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REVIEW PAPER DERLEME MAKALESİ

Exploring the Anticancer Potential of Monoterpenes

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Abstract: Cancer, marked by uncontrolled cell growth and the ability to spread to other tissues, remains a growing global health challenge. Natural compounds are gaining attention in cancer treatment for their potential to improve therapeutic outcomes and reduce harmful side effects. Recent studies have shown that these compounds can improve treatment outcomes while minimizing side effects. Among these, monoterpenes have shown promising anticancer properties, making them valuable candidates for cancer therapy. Due to their wide range of biological activities and natural abundance, monoterpenes are increasingly being explored as promising agents in cancer treatment. Research has shown that monoterpenes can boost the efficacy of conventional anticancer therapies by modulating key signaling pathways and cellular processes. Although preclinical studies strongly support the potential of monoterpenes in cancer therapy, several challenges limit their clinical application such as toxicity and low bioavailability. Continued research on structural modifications and advanced delivery systems is essential to fully realize their therapeutic potential in clinical settings. This review explores the effects of monoterpenes on cancer cells, their potential in combination therapies, the limitations associated with their clinical use, and future directions for their therapeutic development.

Keywords: Natural compounds, monoterpenes, cancer therapy, drug resistance.

Monoterpenlerin Antikanser Potansiyelinin Araştırılması

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Öz: Kontrolsüz hücre büyümesi ve diğer dokulara yayılma yeteneği ile karakterize edilen kanser, giderek büyüyen küresel bir sağlık sorunu olmaya devam etmektedir. Doğal bileşikler, tedavi sonuçlarını iyileştirme ve zararlı yan etkileri azaltma potansiyelleri nedeniyle kanser tedavisinde dikkat çekmektedir. Son çalışmalar, bu bileşiklerin yan etkileri en aza indirirken tedavi sonuçlarını iyileştirebileceğini göstermiştir. Bunlar arasında, monoterpenler umut vadeden antikanser özellikler göstermiş ve bu da onları kanser tedavisi için değerli adaylar haline getirmiştir. Geniş biyolojik aktivite yelpazesi ve doğal bollukları nedeniyle, monoterpenler kanser tedavisinde umut vadeden ajanlar olarak giderek daha fazla araştırılmaktadır. Araştırmalar, monoterpenlerin temel sinyal yollarını ve hücresel süreçleri modüle ederek geleneksel antikanser tedavilerinin etkinliğini artırabileceğini göstermiştir. Preklinik çalışmalar monoterpenlerin kanser tedavisindeki potansiyelini güçlü bir şekilde desteklese de, toksisite ve düşük biyoyararlanım gibi çeşitli zorluklar klinik uygulamalarını sınırlamaktadır. Klinik ortamlarda terapötik potansiyellerini tam olarak gerçekleştirmek için yapısal modifikasyonlar ve gelişmiş dağıtım sistemleri üzerine devam eden araştırmalar şarttır. Bu inceleme, monoterpenlerin kanser hücreleri üzerindeki etkilerini, kombinasyon terapilerindeki potansiyellerini, klinik kullanımlarıyla ilgili sınırlamaları ve terapötik gelişimleri için gelecekteki yönleri ele almaktadır.

Anahtar kelimeler: Doğal bileşik, monoterpenler, kanser tedavisi, ilaç direnci.

INTRODUCTION

Natural compounds (NCs), encompassing a broad range of primary and secondary metabolites derived from plants, marine organisms, and microorganisms, are widely regarded as invaluable resources in drug discovery. For centuries, NCs, particularly those from medicinal plants, have played a foundational role in the treatment of numerous diseases and in the preservation of human health. This deep-rooted medicinal tradition laid the groundwork for modern pharmacotherapy and continues to thrive today, with nature offering a vast chemical reservoir for the identification and development of novel drug candidates.

Traditionally, most pharmaceutical drugs originated directly from natural sources. Before the introduction of advanced screening and genomic technologies, over 80% of medicines were either naturally

derived or chemically designed based on NCs (Harvey, 2008). Their structural diversity and bioactivity have made NCs indispensable across various therapeutic areas, including oncology, infectious diseases, cardiovascular disorders, neurological conditions such as depression, and immune modulation (Atanasov et al., 2021; Chopra & Dhingra, 2021). NCs are therefore still useful places to start when looking for safer, more efficient, and multi-targeted treatments for a variety of illnesses, including cancer.

Cancer is a condition characterized by uncontrolled proliferation of aberrant cells, which can infiltrate nearby tissues and travel to other regions of the body (Brown et al., 2023). It remains a leading global health concern, with its incidence and mortality steadily rising. GLOBOCAN (Global Cancer Observatory) 2020 estimates reported approximately 19.3 million new cancer cases and 10 million cancer-related deaths globally in 2020. By 2040, the annual cancer burden is projected to increase by 47%, reaching 28.4 million new cases (Kamran et al., 2022). Conventional cancer therapies, while effective to a degree, are often limited by systemic toxicity, therapeutic resistance, and tumor recurrence. In this regard, NCs have emerged as promising adjuncts in cancer therapy, not only for their intrinsic anticancer properties but also for their potential to overcome these limitations (Potočnjak et al., 2018; Dehelean et al., 2021). One of the most promising developments in this field is the integration of NCs into combination therapy regimens. By pairing NCs with conventional chemotherapeutics or radiotherapy, researchers aim to harness their anti-proliferative, anti-angiogenic, antioxidant, and immunomodulatory properties to enhance overall therapeutic efficacy while minimizing adverse effects (Cragg & Pezzuto, 2016; Okem et al., 2023). For example, certain phytochemicals have demonstrated the ability to reverse multidrug resistance by resensitizing cancer cells to chemotherapy, thereby reducing the need for high-dose treatments associated with gastrointestinal toxicity, hepatotoxicity, and oral mucositis (Hamzah et al., 2024)

Moreover, some NCs, such as thymoquinone from *Nigella sativa*, can induce immunogenic cell death (ICD), a process that stimulates the immune system to recognize and attack malignant cells, thereby enhancing the antitumor effects of chemotherapy and reducing the likelihood of relapse (Mostofa et al., 2017). These findings support the rationale for integrating NCs into multimodal cancer therapies.

