Bioactive Natural Products as Multitargeted Anticancer Agents: Mechanisms, Preclinical Evidence, and Translational Challenges

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***Abstract*—Cancer remains one of the leading causes of morbidity and mortality worldwide, demanding continuous innovation in treatment strategies. Natural compounds derived from plants, marine organisms, microbes, and animals offer a diverse arsenal of bioactive molecules with potent anticancer properties. These agents act through multiple mechanisms, including induction of apoptosis, cell cycle arrest, inhibition of angiogenesis and metastasis, epigenetic modulation, and immunomodulation. This review examines the therapeutic potential of natural compounds, including curcumin, fucoidan, taccalonolides, honokiol, and others, and discusses their molecular targets and clinical relevance. Furthermore, we discuss their synergistic effects with conventional therapies, the outcomes of key in vivo and clinical trials, and the challenges of translating these agents into clinical applications. Emerging technologies such as nanocarrier-based delivery systems and synthetic biology offer promising solutions to overcome bioavailability and production issues. By integrating traditional pharmacognosy with modern biomedical approaches, natural compounds are poised to become a cornerstone of future oncological therapeutics.**

***Index Terms*—natural compounds; anticancer agents; apoptosis; marine bioactives, phytochemicals; immunomodulation; chemotherapy synergy; drug discovery**

I. INTRODUCTION

Cancer is a multifactorial disease characterized by the uncontrolled proliferation of abnormal cells, evasion of apoptosis, and potential for metastasis. While advances in surgery, radiotherapy, and chemotherapy have improved patient survival, the limitations of these
Treatments such as systemic toxicity, resistance, and high costs underscore the need for novel, safer, and multi-targeted therapeutics.

Historically, nature has served as a wellspring for drug discovery. According to Cragg & Newman (2020), over 60% of current anticancer agents are derived from natural sources or their analogs. Natural products exhibit unparalleled chemical diversity and biological specificity, making them ideal candidates for novel anticancer drugs. The ability of natural compounds to modulate multiple cellular pathways, along with lower toxicity profiles, makes them attractive as both stand-alone agents and as adjuncts to existing therapies. Increasing efforts to screen ethnobotanical sources, marine life, and microbial species for pharmacologically active constituents have further expanded the pool of potential leads.

Given the enormous chemical diversity present in natural sources, this review prioritizes compounds for discussion using three pragmatic criteria: (i) evidence of multi-target activity relevant to canonical cancer hallmarks (apoptosis, angiogenesis, metastasis, epigenetic regulation, immune modulation); (ii) presence of supportive preclinical data (in vitro IC_{50} or in vivo tumour models) and/or early-phase clinical data; and (iii) structural or pharmacological novelty that makes the compound a tractable lead for medicinal chemistry or formulation approaches. The compounds selected (e.g., curcumin, paclitaxel/eribulin class derivatives, trabectedin, fucoidan, salinomycin, psammaplin A, etc.) are therefore representative not exhaustive and were

chosen to illustrate common mechanisms, translational successes, and typical failure modes that shape the field.

The scope of this review is to provide a perspective on natural bioactive molecules, integrating their sources, structural features, and anticancer mechanisms; a graphical abstract summarizing these aspects is provided.

