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REVIEW

Terpenes and isoprenoids: a wealth of compounds for global use

Sarada D. Tetali[1]

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Abstract

Main conclusion **Role of terpenes and isoprenoids has been pivotal in the survival and evolution of higher plants in various ecoregions. These products find application in the pharmaceutical, flavor fragrance, and biofuel industries.**

Fitness of plants in a wide range of environmental conditions entailed (i) evolution of secondary metabolic pathways enabling utilization of photosynthate for the synthesis of a variety of biomolecules, thereby facilitating diverse eco-interactive functions, and (ii) evolution of structural features for the sequestration of such compounds away from the mainstream primary metabolism to prevent autotoxicity. This review summarizes features and applications of terpene and isoprenoid compounds, comprising the largest class of secondary metabolites. Many of these terpene and isoprenoid biomolecules happen to be high-value bioproducts. They are essential components of all living organisms that are chemically highly variant. They are constituents of primary (quinones, chlorophylls, carotenoids, steroids) as well as secondary metabolism compounds with roles in signal transduction, reproduction, communication, climatic acclimation, defense mechanisms and more. They comprise single to several hundreds of repetitive five-carbon units of isopentenyl diphosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP). In plants, there are two pathways that lead to the synthesis of terpene and isoprenoid precursors, the cytosolic mevalonic acid (MVA) pathway and the plastidic methylerythritol phosphate (MEP) pathway. The diversity of terpenoids can be attributed to differential enzyme and substrate specificities and to secondary modifications acquired by terpene synthases. The biological role of secondary metabolites has been recognized as pivotal in the survival and evolution of higher plants. Terpenes and isoprenoids find application in pharmaceutical, nutraceutical, synthetic chemistry, flavor fragrance, and possibly biofuel industries.

Introduction

Isoprenoids, also known as terpenoids, are grouped into natural product categories based on their structure and pathways for their biosynthesis. All terpenoids are derived from the 5-carbon precursor compounds dimethylallyl diphosphate (DMAPP) and its isomer isopentenyl diphosphate (IPP), and exist as single unit hemiterpene (5C) to mono- (C10), sesqui- (C15), di- (C20), sester- (C25), tri- (C30), tetra- (C40) to polyterpenes of $> C40–C5 \times 10^{3–4}$ units. Isoprenoids are ubiquitous in nature, and are essential constituents of all living single cells or multicellular organisms, including bacteria, archaea, protists, and eukaryotes. They are components of both the primary and secondary metabolism in cells (Rodríguez-Concepción 2014). To date, tens of thousands of terpenoid compounds have been identified, the majority encountered in organisms from the plant kingdom, as higher plants possess a vast number of enzymes belonging to the general class of terpenoid synthases (TPS), including the prenylelongase and terpene cyclase families. TPS enzymes have high specificity to various lengths of isoprenoid backbone polymers as their substrates, and synthesize a plethora of chemically variant compounds (Gao et al. 2012). Terpenoids grouped under primary metabolites are the components essential for basic cellular functions, and they include prenyl chains of quinones (ubiquinone and plastoquinone), photosynthetic pigments (phytol in chlorophyll and carotenoid pigments), sterols (the majority of which is responsible for

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✉ Sarada D. Tetali
stetali@uohyd.ac.in; saradakanakagiri@gmail.com

[1] Department of Plant Sciences, School of Life Sciences, University of Hyderabad, C. R. Prof. CR Rao Rd., CUC, Gachibowli, Hyderabad 500046, Telangana, India

membrane stability), growth hormones (gibberellins), and prenylated proteins (Bohlmann and Keeling 2008; Moses et al. 2013). Protein prenylation, a type of posttranslational modification, facilitates their association with cellular membranes, which is highly essential for their function, e.g., GTPases (Bracha-Drori et al. 2008). Terpenoids, which play a crucial role in carrying out various ecological functions in response to both biotic and abiotic factors are classified as products of the secondary metabolism, e.g., pollination attractants, herbivore deterrents, insecticidal/repellants, antibacterial compounds, allelopathic and toxic molecules, antioxidants, thermotolerance and photoprotection molecules, among other functions (Croteau et al. 2000; Gershenzon and Dudareva 2007; Pateraki and Kanellis 2010; Tholl 2015).