However, the co-administration of NCs and chemotherapeutic agents presents a complex pharmacological landscape. While many combinations yield synergistic effects—enhancing drug efficacy and allowing for lower, less toxic doses—others may result in antagonistic interactions. Such outcomes may occur when both agents converge on the same molecular targets or pathways, potentially diminishing therapeutic impact (Okem et al., 2023). Therefore, a thorough understanding of NC–drug interactions is essential to optimize treatment protocols and avoid unintended consequences in clinical applications. Among these natural compounds, monoterpenes—a subclass of terpenes have shown promising potential as adjuncts in cancer therapy.

Terpenes are a large and structurally diverse group of natural compounds (NCs), commonly classified as secondary metabolites (Zielińska-Błajet et al., 2021). More than 80,000 different terpenes have been identified so far (Christianson, 2017). Although terpenes have complex structures, they are made from simple 5-carbon units that connect in a chain to form basic building blocks called isoprenoid units (Christianson, 2017). The number of isoprene units in these compounds determines their grouping. They are classified as hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), triterpenes (C_{30}), sesquarterpenes (C_{35}), tetraterpenes (C_{40}), and polyterpenes (more than C_{40}) (Zielińska-Błajet et al., 2021). Monoterpenes (C_{10}), distinguished by their simple structure and natural abundance, are especially valued for their diverse therapeutic properties.

Monoterpenes are naturally occurring compounds primarily found in essential oils derived from aromatic and medicinal plants. They are especially abundant in plant species from the Lamiaceae, Rutaceae, Verbenaceae, and Myrtaceae families. These compounds are typically concentrated in the leaves, flowers, fruits, and bark of the plants (Silva et al., 2021; Mathur et al., 2024).

In addition to providing flavor and smell, these plant-derived monoterpenes have a variety of biological properties, such as antibacterial, anti-inflammatory, anticancer, and antioxidant properties. Owing to their diverse biological properties and natural abundance, monoterpenes have gained increasing attention as potential adjuvants in cancer therapy. Monoterpenes have been found to enhance the effectiveness of conventional anticancer drugs by influencing multiple signaling pathways and cellular mechanisms involved in cancer development.

Terpenes and terpenoids are closely connected but chemically distinct groups of isoprenoid NCs. Terpenoids that biosynthesize through the enzymatic conversion of terpene precursors into distinct hydrocarbon skeletons. Final form of structural diversification is achieved via a series of oxidative and other functional group modifications (Avalos et al., 2022). Therefore, monoterpenes refer more specifically to C_{10} hydrocarbon structures, whereas monoterpenoids include oxygenated or otherwise modified C_{10} derivatives such as alcohols, aldehydes, ketones, ethers, or esters. This review addresses both monoterpenes and monoterpenoids because many anti-cancer studies evaluate

hydrocarbon monoterpenes such as limonene and pinene, as well as oxygenated monoterpene derivatives such as perillyl alcohol, linalool, citral, geraniol, borneol, thymol, and carvacrol. Therefore, the scope of this review covers monoterpene-related compounds, including both hydrocarbon monoterpenes and their oxygenated derivatives. Where relevant to chemical classification, the terms "monoterpenes" and "monoterpenoids" are used specifically throughout the text.

ANTICANCER MECHANISMS

The therapeutic implications of monoterpenes in cancer therapies can be attributed to their ability to target multiple pathways involved in cancer progression and drug resistance. Key mechanisms include: induction of apoptosis, generation of reactive oxygen species (ROS), disruption of mitochondrial membrane potential (Δψm), alteration of Bax/Bcl-2 and Bax/Bcl-xL ratios, PARP-mediated apoptosis induced by DNA damage, cell cycle arrest and checkpoint regulation, inhibition of metastasis, modulation of autophagy, regulation of intracellular signaling pathways, and influence on cellular antioxidant defenses.

Apoptosis is a form of programmed cell death characterized by unique morphological and biochemical characteristics, including membrane blebbing, DNA breakage, chromatin condensation, and caspase activation (Sheikh et al., 2017). It plays a crucial role in maintaining tissue homeostasis and is a central mechanism targeted in cancer therapy. Inducing apoptosis in tumor cells is considered a key therapeutic strategy for treating various types of cancer. This process occurs via two main pathways: the intrinsic pathway, which is controlled by mitochondrial signals, and the extrinsic pathway, which is started by death receptors on the cell surface. Both routes eventually result in the activation of caspases, which are the enzymes that carry out apoptosis (Sheikh et al., 2017).

In this context, monoterpene-derived compounds may exert anticancer effects not only by promoting apoptosis but also by blocking cell cycle progression. For example, linalool has been shown to downregulate the expression of Cyclin A, Cyclin E, and Cdk4, while upregulating p21 and p27, leading to G_0/G_1 cell cycle arrest in HepG2 hepatocellular carcinoma cells (Rodenak-Kladniew et al., 2018). This combination of pro-apoptotic and antiproliferative actions supports the potential of monoterpenes as effective natural agents in integrative cancer therapy.