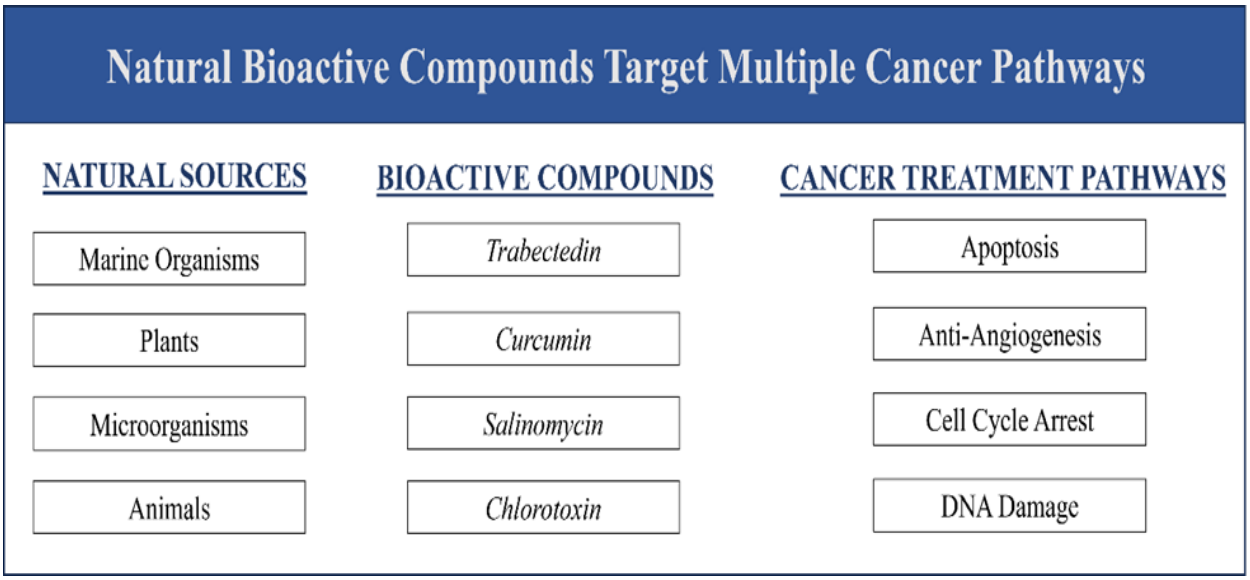

Fig. 1: Natural bioactive compounds from diverse sources target multiple cancer pathways.

Natural sources including marine organisms, plants, microorganisms, and animals yield structurally distinct bioactive molecules such as trabectedin, curcumin, salinomycin, and chlorotoxin. These compounds demonstrate multi-target therapeutic potential by simultaneously affecting key cancer treatment pathways including apoptosis (programmed cell death), anti-angiogenesis (blood vessel formation inhibition), cell cycle arrest (growth inhibition), and DNA damage (genetic material targeting), highlighting the promise of nature-derived compounds for comprehensive cancer therapy.

II. SOURCES OF NATURAL ANTICANCER COMPOUNDS

2.1 Plant-Derived Compounds

Plants have long served as reservoirs for bioactive agents, yielding compounds with unique pharmacophores and therapeutic potential. Some of the most effective chemotherapeutic agents are derived from terrestrial flora. For example, paclitaxel (Taxol), obtained from Taxus brevifolia, exerts its anticancer effect by stabilizing microtubules, thus inhibiting cell division. Vinca alkaloids such as vincristine and vinblastine, extracted from Catharanthus roseus, interfere with microtubule polymerization. Honokiol, a polyphenol from Magnolia officinalis, inhibits Akt, MAPK, and NF-Kb pathways, thereby inducing apoptosis and inhibiting angiogenesis.

Camptothecin from Camptotheca acuminata is another example, acting as a topoisomerase I inhibitor. Taccalonolides from Tacca species are unique in their microtubule-stabilizing properties and remain active even in taxane-resistant cancers. Additional promising plant-derived agents include betulinic acid, resveratrol, curcumin, epigallocatechin gallate (EGCG), and thymoquinone. Structurally, curcumin's α, β-unsaturated β-diketone moiety enables Michael addition with nucleophilic residues in target proteins, contributing to NF-Kb inhibition. Honokiol's biphenolic structure facilitates hydrogen bonding and π–π stacking interactions with signaling enzymes.

2.2 Marine-Derived Compounds

Marine organisms offer a largely untapped and chemically diverse source of bioactive molecules. Trabectedin, isolated from the sea squirt Ecteinascidia turbinata, has DNA-binding properties and is approved for soft tissue sarcoma. Halichondrin B from Halichondria okadai

inspired by eribulin, a microtubule-dynamics inhibitor. Marine polysaccharides such as fucoidan (from brown algae) and carrageenan (from red algae) demonstrate immunomodulatory and anti-angiogenic properties by acting on PI3K/Akt/mTOR and NF-κB pathways. Psammaplin A, from marine sponges, inhibits both DNMT and HDAC, showing promise as an epigenetic modulator.