The universal isoprenoid precursors, isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), are synthesized by two independent pathways that evolved in taxonomically different organisms (Pulido et al. 2012) (Fig. 1). The mevalonic acid (MVA) pathway probably evolved in archaea and is encountered in the cytosol of eukaryotes. The methylerythritol phosphate (MEP) pathway is encountered in most bacteria, all photosynthetic bacteria, and chloroplasts. The end products of both pathways are the isomeric IPP and DMAPP molecules. However, the cellular endogenous substrate input is acetyl-coA for the MVA pathway, whereas it is pyruvate and glyceraldehyde 3-phosphate

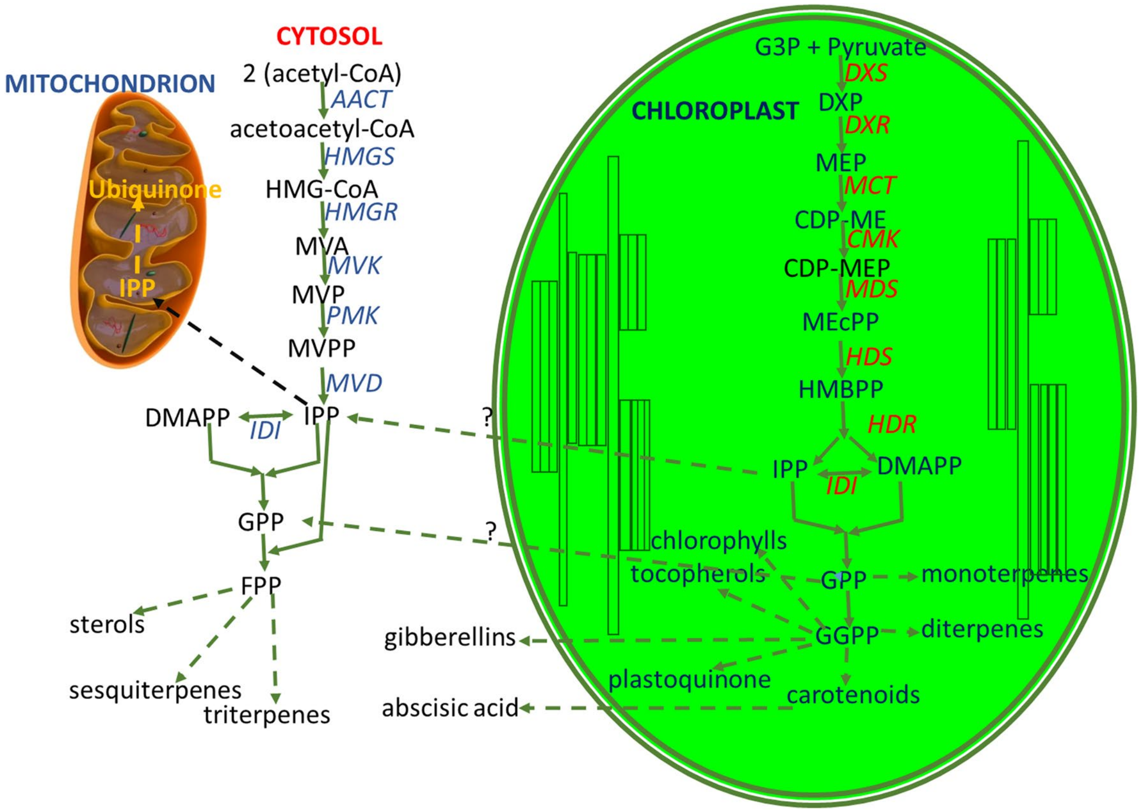

Fig. 1 Biosynthetic pathways for the synthesis of the precursors, isopentenyl diphosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP), used for the subsequent biosynthesis of all terpenes and isoprenoids either in the cytosol or chloroplast of a typical plant cell. The cytosolic MVA pathway enzymes, leading to IPP and DMAPP, are shown in blue, and the chloroplastic MEP pathway enzymes, also leading to IPP and DMAPP, are shown in red. Abbreviations used in this figure are as follows: *CDP-ME* 4-(cytidine 5′-diphospho)-2-*C*-methyl-*D*-erythritol, *CDP-MEP* CDP-ME 2-phosphate, *DMAPP* dimethylallyl diphosphate, *DXP* 1-deoxy-*D*-xylulose 5-phosphate, *FPP* farnesyl diphosphate, *GGPP* geranylgeranyl diphosphate, *GPP* geranyl diphosphate, *HMBPP* 1-hydroxy-2-methyl-2-butenyl 4-diphosphate, *HMG-CoA* 3-hydroxy-3-methylglutaryl CoA, *IPP* isopentenyl diphosphate, *MEcPP* 2-*C*-methyl-*D*-erythritol 2,4-cyclodiphosphate, *MEP* 2-*C*-methyl-*D*-erythritol 4-phosphate, *MVA* mevalonic acid, *MVP* 5-phosphomevalonate, *MVPP* 5-diphosphomevalonate. Enzymes of the MVA pathway are acetoacetyl-CoA thiolase (AACT), 3-hydroxy-3-methylglutaryl CoA synthase (HMGS), 3-hydroxy-3-methylglutaryl CoA reductase (HMGR), mevalonate kinase (MVK), 5-phosphomevalonate kinase (PMK), 5- diphosphomevalonate decarboxylase (MVD). Enzymes of the MEP pathway are 1-deoxy-*D*-xylulose 5-phosphate synthase (DXS), 1-deoxy-*D*-xylulose 5-phosphate reductoisomerase (DXR), 2-*C*-methyl-*D*-erythritol 4-phosphate cytidylyltransferase (MCT), 4-(cytidine 5′-diphospho)-2-*C*-methyl-*D*-erythritol kinase (CMK), 2-*C*-methyl-*D*-erythritol 2,4-cyclodiphosphate synthase (MDS) 1-hydroxy-2-methyl-2-butenyl 4-diphosphate synthase (HDS), 1-hydroxy-2-methyl-2-butenyl 4-diphosphate reductase (HDR). The cross-sectional view of a mitochondrion shown in this figure is modified from Google images (please see supplementary materials)

for the MEP pathway. Both of these pathways operate in plants and some algae, although in different cellular compartments. The MVA pathway operates in the cytosol and originates from the eukaryotic cell, whereas the MEP pathway operates in the chloroplast and was acquired from the cyanobacteria endosymbionts (Lohr et al. 2012). Archaea, bacteria with some exceptions, yeast, fungi, and animal cells possess only the MVA pathway, whereas most fermentative and aerobic bacteria, photosynthetic bacteria, cyanobacteria, micro- and macroalgal chloroplasts, as well as all plant chloroplasts possess the MEP