Monoterpene-derived compounds have been shown to modulate oxygen metabolism. Oxygen metabolism creates free radicals, called ROS (reactive oxygen species), which are linked to diseases like cancer and heart problems. When ROS levels are too high, they can damage important cell parts like DNA, proteins, and fats. Glutathione, a small molecule made of three amino acids (γ-glutamylcysteinylglycine), helps protect cells by removing these harmful ROS and is seen as a sign of healthy cells (Silva et al., 2021).

Carvacrol treatment led to a significant increase in ROS levels in AGS gastric cancer cells, which was accompanied by a notable reduction in intracellular glutathione (GSH) levels. This inverse relationship suggests that the elevated ROS induced by carvacrol overwhelmed the cellular antioxidant system, resulting in the depletion of GSH—a key indicator of oxidative stress and impaired redox balance (Günes-Bayir et al., 2017).

Monoterpene-derived compounds also affect mitochondrial membrane potential. Disrupting mitochondrial membrane potential (Δψm), making mitochondria unstable and leading apoptosis. For instance; Citral induces apoptosis in HCT116 and HT29 colorectal cancer cells by causing a dose- and time-dependent loss of mitochondrial membrane potential (Δψm), a key early event in the intrinsic apoptotic pathway (Sheikh et al., 2017).

Monoterpenoids also influence Bax/Bcl-2 and Bax/Bcl-xL ratios**.** The Bax/Bcl-2 and Bax/Bcl-xL ratios are important indicators of a cell's likelihood to undergo apoptosis. Bax promotes cell death, while Bcl-2 and Bcl-xL prevent it. When the ratio increases-meaning more Bax relative to Bcl-2 or Bcl-xL-the balance shifts toward apoptosis by disrupting mitochondrial membrane integrity and triggering the cell's intrinsic death pathway (Sheikh et al., 2017).

Citral has been shown to trigger mitochondrial-related apoptosis in colorectal cancer cells (HCT116 and HT29). It does this by increasing the

ratio of Bax (a pro-apoptotic protein) to Bcl-2 and Bcl-xL (anti-apoptotic proteins), creating conditions that favor cell death. This change was also linked to other signs of apoptosis, such as a drop in mitochondrial membrane potential and activation of caspase-3, showing that citral promotes cell death by shifting the balance of proteins that control apoptosis (Sheikh et al., 2017).

DNA damage is a critical cellular event that can lead to either repair or programmed cell death, depending on its severity. One of the first responders to DNA strand breaks is poly (ADP-ribose) polymerase (PARP), a nuclear enzyme that detects damage and initiates DNA repair mechanisms. However, when DNA damage is extensive or persistent-such as that induced by oxidative stress-PARP becomes hyperactivated, consuming large amounts of NAD^+ and ATP, thereby depleting the cell's energy reserves. This depletion contributes to mitochondrial dysfunction and triggers the intrinsic apoptotic pathway. Thus, PARP not only acts as a repair enzyme but also functions as a molecular switch between survival and apoptosis in response to genotoxic stress (Miwa et al., 2022).

For instance; citral, a monoterpene aldehyde, was shown to induce apoptosis in breast cancer cell lines (MCF-7 and MDA-MB-231) via activation of PARP-1, in addition to triggering p53 phosphorylation and ROS elevation(Sheikh et al., 2017).

Cell cycle regulation is a critical mechanism that ensures proper cell division, and its disruption is often targeted in cancer therapy to inhibit tumor growth. Compounds that induce cell cycle arrest can effectively halt cancer cell proliferation and promote apoptosis.

Linalool has strong antiproliferative effects through the induction of cell cycle arrest in cancer cells in hepatocellular carcinoma (HepG2) cells. Linalool inhibited DNA synthesis and significantly reduced cell proliferation as promoted G_0/G_1 phase arrest. At the molecular level, this effect was associated with the downregulation of cyclin A, cyclin E, and Cdk4, along with the upregulation of the cyclin-dependent kinase inhibitors p21 and p27. These changes interfered with the progression from G_1 to S phase, effectively halting cell cycle progression. Notably, these effects occurred independently of p53, suggesting a p53-independent mechanism of cell cycle control (Rodenak-Kladniew et al., 2018).

Monoterpenes exhibit significant antimetastatic potential by interfering with key processes that enable cancer cell migration and invasion. A central mechanism involves the downregulation of matrix metalloproteinases (MMPs)—particularly MMP-2 and MMP-9 which are enzymes responsible for degrading the extracellular matrix (ECM). The breakdown of ECM components facilitates tumor cell detachment, local invasion, and eventual dissemination to distant tissues. By suppressing the expression and activity of MMP-2 and MMP-9, monoterpenes hinder ECM remodeling, effectively impairing cancer cell motility and invasive behavior, thereby reducing the risk of metastasis (Mathur et al., 2024). For instance; limonene demonstrated dose-dependent inhibition of both cell migration and invasion in T24 bladder cancer cells (Ye et al., 2020). Monoterpenes also play a role in autophagy pathways. Autophagy is a natural process in which cells break down and recycle their own damaged parts-like proteins and organelles-ean itself and maintain energy balance during difficult conditions (Silva et al., 2021).

Autophagy serves as a survival mechanism that helps cells cope with short-term stress by recycling damaged components and maintaining cellular energy balance. While this process may not prevent apoptosis entirely, it can enable a subset of cells to withstand cytotoxic stress. Over time, these surviving cells-protected in part by autophagic activity-may acquire adaptive changes that enhance their resistance to therapeutic agents. This gradual development of tolerance is referred to as the microevolution of drug resistance.