Squalamine, a compound from dogfish sharks, exhibits anti-angiogenic and antimicrobial properties, making it a dual-function compound under investigation in multiple cancer models.

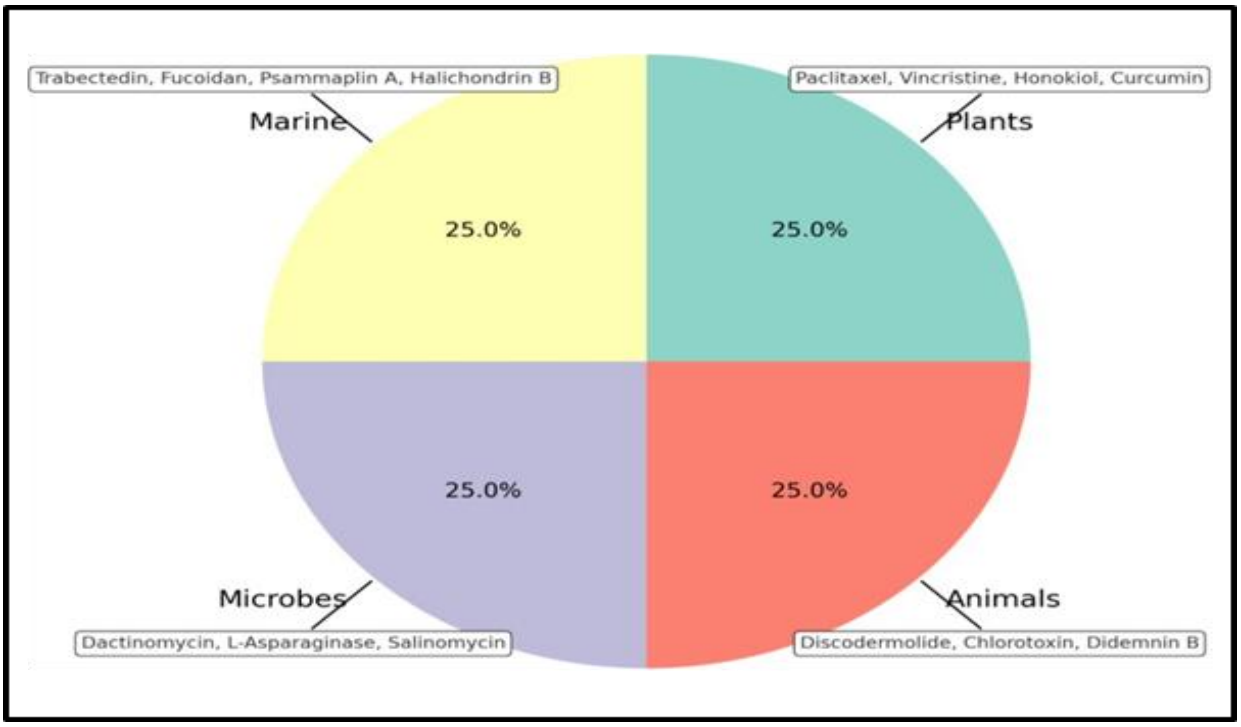

Fig. 2: Distribution of natural anticancer compounds by biological source.

The pie chart illustrates the relative contribution (25% each) of four major natural sources of anticancer agents: marine organisms (Trabectedin, Fucoidan, Psammaplin A, Halichondrin B), plants (Paclitaxel, Vincristine, Honokiol, Curcumin), microbes (Dactinomycin, L-Asparaginase, Salinomycin), and animals (Discodermolide, Chlorotoxin, Didemnin B). Equal distribution highlights the diverse origins of bioactive compounds currently explored for anticancer research and underscores the potential of marine, microbial, plant, and animal resources as drug discovery reservoirs.

