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Terpenoids from Medicinal Plants: Pharmacological Activities and Therapeutic Applications

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Abstract

Terpenoids represent the largest and most structurally diverse class of natural products, derived from five-carbon isoprene units. These compounds, produced through the cytosolic mevalonate (MVA) and plastidic methylerythritol phosphate (MEP) pathways, display a broad spectrum of biological activities, including anticancer, anti-inflammatory, and antimicrobial effects. This review offers a thorough exploration of the molecular mechanisms of action, biosynthetic origins, and challenges faced in the clinical translation of this class of secondary metabolites. Key mechanistic insights include the induction of intrinsic and extrinsic apoptosis, cell cycle arrest at the G1/S and G2/M phases, inhibition of NF-κB signaling, and disruption of microbial membranes. Despite their considerable therapeutic potential, the clinical translation of terpenoids is often hindered by issues such as poor aqueous solubility, low bioavailability, and insufficient pharmacokinetic data. This report assesses the differences in activities across terpenoid classes, discusses current limitations in study designs, and examines the toxicological and pharmacokinetic profiles of prominent lead compounds.

Keywords: Terpenoids, Medicinal plants, Biosynthetic pathways, Anticancer, Anti-inflammatory

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Introduction

Terpenoids, also referred to as isoprenoids, constitute a major class of secondary metabolites, with more than 80,000 structures identified to date. These compounds are found across all life kingdoms, with medicinal plants exhibiting a particularly high abundance and diversity. Structurally, terpenoids are composed of isoprene (C_5H_8) units; however, they undergo extensive enzymatic modifications, such as cyclization, oxidation, and rearrangement, which contribute to their vast functional diversity [1-3]. Historically, medicinal plants have been the primary source of terpenoids used in the healthcare industry. In recent decades, rigorous scientific investigations have validated numerous traditional applications and identified terpenoids as essential scaffolds for contemporary drug development. For instance, the diterpene paclitaxel remains a cornerstone in chemotherapy, whereas the sesquiterpene lactone artemisinin is the gold standard for malaria treatment [2, 4, 5]. This report aims to synthesize current knowledge on these molecules, emphasizing their mechanisms of action and the practicalities of their therapeutic applications.

Classification and Biosynthetic Origins

MVA and MEP Biosynthetic Pathways

The structural diversity of terpenoids arises from two distinct biosynthetic pathways that produce the universal C5 precursors isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) [4, 6].

The mevalonate (MVA) pathway, primarily located in the cytosol, uses acetyl-CoA as its initial substrate and serves as the main source of isopentenyl pyrophosphate (IPP)/dimethylallyl pyrophosphate (DMAPP) for synthesizing sesquiterpenes (C15) and triterpenes (C30) [2, 4].

The methylerythritol phosphate (MEP) pathway, located in the plastids, employs pyruvate and glyceraldehyde-3-phosphate to primarily supply precursors for hemiterpenes (C5), monoterpenes (C10), and diterpenes (C20) [1, 4].

Although these pathways were traditionally viewed as spatially and functionally distinct, recent biosynthetic research has uncovered significant crosstalk, allowing for the exchange of precursors between the cytosol and plastids, depending on the physiological state of the plant and the specific metabolite being synthesized [7, 8]. Understanding these origins is crucial for metabolic engineering and the sustainable production of these compounds.

Classification and Representative Chemical Examples

Terpenoids are classified according to the number of isoprene units they contain. The following table provides a structured overview.

Class	Isoprene Units	Carbon Count	Chemical Examples	Plant Source Example
Hemiterpenes	1	C5	Isoprene	Aromatic plants
Monoterpenes	2	C10	Menthol, Borneol, Linalool	Mentha, Cinnamomum
Sesquiterpenes	3	C15	Artemisinin, Curdione, α-Humulene	Artemisia annua, Curcuma
Diterpenes	4	C20	Paclitaxel, Andrographolide	Taxus, Andrographis paniculata
Sesterterpenes	5	C25	Astellatol, Ansellone A	Marine organisms, Fungi
Triterpenes	6	C30	Ginsenosides, Asiaticoside	Panax, Centella asiatica
Tetraterpenes	8	C40	β-Carotene, Lycopene	Daucus carota

Molecular Mechanisms of Action

Anticancer Mechanisms

Terpenoids exert anticancer effects through a multi-targeted approach that disrupts cancer cell survival and proliferation.