One study showed that autophagy acts as a protective response in T98G glioblastoma cells exposed to the monoterpene α-thujone. While autophagy helped reduce the initial cytotoxic effects, it was not strong enough to fully prevent apoptosis. Interestingly, this partial protection may allow some cancer cells to survive, which over time could lead to microevolution of drug resistance, where surviving cells gradually adapt and become less sensitive to treatment (Pudełek et al., 2019).

Monoterpenes also modulate intracellular signaling pathways that are critical for tumor growth and survival. Specifically, these compounds have been shown to interfere with key molecular cascades such as PI3K/Akt (phosphatidylinositol 3-kinase) and Akt (protein kinase B), MAPK (mitogen-activated protein kinase), and NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells), all of which play pivotal roles in promoting proliferation, inhibiting apoptosis, and fostering chemoresistance (S. R. Lin et al., 2020).

Oxidative stress plays a major role in cancer progression and metastasis by promoting DNA damage, inflammation, and cellular instability. Antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD) form a crucial defense system to neutralize ROS and maintain redox balance. Certain monoterpenes can enhance these endogenous antioxidant pathways, thereby exerting both protective and anticancer effects. For example, hinokitiol, a tropolone-based monoterpenoid, significantly increased CAT and SOD activity in A549 lung adenocarcinoma cells in a dose-dependent manner. This enzymatic upregulation was associated with reduced ROS levels, suppression of migration, and increased apoptosis, supporting the therapeutic relevance of antioxidant modulation in cancer treatment (Jayakumar et al., 2018).

The preceding discussion outlined the multiple anticancer mechanisms of monoterpenes, including the induction of apoptosis, inhibition of metastasis, modulation of autophagy, and enhancement of antioxidant defense. Due to their ability to target diverse cellular pathways, monoterpenes are increasingly recognized not only as potential therapeutic agents but also as valuable adjuvants in cancer treatment. Their combination with conventional chemotherapeutic drugs has shown promise in enhancing treatment efficacy, minimizing adverse effects, and addressing drug resistance. The following section will explore the molecular basis and therapeutic relevance of these synergistic interactions.

COMBINATION with CHEMOTHERAPY

Recent technologies in diagnostic methods and novel chemotherapeutics have improved overall patient survival. However, these improvements are still insufficient to increase long-term survival rates, especially beyond five

years. One of the principal reasons for this limitation is the development of chemoresistance.

Chemoresistance is a multifactorial process which include drug efflux, altered drug metabolism, detoxification mechanisms and changes in survival signaling pathways (Wink et al., 2012).Following the development of chemoresistance to an initial chemotherapeutic agent, tumor cells may also develop resistance to additional chemotherapeutics, ultimately contributing to the emergence of multidrug resistance (MDR) (Maji et al., 2018). MDR is frequently mediated by the overexpression of ATP-binding cassette (ABC) transporters. These include P-glycoprotein (P-gp/ABCB1), MRP1 (ABCC1), and BCRP (ABCG2)—membrane-bound proteins that utilize ATP hydrolysis to efflux chemotherapeutic agents from tumor cells, thereby reducing intracellular drug concentrations and efficacy (Wink et al., 2012). This mechanism often leads to cross-resistance, where cancer cells become resistant to multiple unrelated drugs. Research has therefore focused on identifying chemosensitizers capable of blocking or bypassing ABC transporter activity (S.-R. Lin et al., 2019).

Concequently, chemotherapy remains as a cornerstone in cancer treatment, but its efficacy is often limited by systemic toxicity and the emergence of drug resistance, which compromise long-term therapeutic success. To address these limitations, NCs have gained increasing attention as adjuvants in combination therapy (S. R. Lin et al., 2020).

When combined, NCs and chemotherapeutics can exhibit synergistic effects—enhancing cancer cell sensitivity to treatment, reversing drug resistance, and protecting normal tissues from toxicity (S. R. Lin et al., 2020). Monoterpenes exert their chemosensitizing effects through multiple complementary mechanisms, including inhibition of drug efflux, increased intracellular drug accumulation and modulation of apoptosis-related signaling (S. R. Lin et al., 2020).

Table1. Table of Effects of Selected Monoterpene Derivative Compounds.

Compounds	Cell Line(s)	Mechanism(s)	References
Carvacrol	HeLa	↑p21, ↓Cyclin D1, Caspase-9 activation, PARP cleavage	(Potočnjak et al., 2018)
Carvacrol	AGS	↑ROS, ↓GSH, DNA damage, ↑Bax, Caspase-3/-9, ↓Bcl-2	(Günes-Bayir et al., 2017)
Citral	HCT-116, HT-29	↑ROS, ↓GSH, ↓Δψm, p53 phosphorylation, Caspase-3 activation, ↑Bax, ↓Bcl-2/Bcl-XL	(Sheikh et al., 2017)
Citral	MCF-7	G2/M arrest, COX-2 inhibition	(Chaouki et al., 2009)
Thymol	MDA-MB-231	Oxidative stress, ↓MMP, ↑Bax/Bcl-2, DNA fragmentation, S phase arrest	(Jamali et al., 2018)
Thymol	HL-60	Caspase-8/-9/-3 activation, PARP cleavage, AIF translocation	(Deb et al., 2011)
Linalool	HCT-116, CCD18Co	Selective cytotoxicity via oxidative stress	(Iwasaki et al., 2016)
Myrtenal	B16F0, B16F10, SkMel-5	V-ATPase inhibition, energy stress → autophagy → apoptosis, impairs H+ transport	(Martins et al., 2019)
α-Thujone	T98G	Apoptosis via oxidative stress, inhibits migration, autophagy induction	(Pudełek et al., 2019)
Perillyl Alcohol	HepG2	↓ DNA synthesis, ↑ Caspase-3 (apoptosis)	(Oturanel et al., 2017)
Perillyl Alcohol	A549	↓ DNA synthesis, ↓ mitochondrial membrane potential	(Oturanel et al., 2017)
Perillyl Alcohol	HCT-116 (hypoxia)	↓ HIF-1α, ROS scavenging, ↓ mTOR/4E-BP1/eIF4E phosphorylation, ↓ Cyclin D1, ↑ p53/p21 → G1 arrest	(Ma et al., 2016)
Bakuchiol	NUGC3	↓ Viability, mitochondrial apoptosis, sub-G1 arrest, ↓ PI3K/AKT & MAPK signaling	(Lv & Liu, 2017)