2.3 Microbial-Derived Compounds

Microorganisms, particularly actinomycetes and fungi, are prolific producers of secondary metabolites with diverse biological activities. Dactinomycin, mitomycin C, and L-asparaginase are widely used microbial derivatives. Salinomycin, isolated from Streptomyces albus, has emerged as a selective inhibitor of cancer stem cells, capable of inducing mitochondrial apoptosis. Other notable compounds include streptozotocin for pancreatic cancer and the anthracycline antibiotics (e.g., doxorubicin), which intercalate DNA and generate free radicals to kill cancer cells.

2.4 Animal-Derived Compounds

Animal sources, though less explored, provide potent anticancer candidates. Discodermolide from deep-sea sponges has microtubule-stabilizing effects, often surpassing paclitaxel in potency. Didemnin B from marine tunicates exhibits cell cycle arrest and apoptosis. Chlorotoxin, a peptide from scorpion venom, selectively binds to glioma cells. Additionally, peptides from cone snail venom and amphibian skin secretions are under investigation for their anticancer and immunomodulatory properties.

Table 1: Bioactive Molecules from Different Natural Sources and Their Anticancer Properties

Compound	Source	Primary Target / Pathway	Cancer Type Studied	IC_{50} / MIC (µM or µg/mL)	Reference
Curcumin	Curcuma longa (Plant)	NF-κB, PI3K/Akt, MAPK	Breast, colorectal, pancreatic	5–15 µM	[26]
Resveratrol	Grapes, berries (Plant)	MMP-2/9 inhibition, p53 activation	Colon, prostate	10–25 µM	[23]
Betulinic acid	Betula spp. (Plant)	Mitochondrial apoptosis (Bax↑, Bcl-2↓)	Pancreatic, melanoma	2–10 µM	[11]
Honokiol	Magnolia officinalis (Plant)	Akt, MAPK, NF-κB inhibition	Osteosarcoma, breast	3–8 µM	[28]
Paclitaxel	Taxus brevifolia (Plant)	Microtubule stabilization	Breast, ovarian	5–50 nM	[9]
Fucoidan	Brown algae (Fucus vesiculosus) (Marine)	VEGF, PI3K/Akt, NF-κB	Colon, breast	50–200 µg/mL	[12]
Trabectedin	Ecteinascidia turbinata (Marine)	DNA binding (minor groove)	Soft tissue sarcoma	0.5–1 nM	[1]
Psammaplin A	Marine sponge (Psammaplinidae) (Marine)	DNMT, HDAC inhibition	Breast, leukemia	1–10 µM	[10]
Salinomycin	Streptomyces albus (Microbial)	Mitochondrial apoptosis, CSC inhibition	Breast, prostate	0.2–2 µM	[6]
Dactinomycin	Streptomyces spp. (Microbial)	DNA intercalation	Wilms' tumor, sarcoma	0.01–0.1 µM	[15]
Chlorotoxin	Scorpion venom (Leiurus quinquestriatus) (Animal)	MMP-2 inhibition	Glioma	~1 µM	[5]
Discodermolide	Deep-sea sponge (Discodermia dissoluta) (Animal)	Microtubule stabilization	Lung, breast	5–10 nM	[7]

Panel A–J represent different classes of phytochemicals and natural product–derived molecules: (A) Curcumin (diarylheptanoid), (B) Resveratrol (stilbene), (C) Betulinic acid (triterpene), (D) Honokiol (neolignan biphenol), (E) Paclitaxel (diterpene alkaloid), (F) Genistein (isoflavonoid/soy isoflavone), (G) Harmaline (tetrahydro-β-carboline alkaloid), (H) Salinomycin (polyether ionophore), and (I) Vincristine (vinca alkaloid). Molecular weights (MW) are indicated below each structure in Daltons (Da).