pathway (Lombard and Moreira 2011; Lohr et al. 2012). The MEP pathway operates in the plastidic compartment of plants and algae and supports the synthesis of primary isoprenoids like the phytol tail of chlorophylls (C20), all carotenoids (C40), and the prenyl tail of quinone molecules (C36 and C40). However, higher plants synthesize many more types of terpenoids, often these are species specific, referred to as secondary metabolism terpenoids. The biological significance of many of these specialized compounds is not always understood, though some are recognized as important players in survival, growth and development, pollination, and protection against herbivores and pathogens, among possibly other currently unknown functions. Included in these categories are the mono- and sesquiterpenes, which are components of plant essential oils, triterpenes, phytoalexins, and polyterpenes composed of a large number of isoprene moieties covalently linked to form latex and rubber. Some of the mono- and sesquiterpenes are hydrophobic and volatile in nature and, due to their high vapor pressure at ambient temperatures, are able to cross chloroplast and cellular membranes and to be released into the surrounding atmosphere. The volatile terpenes play important roles in plant physiology including signaling, they attract pollinators and repel or act against predators and other leaf-damaging organisms (Abbas et al. 2017). Plants attract pollinators and animals for seed dispersal by virtue of colored and/or fragrant volatile compounds. Synthesis of most of the secondary metabolism terpenoids occurs in the cytosol of the eukaryotic cell, and is either exclusively supported by the MVA pathway, or aided by the plastidic MEP pathway. The concept of compartmentalization with strict boundaries is being revisited since the recent discoveries that shed the light on (1) movement of IPP and geranyl diphosphate (GPP) across the chloroplast envelope membranes, (2) localization of terpene synthases in several other cellular compartments like the mitochondria, peroxisomes, endoplasmic reticulum, and (3) functional regulation of enzymes by posttranslational modifications (Laule et al. 2003; Pulido et al. 2012). Regulation of terpenoid biosynthesis and its biological significance is highly complex and little understood thus far. Adding to the complexity, interestingly, several noncanonical pathways have been discovered in the recent past (Sun et al. 2016). Applications of several of the primary and secondary terpenoids are being recognized and commercially exploited (Croteau et al. 2000; Betterle and Melis 2018; Chaves and Melis 2018a, b; Lauersen et al. 2018). Isoprenoids, among other natural products, attracted great attention due to their broad spectrum of applications ranging from fragrances for cosmetics, perfumes, space sprays, detergents, deodorants, fabrics, fibers, soap, tobacco, creams, paper products, food products, pharmaceuticals, and perhaps even fuels (Holstein and Hohl 2004; Tippmann et al. 2013; Melis 2017) (Fig. 2). In this review, emphasis is placed on high-value terpenoids in the areas of pharmaceuticals, health care, flavors and fragrances, cosmetics, agriculture, fuels, and useful biomaterials.

