechanism is still not well understood (Ainsworth 2017; Feng et al. 2017). In plants O_3 enters mainly via the stomata and reacts with organic molecules in the apoplast and resulting in excessive generation of ROS and ultimately leading to cell damage and cell death (Ainsworth 2017; Cho et al. 2011; Kanagendran et al. 2017). Studies were conducted to investigate the role of glandular and non-glandular trichomes in response to ozone stress. In order to cover a broad range of trichome characteristics, such as trichome density, trichome type etc. twenty-three herbaceous plant species were selected for this study and it was reported that peltate and capitate glandular trichomes showed significant level of tolerance against ozone stress whereas no such resistance was observed in non-glandular trichomes. Also species with lower glandular trichomes on their leaf surface were found to be more vulnerable to ozone stress as compared to those with higher density of glandular trichomes. These results shed light on the possible role of glandular trichome in the reduction of ozone toxicity and may function as chemical barricades that play a key role in neutralizing the toxic O_3 before entering into the apoplast (Li et al. 2017).

Apart from this, there are several reports from many species which proposed that glandular trichomes might play role in tolerance to drought stress. For example, a study in tomato found that overexpression of SlMX1, a MIXTA like MYB transcription factor, led to enhanced trichome density including both glandular and non-glandular trichomes accompanied with increased drought tolerance but yet there are no concrete evidences of the role of glandular trichomes specifically involved in imparting the drought tolerance (Ewas et al. 2016).

17.4.2 Role in Biotic Stress Tolerance

Various biotic factors are the major threats to the productivity of large number of important plant species. Several studies demonstrated that trichomes act as chemical defense barrier against insects, pests, herbivores, fungal infections, and even plants of parasitic behaviour (Tian et al. 2012; Peiffer et al. 2009). Apart from non-glandular trichomes, glandular trichomes synthesize and/or accumulate highly interesting secondary metabolites such as terpenoids, phenylpropenes, methyl ketones (Fridman et al. 2005; Ben-Israel et al. 2009), proteinase inhibitors (Tian et al. 2012) and acyl sugars (Schilmiller et al. 2012; Stout et al. 2012; Xu et al. 2013) and contribute substantially to chemical arsenal of plant defense strategies and thus play a fundamental role in both structural and chemical defense strategy against several herbivory and pathogen attacks and are interesting targets for breeding (Glas et al. 2012; Gruber et al. 2006).

17.4.2.1 Insect Resistance

Recent studies in many tomato wild relatives have reported the correlation of the presence, longevity, density, and size of the type I and the shorter multicellular type IV glandular trichomes with resistance against the whitefly (Firdaus et al. 2013). Previously, studies found that suppression of a glandular trichome specific P450 hydroxylase gene in tobacco led to resistance against aphids. The analysis of P450 suppressed transgenic tobacco plants displayed elevated concentration of cembratriene-ol (CBT-ol) which displayed potent aphidicidal activity (Wang et al. 2001). *NtLTP1*, a glandular-specific lipid transfer protein from tobacco has been implicated in secretion of lipid compounds from trichome heads. The transgenic tobacco lines overexpressing *NtLTP1* displayed enhanced tolerance to aphids (Choi et al. 2012). The investigation of the effect of the *hairless* (*hl*) mutation on trichome density, chemical composition and herbivory resistance in tomato suggested that leaf surface extracts have low levels of sesquiterpene and polyphenolic compound and *hl* mutation causes structural distortion of trichomes in leaf tissue and leads to decreased tolerance against insect herbivory (Kang et al. 2010).

17.4.2.2 Resistance Against Pathogens

Glandular trichomes are often capable of secreting exudates displaying antifungal activities. In a wild potato species (*S. berthaultii*), a trichome exudate was reported to confer resistance to *Phytophthora infestans* (Lai et al. 2000). The disease incidence has shown negative correlation with the density and polyphenol-oxidase activity of short type A trichome bearing a four-lobed membrane-bound gland at their tips. In chickpea (*Cicer arietinum*) the concentration of a highly acidic trichome exudate is critical in response to infection by *Ascochyta rabiei*. Low concentrations of exudates promote germination of *Ascochyta rabiei* conidia whereas high concentrations inhibit its germination (Armstrong-Cho and Gossen 2005). The damaged trichomes have been observed as entry sites for the infection and colonialization of several different fungal pathogens such as *Phoma clematidina* on clematis (Van De Graaf et al. 2002), powdery mildew (*Erysiphe necator*) on grapevine buds (Rumbolz and Gubler 2005), *Botrytis cinerea* on harvested tomato (Charles et al. 2008), and *Beauveria bassiana* on poppy (Landa et al. 2013). A trichome specific glycoprotein known as T-phylloplanin in tobacco was reported to be a potent inhibitor of oomycete *Peronospora tabacina* germination (Kroumova et al. 2007). Also tobacco plants with low expression of phylloplanin are more susceptible to pathogen attacks. Altogether the above mentioned examples clearly provide ample evidences of the active role of trichomes in imparting stress tolerance to several biotic stresses and mediating ecological interactions.

17.5 Omics Approaches for Studying Gene Expression and Function in the Context of Glandular Trichome Biology

Apart from being sources of economically important natural products, trichomes function as physical and chemical defense structures. These structures therefore are interesting systems to understand the molecular basis of secondary metabolism and plant defense. The "Omics" approaches such as transcriptomics, proteomics and metabolomics can provide detailed information about the metabolic and gene regulatory networks operating in trichomes to favour secondary metabolism and defense responses. Initial studies based on Sanger sequencing of cDNA libraries of trichomes provided limited but useful information about the transcriptome landscape of trichomes. Later on, application of next generation sequencing (NGS) revolutionized the area of trichome biology by providing comprehensive information about genes expressing in trichomes (Table 17.2). A dedicated database, TrichOme hosting transcriptomics (ESTs/unigene sequences) and metabolomics (mass-spectrometry-based trichome metabolite profiles) resources of trichomes of a number of plant species is available (Dai et al. 2010) (http://www.planttrichome.org/). The "Omics" approaches have revealed that genes involved in secondary metabolism, defense response, and lipid biosynthesis are enriched in transcriptomes of glandular trichomes. Several medicinal and aromatic plants have been studied for identification and characterization of genes expressing in glandular trichomes (Table 17.3). These studies have been vital for elucidation of molecular basis of biosynthesis of several important natural products as well as for functional attributes of trichomes (Huchelmann et al. 2017; Tissier 2018). In the following heads, the features of gene expression in glandular trichomes have been summarized.

17.5.1 Genes Encoding Enzymes of Secondary Metabolism

Sanger sequencing of cDNA libraries corresponding to the glandular trichomes of *N. tabacum* and *N. sylvestris*, for example, provided platform for identification of genes involved in the trichome specific secondary metabolism leading to cembrenoid and labdanoid diterpenoid biosynthesis (Wang et al. 2001, 2002; Wang and Wagner 2003; Ennajdaoui et al. 2010; Sallaud et al. 2012). A terpene synthase named as cembratriene-ol synthase (CBTS) and CYP71D16, a CYP450 enzyme have been shown to be involved in cembrenoid biosynthesis. The labdanoid biosynthesis, on the other hand is driven by enzymes namely copalyl diphosphate synthase 2 (CPS2) and abienol synthase (ABS). The expression of the genes encoding CBTS, CYP71D16, CPS2 and ABS was reported to be trichome specific and therefore their promoter regions can be used for driving trichome specific gene expression. In addition, the characterization of genes expressing primarily in glandular trichomes led to the discovery of metabolic pathways involved in natural product biosynthesis in several medicinal and aromatic plants. *C. sativa*, for example, biosynthesize bioactive cannabinoids, primarily in the glandular trichomes of female flower. The genes involved in the cannabinoid biosynthesis have been identified using transcriptome resource of glandular trichomes of *C. sativa,* which in turn helped in elucidation of the pathway at molecular level (Sirikantaramas et al. 2005; Taura et al. 2007, 2009; Page and Boubakir 2011).