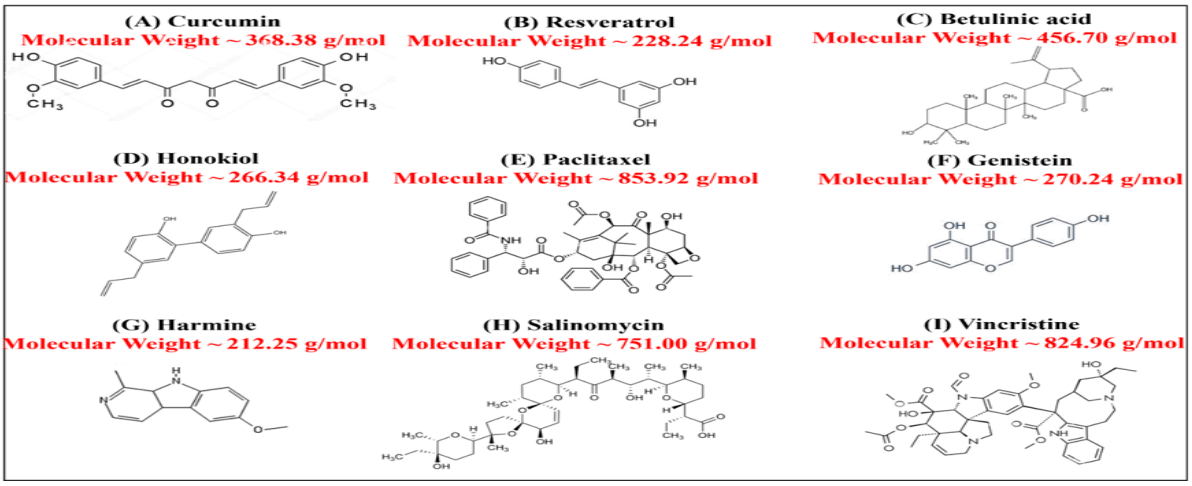

Fig. 3: Chemical structures and molecular weights of selected bioactive compounds investigated in the present study

III. MECHANISMS OF ANTICANCER ACTION

3.1 Apoptosis Induction

Apoptosis is a programmed cell death mechanism often deregulated in cancer. Natural compounds can activate both the intrinsic mitochondrial and extrinsic death receptor pathways. Honokiol and curcumin upregulate pro-apoptotic proteins like Bax and p53 while suppressing Bcl-2. Betulinic acid initiates mitochondrial ROS generation, leading to cytochrome c release and caspase activation. Betulinic acid's pentacyclic triterpenoid scaffold with a C-28 carboxylic acid is essential for mitochondrial membrane permeabilization and cytochrome c release.

3.2 Cell Cycle Arrest

Cancer cells exhibit uncontrolled proliferation. Many natural products target cell cycle regulators. For example, paclitaxel stabilizes microtubules and causes G2/M phase arrest. Camptothecin causes S-phase arrest by inhibiting DNA topoisomerase I. Flavonoids like apigenin and genistein act on CDKs and cyclins to regulate progression at various checkpoints.

3.3 Anti-Angiogenic Effects

Tumor growth depends on neovascularization. Natural agents like thymoquinone, curcumin, and fucoidan inhibit VEGF signaling, HIF-1α expression, and endothelial cell migration. Squalamine inhibits endothelial cell proliferation by disrupting intracellular calcium homeostasis.

3.4 Anti-Metastatic Properties

Natural compounds also target metastasis by inhibiting MMPs, EMT, and cancer cell adhesion. Resveratrol suppresses MMP-2 and MMP-9. EGCG reduces the expression of mesenchymal markers, preventing epithelial cell detachment and migration.

3.5 Epigenetic Modulation

Natural compounds such as curcumin, genistein, and psammaplin A inhibit DNMTs and HDACs. This results in reactivation of silenced tumor-suppressor genes. Sulforaphane from broccoli modulates histone acetylation and affects microRNA expression, contributing to its anticancer effects.

3.6 Immunomodulation

The immune system plays a critical role in recognizing and eliminating tumor cells. Fucoidan enhances NK cell activity, while β-glucans from mushrooms activate macrophages and dendritic cells. Withaferin A enhances Th1 cytokine production and reduces Treg cells, thereby boosting anticancer immunity.