Table2. Table of Selected Monoterpene Derivative and Chemotherapeutic Drug Combinations and Their Major Chemosensitivity-Enhancing Mechanisms.

Compounds	Cell Line(s)	Mechanism(s)	References
Citral + Doxorubicin	MCF-7/ADR, HepG-2/ADR, SKOV-3/ADR resistant cancer cell lines	Enhanced doxorubicin cytotoxicity; reduced doxorubicin IC50; increased intracellular doxorubicin accumulation; downregulated PXR, thereby suppressing downstream CYP3A4, GST, and ABC transporter transcription; contributed to MDR reversal and restoration of drug sensitivity	(Mukhtar et al., 2018)
Borneol + Paclitaxel	TE-1 ,TE-13	Inhibited P-gp function; enhanced paclitaxel uptake; increased apoptosis in a dose- and time-dependent manner; upregulated cleaved caspase-3; downregulated survivin; improved antitumor	(Meng et al., 2018)
Geraniol + 5-Fluorouracil	Ehrlich breast carcinoma mouse model	Showed synergistic antitumor activity with 5-FU; produced 84% tumor growth inhibition; increased caspase-3 activation; decreased autophagy marker expression; enhanced 5-FU sensitivity through apoptosis induction and autophagy modulation	(El-Ganainy et al., 2023)
Carvacrol + 5-Fluorouracil	MCF-7	Increased intracellular 5-FU accumulation; enhanced apoptosis; interacted with the P-gp drug-binding pocket; inhibited P-gp function; showed stronger apoptosis-enhancing activity than verapamil + 5-FU in the reviewed source	(Ghorbanzadeh et al., 2022)
(R)-(+)-Citronellal	LLC-GA5-COL150 cells / P-gp substrate model	Increased intracellular accumulation of [3H] digoxin, a P-gp substrate; directly inhibited P-gp activity without disrupting passive membrane diffusion	(Yoshida et al., 2005)
(S)-β-Citronellol	LLC-GA5-COL150 cells / P-gp substrate model	Increased intracellular digoxin accumulation; reduced P-gp-mediated drug efflux; suggested direct functional inhibition of P-gp rather than nonspecific membrane damage	(Yoshida et al., 2005)

LIMITATIONS

Despite strong preclinical evidence supporting the use of monoterpenes in combination with chemotherapy, several limitations hinder their broader therapeutic application. Most current data are derived from in vitro and animal studies, while well-designed clinical trials remain limited or unpublished (S. R. Lin et al., 2020). Their direct application in clinical settings is often limited by issues such as toxicity, low solubility, and poor bioavailability.

To overcome these limitations, numerous structurally modified derivatives of NCs are being evaluated in clinical trials.

Terpenes, including monoterpenes, sesquiterpenes, diterpenes, triterpenes, and tetraterpenes, are structurally diverse compounds characterized by complex carbon skeletons, multiple chiral centers, and a variety of functional groups. These structural elements contribute significantly to their pharmacological properties but also make their synthesis, purification, and quality control highly challenging. The therapeutic activity of terpenes often depends on subtle features such as stereochemistry, ring conformation, and positional relationships between functional groups (He, 2025).

As a result, despite their potent biological activities, the clinical development of them is often restricted by low reproducibility, variable pharmacokinetics, and scale-up limitations in pharmaceutical production.

Their lipophilic nature hinders efficient passage through cell membranes, and once ingested, they are often degraded by digestive enzymes or expelled via exocytosis mechanisms, resulting in low bioavailability and short circulation time in the bloodstream (He, 2025). These pharmacokinetic limitations represent a major hurdle to the clinical application of terpenoids and have prompted ongoing research into formulation strategies such as nanoencapsulation, liposomal delivery, and structural modification to improve their therapeutic potential (Obeid et al., 2017; Chen et al., 2021; He, 2025).

Although terpenoids are generally regarded as having low toxicity, one of their major clinical limitations is insufficient specificity toward cancer cells. As a result, they may also affect healthy tissues, causing off-target cytotoxicity and undesirable side effects (He, 2025). These compounds may exert cytotoxic effects not only on cancer cells but also on healthy tissues, leading to unintended side effects (Wang et al., 2023). To address this, current research focuses on chemical modification and structural optimization of terpenoids to enhance target specificity, reduce toxicity, and improve their therapeutic window in cancer treatment.

