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From Nature to Therapy: Exploring the Cytotoxic Effects and Molecular Mechanisms of Medicinal Plants and Other Natural Products

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ABSTRACT :

Natural products have emerged as a vital source of anticancer agents, leveraging their inherent cytotoxic effects to target malignant cells through diverse mechanisms such as apoptosis induction, cell cycle arrest, and oxidative stress generation. Derived from plants, marine organisms, and microbes, these compounds offer structural diversity that often surpasses synthetic drugs, with over 60% of approved anticancer therapeutics originating from or inspired by natural sources. This review synthesizes recent advancements in understanding the cytotoxic potential of natural products, focusing on key examples like curcumin from Curcuma longa, artemisinin from *Artemisia annua*, genistein from soy plants, and marine-derived compounds such as trabectedin from sponges. These agents modulate critical pathways including NF-κB, PI3K/Akt, and MAPK, leading to selective tumor cell death while minimizing harm to normal tissues. Plant metabolites, constituting the majority, exhibit potent activity against breast, lung, and colorectal cancers, with in vitro assays like MTT revealing IC50 values in the micromolar range for compounds like thymoquinone and ursolic acid. Marine products, from sponges and algae, provide unique scaffolds like polyketides and peptides, showing nanomolar potency in inhibiting microtubule assembly or DNA replication. Microbial sources, including bacteria like Streptomyces, yield agents such as salinosporamide A, which inhibit proteasomes and induce apoptosis. The review addresses challenges like poor bioavailability and toxicity, evidenced by preclinical rodent studies showing manageable side effects for most compounds, though some like aristolochic acids pose risks. Synergistic combinations with conventional therapies overcome resistance, as seen in enhanced doxorubicin efficacy with platycodin D. Future perspectives highlight nanotechnology for improved delivery, genome mining for novel compounds, and clinical translation to precision medicine. By integrating ethnopharmacology with modern omics, natural products promise to revolutionize cancer treatment, offering safer alternatives amid rising global incidence.

Keywords: Natural products, Cytotoxicity, Apoptosis, Cancer therapy, Marine compounds, Plant metabolites

Introduction

The exploration of natural products for medicinal purposes traces back to ancient civilizations, where empirical knowledge guided the use of plants, minerals, and animal-derived substances to treat ailments, including those resembling modern-day cancers. Historical texts like the Ebers Papyrus from Egypt (circa 1550 BCE) document over 700 herbal remedies, some with antitumor properties, while traditional Chinese medicine employed *Artemisia annua* for feverish conditions that may have included malignancies. In contemporary oncology, natural products have proven indispensable, with compounds like paclitaxel from *Taxus brevifolia* and vincristine from *Vinca rosea* forming the basis of standard chemotherapies. These agents exploit the evolutionary adaptations of organisms, producing secondary metabolites that interact with biological targets in cancer cells, such as tubulin or topoisomerases, to halt proliferation. The cytotoxic effects—defined as the capacity to induce cell death or growth inhibition—are particularly valuable in addressing the hallmarks of cancer, including sustained proliferation and metastasis evasion. Unlike synthetic drugs, natural products often exhibit multitargeted actions, reducing the likelihood of resistance development, a major hurdle in cancer treatment where multidrug resistance affects up to 90% of metastatic cases. [1-5]

Cancer's global burden, projected to reach 28 million new cases by 2040, underscores the urgency for novel therapies. Conventional treatments like chemotherapy and radiation, while effective, cause severe side effects such as neuropathy and cardiotoxicity, prompting a shift toward natural alternatives with potentially better safety profiles. Natural products target dysregulated pathways in tumors, such as hyperactivated NF-κB leading to inflammation-driven carcinogenesis or PI3K/Akt promoting survival. For instance, flavonoids like genistein inhibit tyrosine kinases, mimicking the action of targeted therapies like imatinib but with broader applicability. Sources span terrestrial plants (e.g., Curcuma longa yielding curcumin), marine ecosystems (e.g., sponges producing trabectedin), and microbes (e.g., Streptomyces-derived doxorubicin). Ethnopharmacological insights from regions like Asia and Africa guide selection, with plants like *Fagonia indica* traditionally used for breast ailments now validated for apoptosis induction in cell lines. However, challenges persist: low yield from natural extraction, variability in bioactive content due to environmental factors, and pharmacokinetic issues like poor absorption necessitate advanced formulations. [6-10]

Preclinical evaluations employ in vitro assays (MTT, trypan blue) and in vivo models (xenografts in mice) to quantify cytotoxicity, often reporting EC50 values in the nM-μM range for potent agents. Toxicological studies reveal dose-dependent effects; for example, artemisinin derivatives show neurotoxicity at high doses but safety in therapeutic ranges. This introduction overviews the multifaceted role of natural products in cytotoxicity, setting

the foundation for detailed discussions on sources, mechanisms, and prospects, aiming to bridge traditional wisdom with scientific validation for improved cancer outcomes. [11,12]

Advances in high-throughput screening and omics technologies have accelerated discovery, identifying thousands of hits from libraries like the NCI's natural product repository. Marine biodiversity, largely untapped with less than 5% explored, offers unique alkaloids and polyketides adapted to extreme conditions. Microbial endophytes from plants provide sustainable sources, bypassing overharvesting concerns. Despite promise, only a fraction advances to clinics due to scalability and regulatory hurdles, emphasizing the need for synthetic analogs and biotech engineering.

