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ORIGINAL ARTICLE

A Study on Biosynthesis and Synthetic Approaches to Terpenes

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ABSTRACT

Terpenes constitute one of the most diverse and functionally significant classes of natural products, exhibiting a wide range of structures and biological activities. Derived biosynthetically from isoprene units via the mevalonate (MVA) and methylerythritol phosphate (MEP) pathways, terpenes play crucial roles in plant defense, signaling, and pharmacology. This review explores the structural and functional diversity of terpenes, their biosynthetic precursors, enzymatic catalysts such as prenyltransferases and terpene synthases, and the genetic regulation underlying their biosynthesis. Emphasis is also placed on synthetic strategies-ranging from total synthesis and semi-synthesis to chemoenzymatic methods-used to create or modify terpenoid structures for therapeutic, agricultural, and industrial applications. A comparative analysis of biosynthetic and synthetic approaches highlights the advantages and limitations of each method. Furthermore, the review discusses the growing importance of metabolic engineering and synthetic biology in enhancing terpene yields and diversifying structures. Applications in pharmaceuticals, agrochemicals, cosmetics, and biofuels are outlined, demonstrating the broad relevance of terpene research. The paper concludes with insights into future trends, including enzyme redesign and hybrid synthesis, aimed at unlocking the full potential of terpenes for sustainable and scalable use.

Keywords: *Terpenes, Biosynthesis, Total Synthesis, Mevalonate Pathway, Isoprenoid, Enzymatic Synthesis, Synthetic Biology*

INTRODUCTION

Terpenes are a large and diverse class of naturally occurring organic compounds derived from five-carbon isoprene units arranged in various structural patterns. Based on the number of these isoprene units, terpenes are broadly classified into monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), triterpenes (C_{30}) and tetraterpenes (C_{40}). Each class displays a vast range of structural variations, including linear, monocyclic, bicyclic, and polycyclic frameworks, and contributes to an exceptional diversity of biological functions. Terpenes are often further modified to produce terpenoids, which include functional groups such as alcohols, ketones, or aldehydes, enhancing their reactivity and biological activity.

The historical significance of terpenes can be traced back to ancient civilizations, where plant-derived resins, essential oils, and aromatic compounds were used in traditional medicine, incense, and perfumery. Scientific interest in terpenes began in the 19th century with early isolation and structural elucidation of compounds like camphor, menthol, and limonene. As organic chemistry advanced, terpenes became central to natural product research, stimulating progress in isolation techniques, structural determination, and synthetic methodologies. Today, terpenes are recognized not only as plant secondary metabolites but also as bioactive agents with pharmacological potential.

Terpenes hold considerable value in natural products chemistry, where their complex and chiral structures provide rich templates for the development of drugs, agrochemicals, and flavoring agents. In the pharmaceutical industry, terpenes like artemisinin, taxol, and thapsigargin have revolutionized treatment strategies for diseases such as malaria and cancer. In the flavor and fragrance sectors, terpenes such as linalool, limonene, and geraniol are key components of essential oils used in perfumery and food flavoring. Their versatility, abundance in nature, and biological relevance have made them prime targets for both biosynthetic and synthetic investigation.

The present review aims to provide a comprehensive overview of the biosynthetic and synthetic approaches to terpene production. It discusses the enzymatic pathways and genetic regulation underlying terpene biosynthesis, as well as recent advances in synthetic chemistry, including total synthesis, semi-synthesis, and chemoenzymatic strategies. Additionally, the review compares biosynthetic and synthetic methods, highlights current industrial and pharmaceutical applications, and outlines future directions for terpene research in sustainable production and therapeutic development.