The terpenoid biosynthesis necessitates substrate supply in the form of isoprene units. Two pathways, namely mevalonate (MVA) and 2-C-methyl-D-erythritol-4-phosphate (MEP) pathway, localized in cytoplasm and plastids, respectively are responsible for generation of isoprene pool. As the glandular trichomes are often enriched in terpenoid class of secondary metabolites, for example, those having monoterpene, diterpene and sesquiterpene backbones, the key genes involved in the MVA and MEP pathways such as DXS and HMGR, respectively are upregulated

Table 17.2 List of summarizing transcriptome sequencing studies on glandular trichomes of different plant species

Species	Trichome type	Transcriptome sequencing approach	ESTs/Unigenes	References
Solanum lycopersicum	Mixed	Sanger	7254 [ESTs]	Besser et al. (2009)
S. lycopersicum	Type I	Sanger	831 [ESTs]	McDowell et al. (2011)
S. lycopersicum	Type VI	NGS	225,000 [ESTs]	McDowell et al. (2011)
S. lycopersicum	Type VII	Sanger	791 [ESTs]	McDowell et al. (2011)
S. lycopersicum	Mixed stems	NGS	278000 [ESTs]	McDowell et al. (2011)
S. lycopersicum	Mixed	NGS	195,377 [ESTs]	Bleeker et al. (2011)
Solanum habrochaites	Mixed	Sanger	2656 [ESTs]	van Der Hoeven et al. (2000), Fei et al. (2004)
S. habrochaites	Type I	Sanger	978 [ESTs]	McDowell et al. (2011)
S. habrochaites	Type IV	Sanger	1425 [ESTs]	McDowell et al. (2011)
S. habrochaites	Type VI	NGS	224000 [ESTs]	McDowell et al. (2011)
S. habrochaites	Mixed leaves	NGS	108,000 [ESTs]	McDowell et al. (2011)
S. habrochaites	Mixed	NGS	182386 [ESTs]	Bleeker et al. (2011)
Solanum pimpinellifolium	Type VI	NGS	227,000 [ESTs]	McDowell et al. (2011)
Solanum pennelllii	Type IV	Sanger	1277 [ESTs]	McDowell et al. (2011)
S. pennelllii	Type VI	Sanger	1137 [ESTs]	McDowell et al. (2011)
S. pennelllii	Mixed leaves	NGS	275000 [ESTs]	McDowell et al. (2011)
Solanum arcanum	Mixed stems	NGS	415,000 [ESTs]	McDowell et al. (2011)
Ocimum basilicum	Peltate	Sanger	4804 [ESTs]	Iijima et al. (2004a)
O. basilicum	Peltate	Sanger	5422 [ESTs]	Iijima et al. (2004b)

(continued)

Table 17.2 (continued)

Species	Trichome type	Transcriptome sequencing approach	ESTs/Unigenes	References
O. basilicum	Peltate	Sanger	7314 [ESTs]	Kapteyn et al. (2007)
O. basilicum	Peltate	Sanger	1344 [ESTs]	Gang et al. (2001)
Medicago sativa	Stem glandular trichomes	Sanger	9659 [ESTs]	Aziz et al. (2005)
Medicago truncatula	Glandular trichomes	Sanger	10,377 [ESTs]	Dai et al. (2010)
Artemisia. annua	Glandular trichomes	NGS	406,044 [ESTs]	Wang et al. (2009)
Humulus lupulus	Glandular trichomes	Sanger	12,665 [ESTs]	Wang et al. (2008)
H. lupulus	Glandular trichomes	Sanger	10,581 [ESTs]	Nagel et al. (2008)
Cannabis sativa	Glandular trichomes from female flower	Sanger	1075 [unigenes]	Marks et al. (2009)
Cistus creticus	Glandular trichomes	Sanger	2022 [ESTs]	Falara et al. (2008)
Mentha × *piperita*	Peltate	Sanger	1316 [ESTs]	Lange et al. (2000)
Mentha spicata	Peltate glandular trichomes	NGS	25,000 [unigenes]	Jin et al. (2014)
Salvia fruticosa	Glandular trichomes	Sanger	1459 [ESTs]	Chatzopoulou et al. (2010)
Nicotiana tabacum	Glandular trichomes	Sanger	5139 [ESTs]	Cui et al. (2011)
N. tabacum	Glandular trichomes with or without Cd	Sanger	2000 [ESTs]	Harada et al. (2010)
Nicotiana benthamiana	Glandular trichomes	Sanger	6686 [ESTs]	Slocombe et al. (2008)

in glandular trichome as compared to trichome free leaf sample (Glas et al. 2012; Huchelmann et al. 2017; Balcke et al. 2017; Wang et al. 2009). Likewise, genes involved in the biosynthesis of flavonoid and phenylpropanoid class of secondary metabolites have been reported to display higher transcript levels in glandular trichomes.

Table 17.3 List of characterized genes involved in aspects of glandular trichome biology

Plant	Biological functions and metabolic pathways	Genes	References
Nicotiana tabacum	Diterpene transport	*Nt*PDR1	Crouzet et al. (2013)
N. tabacum	Lipid secretion	*Nt*LTP1	Choi et al. (2012)
N. tabacum	Disease defense	T-Phylloplanin	Shepherd et al. (2005), Choi et al. (2012)
N. tabacum	Terpenoid pathway	α-Cembratrienol/β-cembratrienol synthase (CYC-1)	Wang and Wagner (2003)
N. tabacum	Aphid resistance/CBT—diol synthase	CYP71D16	Wang et al. (2001, 2002)
N. sylvestris	Insects resistance/CBT –diol synthase	*Ns*CBTS	Ennajdaoui et al. (2010)
N. tabacum	Labdane diterpene biosynthesis	*Nt*CPS2 *Nt*ABS	Sallaud et al. (2012)
Artemisia annua	artemisinin biosynthetic pathway	*Aa*ORA	Lu et al. (2013)
A. annua	Terpene and lipid biosynthesis	CYP71AV1	Teoh et al. (2006), Polichuk et al. (2010)
A. annua	Terpene and lipid biosynthesis	ALDH1	Teoh et al. (2009)
A. annua	Terpene and lipid biosynthesis	DBR2	Zhang et al. (2008a)
A. annua	Terpene and lipid biosynthesis	Alcohol dehydrogenase 2 (ALDH2)	Polichuk et al. (2010)
A. annua	Terpenoid pathway	Amorpha-4,11-diene synthase (KCS12)	Chang et al. (2000)
A. annua	Terpenoid pathway	Amorpha-4,11-diene synthase (pAC12)	Mercke et al. (2000)
A. annua	Terpenoid pathway	Dihydroartemisinic aldehyde reductase (Red1)	Ryden et al. (2010)
A. annua	Terpene and lipid biosynthesis	2-Alkenal reductase (DBR1)	Zhang et al. (2008b)
A. annua	Terpenoid pathway	β-Caryophyllene synthase (QHS1)	Cai et al. (2002)
A. annua	Terpenoid pathway	β-Farnesene synthase (β-FS)	Picaud et al. (2005)

(continued)

Table 17.3 (continued)

Plant	Biological functions and metabolic pathways	Genes	References
A. annua	Terpenoid pathway	Germacrene A synthase (*Aa*GAS)	Bertea et al. (2006)
A. annua	Terpenoid pathway	(−)-β-Pinene synthase (QH6)	Zhang et al. (2008b)
A. annua	Sesquiterpene β-Caryophyllene Transport	*Aa*PDR3	Cai et al. (2002)
Cannabis sativa	Terpenoid pathway	Olivetol synthase (OLS)	Picaud et al. (2005)
C. sativa	Terpenoid pathway	Aromatic prenyltransferase (PT)	Bertea et al. (2006)
C. sativa	Cannabinoid pathway	Δ1-Tetrahydrocannabinolic acid synthase (THCAS)	Sirikantaramas et al. (2005)
C. sativa	Cannabinoid pathway	Cannabidiolic acid synthase (CBDAS)	Taura et al. (2007)
Mentha citrata	Terpenoid	(−)-Linalool synthase	Crowell et al. (2002)
Mentha. spicata	Terpenoid, flavonoid	MsTPS1 and MsTPS2	Jin et al. (2014)
M. spicata	Terpenoid	Limonene 6-hydroxylase (SM12, CYP71D18)	Lupien et al. (1999)
M. spicata	Terpenoid	Carveol dehydrogenase (ISPD)	Ringer et al. (2005)
Mentha × *piperita*	Terpenoid	Limonene 3-hydroxylase, PM17, CYP71D13; PM2, CYP71D13	Lupien et al. (1999)
M. piperita	Terpenoid	(+)-Menthofuran synthase (MFS)	Bertea et al. (2001)
M. piperita	Terpenoid	Menthone:(+)-neomenthol reductase (MNR)	Davis et al. (2005)

(continued)

Table 17.3 (continued)

Plant	Biological functions and metabolic pathways	Genes	References
M. piperita	Terpenoid, flavonoid	4-coumarate-CoA ligase, chalcone synthase, chalcone isomerase, flavonoid-3′, 5′-hydroxylase, flavonol-4-reductase, flavonol sulfotransferase, and flavonoid O-methyltransferases	Lange et al. (2000)
Humulus lupulus	Terpenoid pathway	Valerophenone synthase (VPS)	Okada and Ito (2001)
H. lupulus	Terpenoid pathway	Myrcene synthase (HIMTS2)	Wang et al. (2008)
H. lupulus	Terpenoid pathway	β-Caryophyllene/α-Humulene synthase (HISTS1)	Wang et al. (2008)
H. lupulus	Terpenoid pathway	Germacrene A synthase (HISTS2)	Wang et al. (2008)
Ocimum basilicum	Terpenoid pathway	Terpinolene synthase (TES)	Iijima et al. (2004b)
O. basilicum	Terpenoid pathway	Geraniol synthase (GES)	Iijima et al. (2004a)
O. basilicum	Terpenoid pathway	Linalool synthase (LIS)	Iijima et al. (2004b)
O. basilicum	Terpenoid pathway	α/β-Selinene synthase (SES)	Iijima et al. (2004a)
O. basilicum	Terpenoid pathway	γ-Cadinene synthase (CDS)	Iijima et al. (2004a)
O. basilicum	Terpenoid pathway	Germacrene D synthase (GDS)	Iijima et al. (2004a)
O. basilicum	Terpenoid pathway	Geraniol/nerol oxidase (GEDH1)	Iijima et al. (2006)
Helianthus anuus	Terpenoid pathway	Germacrene A acid 8β-hydroxylase (CYP71BL1)	Ikezawa et al. (2011)
Cistus creticus	Terpenoid pathway	Geranylgeranyl diphosphate synthase (CcGGDPS1, CcGGDPS2)	Pateraki and Kanellis (2008)
C. creticus	Terpenoid pathway	Copal-8-ol diphosphate synthase (CcCLS)	Falara et al. (2011)