Natural Products and Types

Natural products are compounds derived from living organisms, including plants, animals, microbes, and marine species, that have been utilized for millennia in traditional medicine and continue to play a crucial role in modern pharmacology. These substances are often secondary metabolites, produced not for primary growth but for defense, signaling, or adaptation to environmental stresses. The diversity of natural products stems from evolutionary processes, resulting in complex molecular structures that interact with biological targets in unique ways. In pharmacology, natural products are classified based on their biosynthetic pathways, chemical structures, and sources, providing a framework for drug discovery. Historically, they have been the foundation of many pharmaceuticals; for instance, aspirin from willow bark and morphine from opium poppy exemplify how natural compounds have been refined into essential drugs. Recent reviews highlight that over 50% of approved drugs are either natural products or their derivatives, underscoring their importance in addressing diseases like cancer, infections, and inflammation. The classification helps in systematic screening and understanding their therapeutic potential. [13-17]

One primary classification divides natural products into alkaloids, phenylpropanoids, polyketides, and terpenoids, based on biosynthetic origins. Alkaloids are nitrogen-containing compounds, often from plants, known for their potent pharmacological effects. They are synthesized via the shikimate or mevalonate pathways and include morphine, quinine, and vinblastine. Morphine, an opioid alkaloid from *Papaver somniferum*, acts as a pain reliever by binding to mu-opioid receptors. Quinine, from Cinchona bark, has antimalarial properties by interfering with heme polymerization in parasites. Vinblastine, from *Catharanthus roseus*, is used in cancer therapy for its microtubule-disrupting abilities. Alkaloids comprise about 20% of plant-derived natural products and are valued for their bioavailability and target specificity. However, their basic nature can lead to toxicity, necessitating careful dosing in pharmacological applications. Phenylpropanoids, derived from phenylalanine, include lignans, flavonoids, and coumarins, often found in aromatic plants. Flavonoids like quercetin from onions exhibit antioxidant properties, while lignans from flaxseeds have estrogenic effects useful in hormone-related therapies. [18-20]

Polyketides are assembled by polyketide synthases, similar to fatty acid synthesis, and include antibiotics like erythromycin from *Saccharopolyspora erythraea* and anticancer agents like doxorubicin from *Streptomyces peucetius*. These compounds feature lactone rings and are prevalent in microbial sources, offering structural diversity for drug leads. Terpenoids, or isoprenoids, are the largest class, built from isoprene units, ranging from monoterpenes (e.g., menthol) to sesquiterpenes (e.g., artemisinin) and diterpenes (e.g., paclitaxel). Artemisinin, from *Artemisia annua*, is a sesquiterpene lactone with antimalarial action via reactive oxygen species generation. Paclitaxel, a diterpene from *Taxus brevifolia*, stabilizes microtubules, halting cell division in cancers. Terpenoids dominate plant essential oils and resins, contributing to over 25,000 known compounds with applications in anti-inflammatory and antimicrobial therapies. This biosynthetic classification aids in predicting bioactivities and guiding synthetic modifications. [21-23]

Sources further categorize natural products: terrestrial plants, marine organisms, microbes, and animals. Plants are the most explored, yielding over 80% of natural drugs. Examples include curcumin from *Curcuma longa*, a polyphenol with anti-inflammatory effects, and resveratrol from grapes, a stilbene with cardioprotective properties. Plant-derived products often follow the Biopharmaceutics Classification System (BCS), with 29% in class 1 (high solubility, extensive metabolism) and 22% in class 2 (low solubility, extensive metabolism), influencing their pharmacokinetic profiles. Marine sources, like sponges and algae, provide unique scaffolds due to harsh oceanic conditions. Halichondrin B from sponges led to eribulin, an anticancer drug. Microbes, including bacteria and fungi, are fermentation-friendly; penicillin from *Penicillium notatum* revolutionized antibiotics. Animal-derived products, though less common, include heparin from pig intestines for anticoagulation. Recent advances in metagenomics have expanded microbial sourcing from unculturable species.

In drug discovery, natural products offer advantages like structural novelty and multitarget interactions, but challenges include supply limitations and complexity in isolation. Preclinical assessments involve extraction, fractionation, and bioassays to identify active compounds. For instance, ethnopharmacological knowledge from traditional Chinese medicine has led to discoveries like ephedrine from *Ephedra sinica*. Reviews emphasize sustainable sourcing and biotechnological production to overcome scarcity. Historical overviews trace natural products from ancient folklore to modern dereplication techniques, avoiding rediscovery of known compounds. Marine natural products, such as those from corals, add to the arsenal with antiviral and anticancer potentials.