Drugs, health care and cosmetic products

Isoprenoids, like many other natural products, show biological activities, which have been exploited in prevention and treatment of human diseases (Wang et al. 2005). Hundreds of isoprenoid compounds and their derivatives have been tested for the cellular and molecular basis of their pharmacological activities. The demonstrated biological activities of various classes of terpenoids from in vitro and in vivo studies include anti-inflammatory, anti-oxidative, anti-aggregatory, anti-coagulative effects, anti-tumor, sedative and analgesic activities of monoterpenes, sesqui-, di-, tri- and tetraterpenes and their glycosides (Kokkiripati et al. 2011, 2013; Zhao et al. 2016). These compounds bring about health benefits by interacting with key molecular players in animal and human physiology, act as immunostimulants, modulate blood coagulation hemostasis, boost antioxidant activity, modulate transcription factors like the nuclear factor kappa B (NF-κB), which regulates a cascade of events in inflammatory pathways associated with various chronic diseases like cardiovascular, diabetes, Alzheimer's, and many others (Wagner and Elmadfa 2003; Nuutinen 2018). Some of the isoprenoid compounds examined showed activity against cancer, malaria, and a variety of infectious viral and bacterial diseases. To date, the anticancer properties of the diterpenoid drug Taxol® and the antimalarial drug artemisinin, a sesquiterpene lactone, are two examples of multibillion dollar pharmaceutical industry directly based on natural products (Wang et al. 2005).

Concepts of aerosol therapy and aromatherapy have evolved from forest bathing, which was later recognized to have beneficial effects on human health via the aerosolic release of isoprenoid substances by the forest trees. Majority of these substances belong to terpenes of low molecular weight including the classes of mono- and sesquiterpenes, which are volatile in nature. Traditionally, terpene-containing plant essential oils have been used to empirically treat various diseases without an understanding of the exact

