JOURNAL OF PLANT RESEARCH AND INNOVATIONS
2023, VOL. 1, ISSUE 1, pp. 1-2
https://doi.org/10.61577/jpri.2023.100001

RESEAPRO JOURNALS

SHORT COMMUNICATION

OPEN ACCESS

# Bioproducts from the microbial metabolization of terpenes

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## ABSTRACT

This paper explores the potential of microbial biotransformation as a sustainable and cost-effective method for generating valuable bioproducts from terpenes, essential components of many plant-derived oils. Terpenes and terpenoids, comprising a diverse group of organic compounds, exhibit various pharmacological activities with applications in pharmaceuticals, cosmetics, and food industries. Traditional chemical extraction methods for obtaining terpenes are often expensive and environmentally unsustainable. In contrast, microbial biotransformation offers an attractive alternative by utilizing biological catalysts to produce complex terpenoid compounds, which are often more biologically active and less toxic. The paper discusses the enzymatic pathways involved in terpene biosynthesis and highlights recent advancements in microbial biotransformation techniques. Additionally, the paper discusses the potential of recombinant microorganism strains in large-scale production of bioactive terpenes, addressing challenges associated with traditional extraction methods. Overall, this paper underscores the significance of microbial biotransformation in unlocking the therapeutic potential of terpenes and terpenoids, paving the way for the development of novel bioproducts with enhanced pharmacological activities and reduced environmental impact.

## KEYWORDS

Terpenes; Terpenoids; Microbial biotransformation; Pharmacological activity; Sustainable production; Bioproducts

## ARTICLE HISTORY

Received 11 June 2023; Revised 11 September 2023; Accepted 29 September 2023

Essential oils are highly concentrated hydrophobic mixtures of aromatic volatile substances derived from plants, which also contain more than 300 organic compounds, such as alkaloids, flavonoids, saponins, and terpenes. They are widely used as flavoring agents by the cosmetic and food industries, respectively. The growing interest of the pharmaceutical industry in essential oils has stimulated pharmacological research in these chemicals that have already demonstrated relevant therapeutic properties such as antimicrobial, antiviral, anthelmintic, antioxidant, anti-inflammatory, insecticidal, larvicidal, immunomodulatory, antinociceptive, and anti-ulcer activities [1].

Some chemical components of essential oils, such as terpenes and terpenoids, which are organic compounds, have been constantly investigated and have shown various pharmacological effects. But what is the difference between terpenes and terpenoids? Terpenes are a large group of compounds with simple hydrocarbons. The isoprene unit, a five-carbon branched chain, gives rise to the different types of terpenes, which include hemiterpenes, (C10) monoterpenes, (C15) sesquiterpenes, (C20) diterpenes, (C30) triterpenes, and (C40) tetraterpenes. Monoterpenes are the most predominant constituents of essential oils. Examples of bioactive monoterpenes are limonene, myrcene, ocimene, menthane, and α-phellandrene, etc. Terpenoids are classified as alcohols, aldehydes, esters, ethers, epoxides, ketones, and phenols because they have an oxygen molecule in their structure. Examples of bioactive terpenoids include carvacrol, linalool, linalyl acetate, menthol, thymol, and myrtenol. Terpenes and terpenoids are produced naturally by the mevalonic acid pathway in the cytoplasm of eukaryotic cells or by the methylerythritol phosphate (MEP) pathway in the cytoplasm of eubacteria [2].

Chemical methods to extract large amounts of terpenes from essential oils are considered expensive because of the need for structured chemical laboratories with High-performance liquid chromatography (HPLC) apparatus to isolate and purify these products. In addition, an exorbitant amount of plant material is required to obtain a good amount of essential oil and its constituents. This implies the risk of extinguishing the plant or species, as it occurred when paclitaxel (a chemotherapeutic agent) was extracted from the yew plant (*Taxus baccata*). Due to the difficulty in obtaining significant quantities of taxol, it was necessary to collect many barks of this plant species, which was used in an unsustainable way, and now it is at risk of extinction in the Pacific [3].

In recent years, the pharmaceutical and chemical industry has recognized biotransformation as an important alternative, where biological catalysts facilitate or even make possible the production of complex by-products, such as terpenoids. Biotransformers make the reaction more specific and eliminate the need for purification that is required in chemical extraction methods. In addition, the use of microbial cells, for example, filamentous fungi, as biotransforming agents is easier and cheaper than using purified enzymes [4].