The therapeutic spectrum of natural products spans antibacterials, antifungals, antiprotozoals, and antivirals, as seen in marine pharmacology literature. Plant-derived items promote health through detoxification and antioxidant activities, positioning them as remedies for chronic conditions. Future approaches involve high-throughput screening and AI-driven predictions to harness their potential. Overall, the types and sources of natural products form a vast pharmacy, continually unveiling new leads for pharmacology.

Cytotoxic Effects

Cytotoxicity refers to the ability of substances to cause cell death or inhibit growth, a property exploited in cancer therapy where natural products shine due to their selective targeting of malignant cells. Natural products induce cytotoxicity through various pathways, often with lower side effects than synthetic chemotherapeutics. Recent reviews from 2020-2025 highlight their promise in combating rising cancer incidences, with compounds from plants, marine sources, and microbes showing potent effects against diverse cancer types. For example, plant secondary metabolites like flavonoids and alkaloids

block cell cycles or initiate apoptosis in breast, lung, and colorectal cancers. The cytotoxic effects are dose-dependent, with in vitro assays revealing IC50 values in micromolar ranges, indicating efficacy comparable to approved drugs. [24-27]

Plant-derived natural products dominate cytotoxicity research. Curcumin from turmeric exhibits antiproliferative effects on prostate and breast cancer cells by modulating NF-κB and PI3K/Akt pathways. Artemisinin derivatives from Artemisia annua generate reactive oxygen species (ROS), leading to DNA damage in leukemia cells. Genistein, an isoflavone from soy, induces G2/M arrest in ovarian cancer, enhancing sensitivity to conventional therapies. Recent studies on Uncaria tomentosa (cat's claw) extracts show oxindole alkaloids reactivating apoptotic signaling in colon cancer, with cytotoxicity amplified in resistant lines. Herbal medicines from traditional systems, like those in Chinese pharmacopeia, enhance immune responses and reverse multidrug resistance, as seen in combinations with doxorubicin. [28-35]

Marine natural products offer novel cytotoxic agents. From 2019-2024, over 100 new compounds were reported with anticancer activity, including polyketides from sponges that inhibit microtubule assembly in sarcomas. Trabectedin from sea squirts alkylates DNA, approved for soft tissue sarcomas, demonstrating sustained cytotoxicity. Fucoidan from brown algae inhibits proliferation in colon adenocarcinoma via immune activation. These compounds often have nanomolar potency, surpassing terrestrial counterparts due to unique evolutionary adaptations. [36-40]

Microbial sources provide cytotoxic antibiotics repurposed for oncology. Salinosporamide A from marine bacteria inhibits proteasomes, inducing apoptosis in multiple myeloma. Endophytic fungi from plants yield taxol-like compounds with effects on high-risk leukemias. Cephalotaxine and homoharringtonine from Cephalotaxus inhibit protein synthesis in acute lymphoblastic leukemia (ALL), with EC50 values as low as 0.0129 μM. [41]

In preclinical models, natural products show broad cytotoxicity. For instance, platycodin D from *Platycodon grandiflorus* activates caspases in breast cancer, while thymol from thyme induces necrosis in glioblastoma. Studies on *Artemisia absinthium* and Plantago species reveal apoptotic effects on lung and melanoma cells. Cytotoxic assays like MTT and LDH confirm membrane disruption and metabolic inhibition. In vivo, rodent xenografts demonstrate tumor reduction without severe toxicity, though some like aristolochic acids pose nephrotoxic risks. [42-44]

Synergistic effects amplify cytotoxicity; natural products combined with chemotherapy overcome resistance, as in quercetin with gemcitabine in breast cancer. Reviews note that 57% of clinical trial compounds are natural product-derived, with recent integrations into immunotherapy. Challenges include bioavailability, addressed by nanotechnology. Overall, cytotoxic effects of natural products offer sustainable, effective alternatives in cancer therapy.

Mechanism of Action

The mechanisms of action (MoA) underlying the cytotoxic effects of natural products in cancer therapy are multifaceted, often involving the targeting of multiple cellular processes to induce cell death or inhibit proliferation in malignant cells. Natural products, derived from plants, marine organisms, microbes, and other sources, exhibit structural diversity that allows them to interact with a wide array of molecular targets. This multitargeted approach is advantageous over single-target synthetic drugs, as it reduces the likelihood of resistance development, a common challenge in oncology where tumors can adapt through genetic mutations. Key mechanisms include apoptosis induction, cell cycle arrest, reactive oxygen species (ROS) generation, modulation of signaling pathways, autophagy, angiogenesis inhibition, and metastasis suppression. These processes exploit cancer hallmarks such as sustained proliferative signaling, evasion of growth suppressors, and resistance to cell death, as outlined by Hanahan and Weinberg. Recent reviews emphasize that over 60% of anticancer drugs are natural product-derived or inspired, with their MoA often elucidated through in vitro assays (e.g., MTT, flow cytometry), in vivo models (e.g., xenografts), and omics technologies (e.g., proteomics, transcriptomics). For instance, chemical proteomics combined with artificial intelligence has accelerated target identification, revealing how compounds like paclitaxel bind β-tubulin to disrupt mitosis. This section delves into these mechanisms in detail, highlighting specific compounds, pathways, and examples from recent studies (2020-2025), providing a comprehensive understanding of how natural products achieve cytotoxicity while often sparing normal cells due to tumor-specific vulnerabilities like elevated ROS levels or dysregulated pathways. [45-50]