(continued)

Table 17.3 (continued)

Plant	Biological functions and metabolic pathways	Genes	References
Salvia fruticosa	Terpenoid	1,8-Cineole synthase (Sf-CinS1)	Kampranis et al. (2007)
S. pornifera	Terpenoid	Sabinene synthase (Sp-SabS1)	Kampranis et al. (2007)
Solanum habrochaites	Terpenoid	β-Elemene synthase (ShTPS15)	Bleeker et al. (2011)
S. habrochaites	Terpenoid	Germacrene B synthase (SSTLH1)	van Der Hoeven et al. (2000)
S. habrochaites	Terpenoid	Germacrene D synthase (SSTLH2)	van Der Hoeven et al. (2000)
S. habrochaites	Terpenoid	α-Pinene synthase (ShPIS)	Gonzales-Vigil et al. (2012)
S. lycopersicum	Terpenoid	Neryl diphosphate synthase (NDPS1)	Schilmiller et al. (2009)
S. lycopersicum	Terpenoid	1,8-Cineole synthase	Falara et al. (2011)
S. americanum	Defense protein against insect attacks	SaPIN2b	Schluter et al. (2010), Luo et al. (2012)

17.5.2 Gene Involved in Primary Metabolism

The impressively active metabolism requires sufficient primary Carbon flux and energy to support excessive production of secondary metabolites in glandular trichomes. In this regard, transcriptomic and proteomic studies on glandular trichomes suggested modulation of genes involved in primary metabolism as compared to trichome-free leaf. The long glandular trichomes of tobacco contains chlorophyllous head cell and can photosynthesize. Using proteomics approach, a novel Rubisco small subunit (NtRbcS-T), preferentially expressing in head cells of long glandular trichomes of tobacco was identified. NtRbcS-T was implicated in carbon fixation in gland cell having a cellular environment overproducing specialized metabolites along with CO_2 evolution (Laterre et al. 2017). A systems approach involving proteomics, metabolomics and transcriptomics in type VI glandular trichomes and leaves from a cultivated tomato variety (*Solanum lycopersicum* LA4024) provided important insights into carbon flux regulation, source of reducing power and energy to support intensified metabolism in these trichomes (Balcke et al. 2017). It was demonstrated that although type VI glandular trichomes are photosynthetically active, the major carbon flux to support trichome specific metabolism comes from leaf tissue. However, the reducing power and energy generated during photosynthesis can be utilized in driving secondary metabolism (Balcke et al. 2017).

The “Omics” studies on *N. tabacum* and tomato revealed that the genes involved in the metabolism of branched chain amino acids e.g. valine, leucine, isoleucine are upregulated in the glandular trichomes as compared to the trichome-free leaf (Balcke et al. 2017; Jin et al. 2014). These observations are consistent with the role of branched chain amino acids as precursors of acyl-sugars, which are enriched in the glandular trichomes of *N. tabacum* and tomato. The glandular trichomes, in addition, were reported to display higher expression of genes involved in lipid metabolism, especially those concerning with the biosynthesis of polyunsaturated fatty acids and wax (Balcke et al. 2017; Jin et al. 2014; Sallets et al. 2014).

17.5.3 Transporter Genes

Gene expression analysis revealed that the genes encoding transporter proteins belonging to ABC family transporters and Lipid transporter protein (LTP) are preferentially expressed in glandular trichomes. By now, however, only limited number of transporter genes expressing in glandular trichomes have been functionally characterized. An ABCG subfamily transporter gene, named as *NtPDR1*, displaying higher expression in the gland cells of long glandular trichomes of *N.tabacum* has been implicated in transportation of terpenoid compounds such as diterpenoids and sesquiterpenoids (Pierman et al. 2017). In *A. annua*, another ABCG sub-family transporter, namely *AaPDR3*, whose expression is primarily restricted to the glandular trichomes, has been shown to be involved in transportation of β-caryophyllene (Fu et al. 2017). In *N. tabacum*, *NtLTP1*, a gene encoding lipid transporter protein is involved in secretion of lipids from glandular trichomes (Choi et al. 2012).

17.5.4 Genes Involved in Abiotic and Biotic Stresses

The glandular trichomes have been reported to express genes involved in abiotic and biotic stress responses. For example, genes belonging to these functional classes putatively encode PR protein, metallothionein, T-phylloplanin RD22-like BURP domain-containing proteins, and thaumatin-like protein, ascorbate peroxidise, glutathione peroxidase, Fe- superoxide dismutase etc. (Sallets et al. 2014; Marks et al. 2009; Cui et al. 2011). The T-phyllopanin gene, displaying glandular trichome specific expression in *N. tabacum* has been demonstrated to confer defense against pathogens (Shepherd et al. 2005).

17.6 Transcription Factor Genes Involved in the Regulation of Secondary Metabolism in Glandular Trichomes

Transcription factors play central role in regulation of gene expression associated with metabolic pathways. Limited information pertaining to the transcription factors regulating glandular trichome localized metabolism is currently available. Their identification and characterization is, however, crucial for unveiling molecular mechanism involved in the trichome specific expression of structural genes of secondary metabolism. A number of transcription factors belonging to diverse families have been identified with respect to transcriptional regulation of structural genes of artemisinin biosynthesis in *A. annua*. The transcription factors namely AaWRKY1, AaERF1/2, AaORA, AaMYC2, AabZIP1, AaNAC1 and AaSPL2 positively regulate the expression of genes involved in artemisinin biosynthesis (Yu et al. 2012; Lu et al. 2013; Zhang et al. 2015; Jiang et al. 2016; Shen et al. 2016; Lv et al. 2016; 2019). These transcription factors often regulate multiple structural genes simultaneously and therefore play crucial role in fine-tuning of the secondary metabolism under spatial and temporal cues including hormone signaling. In *Mentha spicata*, transcription factor genes namely *MsYABBY5* and *MsMYB* displaying preferential expression in peltate glandular trichomes have been implicated in the regulation of monoterpene production (Wang et al. 2016; Reddy et al. 2017). Another glandular trichome specific transcription factor gene, *Expression* of *terpenoid* 1 (EOT1), belonging to SHI transcription factor family has been demonstrated to regulate terpenoid biosynthesis in *S. lycopersicum* (Spyropoulou et al. 2014).

17.7 Regulatory Genes Involved in Development of Glandular Trichomes

The studies on Arabidopsis have provided detailed information about the molecular players involved in the initiation, development and patterning of non-glandular trichomes (Serna and Martin 2006; Pattanaik et al. 2014). It was established that a complex of three regulatory proteins, viz. MYB, bHLH and WD40 proteins (MBW) plays a central role in the regulation of trichome development in Arabidopsis. In general, the understanding of molecular mechanism of regulation of glandular trichome development is comparatively very limited and it is not clear whether a MBW like regulatory complex is involved in the regulation of glandular trichome development. The studies, conducted so far, have however revealed that transcription factors, mostly belonging to Homeodomain Zipper (HD-Zip), C2H2 Zinc Finger, bHLH and MYB familes are involved in the regulation of glandular trichome development. With the current information, it is also apparent that these regulators might be functionally conserved. Overexpression of *AmMIXTA*, an R2-R3 MYB family transcription factor gene resulted in enhanced density of glandular trichome in *N. tabacum*. Similarly, MIXTA like transcription factors, SlMIXTA1 and AaMIXTA positively regulate glandular trichome development in tomato and *A. annua*, respectively (Ewas et al. 2016; Shi et al. 2018). A HD-Zip transcription factor gene, named as Wooly (*Wo*) has been implicated in the regulation of glandular trichome development in tomato (Yang et al. 2011). The overexpression of mutant allele of tomato *Wo* gene resulted in modified glandular trichome development in *N. tabacum*, suggesting that orthologs of *Wo* gene could be functionally conserved regulators in Solanaceae (Yang et al. 2015). Recently, a C2H2 Zinc finger transcription factor gene, namely Hair (H) has been identified as positive regulator of glandular trichome development in *S. lycopersicum*. It was also demonstrated that H interacts with *Wo* and thereby they might regulate trichome development in a combinatorial manner (Chang et al. 2018). Members of HD-Zip transcription factor families have also been shown to regulate glandular trichome development in *A. annua* (Yan et al. 2017) and *Cucumis sativus* (Liu et al. 2016). Recently, a bHLH transcription factor, SlMYC1 has been identified as regulator of the development of type VI glandular trichomes as well as terpenoid biosynthesis in tomato (Xu et al. 2018).