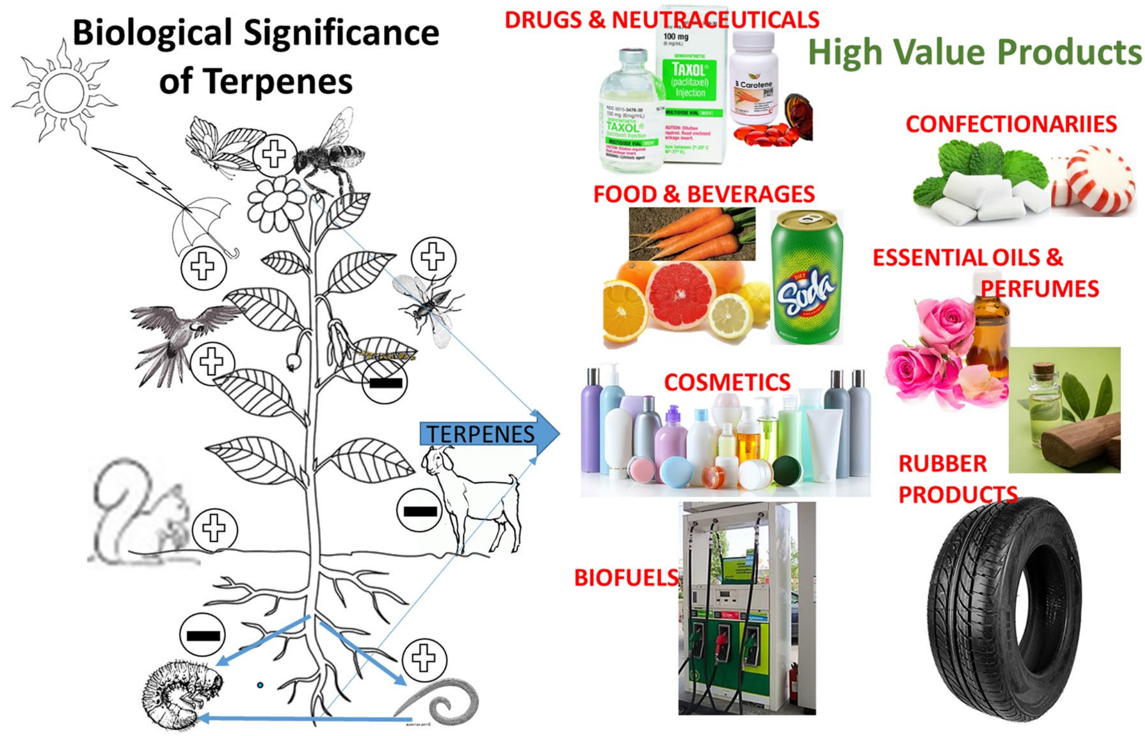

Fig. 2 (Left panel) biological roles of terpenes and isoprenoids in plants. Shown is a presentation of various terpenoid-mediated interactions between plants and their surroundings. These include both above and below ground interfaces upon the release of volatile compounds for thermotolerance, attracting pollinators or insects feeding on herbivores, deterring browsing animals, repelling damaging pests in the soil and attracting certain soil-friendly nematodes, colorants in the fruits to attract birds for dispersal of their seed, and various pigments to protect against damaging high-intensity visible or UV irradiance. (Right panel) examples of terpenoids with commercial applications in the sectors of drugs, nutraceuticals, food and beverage, confectionaries, flavor and fragrances, biofuels and rubber products. Images used in the preparation of this figure, left and right panels, were modified from Google images, clip art and creative commons and these sites are listed in the supplementary materials

functions or the mechanisms of action of the individual bioactive compounds (Cho et al. 2017). Scientific studies showed the molecular mechanism of anti-inflammatory and antioxidant activities of several terpene-based volatile compounds that occur in plant essential oils of several herbs, shrubs and trees like rosemary, *Ocimum*, coniferous trees, *Eucalyptus*, *Citrus*, among other, including compounds like α-pinene, β-limonene, β-phellandrene, p-cymene, linalool, and terpinenes (Cho et al. 2017). Some of these volatile compounds can also cross the blood–brain barrier and are being explored as a treatment against the Alzheimer's disease (Wojtunik-Kulesza et al. 2017).

Terpenes are also important integral components of several human nutritional and health care products like vitamins A, E, K, coenzyme Q10, among others. Dietary carotenoids and tocopherols are the essential sources of vitamins A and E, respectively, in most animals including humans (Shahidi and de Camargo 2016; Laurent 2018; Rodriguez-Concepcion et al. 2018). Carotenoids are tetraterpenoids (C40) and majority of them are bright-colored natural pigments in the yellow to red range and act as natural antioxidants, e.g., β-carotene, β-cryptoxanthin, lycopene, lutein and zeaxanthin. Epidemiologic studies associate a carotenoid-rich diet with health benefits, however, the type of carotenoids with at least one unsubstituted β-ring serve as precursors to vitamin A, an important micronutrient for vision health. Other health-related benefits associated with high carotenoid food products include cardiovascular health and protection against diseases like type-2 diabetes, obesity, cancer and other age-related diseases (Rodriguez-Concepcion et al. 2018). Vitamin E is also a very important antioxidant compound, strongly recommended in the human diet, as it plays a role in maintaining a human well-being. Vitamin E comprises a family of tocopherol and tocotrienols collectively referred to as "tocols", consisting of four tocopherols and two tocotrienols. These molecules possess a polar ring and a phytol tail of various length depending on the number of conjugated isoprene units (Shahidi and de Camargo 2016; Laurent 2018). Dietary sources for vitamin E, or any of its tocopherol and tocrotrienol members, are seeds, nuts, and edible oils of almond, peanut, olive, and sunflower, canola, corn, camelina, linseed, soybean, walnut or palm oil.