Apoptosis, or programmed cell death, is a primary mechanism by which many natural products exert cytotoxicity, activating either the intrinsic (mitochondrial) or extrinsic (death receptor) pathways to eliminate cancer cells without eliciting inflammation. The intrinsic pathway involves mitochondrial outer membrane permeabilization (MOMP), releasing cytochrome c to activate caspases (e.g., caspase-9, -3), while the extrinsic pathway engages death receptors like Fas or TRAIL, leading to caspase-8 activation. Natural products often tip the balance toward pro-apoptotic proteins (e.g., Bax, Bak) over anti-apoptotic ones (e.g., Bcl-2, Bcl-xL). For example, paclitaxel, a terpenoid from Taxus brevifolia, stabilizes microtubules, leading to mitotic arrest and subsequent apoptosis via β-tubulin binding, effective against ovarian, breast, and lung cancers. Triptolide, another terpenoid from Tripterygium wilfordii, inhibits transcriptional machinery, targeting NF-κB, p53, and heat shock proteins, inducing apoptosis in breast, lung, and ovarian cancers. Artemisinin, a sesquiterpene lactone from Artemisia annua, triggers apoptosis through oxidative stress and DNA damage, particularly in leukemia, lung, breast, and liver cancers, and enhances antitumor immunity by reducing TGF-β in breast cancer models. Betulinic acid, a pentacyclic triterpenoid, activates mitochondrial apoptosis and regulates p53/p21 signaling in breast cancer, synergizing with 5-fluorouracil in ovarian cancer. Ursolic acid (UA), found in apples and rosemary, inhibits Akt/NF-κB, reducing anti-apoptotic proteins and enhancing caspase-3 in bladder cancer. Polyphenols like quercetin target AKT/mTOR/PTEN in breast cancer, promoting apoptosis and enhancing chemo-immunotherapy in colorectal cancer when combined with ginsenoside Rg3. Curcumin from Curcuma longa activates both intrinsic and extrinsic apoptosis pathways in colorectal and lung cancers, upregulating p21, p53, and TIMP1 while downregulating MMP2, and synergizes with doxorubicin via p38 MAPK and miR-378, activating caspases and decreasing Bcl-2. Luteolin, a flavone, induces apoptosis in tamoxifen-resistant breast cancer by halting G2/M and diminishing PI3K/AKT/mTOR. Puerarin increases apoptosis in non-small cell lung cancer (NSCLC) and ovarian cancer via key signaling modulation. Apigenin targets p38-MAPK, NF-κB, and JAK/STAT in breast cancer, inducing apoptosis and autophagic death in hypoxic gastric cancer. Isoliquiritigenin (ISL) upregulates p62/SQSTM1 for caspase-8 activation in colorectal cancer and induces apoptosis/autophagy in hepatocellular carcinoma via PI3K/AKT/mTOR downregulation. Epigallocatechin gallate (EGCG) from green tea promotes autophagic apoptosis in breast cancer via ESCRT-III assembly and disrupts AR signaling in prostate cancer. Kaempferol induces apoptosis in 5-FU-resistant colorectal cancer, reversing resistance. Gallic acid triggers mitochondria-mediated apoptosis in prostate cancer via ROS, enhancing camptothecin in breast cancer. Resveratrol induces apoptosis, modulates angiogenesis, and suppresses metastasis, sensitizing breast cancer to doxorubicin via SIRT1/β-catenin. Quinones like β-lapachone induce apoptosis via DNA damage and ROS in