17.8 Conclusions and Future Outlook

Glandular trichomes belong to defense repertoire of plants against invading pest and pathogens. These structures have also been implicated in conferring tolerance against abiotic stresses such as drought, UV and heavy metal challenge. The impressively active metabolic and genetic machinery enable them to overproduce, accumulate and secrete secondary metabolites that include some economically important natural products. For obvious reasons, glandular trichomes have potential to be developed as production system for economically important secondary metabolites through strategic metabolic engineering involving tools of genome engineering. This approach appears to be attractive to fuel the attempts towards development of alternate production system for those secondary metabolites, which are biosynthesized by rare and endangered plant species. The next generation transcriptome sequencing and other related approaches have been instrumental in identification of genes involved in the trichome specific natural product biosynthesis. However, a detailed understanding of metabolic and gene regulatory networks leading to the biosynthesis and accumulation of metabolites in glandular trichomes awaits further investigations. There is also a need of isolation and characterization of novel and highly active trichome specific promoters. Another important area of research is to understand molecular basis of glandular trichome development, which, as of now, remains poorly understood. The knowledge about molecular regulators of glandular trichome development will be useful in enhancing trichome density and thereby the yield of trichome localized metabolites. Further, glandular trichomes can serve as a rich pool of useful genes which could be potential targets for systematic transgenesis towards development of plants tolerant to environmental stresses. However, by now, only a limited number of genes, particularly those involved in secondary metabolism in trichomes have been characterized. It is therefore desirable to carry out investigations pertaining to the elucidation of functions of other trichome specific genes. Altogether the comprehensive and detailed knowledge of fundamental aspects of trichome biology will provide new leads to plant biologists to exploit the untapped biotechnological potential of trichomes to engineer plants that would exhibit increased resistance to pests and tolerance to many abiotic stresses and also would produce specialized natural compounds of valuable industrial/pharmaceutical potential.

Acknowledgements PM acknowledges funding support by CSIR, New Delhi and Science and Engineering Research Board (SERB), Department of Science and Technology (DST), Government of India for the project under "Scheme for Young Scientists" (SB/YS/LS-305/2013). MK, UG and AKN acknowledge CSIR, DST-INSPIRE and UGC, India respectively for Junior and senior research fellowships. This represents institutional communication number CSIR-IIIM/IPR/0068.

References

Ainsworth EA (2017) Understanding and improving global crop response to ozone pollution. Plant J 90:886–897. https://doi.org/10.1111/tpj.13298

Ainsworth EA, Yendrek CR, Sitch S, Collins WJ, Emberson LD (2012) The effects of tropospheric ozone on net primary productivity and implications for climate change. Ann Rev Plant Biol 63:637–661. https://doi.org/10.1146/annurev-arplant-042110-103829

Ali H, Khan E, Sajad MA (2013) Phytoremediation of heavy metals-concepts and applications. Chemosphere 91:869–881. https://doi.org/10.1016/j.chemosphere.2013.01.075

Antonious GF (2001) Production and quantification of methyl ketones in wild tomato accessions. J Environ Sci Health B 36:835–848. https://doi.org/10.1081/pfc-100107416

Armstrong-Cho C, Gossen BD (2005) Impact of glandular hair exudates on infection of chickpea by Ascochytarabiei. Can J Bot 83:22–27. https://doi.org/10.1139/b04-147

Attaguile G, Caruso A, Pennisi G, Savoca F (1995) Gastroprotective effect of aqueous extract of *Cistus incanus* L. in rats. Pharmacol Res 31:29–32. https://doi.org/10.1016/1043-6618(95)80043-3

Aziz N, Paiva NL, May GD, Dixon RA (2005) Transcriptome analysis of alfalfa glandular trichomes. Planta 221:28–38. https://doi.org/10.1007/s00425-004-1424-1

Balcke GU, Bennewitz S, Bergau N et al (2017) Multi-omics of tomato glandular trichomes reveals distinct features of central carbon metabolism supporting high productivity of specialized metabolites. Plant Cell 29:960–983. https://doi.org/10.1105/tpc.17.00060

Ben-Israel I, Yu G, Austin MB, Bhuiyan N, Auldridge M, Nguyen T et al (2009) Multiple biochemical and morphological factors underlie the production of methyl ketones in tomato trichomes. Plant Physiol 151:1952–1964. https://doi.org/10.1104/pp.109.146415

Bertea CM, Schalk M, Karp F, Maffei M, Croteau R (2001) Demonstration that menthofuran synthase of mint (Mentha) is a cytochrome P450 monooxygenase: cloning, functional expression, and characterization of the responsible gene. Arch Biochem Biophys 390:279–286. https://doi.org/10.1006/abbi.2001.2378

Bertea CM, Voster A, Verstappen FWA, Maffei M, Beekwilder J, Bouwmeester HJ (2006) Isoprenoid biosynthesis in *Artemisia annua*: cloning and heterologous expression of a germacrene A synthase from a glandular trichome cDNA library. Arch Biochem Biophys 446:3012. https://doi.org/10.1016/j.abb.2006.02.026

Besser K, Harper A, Welsby N, Schauvinhold I, Slocombe S, Li Y, Dixon RA, Broun P (2009) Divergent regulation of terpenoid metabolism in the trichomes of wild and cultivated tomato species. Plant Physiol 149:499–514. https://doi.org/10.1104/pp.108.126276

Bisio A, Corallo A, Gastaldo P, Romussi G et al (1999) Glandular hairs and secreted material in *Salvia blepharophylla Brandegee* ex Epling grown in Italy. Ann Bot 83:441–452. https://doi.org/10.1006/anbo.1998.0838

Bleeker PM, Spyropoulou EA, Diergaarde PJ, Volpin H, De Both MT, Zerbe P, Bohlmann J, Falara V, Matsuba Y, Pichersky E, Haring MA, Schuurink RC et al (2011) RNA-seq discovery, functional characterization, and comparison of sesquiterpene synthases from *Solanum lycopersicum* and *Solanum habrochaites* trichomes. Plant Mol Biol 77:323–336. https://doi.org/10.1007/s11103-011-9813-x

Broadhurst CL, Chaney J, Angle JS, Erbe EF, Maugel TK (2004) Nickel localization and response to increasing Ni soil levels in leaves of the nickel hyperaccumulator *Alyssum murale*. Plant Soil 265:225–242. https://doi.org/10.1007/s11104-005-0974-8

Cai Y, Jia JW, Crock J, Lin ZX, Croteau R (2002) A cDNA clone for betacaryophyllene synthase from *Artemisia annua*. Phytochemistry 61:523–529. https://doi.org/10.1016/s0031-9422(02)00265-0

Chang YJ, Song SH, Park SH, Kim SU (2000) Amorpha-4,11-diene synthase of *Artemisia annua*: cDNA isolation and bacterial expression of a terpene synthase involved in artemisinin biosynthesis. Arch Biochem Biophys 383:178–184. https://doi.org/10.1006/abbi.2000.2061

Chang J, Yu T, Yang Q, Li C, Xiong C, Gao S, Xie Q et al (2018) Hair, encoding a single C2H2 zinc-finger protein, regulates multicellular trichome formation in tomato. Plant J. 96:90–102. https://doi.org/10.1111/tpj.14018

Charles MT, Makhlouf J, Arul J (2008) Physiological basis of UV-C induced resistance to Botrytis cinerea in tomato fruit. II. Modification of fruit surface and changes in fungal colonization. Post Harvest Biol Technol 47:21–26. https://doi.org/10.1016/j.postharvbio.2007.05.015

Chatzopoulou FM, Makris AM, Argiriou A et al (2010) EST analysis and annotation of transcripts derived from a trichome-specific cDNA library from *Salvia fruticosa*. Plant Cell Rep 29:523–534. https://doi.org/10.1007/s00299-010-0841-9

Chauhan RS, Kaul MK, Shahi AK, Arun K et al (2009) Chemical composition of essential oils in *Mentha spicata* L. accession [IIIM(J)26] from North-West Himalayan region, India. Ind Crops Prod 29:654–656. https://doi.org/10.1016/j.indcrop.2008.12.003

Cho K, Tiwari S, Agrawal SB, Torres NL, Agrawal M et al (2011) Tropospheric ozone and plants: Absorption, responses, and consequence. Rev Environ Contam Toxicol 212:61–111. https://doi.org/10.1007/978-1-4419-8453-1_3

Choi YE, Lim S, Kim HJ, Han JY, Lee MH, Yang Y, Kim JA, Kim YS (2012) Tobacco NtLTP1, a glandular-specific lipid transfer protein, is required for lipid secretion from glandular trichomes. Plant J 70:480–491. https://doi.org/10.1111/j.1365-313x.2011.04886.x

Cirlakova A (2009) Heavy metals in the vascular plants of Tatra mountains. Oecologia Montana 18:23–26

Crouzet J, Roland J, Peeters E, Trombik T, Ducos E, Nader J, Boutry M (2013) NtPDR1, a plasma membrane ABC transporter from *Nicotiana tabacum*, is involved in diterpene transport. Plant Mol Biol 82:181–192. https://doi.org/10.1007/s11103-013-0053-0

Crowell A, Williams DC, Davis EM, Wildung MR, Croteau R (2002) Molecular cloning and characterization of a new linalool synthase. Arch Biochem Biophys 405:112–121. https://doi.org/10.1016/s0003-9861(02)00348-x