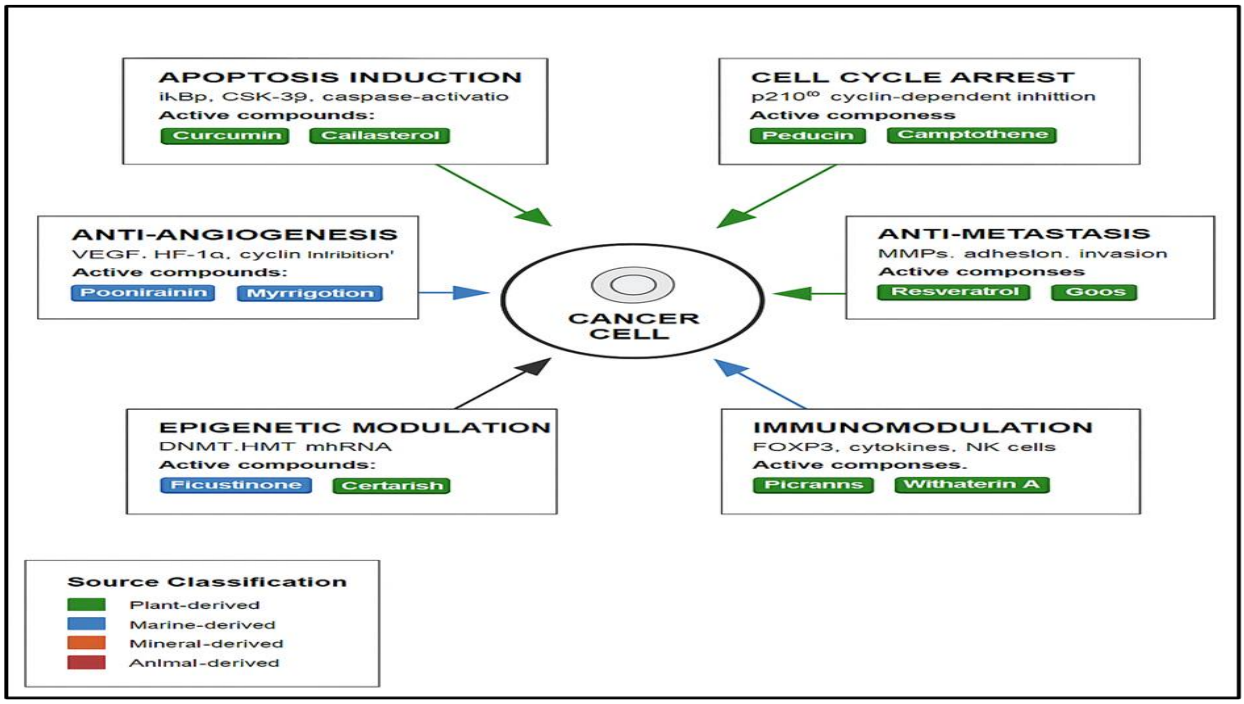

Fig. 4: Mechanistic overview of natural compounds targeting cancer cell pathways.

Plant-, marine-, mineral-, and animal-derived compounds modulate six key cancer hallmarks: apoptosis induction (Curcumin, Callasterol), cell cycle arrest (Peducin, Camptothecin), anti-angiogenesis (Poonirainin, Myrrigoton), anti-metastasis (Resveratrol, Goos), epigenetic modulation (Ficustone, Certarish), and immunomodulation (Picranns, Withaferin A). Source classification is indicated by color coding.

IV. SYNERGISTIC EFFECTS WITH CHEMOTHERAPY

Natural compounds often enhance the efficacy of standard therapies. Curcumin increases the cytotoxicity of cisplatin by downregulating NF-κB, MAPK, and PI3K/Akt signaling, and reducing oxidative stress and nephrotoxicity. Taccalonolides show additive effects with paclitaxel by stabilizing microtubules through different binding sites. Honokiol sensitizes cancer cells to doxorubicin and gemcitabine, reducing required dosages.

Natural agents may also reduce adverse effects. Gingerol and silymarin mitigate chemotherapy-induced nausea and hepatotoxicity, respectively, improving patient compliance and treatment outcomes.