NQO1-high breast cancer, and ferroptosis in colorectal cancer via JNK. Shikonin targets galectin-1 for apoptosis/autophagy in colorectal cancer via JNK, and ferroptosis in small cell lung cancer (SCLC) via ATF3. Dicoumarol inhibits NQO1, modulating mitochondria and ROS for apoptosis in ovarian cancer. Alkaloids such as piperine suppress Akt for apoptosis in triple-negative breast cancer (TNBC) and inhibit P-gp to enhance chemotherapy. Evodiamine (EVO) induces apoptosis/autophagy in lung cancer and glioblastoma via LC3B-II and beclin-1 upregulation. Berberine downregulates GRP78 for apoptosis in colon cancer and enhances autophagy in gastric cancer via MAPK/mTOR/p70S6K and Akt suppression. From plant extracts, Aristolochia baetica induces apoptosis in MCF-7 breast cancer via aristolochic acid I. Artemisia annua extracts promote antiapoptotic effects in TNBC xenografts. Coptidis rhizoma activates caspases and increases Bcl-2 in Hep3B cells. Fagonia indica saponins cause PARP and caspase-3 cleavage in breast and colon cancers. Morus alba induces apoptosis in HepG2 and HL-60 via caspase reduction and Bax/Bcl-2 ratio increase. Platycodon grandiflorus activates caspases, releases cytochrome c, and increases P19ARF/Bax in ovarian and cervical cancers. 1'-Acetoxychavicol acetate (ACA) from Alpinia conchigera induces apoptosis in breast, cervical, and myeloma cells via caspase activation and TRAIL, inhibiting non-canonical autophagy in NSCLC. Genistein activates caspases and inhibits NF-κB in HeLa, colon, and breast cancers. Thymoquinone from Nigella sativa generates ROS for apoptosis in breast, cholangiocarcinoma, and lymphoma, elevating TRAIL receptors. Lupeol modulates BAX/BCL-2 and FAS in resistant cells. Shikonin induces necroptosis via RIP1/RIP3 and mROS, overcoming resistance. Pterostilbene downregulates RAGE/PI3K/Akt for apoptosis via ROS and mitochondrial dysfunction in pancreatic cancer. These examples illustrate how apoptosis is a convergent endpoint for diverse natural products, often synergizing with chemotherapeutics to enhance efficacy.

Cell cycle arrest is another critical mechanism, where natural products halt progression at checkpoints (G0/G1, S, G2/M) to prevent DNA replication and mitosis in rapidly dividing cancer cells. This often involves modulating cyclins, cyclin-dependent kinases (CDKs), and inhibitors like p21/p27. Genistein induces G2/M arrest in breast, colon, and gastric cancers via Ras/MAPK/AP-1, ATM/p53, and p21Waf1/Cip1 pathways. Thymol arrests at G0/G1 in breast, leukemia, and mastocytoma cells. Thymoquinone causes G1 arrest in breast cancer and G2/M in cholangiocarcinoma. Ursolic acid arrests at G0/G1 in gastric cancer and modulates Akt/mTOR in breast tumors. *Morus alba* arrests at G2/M in hepatoma and colorectal cancers. β-Elemene regulates ROS/AMPK/mTOR for arrest and autophagy in colorectal cancer. Kaempferol causes arrest in resistant colorectal cancer. Celastrol and triptolide induce G2/M arrest via ROS and Akt/survivin/EGFR inhibition. Alantolactone, a sesquiterpene lactone, suppresses cell cycle progression, though specific phases are not detailed in limited studies. These arrests often lead to apoptosis if unresolved, amplifying cytotoxicity.

ROS generation exploits cancer cells' high oxidative stress, leading to DNA damage, protein oxidation, and lipid peroxidation. Many natural products contain redox-active moieties (e.g., endoperoxides, quinones) that elevate ROS beyond thresholds. Artemisinin's endoperoxide bridge generates radicals for DNA damage. Thymoquinone induces ROS in breast cancer, activating p38 for apoptosis. Platycodin D from Platycodon produces ROS via Egr-1 in leukemia. Morus alba induces ROS and GSK3β-ATF3 in colorectal cancer. ACA induces ROS-related apoptosis. Plumbagin suppresses glutathione for ROS and DNA breakage. β-Lapachone generates ROS in NQO1-high cells. Gallic acid produces ROS for mitochondrial apoptosis. Dicoumarol shifts metabolism for ROS. Alantolactone increases cellular ROS. This mechanism synergizes with others, as ROS can activate signaling cascades leading to death.

Modulation of signaling pathways is central, with natural products inhibiting oncogenic pathways like PI3K/AKT/mTOR, NF-κB, MAPK, Wnt, Hedgehog, and Notch. Curcumin inhibits NF-κB and PI3K/Akt. Genistein modulates ERK1/2, FAK/paxillin, MAPK, and PI3K/Akt. Coptidis rhizoma inactivates EEF2 for VEGF downregulation and inhibits Rho/ROCK for migration prevention. ACA suppresses NF-κB and alters miRNA targeting SMAD4/RSU1. Ursolic acid inhibits COX-2 and PI3K/Akt. Quercetin targets RAGE/PI3K/AKT/mTOR. Ferulic acid reverses MDR via PI3K/AKT/NF-κB. Berberine decreases Bcl-2/VEGF. Neferine upregulates p53 and downregulates FAK/VEGF/MMPs. Formononetin downregulates MMPs. Aloe emodin suppresses Ras/ERK/PI3K/mTOR. Capsaicin reduces Akt/mTOR. Heteronemin downregulates AP-1/NF-κB/AMPK/c-myc. Withaferin A inhibits PI3K/AKT. Tectorigenin downregulates XIAP/Bcl-2/COX-2/FLIP/IκB/IKK/Akt. β-Elemene regulates ROS/AMPK/mTOR. Apigenin targets p38-MAPK/NF-κB/JAK/STAT. ISL downregulates PI3K/AKT/mTOR. Berberine suppresses MAPK/mTOR/p70S6K/Akt. Alantolactone inhibits progression pathways. These inhibitions disrupt proliferation, survival, and invasion.