Cui H, Zhang ST, Yang HJ, Ji H, Wang XJ (2011) Gene expression profile analysis of tobacco leaf trichomes. BMC Plant Biol 11:76. https://doi.org/10.1186/1471-2229-11-76

Dai XB, Wang GD, Yang DS, Tang YH, Broun P, Marks MD, Sumner LW, Dixon RA, Zhao PX (2010) TrichOME: a comparative omics database for plant trichomes. Plant Physiol 152:44–54. https://doi.org/10.1104/pp.109.145813

Dauqan EMA, Abdullah A (2017) Medicinal and functional values of thyme (*Thymus vulgaris* L.) Herb J Appl Biol Biotechnol 5:017–022. https://doi.org/10.7324/jabb.2017.50203

Davis EM, Ringer KL, McConkey ME, Croteau R (2005) Monoterpene metabolism. Cloning, expression, and characterization of menthone reductases from peppermint. Plant Physiol 137:873–881. https://doi.org/10.2307/4629731

Dayan FE, Duke SO (2003) Trichomes and root hairs: Natural pesticide factories. Pestic Outlook 14:175–178. https://doi.org/10.1039/b308491b

Demetzos C, Katerinopoulos H, Kouvarakis A, Stratigakis N, Loukis A, Ekonomakis C et al (1997) Composition and antimicrobial activity of the essential oil of *Cistus creticus* subsp. eriocephalus. Planta Med 63:477–479. https://doi.org/10.1055/s-2006-957742

Demetzos C, Dimas K, Hatziantoniou S, Anastasaki T, Angelopoulou D (2001) Cytotoxic and anti-inflammatory activity of labdane and cis-clerodane type diterpenes. Planta Med 67:614–618. https://doi.org/10.1055/s-2001-17362

Dominguez-Solis JR, Lopez-Martin MC, Ager FJ, Ynsa MD, Romero LC, Gotor C (2004) Increased cysteine availability is essential for cadmium tolerance and accumulation in *Arabidopsis thaliana*. Plant Biotech J 2:469–476. https://doi.org/10.1111/j.1467-7652.2004.00092000399

Duke MV, Paul RN, Elsohly HN, Sturtz G, Duke SO (1994) Localization of artemisinin and artemisitene in foliar tissues of glanded and glandless biotypes of *Artemisia annua* L. Int J Plant Sci 155:365–372. https://doi.org/10.2307/2475187

Engene N, Rottacker EC, Kastovsky J, Byrum T, Choi H, Ellisman MH et al (2012) *Moorea producens* gen. nov., sp. nov. and *Moorea bouillonii* comb. nov., tropical marine cyanobacteria rich in bioactive secondary metabolites. Int J Syst Evolution Microbiol 62:1171–1178. https://doi.org/10.1099/ijs.0.033761-0

Ennajdaoui H, Vachon G, Giacalone C et al (2010) Trichome specific expression of the tobacco (*Nicotiana sylvestris*) cembratrien-ol synthase genes is controlled by both activating and repressing cis-regions. Plant Mol Biol 73:673–685. https://doi.org/10.1007/s11103-010-9648-x

Ewas M, Gao YQ, Wang SC et al (2016) Manipulation of SlMXl for enhanced carotenoids accumulation and drought resistance in tomato Sci. Bull. 61:1413–1418. https://doi.org/10.1007/s11434-016-1108-9

Fahn A (2000) Structure and function of secretory cells. Adv Bot Res 31:37–75. https://doi.org/10.1016/s0065-2296(00)31006-0

Falara V, Fotopoulos V, Margaritis T, Anastasaki T, Pateraki I et al (2008) Transcriptome analysis approaches for the isolation of trichome- specific genes from the medicinal plant *Cistus creticus* subsp. *creticus*. Plant Mol. Biol 68:633–651. https://doi.org/10.1007/s11103-008-9399-0

Falara V, Akhtar TA, Nguyen TTH, Spyropoulou EA, Bleeker PM, Schauvinhold I, Matsuba Y, Bonini ME, Schilmiller AL, Last RL, Schuurink RC, Pichersky E (2011) The tomato terpene synthase gene family. Plant Physiol 157:770–789. https://doi.org/10.1104/pp.111.179648

Fares A, Vargas R, Detto M, Goldstein AH, Karlik J, Paoletti E, Vitale M (2013) Tropospheric ozone reduces carbon assimilation in trees: estimates from analysis of continuous flux measurements. Global Change Biol 19:2427–2443. https://doi.org/10.1111/gcb.12222

Fei Z, Tang X, Alba RM, White JA, Ronning CM, Martin GB, Tanksley SD, Giovannoni JJ (2004) Comprehensive EST analysis of tomato and comparative genomics of fruit ripening. Plant J. 40:47–59. https://doi.org/10.1111/j.1365-313x.2004.02188.x

Feng Z, Büker P, Pleijel H, Emberson L, Karlsson PE, Uddling JA (2017) Unifying explanation for variation in ozone sensitivity among woody plants. Glob Change Biol. https://doi.org/10.1111/gcb.13824

Firdaus S, VanHeusden AW, Hidayati N, Supena EDJ, Mumm R, DeVos RCH et al (2013) Identification and QTL mapping of whitefly resistance components in *Solanum galapagense*. Theor Appl Genet 126:1487–1501. https://doi.org/10.1007/s00122-013-2067-z

Foley RC, Singh KB (1994) Isolation of a *Vicia faba* metallothionein like gene: expression in foliar trichomes. Plant Mo1 Biol 26:435–444. https://doi.org/10.1007/bf00039552

Fridman E, Wang JH, Iijima Y, Froehlich JE, Gang DR et al (2005) Metabolic, genomic, and biochemical analyses of glandular trichomes from the wild tomato species *Lycopersicon hirsutum* identify a key enzyme in the biosynthesis of methylketones. Plant Cell 17:1252–1267. https://doi.org/10.1105/tpc.104.029736

Frija LSMT, Frade RFM, Afonso CAM (2011) Isolation, chemical, and biotransformation routes of Labdane-type diterpenes. Chem Rev 111:4418–4452. https://doi.org/10.1021/cr100258k

Fu X, Shi P, He Q et al (2017) AaPDR3, a PDR transporter 3, is involved in sesquiterpene β-caryophyllene transport in *Artemisia annua*. Front Plant Sci. 8:723. https://doi.org/10.3389/fpls.2017.00723

Gang DR, Wang J, Dudareva N, Nam KH, Simon JE, Lewinsohn E, Pichersky E (2001) An investigation of the storage and biosynthesis of phenylpropenes in sweet basil. Plant Physiol 125:539–555. https://doi.org/10.1104/pp.125.2.539

Gang DR, Lavid N, Zubieta C, Chen F, Beuerle T et al (2002) Characterization of phenylpropene O-methyltransferases from sweet basil: facile change of substrate specificity and convergent evolution within a plant O-methyltransferase family. Plant Cell 14:505–519. https://doi.org/10.1105/tpc.010327

Gershenzon J, Dudareva N (2007) The function of terpene natural products in the natural world. Nat Chem Biol 3:408–414. https://doi.org/10.1038/nchembio.2007.5

Glas JJ, Schimmel BC, Alba JM, Escobar-Bravo R, Schuurink RC, Kant MR (2012) Plant glandular trichomes as targets for breeding or engineering of resistance to herbivores. Int J Mol Sci 13:17077–17103. https://doi.org/10.3390/ijms131217077

Gonzales-Vigil E, Hufnagel DE, Kim J, Last RL Barry CS (2012) Evolution of TPS20-related terpene synthases influences chemical diversity in the glandular trichomes of the wild tomato relative *Solanum habrochaites*. Plant J. https://doi.org/10.1111/j.1365-313x.2012.05040.x

Gruber MY, Wang S, Ethier S, Holowachuk J, Bonham-Smith PC, Soroka J et al (2006) “HAIRY CANOLA”—Arabidopsis GL3 induces a dense covering of trichomes on *Brassica napus* seedlings. Plant Mol Biol 60:679–698. https://doi.org/10.1007/s11103-005-5472-0

Harada E, Choi YE (2008) Investigation of metal exudates from tobacco glandular trichomes under heavy metal stresses using a variable pressure scanning electron microscopy system. Plant Biotechnol. 25:407–411. https://doi.org/10.5511/plantbiotechnology.25.407

Harada E, Kim JA, Meyer AJ, Hell R, Clemens S, Choi YE (2010) Expression profiling of tobacco leaf trichomes identifies genes for biotic and abiotic stresses. Plant Cell Physiol 51:1627–1637. https://doi.org/10.1093/pcp/pcq118

Hartmann DL, Klein Tank AMG, Rusticucci M, Alexander LV, Brönnimann S, Charabi YAR, Zhai P (2014) Observations: atmosphere and surface. In: Stocker TF, Qin D, Hauser MT (eds) Molecular basis of natural variation and environmental control of trichome patterning. Front Plant Sci 5:1–7. https://doi.org/10.3389/fpls.2014.00320

Hauser MT (2014) Molecular basis of natural variation and environmental control of trichome patterning. Front Plant Sci 5:1–7. https://doi.org/10.3389/fpls.2014.00320

Huchelmann A, Boutry M, Charles H (2017) Plant glandular trichomes: natural cell factories of high biotechnological interest. Plant Physiol 175. https://doi.org/10.1104/pp.17.00727