Breitmaier (2006) provided a comprehensive foundational text on terpenes, outlining their classification, occurrence, and roles in nature as flavors, fragrances, pharmaceutically active compounds, and pheromones. The work emphasized the structural diversity of terpenes and their biosynthetic origin from isoprene units, establishing a chemical basis for further synthetic and biotechnological exploration. Bruckner and Blechert (2007) reviewed major advances in the total synthesis of terpenoids, highlighting strategies to construct complex polycyclic structures with high stereoselectivity. They emphasized the role of retrosynthetic planning and the development of new reactions to efficiently build terpenoid skeletons, which are often challenging due to multiple chiral centers and ring systems. Withers and Keasling (2007) explored the microbial biosynthesis of isoprenoid small molecules, discussing engineering techniques to enhance production in Escherichia coli and Saccharomyces cerevisiae. Their analysis provided insights into gene cloning, promoter optimization, and pathway balancing to improve yields of target terpenoids through metabolic engineering. Anthony et al. (2009) further developed this idea by optimizing the mevalonate pathway in E. coli for increased isoprenoid production. They demonstrated how modular pathway engineering and precise control of gene expression could significantly enhance the flux toward isoprenoid biosynthesis, paving the way for microbial factories producing valuable terpene compounds. Kirby and Keasling (2009) elaborated on the broader context of isoprenoid biosynthesis, focusing on plant-based pathways and their reconstitution in microbial hosts. They analyzed the potential of synthetic biology in rewiring metabolic networks, thus facilitating the heterologous production of diverse plant-derived terpenoids in microbial systems. Brückner and Reissig (2009) provided synthetic chemists with updated methodologies and strategic guidelines for terpene construction. Their work stressed the utility of cascade reactions, cyclizations, and the mimicry of biosynthetic transformations to achieve complex scaffolds with fewer synthetic steps. Vickers et al. (2009) examined the physiological role of isoprene in plants and presented experimental evidence showing that isoprene synthesis in transgenic tobacco conferred protection against oxidative stress. This study highlighted not only the ecological importance of terpenes but also their potential in developing stress-resilient crops through genetic engineering. Ajikumar et al. (2010) presented a landmark study in microbial engineering for terpenoid drug production. They engineered a Saccharomyces cerevisiae strain for high-yield production of taxadiene, a precursor to the anticancer drug paclitaxel. Their work combined pathway optimization, gene stacking, and host strain refinement to achieve unprecedented productivity. Daviet and Schalk (2010) provided a focused discussion on the engineering of terpenoid biosynthetic pathways in plants, particularly for essential oil production. They emphasized the manipulation of terpene synthases and the benefits of metabolic engineering in enhancing oil yield and composition, with applications in flavor, fragrance, and pharmaceutical industries. Peralta-Yahya et al. (2012) advanced the field by demonstrating microbial engineering strategies for producing advanced biofuels derived from terpenes. They underscored the compatibility of terpenoids with existing fuel infrastructure and outlined how synthetic biology tools could be used to redirect carbon flux toward fuel-like molecules. Hamberger and Bak (2013) explored the role of cytochrome P450 monooxygenases in terpene diversification. They presented P450s as evolutionary drivers that expand chemical diversity in plant secondary metabolism. Their discussion focused on how these enzymes perform site-specific oxidation of terpene scaffolds and are valuable targets for metabolic engineering. Zerbe and Bohlmann (2015) reviewed plant diterpene synthases and highlighted their modular domain architecture and catalytic flexibility. They proposed that these enzymes could be harnessed for combinatorial biosynthesis, enabling the generation of novel diterpene scaffolds with potential applications in pharmaceuticals and bioengineering.

STRUCTURAL AND BIOLOGICAL DIVERSITY OF TERPENES

OVERVIEW OF STRUCTURAL TYPES:

Terpenes exhibit a remarkable variety of structures, reflecting their biosynthetic origin from isoprene units (C_5H_8). Based on the number of these isoprene units, terpenes are broadly categorized as:

a. **Hemiterpenes (C_5)**: Consist of a single isoprene unit. Rare and usually volatile (e.g., isoprene itself).
b. **Monoterpenes (C_{10})**: Formed from two isoprene units. They can be acyclic (e.g., geraniol), monocyclic (e.g., limonene), or bicyclic (e.g., pinene).
c. **Sesquiterpenes (C_{15})**: Made from three isoprene units. Examples include farnesene and humulene.
d. **Diterpenes (C_{20})**: Composed of four isoprene units. Important examples include phytol and gibberellins.
e. **Sesterterpenes (C_{25})**: Less common, made of five isoprene units.
f. **Triterpenes (C_{30})**: Built from six isoprene units; include squalene and lanosterol.
g. **Tetraterpenes (C_{40})**: Formed from eight isoprene units. Carotenoids like β-carotene belong to this class.
h. **Polyterpenes**: Composed of many isoprene units (e.g., natural rubber).

This classification underscores the enormous structural flexibility of terpenes, ranging from simple linear chains to complex polycyclic architectures.