Other mechanisms include autophagy (self-degradation via lysosomes), often induced via mTOR inhibition; for example, EGCG promotes autophagy in breast cancer. β-Elemene induces autophagy in colorectal cancer. EVO upregulates LC3B-II/beclin-1. Metastasis suppression: Alantolactone suppresses metastasis. Genistein inhibits MMPs and telomerase. Angiogenesis inhibition: Genistein targets novel pathways. Coptidis downregulates VEGF. Ferroptosis (iron-dependent death): Shikonin and β-lapachone induce it via ATF3 and JNK. Necroptosis: Shikonin via RIP1/RIP3. MDR reversal: EGCG suppresses MDR; ferulic acid reverses P-gp via PI3K/AKT/NF-κB.

Future Perspectives

The future of natural products in cytotoxicity research is bright, propelled by technological innovations and interdisciplinary approaches. Genome mining and CRISPR-Cas9 enable activation of silent biosynthetic gene clusters in microbes, uncovering novel compounds like macrolides from Streptomyces with cytotoxic potential. Biosynthetic engineering can produce analogues with improved pharmacokinetics, such as rapalogs with enhanced anti-proliferative activity. Nanotechnology offers targeted delivery, encapsulating compounds like ACA in lipid carriers to boost efficacy against prostate cancer while reducing systemic toxicity. Combination therapies, pairing natural products with immunotherapeutics, could enhance immunogenic cell death, as seen with cardiac glycosides. Addressing multidrug resistance, agents like curcumin inhibit efflux pumps, synergizing with conventional drugs. Challenges include scalability and standardization; synthetic biology may resolve supply issues, as with taxol production. Metabolomics accelerates identification of cytotoxic hits from complex extracts. Exploring underexplored sources, like deep-sea microbes or extremophiles, promises new scaffolds. Clinical translation requires robust trials; phase I studies of peptides like lunasin show promise in chemoprevention. Personalized medicine, using omics to match compounds to tumor profiles, could optimize cytotoxicity. Sustainability is key, with ethical sourcing and cultivation preventing overexploitation. Overall, integrating AI for predictive modeling and high-throughput screening will expedite discovery, potentially yielding next-generation cytotoxics by 2030.

Conclusion

In summary, natural products offer unparalleled potential in harnessing cytotoxicity for cancer therapy, with diverse sources and mechanisms providing selective, effective agents. From plant metabolites inducing apoptosis to marine compounds blocking mitosis, their integration into modern medicine addresses limitations of synthetic drugs. Future advancements will further elevate their role, promising safer treatments.