DISCUSSION and CONCLUSION

Monoterpenes, a subclass of natural secondary metabolites with diverse biological activities, hold significant potential in cancer therapy through mechanisms such as apoptosis induction, cell cycle arrest, and modulation of oncogenic signaling pathways. When used in combination with conventional chemotherapeutic agents have demonstrated synergistic antitumor effects and the ability to reduce systemic toxicity, offering a promising strategy to overcome drug resistance. Monoterpenes represent promising adjuvant agents capable of enhancing the efficacy of conventional chemotherapeutics while overcoming major resistance mechanisms. Their ability to modulate multidrug resistance pathways, oxidative stress responses, apoptotic signaling, and tumor progression highlights their potential role in future combination therapy strategies.Despite their therapeutic promise, clinical translation has been limited by challenges such as low bioavailability and insufficient target specificity. However, recent advancements in biotechnology—particularly the development of nanocarriers and plant drug-functionalized delivery systems—offer viable solutions to these obstacles. Furthermore, as interest in plant-derived drugs continues to rise, sustainable sourcing and biotechnological production of high-value metabolites become increasingly important to ensure long-term viability. Looking ahead, the integration of monoterpenes into personalized and nanotechnology-driven treatment protocols, supported by robust clinical trials and interdisciplinary collaboration, may pave the way for their effective and sustainable use in modern cancer therapy.

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Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research publishing ethics.

REFERENCES

Atanasov, A. G., Zotchev, S. B., Dirsch, V. M., Orhan, I. E., Banach, M., Rollinger, J. M., Barreca, D., Weckwerth, W., Bauer, R., Bayer, E. A., Majeed, M., Bishayee, A., Bochkov, V., Bonn, G. K., Braidy, N., Bucar, F., Cifuentes, A., D'Onofrio, G., Bodkin, M. (2021). Natural products in drug discovery: advances and opportunities. *Nature Reviews Drug Discovery*, *20*(3), 200-216. https://doi.org/10.1038/S41573-020-00114-Z;SUBJMETA

Avalos, M., Garbeva, P., Vader, L., Van Wezel, G. P., Dickschat, J. S., & Ulanova, D. (2022). Biosynthesis, evolution and ecology of microbial terpenoids. *Natural Product Reports, 39*(2), 249-272. https://doi.org/10.1039/d1np00047k

Brown, J.S., Amend, S.R., Austin, R.H., Gatenby, R.A., Hammarlund, E.U., & Pienta, K.J. (2023). Updating the Definition of Cancer. *Molecular Cancer Research*, *21*(11), 1142-1147. https://doi.org/10.1158/1541-7786.

Chaouki, W., Leger, D. Y., Liagre, B., Beneytout, J.L., & Hmamouchi, M. (2009). Citral inhibits cell proliferation and induces apoptosis and cell cycle arrest in MCF-7 cells. *Fundamental & Clinical Pharmacology*, *23*(5), 549-556. https://doi.org/10.1111/J.1472-8206.2009.00738.X

Chen, T. C., da Fonseca, C. O., Levin, D., & Schönthal, A. H. (2021). The monoterpenoid perillyl alcohol: Anticancer agent and medium to overcome biological barriers. *Pharmaceutics, 13*(12). https://doi.org/10.3390/pharmaceutics13122167

Chopra, B., & Dhingra, A. K. (2021). Natural products: A lead for drug discovery and development. *Phytotherapy Research : PTR*, *35*(9), 4660–4702. https://doi.org/10.1002/PTR.7099

Christianson, D.W. (2017). Structural and Chemical Biology of Terpenoid Cyclases. *Chemical Reviews*, *117*(17), 11570-11648. https://doi.org/10.1021/ACS.CHEMREV.7B00287

Cragg, G.M., & Pezzuto, J.M. (2016). Natural Products as a Vital Source for the Discovery of Cancer Chemotherapeutic and Chemopreventive Agents. *Medical Principles and Practice : International Journal of the Kuwait University, Health Science Centre*, ***25***(Suppl. 2), 41-59. https://doi.org/10.1159/000443404

Deb, D.D., Parimala, G., Saravana Devi, S., & Chakraborty, T. (2011). Effect of thymol on peripheral blood mononuclear cell PBMC and acute promyelotic cancer cell line HL-60. *Chemico-Biological Interactions*, *193*(1), 97-106. https://doi.org/10.1016/j.cbi.2011.05.009

Dehelean, C.A., Marcovici, I., Soica, C., Mioc, M., Coricovac, D., Iurciuc, S., Cretu, O.M., & Pinzaru, I. (2021). Plant-Derived Anticancer Compounds as New Perspectives in Drug Discovery and Alternative Therapy. *Molecules (Basel, Switzerland)*, *26*(4). https://doi.org/10.3390/MOLECULES26041109

El-Ganainy, S. O., Shehata, A. M., El-Mallah, A., Abdallah, D., & Mohy El-Din, M. M. (2023). Geraniol suppresses tumour growth and enhances chemosensitivity of 5-fluorouracil on breast carcinoma in mice: involvement of miR-21/PTEN signalling. *The Journal of Pharmacy and Pharmacology*, *75*(8), 1130-1139. https://doi.org/10.1093/JPP/RGAD060

Ghorbanzadeh, V., Aljaf, K. A. H., Wasman, H. M., Pirzeh, L., Azimi, S., & Dariushnejad, H. (2022). Carvacrol Enhance Apoptotic Effect of 5-FU on MCF-7 Cell Line via inhibiting P-glycoprotein: An In-silco and In-vitro Study. *Drug Research*, *72*(4), 203-208. https://doi.org/10.1055/A-1766-5491

Günes-Bayir, A., Kiziltan, H. S., Kocyigit, A., Güler, E. M., Karataş, E., & Toprak, A. (2017). Effects of natural phenolic compound carvacrol on the human gastric adenocarcinoma (AGS) cells in vitro. *Anti-Cancer Drugs*, *28*(5), 522-530. https://doi.org/10.1097/CAD.0000000000000491