Table 1: Classification of Terpenes

Terpene Type	Carbon Atoms	Examples
Hemiterpenes	C5	Isoprene
Monoterpenes	C10	Geraniol, Limonene, Pinene
Sesquiterpenes	C15	Farnesene, Humulene
Diterpenes	C20	Phytol, Gibberellins
Sesterterpenes	C25	Rare
Triterpenes	C30	Squalene, Lanosterol
Tetraterpenes	C40	β-Carotene
Polyterpenes	C5$\times n$	Natural Rubber

FUNCTIONAL GROUPS AND STEREOCHEMISTRY:

Terpenes incorporate a diverse range of functional groups that define their chemical reactivity and biological interactions. Common functionalities include:

a. Alcohols (e.g., linalool)
b. Aldehydes (e.g., citral)
c. Ketones (e.g., menthone)
d. Carboxylic acids (e.g., abietic acid)
e. (v)Epoxides, ethers, and lactones

Stereochemistry plays a vital role in the activity of terpenes. Many terpene synthases produce chiral centers and cyclic structures with precise stereochemical configurations. For example, (+)-limonene and (−)-limonene have the same molecular formula but distinct odors due to differences in stereochemistry.

BIOLOGICAL ROLES IN PLANTS, MICROBES, AND ANIMALS:

In Plants:

a. Act as phytoalexins (antimicrobial defense compounds)
b. Serve as attractants for pollinators (e.g., floral scent terpenes)
c. Mediate plant-plant communication under herbivore attack
d. Contribute to resin production for wound sealing

In Microorganisms:

a. Terpenoids in fungi and bacteria often function as toxins, antibiotics, or signaling molecules.
b. Example: geosmin in actinomycetes gives soil its earthy smell.

In Animals:

a. Some insects synthesize terpenes for chemical defense or pheromonal communication.
b. Vertebrates, including humans, use terpenoids in hormone synthesis (e.g., cholesterol-derived steroids).

PHARMACOLOGICAL ACTIVITIES:

Terpenes are pharmacologically diverse and form the basis of several clinically important drugs. Major activities include:

a. Anti-cancer:
- *Taxol (paclitaxel)* – a diterpene used for breast and ovarian cancer.
- *Artemisinin* – a sesquiterpene lactone effective against malaria.

b. Anti-inflammatory: *β-Caryophyllene* – binds to CB2 receptors and exhibits potent anti-inflammatory effects.
c. Antimicrobial: Monoterpenes like *thymol* and *carvacrol* disrupt bacterial cell membranes.
d. Antioxidant: Carotenoids such as *lycopene* and *β-carotene* neutralize free radicals.
e. Neuroprotective and Psychotropic: *Linalool* and *myrcene* influence GABAergic pathways and have sedative effects.
f. Analgesic and Anti-anxiety: *Limonene* and *pinene* contribute to anxiolytic and mood-enhancing properties in aromatherapy.

These biological and pharmacological roles underscore the versatility of terpenes as both primary and secondary metabolites with immense therapeutic potential.

BIOSYNTHESIS OF TERPENES

The biosynthesis of all terpenes begins with two key five-carbon building blocks: isopentenyl pyrophosphate (IPP) and its isomer dimethylallyl pyrophosphate (DMAPP). These molecules, derived from the condensation of acetyl-CoA or glyceraldehyde-3-phosphate and pyruvate (depending on the pathway), serve as the fundamental units for assembling more complex terpenoid structures. IPP and DMAPP undergo sequential condensations catalyzed by prenyltransferases to form geranyl pyrophosphate (GPP, C_{10}), farnesyl pyrophosphate (FPP, C_{15}), and geranylgeranyl pyrophosphate (GGPP, C_{20}), which are precursors to monoterpenes, sesquiterpenes, and diterpenes, respectively. The interconversion of IPP and DMAPP, catalyzed by IPP isomerase, maintains the essential balance required for diverse terpene biosynthesis.

Two distinct metabolic routes exist for the production of IPP and DMAPP in living organisms: the Mevalonate (MVA) pathway and the Methylerythritol phosphate (MEP) pathway, also known as the non-mevalonate pathway. The MVA pathway is primarily found in eukaryotes, archaebacteria, and in the cytosol of higher plants. It begins with the condensation of three molecules of acetyl-CoA to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), which is subsequently reduced by HMG-CoA reductase (a key regulatory enzyme) to yield mevalonic acid. Through a series of phosphorylation and decarboxylation steps, mevalonate is then converted into IPP. The MVA pathway is highly regulated and is a crucial control point for the production of sterols and other essential isoprenoids in animals and fungi.