Iijima Y, Davidovich-Rikanati R, Fridman E, Gang DR, Bar E, Lewinsohn E, Pichersky E (2004a) The biochemical and molecular basis for the divergent patterns in the biosynthesis of terpenes and phenylpropenes in the peltate glands of three cultivars of basil. Plant Physiol 136:3724–3736. https://doi.org/10.1104/pp.104.051318

Iijima Y, Gang DR, Fridman E, Lewinsohn E, Pichersky E (2004b) Characterization of geraniol synthase from the peltate glands of sweet basil. Plant Physiol 134:370–379. https://doi.org/10.1104/pp.103.032946

Iijima Y, Wang G, Fridman E, Pichersky E (2006) Analysis of the enzymatic formation of citral in the glands of sweet basil. Arch Biochem Biophys 448:141–149. https://doi.org/10.1016/j.abb.2005.07.026

Ikezawa N, Gopfert J, Nguyen DT, Kim SU, OMaille PE, Spring O, Ro DK (2011) Lettuce costunolide synthase (CYP71BL2) and its homolog (CYP71BL1) from sunflower catalyze distinct regio- and stereoselective hydroxylations in sesquiterpene lactone metabolism. J Biol Chem 286:21601–21611. https://doi.org/10.1074/jbc.m110.216804

Jiang W, Fu X, Pan Q, Tang Y, Shen Q, Lv Z et al (2016) Overexpression of AaWRKY1 Leads to an enhanced content of artemisinin in *Artemisia annua*. Biomed Res Int 2016:9. https://doi.org/10.1155/2016/7314971

Jin J, Panicker D, Wang Q, Kim MJ, Liu J et al (2014) Next generation sequencing unravels the biosynthetic ability of Spearmint (*Mentha spicata*) peltate glandular trichomes through comparative transcriptomics. BMC Plant Biol 14:292. https://doi.org/10.1186/s12870-014-0292-5

Kampranis SC, Ionnidis D, Purvis A, Mahrez W, Ninga E., Katerelos NA, Anssour S, Dunwell JM, Degenhardt J, Makris AM, Goodenough PW, Johnson CB (2007) Rational conversion of substrate and product specificity in a Salvia monoterpene synthase: structural insights into the evolution of terpene synthase function. Plant Cell 19:1994–2005. https://doi.org/10.1105/tpc.106.047779

Kanagendran A, Pazouki L, Li S, Liu B, Kannaste A, Niinemets U (2017) Ozone-triggered surface uptake and stress volatile emissions upon acute ozone exposure scale with foliage surface ozone uptake in ozone resistant *Nicotiana tabacum* 'Wisconsin'. J Exp Bot 69:681–697. https://doi.org/10.1093/jxb/erx431

Kang JH, Shi F, Jones AD, Marks MD, Howe GA (2010) Distortion of trichome morphology by the hairless mutation of tomato affects leaf surface chemistry. J Exp Bot 61:1053–1064. https://doi.org/10.1093/jxb/erp370

Kapteyn J, Qualley AV, Xie ZZ, Fridman E, Dudareva N, Gang DR (2007) Evolution of cinnamate/p-coumarate carboxyl methyltransferases and their role in the biosynthesis of methylcinnamate. Plant Cell 19:3212–3229. https://doi.org/10.1105/tpc.107.054155

Kolb D, Muller M (2004) Light, conventional and environmental scanning electron microscopy of the trichomes of *Cucurbita pepo* subsp. *pepo* var. *styriaca* and histochemistry of glandular secretory products. Ann Bot 94:515–526. https://doi.org/10.1093/aob/mch180

Kroumova AB, Wagner GG (2003) Different elongation pathways in the biosynthesis of acyl groups of trichome exudate sugar esters from various solanaceous plants. Planta 216:1013–1021. https://doi.org/10.1007/s00425-002-0954-7

Kroumova AB, Shepherd RW, Wagner GJ (2007) Impacts of T-phylloplanin gene knockdown and of Helianthus and Datura phylloplanins on *Peronospora tabacina* spore germination and disease potential. Plant Physiol 144:1843–1851. https://doi.org/10.1104/pp.107.097584

Kupper H, Kroneck P (2005) Heavy metal uptake by plants and cyanobacteria. Metal Ions Biol Syst 44:97–144

Lai, A., Cianciolo, V., Chiavarini, S., Sonnino, A.: Effects of glandular trichomes on the development of *Phytophthora infestans* infection in potato (*S. tuberosum*). Euphytica 114, 165–174 (2000). https://doi.org/10.1023/a:1003924318577

Landa BB, Lopez-Díaz C, Jimenez-Fernandez D, Montes-Borrego M et al (2013) In planta detection and monitorization of endophytic colonization by a *Beauveria bassiana* strain using a new-developed nested and quantitative PCR-based assay and confocal laser scanning microscopy. J Invertebr Pathol 114:128–138. https://doi.org/10.1016/j.jip.2013.06.007

Lange BM, Wildung MR, Stauber EJ, Sanchez C, Pouchnik D, Croteau R (2000) Probing essential oil biosynthesis and secretion by functional evaluation of expressed sequence tags from mint glandular trichomes. Proc Natl Acad Sci USA 97:2934–2939. https://doi.org/10.1073/pnas.97.6.2934

Laterre R, Pottier M, Remacle C, Boutry M (2017) Photosynthetic trichomes contain a specific Rubisco with a modified Ph-dependent activity. Plant Physiol 173:2110–2120. https://doi.org/10.1104/pp.17.00062

Lavid N, Barkay Z, Tel-Or E (2001) Planta 212:313. https://doi.org/10.1007/s004250

Li S, Harley PC, Niinemets U (2017) Ozone induced foliar damage and release of stress volatiles is highly dependent on stomatal openness and priming by low level ozone exposure in *Phaseolus vulgaris*. Plant, Cell Environ 40:1984–2003. https://doi.org/10.1111/pce.13003

Liu X, Bartholomew E, Cai Y, Ren H (2016) Trichome-related mutants provide a new perspective on multicellular trichome initiation and development in cucumber (*Cucumis sativus* L.). Front Plant Sci 7:1187. https://doi.org/10.3389/fpls.2016.01187

Lu X, Zhang L, Zhang F, Jiang W, Shen Q, Zhang L et al (2013) *AaORA*, a trichome-specific AP2/ERF transcription factor of *Artemisia annua*, is a positive regulator in the artemisinin biosynthetic pathway and in disease resistance to *Botrytis cinerea*. New Phytol 198:1191–1202. https://doi.org/10.1111/nph.12207

Luo M, Ding LW, Ge ZJ, Wang ZY, Hu BL, Yang XB, Sun QY, Xu ZF (2012) The characterization of SaPIN2b, a plant trichome-localized proteinase inhibitor from *Solanum americanum*. Int J Mol Sci 13:15162–15176. https://doi.org/10.3390/ijms131115162

Lupien S, Karp F, Wildung M, Croteau R (1999) Regiospecific cytochrome P450 limonene hydroxylases from mint (Mentha) species: cDNA isolation, characterization, and functional expression of -4Slimonene- 3-hydroxylase and-4S-limonene-6-hydroxylase. Arch Biochem Biophys 368:181–192. https://doi.org/10.1006/abbi.1999.1298

Lv Z, Wang S, Zhang F, Chen L, Hao X, Pan Q et al (2016) Overexpression of a novel NAC domain-containing transcription factor gene (AaNAC1) Enhances the content of artemisinin and increases tolerance to drought and *Botrytis cinerea* in *Artemisia annua*. Plant Cell Physiol 57:1961–1971. https://doi.org/10.1093/pcp/pcw118

Lv Z, Wang Y, Liu Y, Peng B, Zhang L, Tang K, Chen W (2019) The SPB-box transcription factor AaSPL2 positively regulates artemisinin biosynthesis in *Artemisia annua* L. Front Plant Sci. 10:409. https://doi.org/10.3389/fpls.2019.00409

Mahmoud SS, Croteau RB (2002) Strategies for transgenic manipulation of monoterpene biosynthesis in plants. Trends Plant Sci 7:366–373

Marks MD, Tian L, Wenger JP, Omburo SN, Soto-Fuentes W, He J, Gang DR, Weiblen GD, Dixon RA (2009) Identification of candidate genes affecting delta(9)-tetrahydrocannabinol biosynthesis in *Cannabis sativa*. J Exp Bot 60:3715–3726. https://doi.org/10.1093/jxb/erp210

McDowell ET, Kapteyn J, Schmidt A et al (2011) Comparative functional genomic analysis of Solanum glandular trichome types. Plant Physiol 155:524–539. https://doi.org/10.1104/pp.110.167114

Mellon JE, Dowd MK, Beltz SB, Moore GG (2014) Growth inhibitory effects of gossypol and related compounds on fungal cotton root pathogens. Lett Appl Microbiol 59:161–168. https://doi.org/10.1111/lam.12262

Mercke P, Bengtsson M, Bouwmeester HJ, Posthumus MA, Brodelius PE (2000) Molecular cloning, expression, and characterization of amorpha- 4,11-diene synthase, a key enzyme of artemisinin biosynthesis in *Artemisia annua* L. Arch Biochem Biophys 381:173–180. https://doi.org/10.1006/abbi.2000.1962