Intrinsic (Mitochondrial) Pathway: This pathway is initiated by internal cellular stress. Several terpenoids, such as myrotheciumone A, induce apoptosis by facilitating the release of cytochrome C from mitochondria into the cytosol, thereby activating the caspase cascade [2]. A-Humulene causes mitochondrial dysfunction and depletes intracellular glutathione, a crucial antioxidant, leading to oxidative stress-induced cell death [9].

Extrinsic (death receptor) pathway: This pathway involves the activation of surface receptors. Geraniol has been shown to modulate transcriptional regulation and activate caspases involved in the extrinsic pathway, thereby promoting apoptosis in various cancer cell lines [10].

Cell Cycle Arrest Terpenoids interfere with the cell cycle, preventing the uncontrolled division characteristic of cancer: G2/M phase arrest: Astellatol and α-ekasanthalic acid have been reported to induce arrest at the G2/M checkpoint, preventing cells from entering mitosis [2]. G1/S phase arrest: Monoterpenes, such as geraniol, often target the G1/S transition by modulating p53 and cyclin-dependent kinase (CDK) activities, thereby halting DNA replication [10, 11].

Anti-inflammatory Mechanisms

The anti-inflammatory effectiveness of terpenoids is largely determined by their ability to inhibit key signaling pathways.

NF-κB inhibition The NF-κB signaling pathway acts as a central regulator of immune responses. Terpenoids, such as borneol, linalool, and 86erpinene-4-ol, inhibit the phosphorylation and degradation of IκBα, thereby preventing the nuclear translocation of the NF-κB p65 subunit [12-14]. This mechanism effectively blocks the expression of various pro-inflammatory genes.

Cytokine Suppression By inhibiting NF-κB and related pathways, such as PI3K/Akt/mTOR, terpenoids significantly reduce the production of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. For example, Viquol and Isoegomaketone have shown substantial inhibition of TNF-α and nitric oxide (NO) production in macrophage models [2].

Antimicrobial Mechanisms

Terpenoids act as chemical defenses for plants against pathogens, and these mechanisms can be harnessed for therapeutic use in humans. Membrane disruption The primary antimicrobial action of many monoterpenes and sesquiterpenes, such as 86erpinene-4-ol from tea tree oil, involves the physical disruption of microbial cell membranes [13, 15]. Owing to their lipophilic nature, these compounds integrate into the lipid bilayer, increasing membrane fluidity and permeability. This leads to the leakage of essential ions and metabolites, ultimately causing cell lysis. Enzyme

inhibition In addition to membrane disruption, terpenoids can target specific microbial enzymes. For instance, dysideavarone A inhibits PTP1B, an enzyme involved in various metabolic and signaling pathways [2]. Other terpenoids may interfere with cell wall synthesis or the production of virulence factors, as shown by the antiviral properties of 87erpinene-4-ol [13].

Comprehensive Summary of Terpenoid Pharmacology

The table below summarizes the pharmacological activities and botanical sources of the principal terpenoid compounds discussed in this review.

Compound Name	Plant Source	Primary Pharmacological Activity	References
Paclitaxel	*Taxus* species	Anticancer (Microtubule stabilizer)	[1, 4]
Artemisinin	*Artemisia annua*	Antimalarial, Anticancer (Alkylation)	[4, 5]
Borneol	Various (e.g., *Dryobalanops aromatica*)	Anti-inflammatory, BBB penetration enhancer	[12, 14]
Terpinen-4-ol	*Melaleuca alternifolia*	Antimicrobial, Anti-inflammatory	[13, 15]
Curdione	*Curcuma* species	Anticancer, Anti-thrombotic, Anti-inflammatory	[16]
Andrographolide	*Andrographis paniculata*	Anti-inflammatory, Anticancer, Immunomodulatory	[17]
Geraniol	*Cymbopogon* species (Lemongrass)	Anticancer (Apoptosis, Cell cycle arrest)	[10]
Thapsigargin	*Thapsia garganica*	Anticancer (SERCA pump antagonist)	[2, 4]
Asiaticoside	*Centella asiatica*	Wound healing, Skin disease treatment	[2]
Ginsenosides	*Panax* species	Multi-target (Cardiometabolic, Anticancer)	[18]
Linalool	*Cinnamomum* species	Anti-inflammatory, Anticancer (Apoptosis)	[12]
Salvinorin A	*Salvia divinorum*	Psychoactive (κ-opioid receptor agonist)	[2]