Thus, biotransformation is considered an economical and ecologically viable technology. Some studies have shown that the biotransformation of bioactive substances generates more biologically active products with reduced toxicity, such as cyclic monoterpenes with antimicrobial potential. After biotransformation, the bioproducts have low molecular weight and more potent antimicrobial activity. Monoterpenes with antioxidant, anti-inflammatory, and antimicrobial activity are valuable raw materials for the pharmaceutical industry. However, large-scale production of these compounds is very costly [5]. Currently, biotechnology has

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been working with microbiology to overcome this problem. Different types of recombinant microorganism strains can be obtained using biotechnological methods to produce different types of monoterpenes with biological properties of interest to the pharmaceutical, cosmetic, and food industries.

Terpenes form a class of more than 20000 structurally and functionally different metabolites. The production of these different terpenoid metabolites occurs through the activity of prenyltransferases, which convert the substrates isopentenyl diphosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP) into the allylic prenyldiphosphate whereby through the catalytic action of specific terpene synthases, the terpene skeleton is formed and, finally, secondary enzymatic modifications establish the functional properties of the 42 different terpenes (Figure 1). Amongst them, the main terpenes are monoterpenes with 10 carbon atoms, sesquiterpenes with 15 carbon atoms, hemiterpenes with 5 carbon atoms, diterpenes with 20 carbon atoms, and triterpenes with 30 carbon atoms [6].

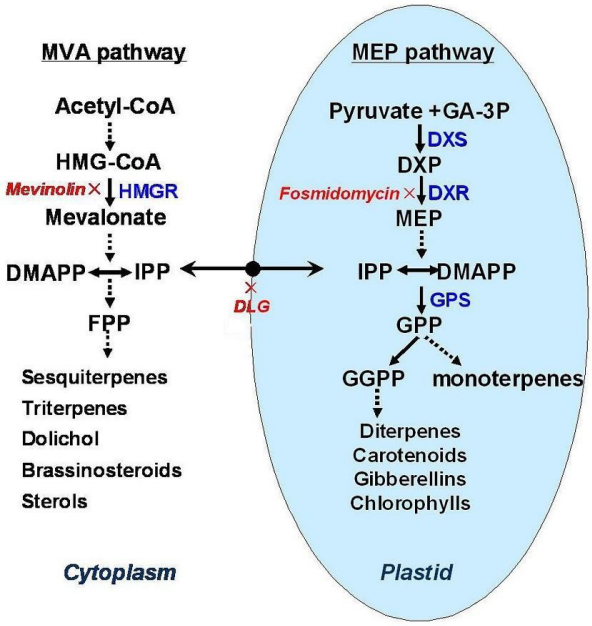


**Figure 1.** The mevalonate (MVA) and methylerythritol phosphate (MEP) pathways in the biosynthesis of terpenoid [7].

Monoterpenes have two isoprenoid units and 10 carbon atoms. They are aromatic and odorous molecules and make up the majority of 90% of essential oils. Monoterpenes are divided into three main subgroups: linear monoterpenes (myrcene, linalool, and neral), monocyclic monoterpenes (p-cinene, menthol, and carveol), and bicyclic monoterpenes: ((-)-myrtenol, α-pinene and borneol). Within these subgroups, monoterpenes can also be divided according to their functional group into alcohols, hydrocarbons, aldehydes, ketones, ethers, and esters [8].

Monoterpenoids are generally extracted from plant species, and the isolation of these compounds is difficult and expensive due to their purity and the fact that they are obtained in low quantities. Furthermore, the supply of plant materials can become limited due to seasonal variations and diseases. Another way of obtaining monoterpenes of economic and pharmaceutical interest is through the oxidative transformation of monoterpenes that are more abundant and cheaper, such as α-pinene [9]. A study by Schewe Holtmann and Schrader showed promising results in obtaining satisfactory quantities of (-)-myrtenol through the oxidation of α-pinene using bacterial biocatalysts, recombinant *Escherichia coli* [10]. These results are extremely important since (-)-myrtenol is a monoterpene widely used in the cosmetics industry and has shown promising results in pharmacological research. In addition, the bicyclic monoterpene, α-pinene, present in the essential oil of plants of the genus *Hyptis*, showed a gastroprotective effect in protocols of ulcer induced by ethanol and indomethacin by increasing mucus content and reducing gastric H+ secretion [11].

Finally, knowledge of the pharmacological activity of terpenes or terpenoids becomes the starting point to inspire the development of new products by means of biotransformers that are more effective, specific, and have fewer adverse effects as well as greater pharmacological activity at the target studied. The microbiological transformation of organic compounds is already used for the industrial production of several compounds that enhance flavor and aroma, and it has become " an apple of the eye" of the pharmaceutical industry for the production of more biologically active terpenes and terpenoids [12].

## Disclosure statement

No potential conflict of interest was reported by the authors.

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https://doi.org/10.61577/jpri.2023.100001