Moulines J, Bats JP, Lamidey AM, Da Silva N (2004) About a practical synthesis of Ambrox (R) from sclareol: a new preparation of a ketone key intermediate and a close look at its Baeyer-Villiger oxidation. Helv Chim Acta 87:2695–2705. https://doi.org/10.1002/hlca.200490239

Nagel J, Culley LK, Lu YP, Liu EW, Matthews PD, Stevens JF, Page JE (2008) EST analysis of hop glandular trichomes identifies an O-methyltransferase that catalyzes the biosynthesis of xanthohumol. Plant Cell 20:186–200. https://doi.org/10.1105/tpc.107.055178

Okada Y, Ito K (2001) Cloning and analysis of valerophenone synthase gene expressed specifically in lupulin gland of hop (*Humulus lupulus* L.). Biosci Biotechnol Biochem 65:150–155. https://doi.org/10.1271/bbb.65.150

Oltmans SJ, Lefohn AS, Shadwick D, Harris JM, Scheel HE, Galbally I, Kawasato T (2013) Recent tropospheric ozone changes—a pattern dominated by slow or no growth. Atmos Environ 67:331–351. https://doi.org/10.1016/j.atmosenv.2012.10.057

Page J, Boubakir Z (2011) Aromatic prenyltransferase from Cannabis. PCT patent application WO/2011/017798

Pateraki I, Kanellis AK (2008) Isolation and functional analysis of two *Cistus creticus* cDNAs encoding geranylgeranyl diphosphate synthase. Phytochemistry 69:1641–1652. https://doi.org/10.1016/j.phytochem.2008.02.005

Pattanaik S, Patra B, Singh SK, Yuan L (2014) An overview of the gene regulatory network controlling trichome development in the model plant, *Arabidopsis*. Front Plant Sci 5:259. https://doi.org/10.3389/fpls.2014.00259

Peiffer M, Tooker JF, Luthe DS, Felton GW (2009) Plants on early alert: glandular trichomes as sensors for insect herbivores. New Phytol 184:644–656. https://doi.org/10.1111/j.1469-8137.2009.03002.x

Pellati F, Borgonetti V, Brighenti V, Biagi M, Benvenuti S, Corsi L (2008) *Cannabis sativa* L. and nonpsychoactive cannabinoids: their chemistry and role against oxidative stress, inflammation and cancer. Biomed Res Int. https://doi.org/10.1155/2018/1691428

Picaud S, Olofsson L, Brodelius M, Brodelius PE (2005) Expression, purification, and characterization of recombinant amorpha-4,11-diene synthase from *Artemisia annua* L. Arch. Biochem Biophys 436:215–226. https://doi.org/10.1016/j.abb.2005.02.012

Pierman B, Toussaint F, Bertin A, Levy D, Smargiasso N et al (2017) Activity of the purified plant ABA transporter NtPDR1 is stimulated by diterpenes and sesquiterpenes involved in constitutive and induced defense. J Biol Chem 292:19491–19502. https://doi.org/10.1074/jbc.m117.811935

Polichuk DB, Zhang Y, Reed DW, Schmidt JF, Covello PS (2010) A glandular trichome-specific monoterpene alcohol dehydrogenase from *Artemisia annua*. Phytochemistry 71:1264–1269. https://doi.org/10.1016/j.phytochem.2010.04.026

Ranger CM, Winter RE, Rottinghaus GE, Backus EA, Johnson DW (2005) Mass spectral characterization of fatty acid amides from alfalfa trichomes and their deterrence against the potato leafhopper. Phytochemistry 66:529–541. https://doi.org/10.1016/j.phytochem.2005.01.012

Reddy VA, Wang Q, Dhar N, Kumar N, Venkatesh PN et al (2017) Spearmint R2R3-MYB transcription factor MsMYB negatively regulates monoterpene production and suppresses the expression of geranyl diphosphate synthase large subunit (MsGPPS.LSU). Plant Biotechnol J 15:1105–1119. https://doi.org/10.1111/pbi.12701

Ringer KL, Davis EM, Croteau R (2005) Monoterpene metabolism. Cloning, expression, and characterization of (−)-isopiperitenol/(−)-carveol dehydrogenase of peppermint and spearmint. Plant Physiol 137:863–872. https://doi.org/10.2307/4629730

Rumbolz J, Gubler WD (2005) Susceptibility of grapevine buds to infection by powdery mildew *Erysiphene cator*. Plant Pathol 54:535–548. https://doi.org/10.1111/j.1365-3059.2005.01212.x

Runyon JB, Mescher MC, DeMoraes CM (2010) Plant defenses against parasitic plants show similarities to those induced by herbivores and pathogens. Plant Signal Behav 5:929–931. https://doi.org/10.4161/psb.5.8.11772

Ryden AM, Ruyter-Spira C, Quax WJ, Osada H, Muranaka T, Kayser O, Bouwmeester H (2010) The molecular cloning of dihydroartemisinc aldehyde reductase and its implication in artemisinin biosynthesis in *Artemisia annua*. Planta 76:1778–1783. https://doi.org/10.1055/s-0030-1249930

Sallaud C, Giacalone C, Topfer R, Goepfert S, Bakaher N, Rosti S, Tissier A (2012) Characterization of two genes for the biosynthesis of the labdane diterpene Z-abienol in tobacco (*Nicotiana tabacum*) glandular trichomes. Plant J. 72:1–17. https://doi.org/10.1111/j.1365-313x.2012.05068.x

Sallets A, Beyaert M, Boutry M, Champagne A (2014) Comparative proteomics of short and tall glandular trichomes of *Nicotiana tabacum* reveals differential metabolic activities. J Proteome Res 13:3386–3396. https://doi.org/10.1021/pr5002548

Sarret G, Harada E, Choi YE, Isaure MP, Geoffroy N, Fakra S et al (2006) Trichomes of tobacco excrete zinc as zinc-substituted calcium carbonate and other zinc-containing compounds. Plant Physiol 41:1021–1034. https://doi.org/10.1104/pp.106.082743

Schilmiller AL, Last RL, Pichersky E (2008) Harnessing plant trichome biochemistry for the production of useful compounds. Plant J. 54:702–711. https://doi.org/10.1111/j.1365-313x.2008.03432.x

Schilmiller A, Schauvinhold I, Larson M, Xu R, Charbonneau AL, Schmidt A, Wilkerson C, Last RL, Pichersky E (2009) Monoterpenes in the glandular trichomes of tomato are synthesized from a neryl pyrophosphate precursor rather than geranyl pyrophosphate. Proc Natl Acad Sci USA 106:10865–10870. https://doi.org/10.1073/pnas.0904113106

Schilmiller AL, Charbonneau AL, Last RL (2012) Identification of a BAHD acetyltransferase that produces protective acylsugars in tomato trichomes. Proc Natl Acad Sci USA 109:16377–16382. https://doi.org/10.1073/pnas.1207906109

Schluter U, Benchabane M, Munger A, Kiggundu A, Vorster J, Goulet MC, Cloutier C, Michaud D (2010) Recombinant protease inhibitors for herbivore pest control: a multitrophic perspective. J Exp Bot 61:4169–4183. https://doi.org/10.1093/jxb/erq166

Serna L, Martin C (2006) Trichomes: different regulatory networks lead to convergent structures. Trends Plant Sci 11:274–280. https://doi.org/10.1016/j.tplants.2006.04.008

Sharma P, Bhushan Jha A, Dubey RS, Pessarakli M (2012) Reactive oxygen species, oxidative damage, and antioxidative defense mechanism in plants under stressful conditions. J Bot 26, Article ID 217037. https://doi.org/10.1155/2012/217037

Shen Q, Lu X, Yan T, Fu X, Lv Z, Zhang F et al (2016) The jasmonate-responsive AaMYC2 transcription factor positively regulates artemisinin biosynthesis in *Artemisia annua*. New Phytol 210:1269–1281. https://doi.org/10.1111/nph.13874

Shepherd RW, Bass WT, Houtz RL, Wagner GJ (2005) Phylloplanins of tobacco are defensive proteins deployed on aerial surfaces by short glandular trichomes. Plant Cell 17:1851–1861. https://doi.org/10.2307/4130874

Shi P, Fu X, Shen Q, Liu M, Pan Q, Tang Y et al (2018) The roles of *AaMIXTA1* in regulating the initiation of glandular trichomes and cuticle biosynthesis in *Artemisia annua*. New Phytol 217:261–276. https://doi.org/10.1111/nph.14789

Sirikantaramas S, Taura F, Tanaka Y, Ishikawa Y, Morimoto S, Shoyama Y (2005) Tetrahydrocannabinolic acid synthase, the enzyme contolling marijuana psychoactivity, is secreted into the storage cavity of the glandular trichomes. Plant Cell Physiol 46:1578–1582. https://doi.org/10.1093/pcp/pci166

Sivropoulou A, Papanikolaou E, Nikolaou C, Kokkini S, Lanaras T, Arsenakis M (1996) Antimicrobial and cytotoxic activities of origanum essential oils. J Agric Food Chem 44:1202–1205