V. CLINICAL AND PRECLINICAL EVIDENCE

Extensive preclinical investigations demonstrate that numerous bioactive natural products exert potent anticancer activity through multiple mechanisms triggering apoptosis, inhibiting angiogenesis, and modulating key signaling pathways such as PI3K/AKT and NF-κB. Compounds including curcumin, resveratrol, and fucoidan have repeatedly reduced tumor volumes by 40–60 % in murine xenograft models of breast, colon, and liver cancers, while marine-derived metabolites such as trabectedin and halichondrin analogues display nanomolar IC_{50} values against a wide range of solid tumors. Translation of these findings to the clinic, however, is uneven. Trabectedin (ET-743) achieved regulatory approval after a randomized phase III trial comparing it with dacarbazine in previously treated advanced soft-tissue sarcoma demonstrated a significant improvement in investigator-assessed progression-free survival median PFS 4.2 months versus 1.5 months (hazard ratio 0.55; $p < 0.001$) although overall-survival differences were not significant in the overall population (FDA access data). Likewise, the halichondrin-derived microtubule inhibitor eribulin has shown meaningful benefit in specific histologic subtypes: in a phase III analysis of liposarcoma, median overall survival reached ~15.6 months with eribulin versus 8.4 months with the comparator, confirming that certain marine-derived analogues can achieve clinically significant survival advantages when used in the appropriate disease context (Eisai clinical media release). In contrast, many promising polyphenols such as curcumin and epigallocatechin gallate remain confined to early-phase human studies because of poor oral bioavailability and formulation variability, which lead to inconsistent pharmacokinetics and lack of reproducible survival benefit. Combination approaches for example, curcumin with doxorubicin or cisplatin, or fucoidan with platinum agents demonstrate synergistic cytotoxicity and reduced toxicity in animal models but are still largely preclinical or in small phase I/II pilot trials. Collectively, these data underscore both the promise and the translational gap: while mechanistic synergy and robust in-vivo efficacy are well established, only a limited number of natural compounds have produced statistically significant improvements in patient outcomes, and most combination regimens await rigorous phase III validation.

Other examples include:

- EGCG in prostate cancer chemoprevention
- Resveratrol in reducing colon polyp formation
- Withaferin A in suppressing osteosarcoma growth in xenograft models

However, many trials are limited by small sample sizes and a lack of standardization, necessitating further investigation.

Table 2: Clinical and Key Preclinical Studies of Bioactive Natural Compounds

Compound	Model / Trial	Dose / Regimen	Primary quantitative outcome (e.g., median PFS/OS or % tumor reduction)	Stage (preclinical / phase I / II / III / approved)	Reference
Trabectedin	Phase III vs dacarbazine (advanced STS)	1.5 mg/m² 24-h IV q3w	Median PFS 4.2 vs 1.5 mo (HR 0.55; p<0.001); OS no significant difference overall	Phase III / approved for some STS settings	[ref — FDA & JCO]. (FDA Access Data)
Eribulin (halichondrin-derived)	Phase III subgroup (liposarcoma)	standard dosing schedule	Median OS 15.6 vs 8.4 mo (subgroup analysis)	Phase III / approved	(Eisai Media)
Curcumin (example)	multiple small RCTs / pilot studies	variable formulations/doses	Mostly mixed endpoints; limited consistent PFS/OS benefit; bioavailability a major confounder	Phase I/II / varied	(MDPI)
β-Carotene (supplement)	ATBC / CARET RCTs (smokers)	chronic supplementation	Increased lung-cancer incidence in smokers (RR ~1.28 in CARET/ATBC subgroups)	Phase III (prevention) negative/harmful	(GO2 for Lung Cancer)

Table 3: Natural Compounds with Strong Preclinical Promise but Limited or Negative Clinical Translation

Compound	Preclinical promise	Why it failed in clinic / controversy	Key refs
β-Carotene	Epidemiologic association with reduced cancer risk	Large RCTs showed increased lung cancer & mortality in smokers highlights risk of high-dose supplementation	(PMC)
Bryostatin-1	PKC modulator; in vitro activity	Phase II single-agent trials showed limited efficacy; future interest remains in combinations	(PMC)
Curcumin (formulations)	Potent pleiotropic activity in vitro	Poor oral bioavailability and inconsistent formulations inconclusive clinical outcomes	(MDPI)

VI. CHALLENGES IN THERAPEUTIC APPLICATION

Despite promising results, several obstacles impede clinical translation:

Bioavailability: Compounds like curcumin and resveratrol suffer from poor absorption and rapid metabolism.