Hamzah, E. F., Neema Al-Mussawy, A., Al-Azawi, R. S. A., & Al-Shukri, H. H. K. (2024). The Role of Herbals in Complementary and Alternative Cancer Therapies: A Critical Review. *South Asian Res J App Med Sci*, *6*(4), 122-127. https://doi.org/10.36346/sarjams.2024.v06i04.007

Harvey, A. L. (2008). Natural products in drug discovery. *Drug Discovery Today*, *13*(19-20), 894-901. https://doi.org/10.1016/J.DRUDIS.2008.07.004

He, H. (2025). Potential and Challenges of Terpenoids in Cancer Therapy: Mechanistic Review and Future Perspectives. *Theoretical and Natural Science*, *75*(1), 13-19. https://doi.org/10.54254/2753-8818/2024.LA19342

Iwasaki, K., Zheng, Y. W., Murata, S., Ito, H., Nakayama, K., Kurokawa, T., Sano, N., Nowatari, T., Villareal, M. O., Nagano, Y. N., Isoda, H., Matsui, H., & Ohkohchi, N. (2016). Anticancer effect of linalool via cancer-specific hydroxyl radical generation in human colon cancer. *World Journal of Gastroenterology*, *22*(44), 9765-9774. https://doi.org/10.3748/wjg.v22.i44.9765

Jamali, T., Kavoosi, G., Safavi, M., & Ardestani, S. K. (2018). In-vitro evaluation of apoptotic effect of OEO and thymol in 2D and 3D cell cultures and the study of their interaction mode with DNA. *Scientific Reports*, *8*(1), 15787. https://doi.org/10.1038/s41598-018-34055-w

Jayakumar, T., Liu, C. H., Wu, G. Y., Lee, T. Y., Manubolu, M., Hsieh, C. Y., Yang, C. H., & Sheu, J. R. (2018). Hinokitiol Inhibits Migration of A549 Lung Cancer Cells via Suppression of MMPs and Induction of Antioxidant Enzymes and Apoptosis. *International Journal of Molecular Sciences*, *19*(4), 939. https://doi.org/10.3390/IJMS19040939

Kamran, S., Sinniah, A., Abdulghani, M. A. M., & Alshawsh, M. A. (2022). Therapeutic Potential of Certain Terpenoids as Anticancer Agents: A Scoping Review. *Cancers*, *14*(5), 1100. https://doi.org/10.3390/CANCERS14051100/S1

Lin, S. R., Chang, C. H., Hsu, C. F., Tsai, M. J., Cheng, H., Leong, M. K., Sung, P. J., Chen, J. C., & Weng, C. F. (2020). Natural compounds as potential adjuvants to cancer therapy: Preclinical evidence. *British Journal of Pharmacology*, *177*(6), 1409-1423. https://doi.org/10.1111/BPH.14816

Lv, L., & Liu, B. (2017). Anti-tumor effects of bakuchiol on human gastric carcinoma cell lines are mediated through PI3K/AKT and MAPK signaling pathways. *Molecular Medicine Reports*, *16*(6), 8977-8982. https://doi.org/10.3892/MMR.2017.7696/ABSTRACT

Ma, J., Li, J., Wang, K. S., Mi, C., Piao, L. X., Xu, G. H., Li, X., Lee, J. J., & Jin, X. (2016). Perillyl alcohol efficiently scavenges activity of cellular ROS and inhibits the translational expression of hypoxia-

inducible factor-1α via mTOR/4E-BP1 signaling pathways. *International Immunopharmacology*, *39*, 1-9. https://doi.org/10.1016/J.INTIMP.2016.06.034

Maji, S., Panda, S., Samal, S. K., Shriwas, O., Rath, R., Pellecchia, M., Emdad, L., Das, S. K., Fisher, P. B., & Dash, R. (2018). Chapter Three. Bcl-2 Antiapoptotic Family Proteins and Chemoresistance in Cancer. In *Advances in Cancer Research, 137*, 37-75. Academic Press Inc. https://doi.org/10.1016/bs.acr.2017.11.001

Martins, B. X., Arruda, R. F., Costa, G. A., Jerdy, H., de Souza, S. B., Santos, J. M., de Freitas, W. R., Kanashiro, M. M., de Carvalho, E. C. Q., Sant'Anna, N. F., Antunes, F., Martinez-Zaguilan, R., Souad, S., Okorokova-Façanha, A. L., & Façanha, A. R. (2019). Myrtenal-induced V-ATPase inhibition - A toxicity mechanism behind tumor cell death and suppressed migration and invasion in melanoma. *Biochimica et Biophysica Acta (BBA) - General Subjects*, *1863*(1), 1-12. https://doi.org/10.1016/J.BBAGEN.2018.09.006

Mathur, A., Meena, A., & Luqman, S. (2024). Monoterpenoids: An upcoming class of therapeutic agents for modulating cancer metastasis. In *Phytotherapy Research* (Vol. 38, Number 2, pp. 939-969). John Wiley and Sons Ltd. https://doi.org/10.1002/ptr.8081

Meng, X., Dong, X., Wang, W., Yang, L., Zhang, X., Li, Y., Chen, T., Ma, H., Qi, D., & Su, J. (2018). Natural Borneol Enhances Paclitaxel-Induced Apoptosis of ESCC Cells by Inactivation of the PI3K/AKT. *Journal of Food Science*, *83*(5), 1436-1443. https://doi.org/10.1111/1750-3841.14143