In contrast, the MEP pathway operates in most bacteria, algae, and the plastids of higher plants. This pathway utilizes pyruvate and glyceraldehyde-3-phosphate (G3P) as starting materials. The first committed step involves the condensation of these two substrates to form 1-deoxy-D-xylulose-5-phosphate (DXP), which is then rearranged and reduced to form 2-C-methyl-D-erythritol-4-phosphate (MEP). Subsequent reactions involving phosphorylation, cyclization, and reduction lead to the formation of IPP and DMAPP. Unlike the MVA pathway, the MEP pathway is not inhibited by statins and has become a target for the development of novel antibiotics and herbicides due to its absence in humans.

Both pathways operate independently but may coexist in the same organism (notably in plants), where they compartmentalize terpene biosynthesis for different functional needs. For example, monoterpenes and diterpenes are often derived from the MEP pathway in plastids, whereas sesquiterpenes and sterols are produced via the MVA pathway in the cytosol. This metabolic diversity and spatial separation allow for the intricate regulation of terpene biosynthesis in multicellular organisms.

ENZYMES INVOLVED:

A fundamental class of enzymes responsible for initiating terpene biosynthesis is the prenyltransferases. These enzymes catalyze the sequential condensation of the five-carbon precursors isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) to form linear isoprenoid intermediates such as geranyl pyrophosphate (GPP, C_{10}), farnesyl pyrophosphate (FPP, C_{15}), and geranylgeranyl pyrophosphate (GGPP, C_{20}). These intermediates serve as direct precursors to monoterpenes, sesquiterpenes, and diterpenes, respectively. Prenyltransferases exhibit remarkable substrate specificity and chain-length determination, which are critical for the structural diversity of terpenes. For instance, geranyltransferase catalyzes the formation of GPP, while farnesyltransferase leads to FPP synthesis. These reactions set the stage for downstream cyclization and rearrangement processes.

The next pivotal group of enzymes in terpene biosynthesis are the terpene synthases (TPSs), also known as terpene cyclases. These enzymes are responsible for converting linear prenyl diphosphates into a vast array of complex hydrocarbon skeletons through ionization, cyclization, hydride shifts, and rearrangements. Terpene synthases are categorized based on the substrate (e.g., GPP, FPP, GGPP) and the type of reaction they catalyze. For example, limonene synthase catalyzes the cyclization of GPP to form the monocyclic monoterpene limonene, while taxadiene synthase converts GGPP into taxadiene, a key intermediate in the biosynthesis of Taxol. These enzymes are highly promiscuous, capable of generating multiple products from a single substrate, contributing significantly to terpene chemical diversity.

Following the core cyclization events, many terpenes undergo further modifications catalyzed by tailoring or modifying enzymes, which add functional groups to the hydrocarbon skeleton, enhancing biological activity and solubility. Among these, the cytochrome P450 monooxygenases (P450s) are especially important. They introduce hydroxyl, epoxy, or other oxygen-containing groups via regio- and stereoselective oxidation reactions. For example, the hydroxylation of taxadiene by P450 enzymes is a critical step in the biosynthesis of Taxol. In addition, glycosyltransferases catalyze the attachment of sugar moieties to hydroxylated terpenes, increasing their stability, water solubility, and in some cases, altering their bioactivity or cellular transport properties. These modifying enzymes work in tandem to fine-tune terpene structures, thereby diversifying their functional roles in ecological interactions and therapeutic applications.

GENETIC AND METABOLIC REGULATION:

The biosynthesis of terpenes in natural systems is tightly regulated at the genetic level, often through the coordinated expression of biosynthetic gene clusters (BGCs). These clusters typically encode all the enzymes required for the sequential conversion of primary metabolites (like IPP and DMAPP) into complex terpenoids, including prenyltransferases, terpene synthases, and modifying enzymes such as cytochrome P450s and glycosyltransferases. The organization of genes into operons or tightly linked clusters allows for co-regulation, which ensures synchronized production in response to environmental stimuli or developmental cues. In microbes like Streptomyces and Aspergillus species, the transcription of terpene BGCs is often regulated by pathway-specific activator proteins or global regulators sensitive to nutrient levels or stress signals. In plants, although genes are less frequently clustered, transcriptional regulation is achieved through transcription factors, epigenetic modifications, and hormone signaling pathways. Recent advances in transcriptomics and CRISPR-based gene activation or suppression tools have enhanced our understanding of how these gene clusters are regulated, allowing for better control over terpene production.