Critical Evaluation and Comparative Discussion

Differences in Activities Among Classes

- The biological profile of a terpenoid is primarily determined by its molecular weight and functional groups. Monoterpenes (C10), which are often small and volatile, are notable for their ability to penetrate biological membranes, such as the blood–brain barrier. They typically exhibit rapid but short-lived anti-inflammatory and antimicrobial effects [14, 19]. Sesquiterpenes (C15), including compounds such as artemisinin and α-humulene, demonstrate potent cytotoxic activities and are more likely to target intracellular proteins and organelles because of their balanced lipophilicity [5, 9]. Diterpenes (C20) encompass highly complex molecules, such as paclitaxel and andrographolide, which often have very specific targets, such as tubulin, and exhibit high potency, although they may also present higher toxicity [1, 17]. Triterpenes (C30), frequently found as glycosides (saponins), are recognized for their multi-target and systemic effects, such as immunomodulation and cardiometabolic protection, although their large size can limit absorption [2, 18].

Limitations of Existing Studies

- Despite the extensive literature on terpenoids, numerous studies have methodological limitations.
- In Vitro Dominance: A significant portion of mechanistic insights is derived from cell culture models, which fail to replicate the complex physiological environment, metabolism, and bioavailability observed in vivo [11, 12].
- Lack of Standardization: Plant extracts often exhibit variable concentrations of active terpenoids, leading to inconsistent outcomes across different batches and studies [15].
- Inadequate clinical evidence: For many promising compounds, such as geraniol, there is a notable absence of human clinical trials, leaving their therapeutic efficacy and safe dosage ranges unverified [10].

Toxicity and Pharmacokinetic Considerations

- The pharmacological development of terpenoids is often impeded by less-than-ideal safety profiles or pharmacokinetic properties. Andrographolide has been associated with nephrotoxicity and reproductive toxicity [17]. Thapsigargin is highly toxic, even at low concentrations, necessitating the use of targeted prodrug formulations to reduce off-target effects [2]. In terms of pharmacokinetics, terpenoids generally undergo rapid metabolism and clearance. For example, curdione suffers from poor water solubility and metabolic instability, reducing its effective concentration in the body [16]. Similarly, the rapid biotransformation of monoterpenes often limits their systemic therapeutic efficacy.

Challenges in Clinical Translation

The clinical application of terpenoids faces several significant challenges.

1. Solubility and Bioavailability: The strong lipophilicity of most terpenoids, such as curdione and α-humulene, results in poor aqueous solubility and limited oral bioavailability [9, 16].
2. Standardization and Quality Control: The inherent "variable composition" of plant-derived materials complicates the establishment of consistent dosing regimens, which is crucial for clinical approval [15].
3. Safety and Pharmacokinetic Limitations: The lack of comprehensive summaries on pharmacokinetics and long-term toxicity, including the reproductive toxicity of andrographolide, poses a major obstacle [17].
4. Economic and Isolation Challenges: The presence of many highly potent terpenoids in trace amounts within their natural sources renders large-scale isolation or synthesis economically unfeasible [9].

Conclusion and Future Perspectives

Terpenoids derived from medicinal plants represent a highly promising area for natural product drug discovery. Their ability to modulate apoptosis, the cell cycle, and inflammatory signaling pathways through distinct molecular mechanisms makes them invaluable candidates for anticancer and anti-inflammatory therapies. However, to fully realize their clinical potential, it is crucial to move beyond basic in vitro screening. Future research should focus on developing advanced delivery systems, such as nanoformulations, to address solubility challenges, conduct systematic pharmacokinetic and toxicity profiling, and implement rigorous clinical trials. By addressing these challenges, the unique chemical diversity of terpenoids can be effectively translated into safe and efficacious therapeutic applications.

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