Vitamin E has been shown to reduce the risk of cancer, ageing, and cardiovascular diseases. Vitamin E deficiency is associated with anemia, retinopathy, neurological diseases and can cause miscarriage in pregnant women (Shahidi and de Camargo 2016).

The global cosmetic products market was valued at over US$500 billion in 2017. Natural products, terpenes and terpenols in specific, contribute substantially to the overall market value. Carotenoids, tocols and few other terpenes are in high demand as skin care and cosmetic industry product ingredients due to their fragrance and benefits associated with beauty enhancement by making the skin wrinkle free, healthy and radiant. They are widely used in cosmetics in view of their antioxidant effect in protecting against ageing, damage by UV radiation of skin cells and also preventing melanogenesis. Role of various carotenoids like astaxanthin, fucoxanthin and β-carotene in keeping the skin cells young and healthy and their mechanism of action has been a focus of research in view of the benefits they afford and their commercial application (Sathasivam and Ki 2018). Retinoids, the metabolites of vitamin A and the various forms of vitamin E are also being exploited in the cosmetics industry due to their antioxidant effect, i.e., their use as topical antioxidants. They can prevent photoaging by modulating keratinization of epidermis via inhibition of UV-induced matrix metalloproteinases and also suppress pigmentation by inhibiting tyrosinase enzymes involved in the synthesis of melanin pigments (Nolan and Marmur 2012; Lee 2016). Carotenoids, vitamin E, and other terpenes such as carnosic acid, squalene, coenzyme Q10 (CoQ10) are used in functional foods, as well as for skin and other health benefits (Pérez-Sánchez et al. 2018).

Flavor and fragrance agents

The worldwide flavor and fragrance market has grown to be worth an estimated US$30 billion in 2017 (Kutyna and Borneman 2018). Terpenes and isoprenoids are the most divergent and abundant compounds responsible for the characteristic scent of essential oils emanating from flowers, fruits, leaves, bark, and underground plant parts like rhizomes. Essential oils have been commercially exploited for their characteristic flavor by the food, beverage, and perfume industries. To name a few, valencene is a sesquiterpene, an aroma component of citrus fruit and its derivative, nootkatone is one of the main components of the aroma and flavor of grapefruit (Kutyna and Borneman 2018). Monoterpenes like limonene, linalool, 1,8-cineole are used for the aroma of lemon or lime beverages (Hausch et al. 2015). The aroma of mango fruit depends on terpenes like terpinolene, 3-carene, caryophyllene and α-pinene, β-myrcene, among others (Li et al. 2017). Similarly, several terpenes are detected in strawberry volatiles, and a terpene alcohol, nerolidol was identified as a strawberry-associated aroma compound (Schwieterman et al. 2014). Also, several other terpenes, identified from herbs and spices, are responsible for their characteristic flavor and have been commercially exploited not only by the food industry but also in the consumer products of soaps, shampoos, toothpastes, cleaning liquids, and even insect repellants of household and as insecticides in agriculture (Croteau et al. 2000).

Floral scents play a very important ecological role in attracting pollinators and have gained market interest due to their pleasant fragrance for human use. Understanding the biology of floral scent is at an early stage, as these are mixtures of tens to hundreds of volatile organic compounds, with terpenes and isoprenoids being one of the major classes associated with the scent (Raguso 2016). A monoterpene alcohol linalool and its enantiomers are ubiquitously associated with several floral scents, for example, rose, lavender, and jasmine (Sugawara et al. 2000; Raguso 2016; Pragadheesh et al. 2017). Also, essential oils from trees, e.g., sandalwood oil from *Santalum* and frankincense from *Boswellia* have gained high market value due to their pleasant scents. These essential oils contain several volatiles including mono- and sesquiterpnes. Sandalwood oil contains several terpenes like sesquiterpene olefins and alcohols, including variable levels of the valuable sesquiterpene alcohols α- and β-santalol, and often high levels of *E,E*-farnesol (Moniodis et al. 2015). Major odorants of frankincense are monoterpenes like α-pinene, β-myrcene, p-cymene and oxygenated monoterpenoids of 1,8-cineole, linalool, verbenone, trans-carveol, carvone, and thymoquinone (flatbread, black cumin) and few other sesqui- and diterpenoids (Niebler and Buettner 2015).