In parallel, major strides in synthetic biology and metabolic engineering have revolutionized terpene biosynthesis by enabling the reconstruction of entire biosynthetic pathways in heterologous hosts such as Escherichia coli, Saccharomyces cerevisiae, and Yarrowia lipolytica. By inserting optimized BGCs into microbial or plant chassis, researchers can now produce high-value terpenes in a sustainable and scalable manner. Metabolic engineering strategies such as pathway refactoring, codon optimization, promoter tuning, and dynamic regulation have significantly improved precursor flux toward terpene synthesis. Additionally, the use of synthetic regulatory circuits, modular cloning systems, and genome-scale metabolic models has enabled the fine-tuning of gene expression and pathway balancing. Integration of computational tools and machine learning has further accelerated strain development by predicting enzyme kinetics, pathway bottlenecks, and optimal chassis-host combinations. These approaches not only enhance yield but also allow for the generation of novel terpenoid analogs by combinatorial biosynthesis, expanding the scope of terpenes for pharmaceutical, agricultural, and industrial applications.

SYNTHETIC APPROACHES TO TERPENES

TOTAL SYNTHESIS:

Total synthesis refers to the complete chemical construction of complex natural products like terpenes from simple, commercially available starting materials. A fundamental tool in total synthesis is retrosynthetic analysis, which involves working backward from the target molecule to identify simpler precursor structures and viable disconnection strategies. For terpenes, retrosynthetic planning is especially challenging due to their densely packed carbon frameworks, multiple chiral centers, and polycyclic skeletons. Chemists often identify key bonds to break-usually C–C or C–O bonds-based on known reactivity patterns or biomimetic logic. For example, the retrosynthesis of complex diterpenes or triterpenes may involve strategic ring-opening steps and recognition of biosynthetically relevant intermediates like epoxides or allylic alcohols. This analytical process is essential for designing an efficient forward synthesis that minimizes steps, maximizes yield, and ensures stereochemical fidelity.

Over the past few decades, synthetic chemists have developed key synthetic routes to access major terpene molecules with significant therapeutic importance. One of the most notable examples is the total synthesis of Taxol (paclitaxel), a complex diterpenoid used in cancer therapy. Taxol's synthesis involves over 20 steps, including crucial stereoselective oxidations, cyclizations, and side-chain installations. Pioneering work by Nicolaou and Holton showcased the feasibility of constructing such a molecule entirely from scratch. Another prominent example is artemisinin, a sesquiterpene lactone effective against malaria. While the natural extraction of artemisinin from Artemisia annua is low-yielding, synthetic efforts-both total and semi-synthetic-have led to scalable production pathways. The semi-synthetic route developed by Keasling's group, involving engineered yeast and chemical derivatization, represents a breakthrough in combining biology with chemical synthesis for commercial drug production.

Despite these successes, total synthesis of terpenes faces several challenges, particularly related to stereocontrol and scalability. Many terpenes contain multiple contiguous stereocenters and polycyclic frameworks, which require highly selective reactions to ensure the correct three-dimensional arrangement of atoms. Achieving this level of control often necessitates chiral catalysts, protecting group strategies, and sophisticated reaction sequences, which increase complexity and cost. Moreover, the overall yield across multistep syntheses tends to be low, making industrial-scale production economically unviable for many terpene drugs. Environmental concerns related to reagent use, purification steps, and waste generation also hinder the practical application of classical total synthesis routes. As a result, many modern strategies focus on hybrid approaches-such as chemoenzymatic synthesis or semi-synthesis from biosynthetic intermediates-to balance precision and sustainability.

SEMI-SYNTHESIS:

Semi-synthesis serves as a powerful and practical strategy in terpene chemistry, especially when total synthesis is too complex or cost-prohibitive. This approach involves using naturally derived

terpene skeletons-often extracted from plants, microbes, or marine organisms-as starting materials. These naturally occurring compounds already possess the core structural framework, including the desired ring systems and stereochemistry, which significantly reduces synthetic complexity. By building upon these bioavailable templates, chemists can perform targeted transformations to yield pharmacologically active derivatives with improved bioavailability, potency, or stability. A well-known example includes the modification of the plant-derived compound 10-deacetylbaccatin III, a precursor to the anticancer drug Taxol, where a synthetic side chain is appended to produce the final active compound.