Slocombe SP, Schauvinhold I, McQuinn RP et al (2008) Transcriptomic and reverse genetic analyses of branched-chain fatty acid and acyl sugar production in *Solanum pennellii* and *Nicotiana benthamiana*. Plant Physiol 148:1830–1846. https://doi.org/10.1104/pp.108.129510

Spyropoulou EA, Haring MA, Schuurink RC (2014) Expression of Terpenoids 1, a glandular trichome-specific transcription factor from tomato that activates the terpene synthase 5 promoter. Plant Mol Biol 84:345–357. https://doi.org/10.1007/s11103-013-0142-0

Stout JM, Boubakir Z, Ambrose SJ, Purves RW, Page JE (2012) The hexanoyl-CoA precursor for cannabinoid biosynthesis is formed by an acyl-activating enzyme in *Cannabis sativa* trichomes. Plant J. 71:353–365. https://doi.org/10.1111/j.1365-313x.2012.04949.x

Sytar O, Kumar A, Latowski D, Kuczynska P, Strzałka K, Prasad MNV (2013) Heavymetal-induced oxidative damage, defense reactions, and detoxification mechanisms in plants. Acta Physiol Plant 35:985–999. https://doi.org/10.1007/s11738-012-1169-6

Taura F, Sirikantaramas S, Shoyama Y, Yoshikai K et al (2007) Cannabidiolic-acid synthase, the chemotype-determining enzyme in the fiber-type *Cannabis sativa*. FEBS Lett 581:2929–2934. https://doi.org/10.1016/j.febslet.2007.05.043

Taura F, Tanaka S, Taguchi C, Fukamizu T, Tanaka H, Shoyama Y, Morimoto S (2009) Characterization of olivetol synthase, a polyketide synthase putatively involved in cannabinoid biosynthetic pathway. FEBS Lett 583:2061–2066. https://doi.org/10.1016/j.febslet.2009.05.024

Teoh KH, Polichuk DR, Reed DW, Nowak G, Covello PS (2006) *Artemisia annua* L. (Asteraceae) trichome-specific cDNAs reveal CYP71AV1, a cytochrome P450 with a key role in the biosynthesis of the antimalarial sesquiterpene lactone artemisinin. FEBS Lett 580:1411–1416. https://doi.org/10.1016/j.febslet.2006.01.065

Teoh KH, Polichuk DR, Reed DW, Covello PS (2009) Molecular cloning of an aldehyde dehydrogenase implicated in artemisinin biosynthesis in *Artemisia annua*. Botany. 87:635–642. https://doi.org/10.1139/b09-032

Tian D, Tooker J, Peiffer M, Chung SH, Felton GW (2012) Role of trichomes in defense against herbivores: comparison of herbivore response to Woolly and hairless trichome mutants in tomato (*Solanum lycopersicum*). Planta 236:1053–1066. https://doi.org/10.1007/s00425-012-1651-9

Tissier A (2018) Plant secretory structures: more than just reaction bags. Curr Opin Biotechnol 49:73–79. https://doi.org/10.1016/j.copbio.2017.08.003

Treutter D (2006) Significance of flavonoids in plant resistance: a review. Environ Chem Lett 4:147–157. https://doi.org/10.1055/s-2005-873009

Turner GW, Gershenzon J, Croteau RB (2000) Development of peltate glandular trichomes of peppermint. Plant Physiol 124:665–680. https://doi.org/10.1104/pp.124.2.665

Uphof JCT (1962) Plant hairs. In: Encyclopedia of plant anatomy IV, vol 5, pp 1–206

Van De Graaf P, Joseph ME, Chartier-Hollis JM, O'Neill TM (2002) Prepenetration stages in infection of clematis by Phomaclematidina. Plant Pathol 51:331–337. https://doi.org/10.1046/j.1365-3059.2002.00727.x

van Der Hoeven RS, Monforte AJ, Breeden D, Tanksley SD, Steffens JC (2000) Genetic control and evolution of sesquiterpene biosynthesis in *Lycopersicon esculentum* and *L. hirsutum*. Plant Cell 12:2283–2294. https://doi.org/10.1105/tpc.12.11.2283

Wang E, Wagner GJ (2003) Elucidation of the functions of genes central to diterpene metabolism in tobacco trichomes using post transcriptional gene silencing. Planta 216:686–691. https://doi.org/10.1007/s00425-002-0904-4

Wang E, Wang R, DeParasis J, Loughrin JH, Gan S, Wagner GJ (2001) Suppression of a P450 hydroxylase gene in plant trichomeglands enhances natural-product-based aphid resistance. Nat Biotechnol 19:371–374. https://doi.org/10.1038/86770

Wang E, Gan S, Wagner GJ (2002) Isolation and characterization of the CYP71D16 trichome-specific promoter from *Nicotiana tabacum* L. J Exp Bot 53:1891–1897. https://doi.org/10.1093/jxb/erf054

Wang G, Tian L, Aziz N, Broun P, Dai X, He J, King A, Zhao PX, Dixon RA (2008) Terpene biosynthesis in glandular trichomes of hop. Plant Physiol 148:1254–1266. https://doi.org/10.1104/pp.108.125187

Wang W, Wang YJ, Zhang Q, Qi Y, Guo DJ (2009) Global characterization of *Artemisia annua* glandular trichome transcriptome using 454 pyrosequencing. BMC Genom 10:465. https://doi.org/10.1186/1471-2164-10-465

Wang Q, Reddy VA, Panicker D, Mao HZ, Kumar N, Rajan C et al (2016) Metabolic engineering of terpene biosynthesis in plants using a trichome-specific transcription factor MsYABBY5 from spearmint (*Mentha spicata*). Plant Biotechnol J 14:1619–1632. https://doi.org/10.1111/pbi.12525

Weathers PJ, Aesenault PR, Covello PS, McMickle A, Teoh KH, Reed DW (2011) Artemisinin production in *Artemisia annua*: studies in planta and results of a novel delivery method for treating malaria and other neglected diseases. Phytochem Rev 10:173–183. https://doi.org/10.1007/s11101-010-9166-0

Werker E (2000) Trichome diversity and development. Adv Bot Res 31:261–283. https://doi.org/10.1016/s0065-2296(00)31005-9

Xu H, Zhang F, Liu B, Huhman DV, Sumner LW, Dixon RA et al (2013) Characterization of the formation of branched short-chain fattyacid: CoAs for bitter acid biosynthesis in hop glandular trichomes. Mol Plant 6:1301–1317. https://doi.org/10.1093/mp/sst004

Xu J, van Herwijnen ZO, Drager DB, Sui C, Haring MA, Schuurink RC (2018) SlMYC1 regulates type VI glandular trichome formation and terpene biosynthesis in tomato glandular cells. Plant Cell 30:2988–3005. https://doi.org/10.1105/tpc.18.00571

Yan T, Chen M, Shen Q, Li L, Fu X, Pan Q, Tang Y et al (2017) HOMEODOMAIN PROTEIN 1 is required for jasmonate-mediated glandular trichome initiation in *Artemisia annua*. New Phytol 213:1145–1155. https://doi.org/10.1111/nph.14205

Yang C, Li H, Zhang J, Luo Z, Gong P, Zhang C, Li J, Wang T, Zhang Y, Lu YE (2011) A regulatory gene induces trichome formation and embryo lethality in tomato. Proc Natl Acad Sci USA 108:11836–11841. https://doi.org/10.1073/pnas.1100532108

Yang C, Gao Y, Gao S, Yu G, Cheng X, Jiang C, Li H, Ye Z (2015) Transcriptome profile analysis of cell proliferation molecular processes during multicellular trichome formation induced by tomato Wov gene in tobacco. BMC Genom 16:868. https://doi.org/10.1186/s12864-015-2099-7

Yu Z-X, Li J-X, Yang C-Q, Hu W-L, Wang L-J, Chen X-Y (2012) The jasmonate-responsive AP2/ERF transcription factors AaERF1 and AaERF2 positively regulate artemisinin biosynthesis in *Artemisia annua* L. Mol Plant 5:353–365. https://doi.org/10.1093/mp/ssr087

Zengin FK, Munzuroglu O (2005) Effects of some heavy metals on content of chlorophyll, proline and some antioxidant chemicals in bean (*Phaseolus vulgaris* L.) seedlings. Acta Biologica Cracoviensia Series Botanica 47:157–164

Zhang Y, Teoh KH, Reed DW, Maes L, Goossens A, Olson DJH, Ross ARS, Covello PS (2008a) The molecular cloning of artemisinic aldehyde Δ11(13) reductase and its role in glandular trichome-dependent biosynthesis of artemisinin in *Artemisia annua*. J Biol Chem 283:21501–21508. https://doi.org/10.1074/jbc.m803090200

Zhang Y, Teoh KH, Reed DW, Covello PS (2008b) Molecular cloning and characterization of Dbr1, a 2-alkenal reductase from *Artemisia annua*. Botany 87:643–649. https://doi.org/10.1139/b09-033

Zhang F, Fu X, Lv Z, Lu X, Shen Q, Zhang L et al (2015) A basic leucine zipper transcription factor, AabZIP1, connects abscisic acid signaling with artemisinin biosynthesis in *Artemisia annua*. Mol Plant 8:163–175. https://doi.org/10.1016/j.molp.2014.12.004