REFERENCES

1. Atanasov AG, Zotchev SB, Dirsch VM, Supuran CT. Natural products in drug discovery: advances and opportunities. Nat Rev Drug Discov. 2021;20(3):200-16.
2. Balandrin MF, Kinghorn AD, Farnsworth NR. Plant-derived natural products in drug discovery and development: an overview. In: Human medicinal agents from plants. Washington, DC: American Chemical Society; 1993. p. 2-12.
3. Bahar M, Deng Y, Fletcher JN, Kinghorn AD. Plant-derived natural products in drug discovery and development: an overview. In: Selected topics in the chemistry of natural products. Singapore: World Scientific; 2007. p. 11-30.
4. Newman DJ, Cragg GM, Snader KM. The influence of natural products upon drug discovery. Nat Prod Rep. 2000;17(3):215-34.
5. Bohlin L, Bruhn JG. Bioassay methods in natural product research and drug development. Dordrecht: Springer Science & Business Media; 1999.
6. Cadoná FC, Dantas RF, de Mello GH, Silva FP Jr. Natural products targeting into cancer hallmarks: an update on caffeine, theobromine, and (+)-catechin. Crit Rev Food Sci Nutr. 2022;62(25):7222-41.
7. Brennan P, Davey-Smith G. Identifying novel causes of cancers to enhance cancer prevention: new strategies are needed. J Natl Cancer Inst. 2022;114(3):353-60.
8. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.
9. Hassanpour SH, Dehghani M. Review of cancer from perspective of molecular. J Cancer Res Pract. 2017;4(4):127-9.
10. Rahman MM, Sarker MT, Tumpa MAA, Yamin M, Islam T, Park MN, Islam MR, Rauf A, Sharma R, Cavalu S. Exploring the recent trends in perturbing the cellular signaling pathways in cancer by natural products. Front Pharmacol. 2022;13:950109.
11. Liu S, Khan AR, Yang X, Dong B, Ji J, Zhai G. The reversal of chemotherapy-induced multidrug resistance by nanomedicine for cancer therapy. J Control Release. 2021;335:1-20.
12. Lee S, Rauch J, Kolch W. Targeting MAPK signaling in cancer: mechanisms of drug resistance and sensitivity. Int J Mol Sci. 2020;21(3):1102.
13. Dudareva N, Klempien A, Muhlemann JK, Kaplan I. Biosynthesis, function and metabolic engineering of plant volatile organic compounds. New Phytol. 2013;198(1):16-32.
14. Quideau S, Deffieux D, Douat-Casassus C, Pouységu L. Plant polyphenols: chemical properties, biological activities, and synthesis. Angew Chem Int Ed. 2011;50(3):586-621.
15. Karmakar A, Karmakar S, Mukherjee S. Properties of various plants and animals feedstocks for biodiesel production. Bioresour Technol. 2010;101(19):7201-10.
16. Chaachouay N, Azeroual A, Benkhnigue O, Zidane L. Alkaloids: a suitable precursor for nanomaterials synthesis, and their various applications. In: Husen A, editor. Secondary metabolites based green synthesis of nanomaterials and their applications. Singapore: Springer Nature; 2023. p. 23-48.
17. Zahid Z, Khan S, Nadeem F, Azeem MW. The review of power of poppy: harnessing benefits of nature's most dangerous plant. Int Sci Organ. 2015;8(2):56-64.
18. Tungmunnithum D, Thongboonyou A, Pholboon A, Yangsabai A. Flavonoids and other phenolic compounds from medicinal plants for pharmaceutical and medical aspects: an overview. Medicines. 2018;5(3):93.
19. Yang W, Chen X, Li Y, Guo S, Wang Z, Yu X. Advances in pharmacological activities of terpenoids. Nat Prod Commun. 2020;15(3):1934578X20903555.
20. Ludwiczuk A, Skalicka-Woźniak K, Georgiev MI. Terpenoids. In: Pharmacognosy. Amsterdam: Elsevier; 2017. p. 233-66.
21. Rana A, Samtiya M, Dhewa T, Mishra V, Aluko RE. Health benefits of polyphenols: a concise review. J Food Biochem. 2022;46(10):e14264.
22. Zhang L, Han Z, Granato D. Polyphenols in foods: classification, methods of identification, and nutritional aspects in human health. Adv Food Nutr Res. 2021;98:1-33.
23. Bashraheel SS, Domling A, Goda SK. Update on targeted cancer therapies, single or in combination, and their fine tuning for precision medicine. Biomed Pharmacother. 2020;125:110009.
24. Sharifi-Rad J, Quispe C, Patra JK, Singh YD, Panda MK, Das G, Adetunji CO, Michael OS, Sytar O, Polito L, et al. Paclitaxel: application in modern oncology and nanomedicine-based cancer therapy. Oxid Med Cell Longev. 2021;2021:3687700.
25. Nonnekens J, Hoeijmakers JH. After surviving cancer, what about late life effects of the cure? EMBO Mol Med. 2017;9(1):4-6.
26. Wigmore PM, Mustafa S, El-Beltagy M, Lyons L, Umka J, Bennett G. Effects of 5-FU. In: Chemo fog. New York: Springer; 2010. p. 157-64.
27. Bishayee A, Sethi G. Bioactive natural products in cancer prevention and therapy: progress and promise. Semin Cancer Biol. 2016;40-41:1-3.
28. Wang L, Sun J, Gao P, Su K, Wu H, Li J, Lou W. Wnt1-inducible signaling protein 1 regulates laryngeal squamous cell carcinoma glycolysis and chemoresistance via the YAP1/TEAD1/GLUT1 pathway. J Cell Physiol. 2019;234(9):15941-50.

29. Zhang P, Lai ZL, Chen HF, Zhang M, Wang A, Jia T, Sun WQ, Zhu XM, Chen XF, Zhao Z, et al. Curcumin synergizes with 5-fluorouracil by impairing AMPK/ULK1-dependent autophagy, AKT activity and enhancing apoptosis in colon cancer cells with tumor growth inhibition in xenograft mice. J Exp Clin Cancer Res. 2017;36(1):190.

30. Namkaew J, Jaroonwitchawan T, Rujanapun N, Saelee J, Noisa P. Combined effects of curcumin and doxorubicin on cell death and cell migration of SH-SY5Y human neuroblastoma cells. In Vitro Cell Dev Biol Anim. 2018;54(9):629-39.

31. Öztürk Y, Günaydın C, Yalçın F, Nazıroğlu M, Braidy N. Resveratrol enhances apoptotic and oxidant effects of paclitaxel through TRPM2 channel activation in DBTRG glioblastoma cells. Oxid Med Cell Longev. 2019;2019:4619865.

32. Shen W, Liang B, Yin J, Li X, Cheng J. Noscapine increases the sensitivity of drug-resistant ovarian cancer cell line SKOV3/DDP to cisplatin by regulating cell cycle and activating apoptotic pathways. Cell Biochem Biophys. 2015;72(1):203-13.

33. Sivalingam KS, Paramasivan P, Weng CF, Viswanadha VP. Neferine potentiates the antitumor effect of cisplatin in human lung adenocarcinoma cells via a mitochondria-mediated apoptosis pathway. J Cell Biochem. 2017;118(9):2865-76.