One of the main advantages of semi-synthesis lies in the ability to introduce specific chemical modifications to the terpene backbone, enabling structure-activity relationship (SAR) studies and the optimization of therapeutic profiles. Among the most common modifications are oxidation reactions, which install hydroxyl, ketone, or epoxide functionalities that often enhance solubility or receptor binding. For instance, hydroxylation of triterpenes can improve anti-inflammatory or antiviral properties. Glycosylation is another critical transformation in semi-synthesis, wherein sugar moieties are enzymatically or chemically attached to hydroxyl groups on the terpene core. This not only improves water solubility and pharmacokinetics but also affects bio-distribution and cellular uptake. Additionally, modifications such as acylation, halogenation, and hydrogenation are frequently used to tailor the chemical properties and biological activities of terpenoid drugs.

Semi-synthesis thus represents a versatile bridge between nature and laboratory synthesis. By leveraging the inherent complexity and stereochemistry of natural terpenes, researchers can generate libraries of analogs with enhanced pharmacological potential while minimizing synthetic effort and environmental impact. This strategy is particularly valuable in the pharmaceutical industry, where access to rare or complex terpene derivatives in sufficient quantities is crucial for drug development.

CHEMOENZYMATIC SYNTHESIS:

Chemoenzymatic synthesis combines the precision of enzymatic catalysis with the flexibility of organic synthesis, offering a highly selective and environmentally friendly approach to modifying terpene structures. This strategy involves the use of isolated enzymes or whole-cell biocatalysts to perform specific chemical transformations on terpene substrates, often under mild conditions and with high regio- and stereoselectivity. Enzymes such as cytochrome P450 monooxygenases, glycosyltransferases, and oxidoreductases are frequently employed for hydroxylation, epoxidation, and glycosylation of terpene scaffolds. Alternatively, whole-cell systems like engineered strains of E. coli, S. cerevisiae, or Yarrowia lipolytica can be used to express terpene biosynthetic enzymes in vivo, providing a self-contained environment for multiple enzymatic steps. These systems are particularly advantageous for large-scale applications, as they reduce the need for costly enzyme purification and can recycle cofactors like NADPH internally.

A significant advantage of chemoenzymatic synthesis lies in its ability to carry out site-specific modifications that are challenging to achieve using traditional chemical methods. Enzymes can recognize subtle differences in molecular geometry and electronic environment, enabling them to target a particular position on a complex terpene skeleton with exquisite precision. For example, selective hydroxylation of inert C–H bonds on a triterpene can be achieved by engineered P450 enzymes without affecting other functional groups. This level of specificity allows for the production of rare or otherwise inaccessible analogs that exhibit unique biological activities. Additionally, glycosyltransferases can selectively attach sugar moieties to certain hydroxyl groups, modulating solubility, stability, and pharmacodynamics. By controlling the enzyme-substrate pairing, chemists can fine-tune reaction outcomes to generate desired products with minimal by-products and waste.

Chemoenzymatic synthesis is rapidly emerging as a powerful tool in terpene derivatization, especially with recent advances in protein engineering and synthetic biology. The development of tailor-made enzymes with expanded substrate scopes and enhanced catalytic efficiency continues to broaden the range of accessible terpene derivatives. As the demand for sustainable and selective chemical processes grows, chemoenzymatic methods are likely to play an increasingly important role in the industrial production and diversification of valuable terpenoid compounds.