Miwa, S., Kashyap, S., Chini, E., & von Zglinicki, T. (2022). Mitochondrial dysfunction in cell senescence and aging. *The Journal of Clinical Investigation*, *132*(13). https://doi.org/10.1172/JCI158447

Mostofa, A. G. M., Hossain, M. K., Basak, D., & Sayeed, M. S. Bin. (2017). Thymoquinone as a potential adjuvant therapy for cancer treatment: Evidence from preclinical studies. *Frontiers in Pharmacology*, *8*, 268913. https://doi.org/10.3389/fphar.2017.00295

Mukhtar, Y. M., Adu-Frimpong, M., Xu, X., & Yu, J. (2018). Biochemical significance of limonene and its metabolites: future prospects for designing and developing highly potent anticancer drugs. *Bioscience Reports*, *38*(6). https://doi.org/10.1042/BSR20181253

Obeid, M. A., Al Qaraghuli, M. M., Alsaadi, M., Alzahrani, A. R., Niwasabutra, K., & Ferro, V. A. (2017). Delivering Natural Products and Biotherapeutics to Improve Drug Efficacy. *Therapeutic Delivery*, *8*(11), 947-956. https://doi.org/10.4155/TDE-2017-0060

Okem, A., Henstra, C., Lambert, M., & Hayeshi, R. (2023). A review of the pharmacodynamic effect of chemo-herbal drug combinations therapy for cancer treatment. *Medicine in Drug Discovery*, *17*, 100147. https://doi.org/10.1016/J.MEDIDD.2022.100147

Oturanel, C. E., Kıran, İ., Özşen, Ö., Çiftçi, G. A., & Atlı, Ö. (2017). Cytotoxic, Antiproliferative and Apoptotic Effects of Perillyl Alcohol and Its Biotransformation Metabolite on A549 and HepG2 Cancer Cell Lines. *Anti-Cancer Agents in Medicinal Chemistry*, *17*(9), 1243-1250. https://doi.org/10.2174/1871520617666170103093923

Potočnjak, I., Gobin, I., & Domitrović, R. (2018). Carvacrol induces cytotoxicity in human cervical cancer cells but causes cisplatin resistance: Involvement of MEK–ERK activation. *Phytotherapy Research*, *32*(6), 1090-1097. https://doi.org/10.1002/PTR.6048

Pudełek, M., Catapano, J., Kochanowski, P., Mrowiec, K., Janik-Olchawa, N., Czyż, J., & Ryszawy, D. (2019). Therapeutic potential of monoterpene α-thujone, the main compound of Thuja occidentalis L. essential oil, against malignant glioblastoma multiforme cells in vitro. *Fitoterapia*, *134*, 172-181. https://doi.org/10.1016/J.FITOTE.2019.02.020

Rodenak-Kladniew, B., Castro, A., Stärkel, P., De Saeger, C., García de Bravo, M., & Crespo, R. (2018). Linalool induces cell cycle arrest and apoptosis in HepG2 cells through oxidative stress generation and modulation of Ras/MAPK and Akt/mTOR pathways. *Life Sciences*, *199*, 48-59. https://doi.org/10.1016/j.lfs.2018.03.006

Sheikh, B. Y., Sarker, M. M. R., Kamarudin, M. N. A., & Mohan, G. (2017). Antiproliferative and apoptosis inducing effects of citral via p53 and ROS-induced mitochondrial-mediated apoptosis in human colorectal HCT116 and HT29 cell lines. *Biomedicine & Pharmacotherapy*, *96*, 834-846. https://doi.org/10.1016/J.BIOPHA.2017.10.038

Silva, B. I. M., Nascimento, E. A., Silva, C. J., Silva, T. G., & Aguiar, J. S. (2021). Anticancer activity of monoterpenes: a systematic review. *Molecular Biology Reports 2021 48:7*, *48*(7), 5775–5785. https://doi.org/10.1007/S11033-021-06578-5

Wang, Y., Zhang, Z., Cheng, Z., Xie, W., Qin, H., & Sheng, J. (2023). Astragaloside in cancer chemoprevention and therapy. *Chinese Medical Journal*, *136*(10), 1144-1154. https://doi.org/10.1097/CM9.0000000000002661

Wink, M., Ashour, M. L., & El-Readi, M. Z. (2012). Secondary metabolites from plants inhibiting ABC transporters and reversing resistance of cancer cells and microbes to cytotoxic and antimicrobial agents. *Frontiers in Microbiology*, *3*, 22157. https://doi.org/10.3389/fmicb.2012.00130

Ye, Z., Liang, Z., Mi, Q., & Guo, Y. (2020). Limonene terpenoid obstructs human bladder cancer cell (T24 cell line) growth by inducing cellular apoptosis, caspase activation, G2/M phase cell

cycle arrest and stops cancer metastasis. *JBUON*, *25*(1), 280-285.

Yoshida, N., Takagi, A., Kitazawa, H., Kawakami, J., & Adachi, I. (2005). Inhibition of P-glycoprotein-mediated transport by extracts of and monoterpenoids contained in Zanthoxyli Fructus. *Toxicology and Applied Pharmacology*, *209*(2), 167-173. https://doi.org/10.1016/J.TAAP.2005.04.001

Zielińska-Błajet, M., Pietrusiak, P., & Feder-Kubis, J. (2021). Selected Monocyclic Monoterpenes and Their Derivatives as Effective Anticancer Therapeutic Agents. *International Journal of Molecular Sciences 2021, Vol. 22, Page 4763*, *22*(9), 4763. https://doi.org/10.3390/IJMS22094763