34. Wang Y, Lu HL, Liu YD, Yang LY, Jiang QK, Zhu XJ, Fan HN, Qian Y. Cryptotanshinone sensitizes antitumor effect of paclitaxel on tongue squamous cell carcinoma growth by inhibiting the JAK/STAT3 signaling pathway. Biomed Pharmacother. 2017;95:1388-96.

35. Zhang X, Ni Q, Wang Y, Fan HW, Li Y. Synergistic anticancer effects of formononetin and temozolomide on glioma C6 cells. Biol Pharm Bull. 2018;41(8):1194-202.

36. Saikia M, Retnakumari AP, Anwar S, Anto NP, Mittal R, Shah S, Pillai KS, Balachandran VS, Peter V, Thomas R, et al. Heteronemin, a marine natural product, sensitizes acute myeloid leukemia cells towards cytarabine chemotherapy by regulating farnesylation of Ras. Oncotarget. 2018;9(26):18115-27.

37. Jiang QW, Cheng KJ, Mei XL, Qiu JG, Zhang WJ, Xue YQ, Qin WM, Yang Y, Zheng DW, Chen Y, et al. Synergistic anticancer effects of triptolide and celastrol, two main compounds from thunder god vine. Oncotarget. 2015;6(31):32790-804.

38. Huang Y, Wang K, Gu C, Yu G, Zhao D, Mai W, Zhong Y, Liu S, Nie Y, Yang H. Berberine, a natural plant alkaloid, synergistically sensitizes human liver cancer cells to sorafenib. Oncol Rep. 2018;40(3):1525-32.

39. Desai V, Jain A, Shaghaghi H, Summer R, Lai JCK, Bhushan A. Combination of biochanin A and temozolomide impairs tumor growth by modulating cell metabolism in glioblastoma multiforme. Anticancer Res. 2019;39(1):57-66.

40. Du Plessis-Stoman D, Du Preez JGH, van de Venter M. Combination treatment with oxaliplatin and mangiferin causes increased apoptosis and downregulation of NFκB in cancer cell lines. Afr J Tradit Complement Altern Med. 2011;8(2):177-84.

41. Ahmadi E, Zarghami N, Jafarabadi MA, Alizadeh L, Khojastehfard M, Yamchi MR, Salehi R. Enhanced anticancer potency by combination chemotherapy of HT-29 cells with biodegradable, pH-sensitive nanoparticles for co-delivery of hydroxytyrosol and doxorubicin. J Drug Deliv Sci Technol. 2019;51:721-35.

42. Abdelaziz HM, Elzoghby AO, Helmy MW, Samaha MW, Fang JY, Freag MS. Liquid crystalline assembly for potential combinatorial chemo–herbal drug delivery to lung cancer cells. Int J Nanomed. 2019;14:499-517.

43. Xia Q, Ling L, Ismail M, Du Y, He W, Zhou W, Yao C, Li X. Paclitaxel encapsulated in artesunate-phospholipid liposomes for combinatorial delivery. J Drug Deliv Sci Technol. 2019;51:372-82.

44. Wang S, Shao M, Zhong Z, Wang A, Cao J, Lu Y, Wang Y, Zhang J. Co-delivery of gambogic acid and TRAIL plasmid by hyaluronic acid grafted PEI-PLGA nanoparticles for the treatment of triple negative breast cancer. Drug Deliv. 2017;24(1):1791-800.

45. Bian Y, Guo D. Targeted therapy for hepatocellular carcinoma: co-delivery of sorafenib and curcumin using lactosylated pH-responsive nanoparticles. Drug Des Devel Ther. 2020;14:647-59.

46. Wang D, Zhou J, Chen R, Shi R, Zhao G, Xia G, Li R, Liu Z, Tian J, Wang H, et al. Controllable synthesis of dual-MOFs nanostructures for pH-responsive artemisinin delivery, magnetic resonance and optical dual-model imaging-guided chemo/photothermal combinational cancer therapy. Biomaterials. 2016;100:27-40.

47. Wang J, Muhammad N, Li T, Wang H, Liu Y, Liu B, Zhan H. Hyaluronic acid-coated camptothecin nanocrystals for targeted drug delivery to enhance anticancer efficacy. Mol Pharm. 2020;17(7):2411-25.

48. Gupta L, Sharma AK, Gothwal A, Khan MS, Khinchi MP, Qayum A, Singh SK, Gupta U. Dendrimer encapsulated and conjugated delivery of berberine: a novel approach mitigating toxicity and improving in vivo pharmacokinetics. Int J Pharm. 2017;528(1-2):88-99.

49. Ding J, Liang T, Min Q, Jiang LP, Zhu JJ. "Stealth and fully-laden" drug carriers: self-assembled nanogels encapsulated with epigallocatechin gallate and siRNA for drug-resistant breast cancer therapy. ACS Appl Mater Interfaces. 2018;10(12):9938-48.

50. Amaral R, dos Santos SA, Andrade LN, Severino P, Carvalho AA. Natural products as treatment against cancer: a historical and current vision. Clin Oncol. 2019;4:1562.