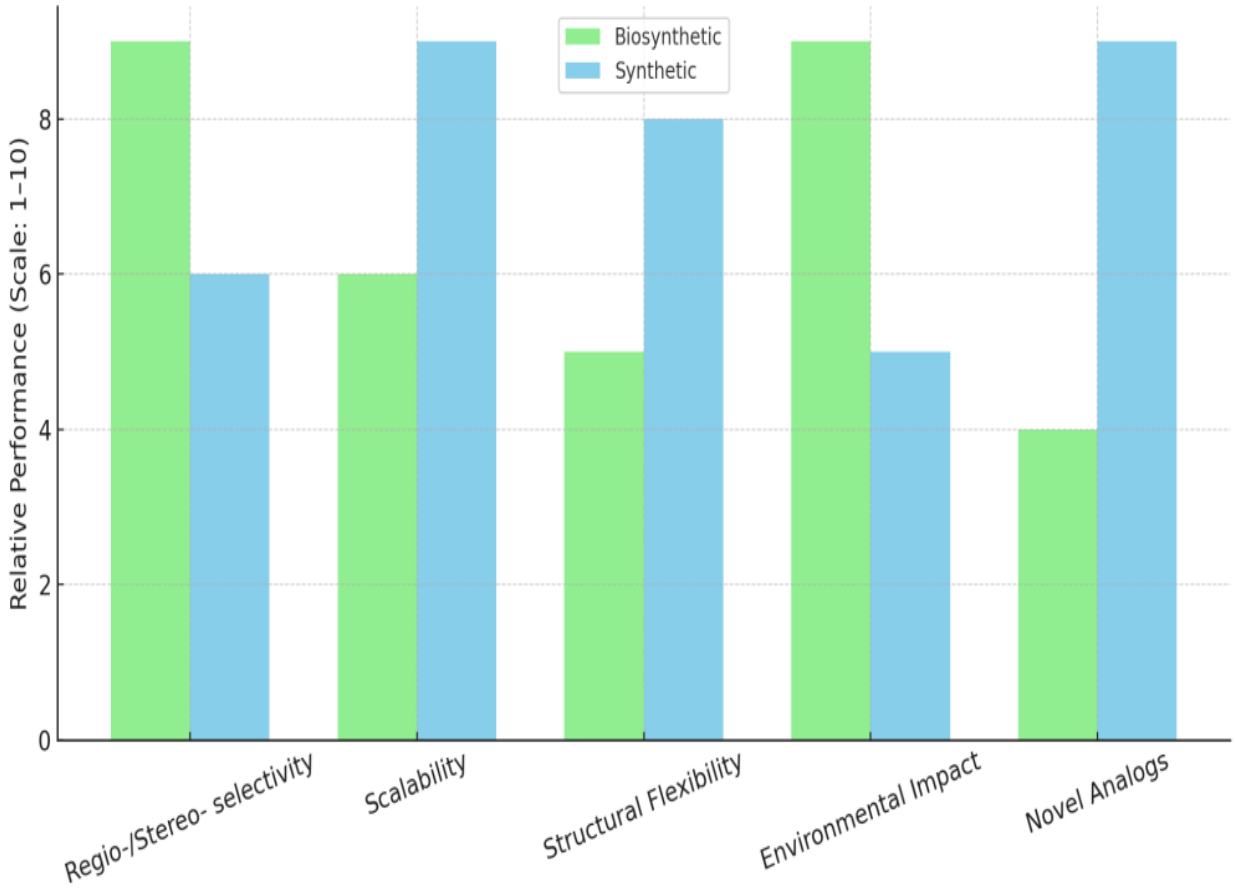
COMPARISON OF BIOSYNTHETIC VS SYNTHETIC APPROACHES

The production of terpenes can be achieved through both biosynthetic (natural or engineered biological systems) and synthetic (chemical laboratory synthesis) routes, each offering distinct advantages and limitations. Biosynthetic approaches rely on natural pathways such as the mevalonate (MVA) or methylerythritol phosphate (MEP) pathways within living organisms to generate terpenes from primary metabolites. These methods are often praised for their high regio- and stereoselectivity, environmental friendliness, and ability to produce complex molecules with minimal chemical waste. Advances in metabolic engineering and synthetic biology have further enhanced the potential of microbial factories such as E. coli, Saccharomyces cerevisiae, and plant-based systems to produce rare or high-value terpenes. However, biosynthetic production is sometimes limited by low yields, long fermentation times, and complex regulation of gene expression and metabolic flux.

In contrast, chemical synthetic approaches, including total synthesis and semi-synthesis, offer greater control over reaction conditions, scalability, and functional group transformations. They allow for the design of entirely new terpene analogs not found in nature, thus expanding the chemical diversity available for pharmaceutical and industrial applications. Moreover, chemical synthesis can be performed independently of biological systems, which eliminates the need for gene cloning, enzyme expression, or fermentation infrastructure. Nonetheless, these methods often suffer from low overall yield due to lengthy multistep processes, high cost of reagents, and difficulties in controlling stereochemistry-particularly for highly complex and chiral terpenes.