Standardization: Variability in natural product content due to differences in extraction and cultivation methods.

Toxicity and Interactions: Although generally safer, some compounds may potentiate or antagonize conventional drugs.

Regulatory Hurdles: Lack of large-scale randomized trials delays approval.

Solutions include nanocarriers, liposomes, micelles, and prodrug formulations to enhance delivery. Co-crystal engineering and synthetic analogs also offer strategies to improve stability and pharmacokinetics.

VII. CLINICAL FAILURES AND UNRESOLVED CONTROVERSIES

While natural products have produced clinically approved agents (e.g., trabectedin and eribulin/halichondrin-derived agents), many promising leads have not translated into patient benefit because of poor pharmacokinetics, toxicity at therapeutic doses, inconsistent study design, or unexpected adverse outcomes. A classic safety example is β-carotene supplementation, which paradoxically increased lung-cancer incidence in randomized trials of smokers (ATBC/CARET). Similarly, bryostatin-1 showed limited single-agent efficacy in several phase II cancer trials, illustrating that strong preclinical activity does not guarantee clinical benefit. For polyphenols such as curcumin and resveratrol, poor oral bioavailability and inconsistent formulations have limited reproducible clinical

outcomes despite many positive preclinical reports; recent systematic reviews emphasize the need for standardized, pharmacokinetically-aware trial designs. These cases illustrate the importance of rigorous PK/PD characterization, randomized controlled designs, and improved formulations in translating natural leads to clinical success.

Key unresolved questions include: (i) whether multi-target activity yields durable clinical benefit or merely broader off-target toxicity; (ii) how best to standardize extracts and define active principle(s) for clinical testing; (iii) the impact of interpatient pharmacokinetic variability on efficacy; and (iv) the optimal trial endpoints for natural product–based adjuvants (survival vs. quality-of-life vs. response rate). Addressing these requires coordinated preclinical-to-clinical pipelines, standardized formulations, and larger randomized studies.

VIII. FUTURE PERSPECTIVES

The future of natural product-based therapy is intertwined with advances in synthetic biology, nanotechnology, and personalized medicine. Multi-omics approaches can identify predictive biomarkers for selecting appropriate patients. Deep-sea mining and metagenomic exploration of rare microbial species are opening new avenues for discovery.

CRISPR-Cas systems and AI-driven drug design can accelerate the synthesis of potent analogs. Moreover, integrating traditional knowledge systems with modern pharmacology offers a holistic approach to cancer therapy.

IX. CONCLUSION

Natural compounds represent a vast and valuable repository of structurally diverse molecules with significant anticancer potential. Their ability to act on multiple cellular pathways including apoptosis, angiogenesis, metastasis, and immune modulation makes them ideal candidates for comprehensive cancer treatment strategies. These agents not only offer therapeutic alternatives but also augment the efficacy and safety profiles of conventional chemotherapeutics when used in combination. Despite the challenges posed by issues like poor bioavailability, standardization, and regulatory barriers, advances in drug delivery systems, synthetic biology, and integrative medicine are progressively addressing these limitations. Moving forward, the continued exploration and clinical validation of natural compounds will likely contribute significantly to the development of next-generation, personalized, and holistic cancer therapies.

Author's Contribution

Bhavya Saraf: Drafted initial manuscript sections, performed literature review on plant-derived compounds.

Shreosee Ghosh: Compiled marine and microbial compound data, created figures and tables, and edited final text.

Pranati Das: Conducted data analysis, organized clinical evidence tables, and contributed to discussion and future perspectives.

Rupak Roy: Conceived the study, supervised research, provided critical revisions, and approved the final manuscript as corresponding author.

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