Biofuels

Alternative sources of fuels that are low cost and eco-friendly are rising in demand. Terpene hydrocarbons offer a number of compounds that can be used as renewable biofuels. Monoterpenes can be viewed as biogasoline analogs (Melis 2017). Sesquiterpenes have properties similar to conventional aviation fuels such as Jet A and Jet A-1, whereas sesquiterpenes and diterpenes could find application as biodiesels (Tippmann et al. 2013). Their low hygroscopy, high-energy density, and good fluidity at low temperatures place them at the forefront of potentially useful transportation fuel alternatives (Phulara et al. 2016; Melis 2017). The most promising examples include the monoterpenes limonene and β-phellandrene, the sesquiterpenes farnesene and bisabolene and the diterpenes phytene and cambrene, which can either be used as fuel additives or directly as replacements of gasoline, jet fuel, and diesel, respectively (Tippmann et al. 2013).

Metabolic engineering of microbial factories for the production of terpenes and isoprenoids

Even though plants are the green laboratories synthesizing diverse structures of isoprenoids having a broad spectrum of applications, it is not always economically feasible to extract isoprenoids from plants to meet demands of the global market. Therefore, microbial systems of fermentative organisms like *Escherichia coli*, *Saccharomyces cerevisiae* (Tippmann et al. 2013; Phulara et al. 2016), green microalgae such as *Chlamydomonas reinhardtii* (Wichmann et al. 2018) and cyanobacteria such as *Synechocystis* PCC 6803 (Melis 2017; Chaves and Melis 2018b), which can be genetically manipulated, have attracted attention for large-scale production of terpene and isoprenoid compounds. Other investigators have genetically manipulated *Synechocystis* for terpenoid biosynthesis (Formighieri and Melis 2016, 2017, 2018; Englund et al. 2018). Also, production of artemisinic acid in yeast, which is a precursor of artemisinin, a sesquiterpene endoperoxide produced by the plant *Artemisia annua*, paved the way for its sustainable production and affordable antimalarial drug (Paddon et al. 2013). Thus, synthetic biology approaches have been developed to produce several mono-, sesqui- or diterpenoids in larger quantities for commercial exploitation in the pharmaceutical, nutraceutical, flavor, fragrance, and colorants sectors of compounds that are either produced in a low quantity by host plants and/or are difficult to be isolated and purified from the host complex matrices (Vickers et al. 2017).

Conclusions

Higher plants can produce an array of terpenes and isoprenoids, with broad spectrum applications in medicinal drugs and health care products including nutraceuticals, cosmetics, food and beverages, confectionaries, biofuel, and rubber derivatives. Many of these compounds are family or genera specific and also tissue specific within a plant species. Their biosynthetic pathways in several plants, and especially so in trees, have not yet been thoroughly investigated. Genetic and metabolomic profiling for the biosynthesis of such plant products would offer insight into the regulation of their gene expression and also explain their regulation by environmental cues. Such information would enable the genetic and metabolic engineering of plants for terpene and isoprenoids production. However, molecular genetic manipulations and transformation protocols are not available for the many interested in these respective plants. As the vast majority of terpenes and isoprenoids cannot be chemically synthesized, alternative technologies may assist in the commercially viable synthesis of these compounds. Synthetic biology approaches, including manipulation of microorganisms by metabolic engineering approaches is promising for terpenes and isoprenoids production. In this respect, fermentative microorganisms like *E. coli* and yeast, as well as photosynthetic microorganisms like the green microalgae *Chlamydomonas reinhardtii* and the cyanobacteria *Synechocystis* and *Synechococcus* have been applied in the heterologous production of terpenes and isoprenoids. Recent interest was focused on the development of economical and eco-friendly technologies for the generation of various high-value terpenoids, e.g., low molecular weight terpenes like mono-, sesqui-, di- and tri-terpenoids. Notable success stories like the generation of artemisinin are encouraging in this line of research. The present scenario asserts the need to elucidate the pathways of synthesis of terpenoids in their natural hosts, especially of medicinal and aromatic plants, including the dynamics of gene expression, and metabolic flow in response to environmental cues. Knowledge in this domain would open the gateways for the generation of an abundance and variety of terpenes and isoprenoids useful in human health and welfare.

Author contribution statement SDT conceived of the idea, surveyed and collected the relevant literature, wrote the review article.

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Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

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