Ultimately, both approaches are complementary rather than competing. Biosynthesis offers precision and sustainability, especially for complex scaffolds, while synthetic chemistry offers versatility and modularity. Hybrid strategies such as chemoenzymatic synthesis or semi-synthesis-which combine the selectivity of enzymes with the flexibility of synthetic chemistry-represent a promising middle ground, enabling more efficient and tailored production of terpene-based compounds.

Fig. 1: Comparison of Biosyntheticvs Synthetic Approaches



APPLICATIONS OF TERPENES

Terpenes hold immense value across multiple sectors owing to their structural diversity and wide range of bioactivities. One of the most important areas of application is in the pharmaceutical industry, where terpenes and their derivatives serve as potent therapeutic agents. Notable examples include artemisinin, a sesquiterpene lactone with powerful antimalarial activity, and paclitaxel (Taxol), a diterpene widely used in cancer chemotherapy for breast and ovarian cancers. Other terpenes such as camphor, menthol, and linalool are used in over-the-counter formulations for their analgesic, anti-inflammatory, and antimicrobial effects. Their ability to interact with various biological targets, including enzymes, ion channels, and receptors, makes them valuable leads for drug discovery and development.

In the field of agriculture, terpenes play crucial roles as agrochemicals, particularly as natural pesticides, herbicides, and insect repellents. For instance, monoterpenes such as limonene, carvone, and citral exhibit strong insecticidal and antifungal activities, providing an eco-friendly alternative to synthetic agrochemicals. Terpenoids also function as allelopathic agents, suppressing the growth of competing plant species and pathogens in the rhizosphere. Moreover, engineered production of terpenes in transgenic plants is being explored to enhance pest resistance and reduce reliance on chemical treatments.

The food and cosmetic industries have long capitalized on the aromatic and flavoring properties of terpenes. Compounds like vanillin, menthol, pinene, and myrcene are used to enhance the scent and taste of a wide range of products-from beverages and baked goods to perfumes and personal care items. In cosmetics, terpenes serve not only as fragrances but also as bioactive ingredients due to their antioxidant and skin-soothing properties. Their natural origin makes them attractive to consumers seeking clean-label, plant-derived products.

In addition to these uses, terpenes are increasingly recognized for their role in industrial applications, particularly in the development of biofuels and green chemicals. Large, energy-dense terpenes like farnesene, limonene, and pinene are being investigated as renewable hydrocarbon fuels and lubricants, offering a sustainable alternative to petroleum-based compounds. Through microbial fermentation and chemical conversion, these terpenes can be transformed into jet fuel, diesel, and other industrial solvents. Their high energy content, low toxicity, and biodegradability further enhance their suitability as next-generation industrial bioresources.

CONCLUSION

The study of terpenes continues to be a vibrant and multidisciplinary field, bridging natural product chemistry, biotechnology, and synthetic organic chemistry. This review has highlighted the remarkable structural and functional diversity of terpenes, driven by nature's use of simple five-carbon precursors-IPP and DMAPP-through the mevalonate (MVA) and methylerythritol phosphate (MEP) pathways. The role of key enzymes such as prenyltransferases, terpene synthases, and modifying enzymes further underscores the complexity and elegance of terpene biosynthesis. On the other hand, chemical approaches such as total synthesis, semi-synthesis, and chemoenzymatic synthesis have enabled the creation and diversification of terpene-based compounds beyond natural limits, often improving bioactivity and pharmacokinetics.

The integration of biosynthetic and synthetic strategies offers immense potential for advancing terpene research and applications. While biosynthesis provides high specificity, environmental sustainability, and access to structurally complex scaffolds, chemical synthesis enables the fine-tuning of functional groups and the development of novel analogs. Recent advances in synthetic biology, metabolic engineering, and enzyme redesign are blurring the boundaries between the two fields, allowing for hybrid approaches where engineered microbial hosts produce complex terpenoids, which are then selectively modified through chemical or enzymatic transformations.

Looking ahead, the future of terpene research lies in addressing key challenges such as improving yields, reducing costs, and expanding structural diversity. The development of robust biocatalysts, high-throughput screening platforms, and computational modeling will be instrumental in optimizing terpene biosynthetic pathways. Moreover, the increasing demand for sustainable alternatives to petrochemical-derived products positions terpenes as valuable candidates for green pharmaceuticals, biodegradable materials, and biofuels. Interdisciplinary collaboration between

chemists, biologists, and engineers will be crucial in unlocking the full potential of terpenes and translating laboratory innovations into real-world applications.

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